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Editorial

EDITORIAL

# Current challenges in vascular anaesthesia

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The *British Journal of Anaesthesia* is delighted to offer this special issue on Current Challenges in Vascular Anaesthesia. Vascular diseases are responsible for 17.3 million deaths per year worldwide; that is, 31% of global mortality. Cardiovascular disease remains a huge burden worldwide. Even as the rates of cardiovascular mortality have decreased in more economically developed countries, they have continued to increase elsewhere. Cardiovascular mortality rates in Western Europe and North America are in the range of 120–238 deaths per 100 000. This compares with death rates of 240 to 362 per 100 000 in China and rates of over 360 per 100 000 in India and several South East Asian countries.[1]

This special issue is linked to the 2016 World Congress of Anaesthesia being held in Hong Kong. As a leading international journal of anaesthesia, we are proud to have a strong presence in China, South East Asia, and Australia. The *BJA* is affiliated with the Hong Kong College of Anaesthetists. In 2015, the Journal published papers from China, Hong Kong, Taiwan, Japan, South Korea, Australia, and New Zealand.

The special issue is edited by Professors Simon Howell (Editorial Board Member, *BJA*), Jonathan Thompson (Editor, *BJA*), and Michael Irwin (Guest Editor for the special issue). It is with Michael's help and support that we have been able to include reviews by leading authors in Hong Kong and Australia for this special issue in addition to contributions from leading figures in Europe and the UK.

The special issue covers a range of vascular topics. The challenges presented by new endovascular and aortic surgery techniques are outlined by Professor Stephen Cheng[2] of the University of Hong Kong. Drs So and Poon[3] of the Department of Anaesthesiology of Queen Mary Hospital, Hong Kong give a detailed account of the neuromonitoring strategies available for carotid and aortic surgery and highlight the fact that intraoperative management and the choice of anaesthetic technique can have a direct impact on the effectiveness of such monitoring. This review of neuromonitoring complements an overview by Professors Scott and Denton[4] from Melbourne of strategies for spinal cord protection in patients undergoing major aortic surgery. Their review examines the translation into clinical practice of the recent position statement on spinal cord monitoring from the European Association of Cardiothoracic Surgery. Yang and colleagues[5] from Dr Daqing Ma's group at Imperial College in the UK give an overview of organ protection strategies, and Xia and Irwin[6] explore the impact of ischaemic pre- and postconditioning. Moving to specific organ protection, Wong and colleagues[7] examine the pathophysiology and prevention of contrast-induced nephropathy in patients undergoing vascular surgery. The development of new antiplatelet and anticoagulant drugs has added significant complexity to perioperative coagulation management in vascular surgery patients. These challenges are explored in a review by Koenig-Oberhuber and Filipovic[8] of St Gallen in Switzerland. They point out that many accepted practices, such as the use of bridging therapy in patients on systemic anticoagulation for atrial fibrillation, are not supported by new evidence. The common use of such drugs together with the potential for significant haemorrhage during surgery has motivated a review on the management of bleeding in vascular surgery by Chee and colleagues.[9] Finally, a significant proportion of patients undergoing major vascular surgery have severe or chronic pain as a result of their disease. A review by Dr Colvin of Edinburgh, an editor of the *British Journal of Anaesthesia*, writing with Dr Serenty, examines the often vexed issue of the management of pain patients with major vascular disease.[10]

The *British Journal of Anaesthesia* is delighted to launch this special issue on the state of the art in vascular anaesthesia. We hope meets that it meets the needs of clinicians and scientists in equal measure and helps to improve the care of patients undergoing vascular surgery around the world.

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Special Issue

SPECIAL ISSUE

# Novel endovascular procedures and new developments in aortic surgery

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## Abstract

Endovascular repair has evolved to become a viable mainstream treatment for aortic pathology in both acute and elective settings. As technology advanced, traditional anatomical barriers were progressively tackled using new devices and novel procedures, and there are now multiple options available to the vascular surgeon. In the abdominal aorta, advances in endovascular aneurysm repair have been in the treatment of hostile aortic necks using new sealing concepts and ancillary procedures, and in branch preservation using fenestrations and snorkels. Access challenges have been met with a percutaneous approach and low-profile devices, and standard protocols have improved mortality for ruptured aneurysms. In the thoracic aorta, more invasive hybrid procedures have given way gradually to branched endografts. Particular challenges to the anaesthetist include blood pressure control and the prevention of stroke and paraplegia. Current focus in the thoracic aorta is in treating aortic arch pathology and in optimal management of acute and chronic dissections. This review describes the latest trends in the endovascular treatment of aortic diseases and examines the current evidence for different modalities of management.

**Key words:** aorta; aortic aneurysm; endovascular procedures

**Editor's key points**

- In most vascular surgery centres, 60–80% of abdominal aortic aneurysm repairs are now endovascular.
- New stent designs make it likely that the use of endovascular repair for abdominal aortic aneurysm will increase further.
- Thoracic endovascular aneurysm repair is increasingly used to treat type B thoracic aortic dissections.
- Fenestrated endografts have transformed the treatment of thoracoabdominal aneurysms.

Endovascular repair of major aortic pathology, such as aneurysms, dissections, and traumatic rupture, has gained wide patient and surgeon acceptance during the last two decades because of lower morbidity and mortality. Advanced catheter skills have become a requirement for training in vascular surgery. This rapid transformation in the practice of vascular surgery has also had a significant impact on the provision of anaesthesia and intensive care. As endovascular surgery matures, major developments focus on product improvements to enhance delivery, ensure durability, and meet challenging anatomy. Technological advances have been complemented by the continuing refinement of surgical skills and innovation by pioneers in the field. This article gives an overview of these advances in endovascular treatment in the thoracic and abdominal aorta and the potential influence on anaesthetic practice.

## Endovascular repair of abdominal aortic aneurysms

Since its introduction in the early 1990s, endovascular aneurysm repair (EVAR) has become firmly established as a viable treatment

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for abdominal aortic aneurysms. Current commercial aortic stent grafts are in their third to fourth generation. Most endografts are based on a modular bifurcated system, with self-expanding stents on low-porosity fabric and supra- or infrarenal fixation. The graft is introduced via flexible hydrophilic sheaths through bilateral common femoral arterotomies.

The benefits of avoiding laparotomy and aortic cross-clamping, intensive care stay, reduced blood loss, and lower morbidity and mortality compared with open surgery have been well established in randomized trials.[1] In most vascular surgery centres, 60–80% of abdominal aortic aneurysm repairs are now endovascular. The EVAR involves very little physiological perturbation and can be completed under monitored anaesthesia care, with regional or general anaesthesia. A preference for the latter mainly pertains to control of respiration and better digital subtraction images.

Modern developments in EVAR focus on several key areas, as follows: (i) refinement of existing stent graft materials to enable a lower-profile delivery system yet maintaining endograft strength and durability; (ii) simplifying steps in delivery; (iii) allowing for adjustments in positioning for accuracy of placement; (iv) minimizing endoleak and stent graft migration with improved and assisted fixation and seal; (v) improving performance in instances of adverse aortic anatomy; and (vi) extended coverage, with branch preservation.

## Percutaneous approach and lower-profile devices

Most endograft manufacturers are moving towards lower-profile endografts that can be introduced percutaneously. With new material, thinner fabrics, and better sheaths, the latest generation of EVAR delivery systems have reduced significantly in size from 20–22 Fr to as low as 14 Fr gauge, and they can be introduced into narrow access vessels <6 mm in diameter. Percutaneous EVAR (PEVAR) is a completely percutaneous procedure that involves a pre-close technique, in which percutaneously placed closure device(s) are applied before the introduction of the stent graft. PEVAR has been shown to be equally effective and safe, with minimal access-related complications, and is non-inferior to standard femoral cut-down.[2 3] With PEVAR, the hospital stay can be further reduced to a 1 day procedure in selected patients.

## Endovascular aneurysm repair for ruptured aneurysms

Where expertise and equipment are available, EVAR has fast become the gold standard and preferred choice for treating ruptured aneurysms. Multiple randomized studies have shown equivalent results to open repair, with lower morbidity and blood loss in favour of EVAR.[4 5] Recent randomized trials have confirmed that EVAR had similar 30 day and 1 yr mortality when compared with open surgical repair, yet incurred less complications, blood transfusions, and intensive care unit stay.[6] Endovascular aneurysm repair also consumes less hospital resources, with better quality of life and cost-effectiveness, leading to long-term socio-economic gains.[7]

Modern management of patients with ruptured abdominal aortic aneurysms advocates permissive hypotension and a percutaneously introduced suprarenal aortic balloon to effect temporary haemostasis before EVAR. In extremely unstable patients, an aorto-uni-iliac stent graft can achieve an instant seal of the aneurysm, although a femoral–femoral bypass is then required. Most experienced clinicians would now prefer to use a standard bifurcated device. The main limitation of emergency EVAR is postoperative abdominal compartment syndrome, and occasionally, a laparotomy for decompression has to be carried out after successful EVAR. Patients requiring laparotomy after emergency EVAR generally have worse prognosis.

## Branch preservation and extension of seal: fenestrated endovascular aneurysm repair

Traditional EVAR requires a healthy infrarenal 'neck' length of about 10–15 mm below the lowest renal artery origin for secure proximal fixation. Inadequate neck length or excessive angulation are key causes of attachment (type Ia) endoleaks and graft migration. In patients with a short or unhealthy aneurysm neck, the proximal landing zone has to be extended upwards. Fenestrated endografts were designed to land in the suprarenal aorta, with preservation of vital visceral branches of juxtarenal aneurysms. These endografts are custom manufactured to contain scallops (gaps in the fabric on the top of an endograft, reinforced on three sides) or fenestrations (small circular or oval 'holes' in the graft body reinforced by a nitinol wire ring) in the fabric to match the origin of 'target' vessels, such as the coeliac axis, superior mesenteric artery, and both renal arteries. The main graft is unsheathed, yet restrained by diameter-reducing wires to allow adjustments of position. The target vessels are then individually accessed via a contralateral femoral (or brachial) approach and bridged to the main graft body with a balloon-expandable covered stent (Fig. 1). Large series have confirmed that this is a viable approach, with low mortality and

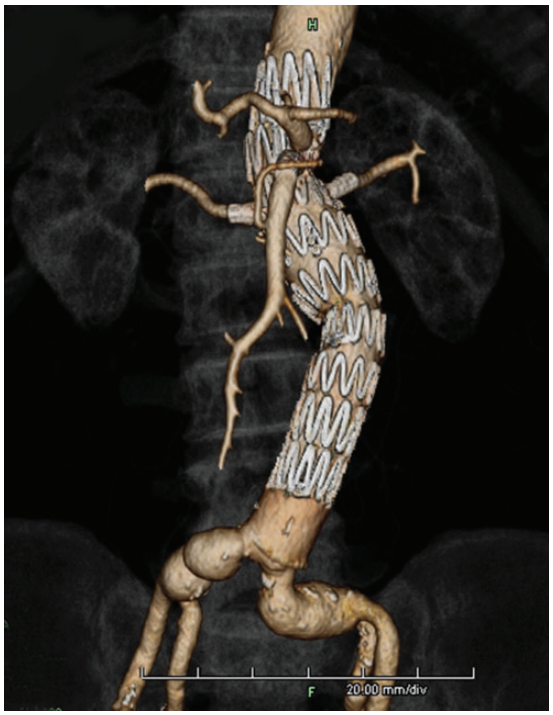


Fig 1 A juxtarenal aneurysm treated with a fenestrated endograft. The coeliac axis was preserved by a scallop, and three fenestrations to the superior mesenteric artery and renal arteries were bridged by covered stents.

morbidity.[8] Long-term mortality is largely not aorta related, despite the need for some secondary interventions to address stent migration and occlusion.[9]

The limitations of fenestrated endovascular aneurysm repair (FEVAR) are the requirement to develop appropriate technical skills and the long duration of the procedure. Large-diameter or multiple femoral sheaths accommodating several catheters may lead to substantial but unrecognized blood loss from the valves in a lengthy procedure. There are also increased risks of target organ (bowel, kidneys) and lower limb ischaemia because occlusive sheaths are left for extended periods of time. When a difficult procedure is anticipated, some operators may construct a temporary axillo-femoral bypass or place a femoral artery perfusion catheter distally to maintain lower limb flow and minimize reperfusion injury and mortality.[10]

Currently, fenestrated grafts are custom-ordered according to individual anatomy, with a 3–6 week manufacture time, and are, therefore, unsuitable for urgent procedures. An off-the-shelf design has been proposed to cater for a proportion of juxtarenal or suprarenal aneurysms.[11] This endograft has a standard scallop for the superior mesenteric artery and two pivoted renal fenestrations at dedicated clock positions to allow for varying renal artery origins in two available designs. Anatomical studies indicate that they are suitable in as many as 70% of patients.[12 13]

## Chimneys and snorkels

Fenestrated grafts are not universally available and also require a higher level of catheter skills. An alternative to FEVAR for treating juxtarenal aneurysms is the 'chimney' or 'snorkel' technique, where the target (usually renal) vessels are first cannulated from the proximal end via a transbrachial (or transaxillary) wire and long sheaths. A standard abdominal stent graft is then advanced above the renal origin and deployed, while the patency of the renal artery(s) is protected by expanding a parallel covered stent alongside the oversized EVAR graft (Fig. 2).[14] This procedure is simpler to perform and is suitable when FEVAR is not feasible technically or the urgency of the patient's condition precludes waiting for graft manufacture. The obvious concerns are the durability of these chimneys and the 'gutter' leaks between the parallel grafts. Anatomical considerations also limit the number of chimneys to be generally not more than two. Mid-term results, albeit from non-randomized data, support this approach, and few complications have been reported.[15]

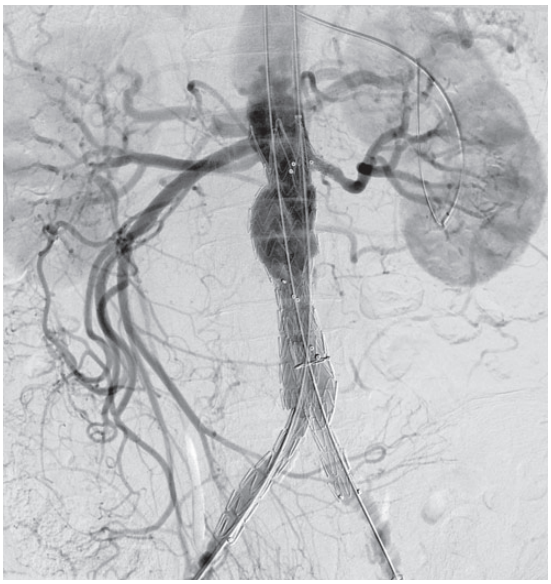

Fig 2 A 'chimney' covered stent preserves blood flow to the left renal artery, with a standard abdominal endograft landing above its origin.

Some physicians have embarked on on-table modification of standard endografts, constructing fenestrations or side-branches as a temporary measure. These physician-modified devices have also proved to be viable, at least in the short term.[16 17]

## Internal iliac artery preservation

The distal landing zone of EVAR is also critical, with a requirement to preserve pelvic blood flow by maintaining patency of at least one internal iliac artery. In patients with an aneurysmal common iliac artery, the distal graft fixation has to be within the external iliac artery. The internal iliac artery will have to be sacrificed by coil embolization; this carries a risk of disabling gluteal claudication or bowel ischaemia. The historical external-to-internal iliac bypass has largely been superseded by the placement of a side-branch endograft incorporating a covered stent into the vessel.

The most widely used device is the iliac branched device. The iliac branched device is essentially an iliac extension graft with a small downward-pointing side-branch in a helical or angled configuration. It is first introduced as a modular component and the target internal iliac artery accessed in a crossover manner by contralateral (or transbrachial) cannulation. The branch and the target internal iliac are then bridged by a covered stent (Fig. 3).[18] Several custom variants and improved second-generation devices are now available.[19–21] In centres where the iliac branched device is not available, an ingenious crossover chimney technique has been used to preserve internal iliac flow.[22]

## Alternative approaches for short-neck aneurysms

As techniques of EVAR improve, vascular surgeons strive to expand its application to younger patients and to those with adverse anatomy, outside the standard 'instructions for use'. In this arena, long-term durability and freedom from secondary interventions and conversions are paramount considerations.

Those who prioritize a healthy neck for landing a stent graft believe that one should not compromise on neck length, as there is ample evidence that a neck length of <15 mm, particularly with angulation, is associated with significantly increased risk of proximal type I endoleaks and a higher incidence of reintervention and rupture.[23] There is also evidence that almost 30% of infrarenal aortic necks will dilate in as short a time as 24 months after open and endovascular repair.[24] Advocates of this approach argue that a secure proximal landing equates with good long-term results and that short necks should be treated with fenestrated endografts.

Recently, newer stent grafts with improved seal characteristics have emerged, using a modification of proximal stent design to accommodate a short (8–10 mm) aortic neck.[25] Another approach goes with a series of nitinol rings instead of the traditional vertical stents in the stent grafts for better conformance and kink resistance, and seal aneurysms with highly angulated necks.[26] Registry follow-up data on these new grafts are relatively short term, but they do present another option in adverse neck anatomy.

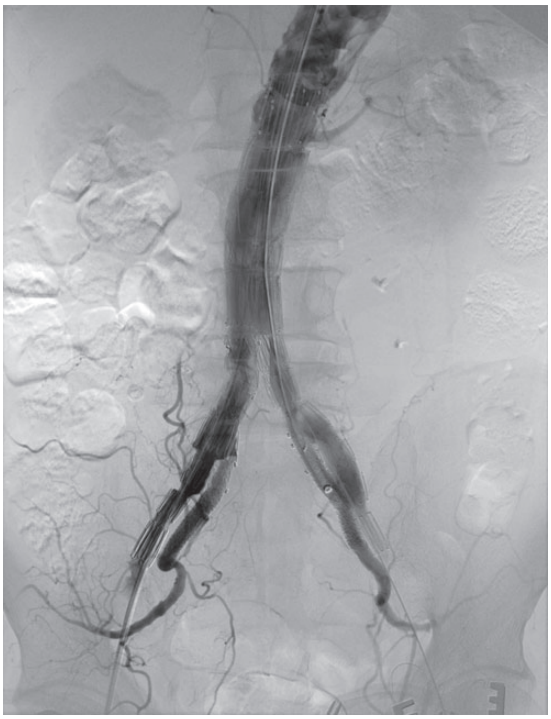

Fig 3 A patient with bilateral common iliac aneurysms, and both internal iliac arteries were preserved after endovascular aneurysm repair with two iliac branched devices.

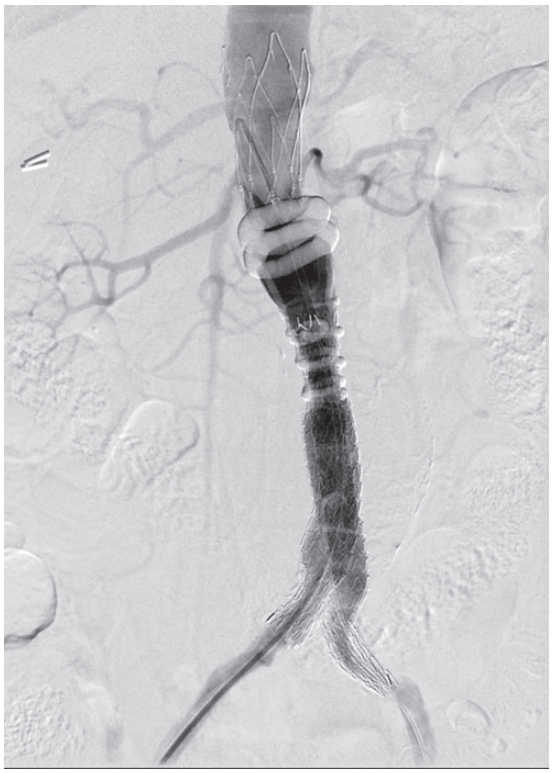

Fig 4 Polymer-filled sealing rings in the Ovation Prime endograft system.

To supplement endograft fixation in questionable landing zones that are short, dilated, or angled, small helical endoanchors have been developed to be placed via a 16 Fr motor-driven transfemoral delivery system into traditional endografts.[27] When applied in numbers in the aortic neck, these small screw-like endoanchors appose the graft and aortic wall, with the goal being to improve the seal and fixation. Early results of these transmural fixations are promising, and they have been extended to treat proximal type Ia endoleaks after both EVAR and thoracic endovascular aneurysm repair (TEVAR), with a 98% technical success rate.[28] These anchors have not been approved for use in the iliac arteries for fear of vessel penetration and bowel injury.

## Polymers and endovascular aneurysm sealing

The traditional model of a modular, covered stent graft supported by a stainless-steel or nitinol self-expanding skeleton is now being challenged. The radial force exerted by traditional sealing stents on the aorta was thought to cause continuing aneurysm neck expansion and ultimate failure of the seal. The Ovation Prime device (Endologix Inc., Irvine, CA, USA) offers a 'neck protection' theory. Instead of self-expanding metal stents, a polymer-filled non-expansile ring is used for sealing the neck. The fast-cure polymer is injected via a side-channel on a collapsible polytetrafluoroethylene body after insertion. The polymer opens the graft body and forms a ring at the neck to achieve a proximal seal. A long suprarenal nitinol stent at the top of the graft provides fixation (Fig. 4). Initial 1 yr results of this very low-profile device showed 99% success, with no migration and very low endoleak rates.[29] This technology may have a special application in reverse-tapering aneurysm necks but remains to be proved in time.

A completely novel concept of endovascular aneurysm sealing (EVAS) has recently emerged to challenge the EVAR principle. Two side-by-side balloon-expandable stents are introduced into the abdominal aortic aneurysm. The stents are attached to two endobags, which are then filled with predetermined volumes of polymer using an injection system under intraluminal pressure monitoring. The cured polymer inside the endobag fills the aneurysm sac completely and obliterates retrograde type II endoleaks from lumbar or inferior mesenteric arteries (Fig. 5). Despite minor concerns of potential rupture, limb occlusion, and polymer leaks, initial results have been promising.[30] This graft has the added potential of allowing sealing in challenging anatomy, such as shorter necks, combined with the use of renal artery 'chimneys',[31] and in accommodating common iliac aneurysms up to 35 mm in diameter without sacrificing the internal iliac artery.[32]

These new technologies open entirely new potential areas of revolutionizing abdominal aortic aneurysm treatment in the future, and are testimony to the rapid developments in EVAR. Although long-term efficacy remains to be proved in larger studies, their immediate impact on endovascular repair places demands for new troubleshooting and imaging techniques.

## Thoracic endovascular stent grafts

The advantages of TEVAR compared with traditional open repair for thoracic aortic disease are potentially even greater than those of EVAR for abdominal aneurysms. Proximal thoracic aortic surgery requires tactics for blood-pressure control, cerebral

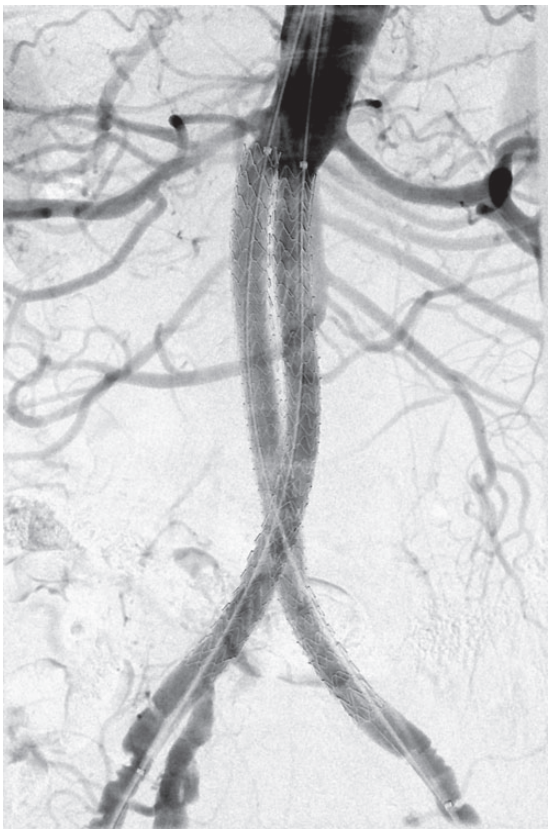

Fig 5 Endovascular aneurysm sealing with the Nellix system, showing two balloon-expandable stents and a polymer-sealed aneurysm sac.

preservation, and distal end-organ perfusion in patients who often have significant pre-existing co-morbidities. Cardiopulmonary bypass, extracorporeal circulation, and hypothermic circulatory arrest often pose prohibitory risks of cardiac complications and stroke. Extensive thoracic replacement with a graft may result in paraplegia. Thoracic endovascular aneurysm repair with a tube thoracic endograft has revolutionized the treatment of certain thoracic aortic pathologies, and has become the undisputed treatment of choice for descending thoracic aortic aneurysms and traumatic thoracic aortic rupture. The profile of thoracic delivery systems has come down to as small as 18 Fr (6 mm), and complete percutaneous delivery is now a reality. During TEVAR deployment, transient induced hypotension is usually advisable to avoid inadvertent distal displacement of the stent graft.

## Preserving supra-aortic branches: hybrid procedures

The proximal seal zone for TEVAR required for a secure landing, normally no less than 2 cm, is often short and subject to further degeneration when the pathology is close to the arch. Purposefully covering the great arch vessels becomes necessary in pursuit of a healthy segment to land the graft. Sacrificing the left subclavian artery by covering its origin may be acceptable in emergency situations, but the current consensus is moving towards preserving the left subclavian (and, therefore, left vertebral) artery blood flow to reduce the risks of posterior territory stroke and paraplegia. A number of approaches have been proposed, and the most widely practised is a left carotid–subclavian bypass using a supraclavicular incision, performed either simultaneously with TEVAR or as a staged procedure. Sometimes a right axillary-to-left axillary artery subcutaneous bypass is used instead (usually by cardiac surgeons less familiar with the neck). The option of placing a left subclavian 'chimney' parallel to the main graft has not been widely accepted for fear of compromising the seal and increasing the risk of retrograde type A dissection. These procedures may also have a bearing on the siting of arterial pressure-monitoring lines during anaesthesia.

In patients for whom the anatomy of the landing zone requires coverage of the left common carotid artery, a carotid–carotid bypass or carotid–carotid–left subclavian bypass can be performed, using a prosthetic graft placed in a retropharyngeal route and two oblique neck incisions. While technically simple, this 'hybrid' approach has the disadvantage of complications associated with carotid artery clamping (stroke) and the risk of later occlusions from the single supplying artery.

Addressing true aortic arch pathologies, such as arch aneurysms, in high-risk patients unsuitable for total open arch replacement, a hybrid 'total debranching' procedure can be performed. This involves a median sternotomy, side-clamping, and construction of a bifurcated prosthetic bypass graft from the ascending aorta to the innominate and left common carotid arteries (with or without left subclavian). This is followed by total coverage of the aortic arch with a retrogradely placed transfemoral TEVAR or, in those with access difficulties or a tortuous aorta, anterogradely from a side-branch.[33] Although less invasive than a total arch replacement, morbidity of this procedure is still high, with immediate concerns of stroke and retrograde aortic dissection, especially in a diseased ascending aorta. Late branch occlusions as a result of kinking in the limited retrosternal space have been reported.

Challenges to anaesthesia in these situations include the added blood loss from a sternotomy, and the need for cerebral perfusion monitoring and control during carotid clamping. Hybrid debranching has been losing favour to less invasive options. Interim solutions using carotid artery chimney(s) or snorkel(s) have been tried with varying success. *In situ* fenestration techniques have also been attempted in the arch but have not stood the test of time.

## Branched aortic arch endografts

The ultimate challenge in endovascular aortic repair is in the aortic arch. Obstacles to successful placement of the stent graft include access issues (large-calibre delivery systems), tortuous descending aortic anatomy, branch preservation, 'beaking' and collapse of the stent graft, accurate placement, cerebral protection, blood pressure control, prevention of retrograde dissection, and preservation of coronary and valve function.

Innovative advances include a single-branched thoracic endograft developed in China, in which a small side-branch (or fenestration) can be snared into the left subclavian artery on a preloaded guide wire.[34] Similar attempts in other countries have, so far, not matured into a viable commercial product. Another approach is with custom-made scalloped grafts[35] or a home-made fenestrated graft in the arch to accommodate the supra-aortic branches that is available in Japan.[36]

Currently, the most promising product is the branched aortic arch endograft. The prevailing design consists of a tube graft with one or two proximal sealing stents with a maximum of 46 mm diameter in the ascending aorta, with a middle recessed segment containing two internal forward-directed side-branches

accessible through two diamond-shaped depressions. The graft is introduced via the femoral artery on a stiff wire into the left ventricle through the aortic valve and deployed. Owing to the proximity to the heart, accurate positioning is achieved with blood pressure control using either rapid cardiac pacing or inferior vena cava occlusion. The latter preload reduction method involves inflating a balloon in the right atrium placed via the femoral vein and occluding the inferior vena cava return. After the graft is deployed, the recessed section allows blood flow into the cerebral circulation while the left common carotid and innominate arteries are bridged with covered stents[37] (Fig. 6). Preliminary short-term success rates are promising, although there are concerns about the risk of stroke from air or thrombus embolization. About 200 of these procedures have been performed worldwide, with a stroke rate of ~10% in major centres.[38] Two companies produce similar grafts, and it is expected that an off-the-shelf design will be available in the near future. These grafts are still currently custom-made and require a staged left carotid–subclavian bypass. They remain large-calibre systems and, currently, their use is limited to high-risk patients unsuitable for open surgery.

## Ascending aorta

Owing to the short length, complex pathology, and proximity to the heart, TEVAR in the ascending aorta remains a largely uncharted territory. Small case series reporting the use of short tube stent grafts demonstrated early feasibility only in highly selected patients.[39 40]

## Thoracic endovascular aneurysm repair in aortic dissections

One of the increasing indications of TEVAR is in treating type B aortic dissections. A stent graft covering the primary entry tear will depressurize the false lumen while re-establishing true lumen and visceral blood flow. Thoracic endovascular aneurysm repair in the acute stage is generally limited to patients with rupture or end-organ malperfusion, because complications rates are higher. Generally, TEVAR is preferably performed in the subacute setting (<14 days). Used alone or with an adjunct renal or visceral stent, TEVAR is very effective in achieving true lumen re-expansion in the acute stage. The current trend is to place a long, tapered covered stent graft from the left subclavian origin to extend the distal coverage to the lower descending thoracic aorta in order to minimize the chance of a late stent graft-induced new entry tear in the dissection flap (SINE; Fig. 7).

There are a number of choices to treat the distal landing site. Most surgeons would place a single stent graft first and deal with retrograde false-lumen flow on follow-up. Long-term data have emerged from randomized studies inidcating that, although the incidence of initial complications and early mortality of TEVAR obviate any advantages compared with medical therapy,[41] after 5 yr there is a distinct survival advantage in type B dissection patients treated with TEVAR compared with best medical management.[42] Thoracic endovascular aneurysm repair also promotes better false-lumen thrombosis and aortic remodelling than medical treatment.[43]

Some surgeons prefer a more aggressive approach to extend the stent graft with a distal bare stent segment all the way into the abdominal aorta, referred as the PETTICOAT procedure, in

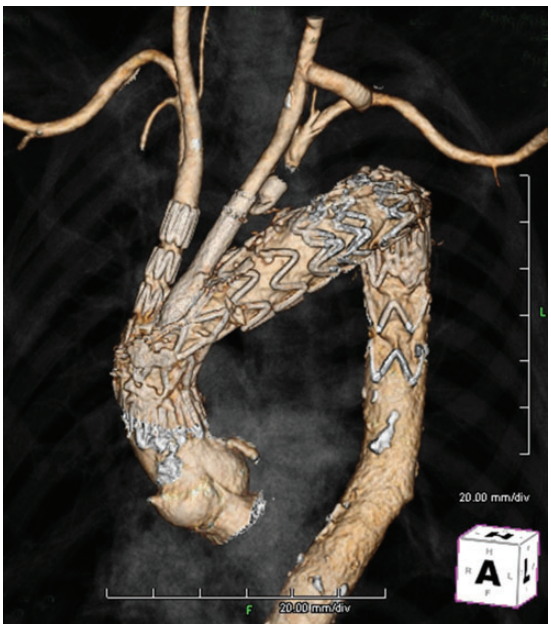


Fig 6 A patient with a large arch aneurysm treated with the Cook arch-branch device. A staged left carotid–subclavian bypass is evident, with the left subclavian origin plugged with an Amplatzer occluder.

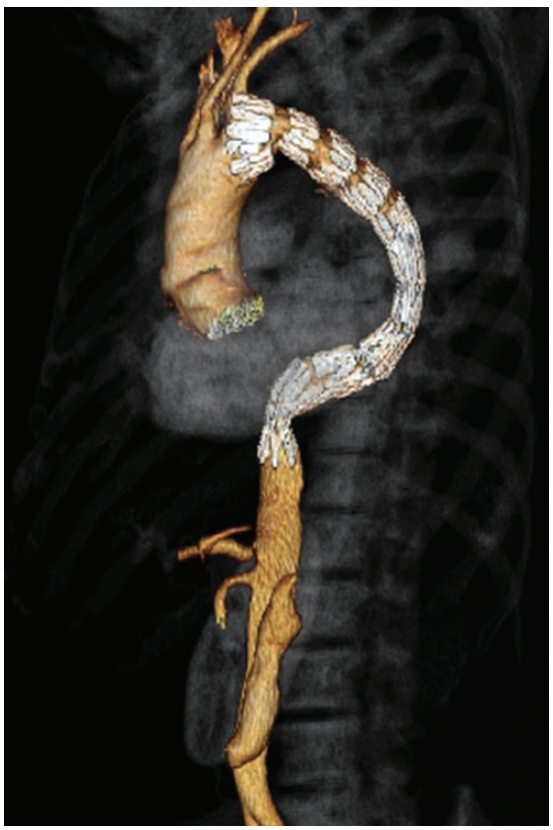

Fig 7 Thoracic endovascular aneurysm repair for type B dissection. A stent graft covers the primary entry tear and distal bare stents expand the true lumen.

an attempt to achieve total true lumen re-expansion or 'complete attachment'.[44] This may be combined with additional covered stents distally to cover any secondary fenestrations.

Although TEVAR is an effective treatment for complicated procedures, it remains controversial as to whether this should be extended to treat uncomplicated type B dissections. The IRAD (International Registry of acute Aortic Dissections) registry showed a continued survival disadvantage of patients on conservative treatment, because of late mortality from aneurysm formation and rupture. Early treatment by TEVAR may prevent this continuing mortality. There are no definitive randomized studies to address this issue, as some may argue that the theoretical advantage of TEVAR is temporary. Interestingly, with the increase in the use of TEVAR, the literature has also shown a corresponding increase in stent graft-related mortality rates over time.[45]

Chronic dissection is more difficult to treat, and the results are generally less favourable. The dissection flap becomes rigid over time, and retrograde filling of the false lumen, despite TEVAR, can lead to persistent pressurization and expansion.[46 47] Generally, a proximal thoracic endograft is placed first, while subsequent staged endovascular procedures or fenestrated grafts may be used later to seal additional distal tears. A new innovative approach is to introduce a large-calibre, blind-ended occluder into the false lumen adjacent to the main stent graft to prevent retrograde false lumen fill. Alternatively, a wide-bottomed stent graft may be used to expand the distal landing zone forcefully in order to seal the false lumen (the 'knickerbocker' procedure).

Currently, TEVAR for treating type A dissection has been limited to very selected patients, and the use of devices in the ascending aorta remains experimental. In major cardiovascular centres, a hybrid procedure may be contemplated for complicated type A dissections. The ascending aorta and arch may be replaced by an open 'frozen elephant trunk' procedure under cardiopulmonary bypass, and a hybrid prosthetic branched graft is sutured proximally. Its distal end consists of a self-expanding stent graft, which is introduced under direct vision (or guide-wire guidance) into the false lumen. This may be the best one-step treatment for suitable patients.

## Thoracoabdominal aneurysms and branched stent grafts

The use of TEVAR or EVAR in patients with true thoracoabdominal aneurysms has evolved rapidly. In the past, an abdominal debranching procedure has been used, whereby separate bypasses are constructed from the healthy lower abdominal aorta or iliac artery to the visceral and renal arteries via a laparotomy. Tube endografts are then deployed to seal the aneurysm and cover the native origins of these vessels. This tedious procedure is not without morbidity and has largely been abandoned in favour of fenestrated and branched devices.

Custom multifenestrated endografts have been used to treat thoracoabdominal aneurysms and dissections. A large contralateral femoral sheath is needed to allow the operator to access multiple target vessels with smaller sheaths and bridge these with covered stents. A high degree of accuracy and planning is necessary, and placement errors and misalignment can have disastrous consequences and even death.

If the aneurysm is large enough, an alternative approach is to design an endograft with multiple downward-pointing side-branches (either angled or helical). This 'branched' endograft can be placed first, and the femoral arteriotomy is then closed to preserve lower limb blood flow. Meanwhile, the side-branches would allow visceral vessel perfusion. The target vessels are then cannulated individually from above via the left brachial artery or axillary artery (Fig. 8). The obvious advantages of this procedure are fewer concerns for visceral and lower limb ischaemia, and more flexible positioning of the stent graft. Cannulation from above is also technically easier, and there will be less instrument clutter. There may also be a durability advantage compared with fenestrated grafts because of the more anatomical position of the caudally directed side-branches. A recent large series on fenestrated and branched grafts for treating type II and III thoracoabdominal aneurysms incorporating 1305 fenestrations and branches reported 96% target vessel preservation, low mortality (7% for type II and 3.5% for type III), spinal cord ischaemia incidence of 4%, and a 7.6% reintervention rate.[48]

Branched thoracic endografts can be combined with a number of fenestrations as a custom design to accommodate various anatomies. A standard off-the-shelf T-branch option has also been developed with a choice of tube extensions and has proved to be equivalent to custom branched grafts in terms of performance and operating time.[49]

As in all instances of extensive thoracoabdominal aortic coverage, paraplegia is the main concern for endovascular repair. Experienced clinicians in some centres have adopted the routine insertion of a cerebrospinal fluid drain for 48 h, controlled hypertension, and preservation of vital side-branches (left subclavian and internal iliacs) to reduce the risk of paraplegia.

In centres where these endografts are not available, surgeons have come up with innovative solutions, including the placement of multiple covered stents in the contralateral limb of a standard bifurcated endograft to act as 'branches', on-table

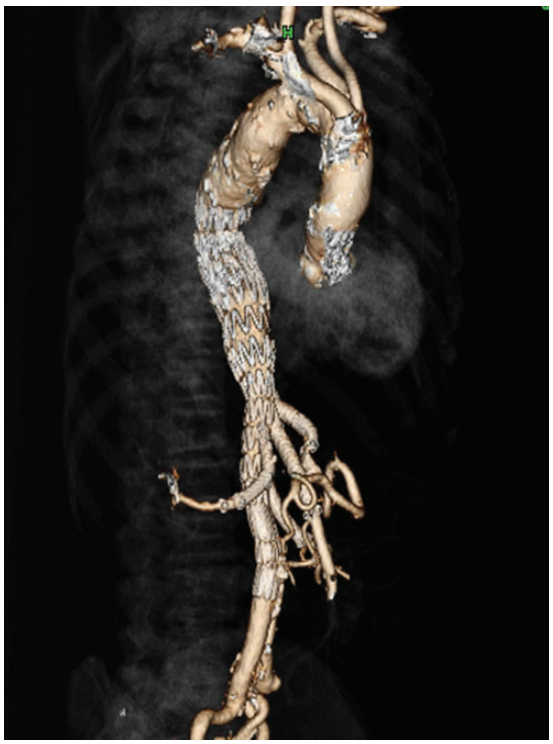

Fig 8 A four-vessel branched endograft, with covered stents to visceral vessels, successfully excludes a thoracoabdominal aneurysm.

physician modifications, or a parallel 'sandwich' technique incorporating multiple covered stents. Although ingenious, the durability of these devices is in question, and no doubt they will be replaced by commercial devices once they are available.

## Multilayer flow modulators

In certain patients with complicated thoracoabdominal aneurysms but who are unfit for open surgery or even endovascular stent grafts, a company has proposed a concept of placing a series of multilayer bare stents in an overlapping fashion in the aorta. The concept is based on haemodynamic principles, and the stents act as a flow modulator to preserve side-branch perfusion yet allow thrombosis in the aneurysm. Reports after years of trials have yielded inconsistent results to justify widespread usage. A recent UK pilot study on 14 patients could not confirm the efficacy to prevent aneurysm expansion, while the rate of stent dislocation was high.[50] Further review of this concept is necessary.

## Hybrid interventional operating theatre

In view of these developments, intraoperative imaging demands are on the increase, and image quality and field of view are vital to successful modern vascular surgery. The vascular surgeons of today work in a purpose-built hybrid operating room environment. Modern fixed C-arm equipment includes software for preoperative planning and fusion of computed tomography (CT) images to intraoperative fluoroscopy. On-table CT scanning can be done on completion of the procedure to check for anatomical positions and endoleaks before the patient leaves the operating table.

Complex endovascular procedures often involve multiple access sites, such as the femoral, left infra- or supraclavicular, and right cervical incisions. One or two teams of operators may need to occupy these positions, coupled with the C-arm and multiple monitors. The placement of the anaesthetic machine and tubes should be anticipated in positioning the patient and discussed before surgery.

As procedures become lengthy, radiation protection is essential both for the patient and for the operators, anaesthetists, and nurses. Although there have been a number studies on radiation exposure in endovascular procedures that confirm operator safety, it is good practice to adhere to rigid screening protection, wear radiation aprons and glasses, and avoid angled C-arm projections. The radiation dose is generally higher in TEVAR than EVAR, and also during digital subtraction acquisition runs. Basic knowledge of radiation protection and good practice are required to minimize the risks of radiation exposure.

## Conclusion

Vascular surgery has undergone an unprecedented transformation in the last two decades, largely driven by technology and physician innovation. The plethora of procedures and theories described are but a proportion of what is possible. Endografts and procedures may become outdated or superseded by improved versions within a short time, and large-scale randomized trials are difficult to perform. Although not all these technologies are available and operator skills and equipment may vary, everyone involved in managing patients undergoing vascular surgery should strive to keep themselves informed of the latest evidence and exercise meticulous planning and patient selection to ensure continuing success.

## Declaration of interest

None declared.

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Special Issue

# Intraoperative neuromonitoring in major vascular surgery

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## Abstract

There has been a growing interest in using intraoperative neuromonitoring to reduce the incidence of stroke and paralysis in major vascular interventions. Electroencephalography, various neurophysiological evoked potential measurements, transcranial Doppler, and near-infrared spectroscopy are some of the modalities currently used to detect neural injuries. A good understanding of these modalities and their interactions with anaesthesia is important to maximize their value and to allow meaningful interpretation of their results. In view of the inter-individual differences in anatomy, physiological reserves, and severity of pathological processes, neuromonitoring may be a valuable method to evaluate the well-being of the nervous system during and after surgical interventions. In this review, we summarize some of their applications, efficacies, and drawbacks in major carotid and aortic surgeries.

**Key words:** aortic surgery; carotid surgery; intraoperative neurophysiological monitoring; neurological injury; vascular surgical procedures

**Editor's key points**

- Carotid surgery and carotid stenting are associated with stroke rates of between 3.2 and 7.0%.
- No neuromonitoring modality has been conclusively proved to be superior when used in carotid surgery.
- The T4–T8 segment of the spinal cord is particularly susceptible to reduced perfusion during aortic procedures.
- Volatile anaesthetic agents may interfere with the monitoring of evoked potentials, and total i.v. anaesthesia is generally preferred in this setting.

Neurological complications, including stroke and spinal cord ischaemia, are some of the most devastating complications in major vascular procedures for carotid and aortic diseases, significantly increasing intensive care unit and hospital length of stay, morbidities and mortality.[1–3]

The International Carotid Stenting Study (ICSS) reported procedural stroke rates of 7 and 3.2%, and 120 day stroke rates of 7.7 and 4.1% for carotid stenting and endarterectomy, respectively.[4 5] The incidence of finding new ischaemic lesions on magnetic resonance imaging after such interventions can be as high as 50%.[5 6] Aortic surgery, even with recent advances in surgical techniques, is associated with a significant risk of stroke (3.1–6%)[1 7–10] and spinal cord ischaemia (2.5–28%).[2 7–9 11–13] The reported rate of cerebral ischaemia in thoracic aortic surgery varies from 2.2 to 10.5% for thoracic endovascular procedures, and the paraparesis rate is reported as anything from 0.5 to 48% for open procedures.

Although of concern, these high incidences are perhaps not surprising because several features known to be associated with perioperative stroke in non-vascular surgeries are prevalent in vascular patients.[14–16] Furthermore, surgical manipulation of diseased vessels, together with procedure-related hypotension, can cause global hypoperfusion and embolic events leading to

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iatrogenic neurological injuries.[17] Activation of the neurotoxicity cascade and reperfusion injury from hyperaemia, tissue oedema, and inflammatory response can also perpetuate the process, which sometimes manifests in the postoperative period as new or worsening neurological deficits.

There has been substantial interest in using intraoperative neuromonitoring (IONM) to reduce the incidence of stroke and paralysis. It is an appealing option, because the risk of injury varies with individual anatomical and physiological differences. For example, variation in the cerebral collateral circulation, in particular the circle of Willis, is common.[18 19] Anomalies of the great vessels and their branches, with different degrees of dominance in blood supply, can result in variable extents of ischaemia should one of them be hypoperfused. The number of radiculomedullary arteries and the location of the artery of Adamkiewicz may also differ significantly.[20] Although preoperative radiological investigations can delineate such inter-individual variability, perfusion augmentation via collateral circulations can be a dynamic process, which is difficult to determine in advance of surgery. Furthermore, the robustness of pressure autoregulation and vascular reserve can be modified by pathological processes and the metabolic state of the tissue. Hence, IONM is an attractive option to ascertain, in real time, the well-being of the nervous system during high-risk vascular interventions. A useful IONM modality would be one capable of identifying injuries early enough to trigger aggressive measures to preserve the tissue of interest. It may also help to clarify physiological targets, to assist in clinical decision-making, and to provide prognostication guiding subsequent care. However, it is important to appreciate that patient outcome can only be improved if the appropriate monitoring modalities are selected, the interpretation of data is accurate, and effective management is initiated in a timely manner when necessary.

In this review, we discuss some of the commonest modalities of neuromonitoring and their applications in carotid and major aortic surgery. We examine some of the current evidence regarding their efficiency, limitations, and challenges.

## Methods

The search engines used included Ovid, Medline, and PubMed, last accessed March 2015. The keywords used included the following: neuromonitoring, intraoperative monitoring, cerebral monitoring, spinal cord monitoring, brain protection, spinal cord protection, electroencephalography, evoked potentials, transcranial Doppler, near-infrared spectroscopy, vascular surgery, carotid surgery, aortic surgery, and endovascular surgery. These keywords were used in combination such that terms related to monitoring type were paired with surgery type. Exclusion criteria were animal studies and articles published in non-English language journals. Perioperative clinical outcome measures were restricted to neurological deficits such as stroke, paraplegia or paraparesis, and death.

## Neuromonitoring modalities and the effects of general anaesthesia on neuromonitoring modalities

In general, modalities can be classified into those that monitor the neurophysiological function [electroencephalography (EEG) and evoked potential measurements], assess haemodynamic status [transcranial Doppler (TCD) and stump pressure], or measure cerebral oxygenation status [near-infrared spectroscopy (NIRS)]. Features of an ideal neuromonitor are summarized in Table 1.

### Awake neurological monitoring

Continuous clinical monitoring of awake, cooperative patients is generally regarded as the gold standard for neuromonitoring during surgical interventions. Awake monitoring must be done

**Table 1** Features of an ideal monitor

| | Brain monitoring | Spinal cord monitoring |
|---|---|---|
| General | • Minimally invasive and no complications from its use<br>• Non-obstructive to surgical field<br>• Measureable in all patients<br>• Can be used both intraoperatively and postoperatively<br>• High sensitivity and specificity in detecting ischaemia<br>• Immediate detection when ischaemia occurs to guide rescue measures before permanent damage<br>• Clear cut-offs for ischaemia<br>• Easy interpretation even by inexperienced personnel, non-operator dependent<br>• Objective, quantitative, continuous measurement<br>• Minimally affected by anaesthetic agents<br>• Prognostic value in predicting postoperative neurological recovery after injury | |
| Carotid surgery | • Differentiation of cortical and subcortical ischaemia<br>• Differentiation of localised versus global ischaemia<br>• Detection of hypoperfusion, thromboembolism and hyperperfusion<br>• Detection of emboli and quantification of emboli load<br>• Assurance of adequate physiological and pharmacological cerebral protection | |
| Aortic surgery | • Detection of emboli and quantification of emboli load<br>• Assurance of adequate physiological and pharmacological cerebral protection | • Option of detecting deficits in various neural pathways depending on surgical need<br>• Can be used postoperatively to detect delayed neural deficits |

properly at the appropriate time to detect subtle dysfunction and guide surgical decision-making. Patients are asked to perform tasks to check their orientation in time and place, language and mental capacity (e.g. counting backwards), motor activity (e.g. squeezing a squeaky toy or fluid-filled pressure transducer), and level of consciousness. Focal neurological deficits, confusion, restlessness, or a decreased level of consciousness are markers of possible ischaemia. The major limitation of this method is that awake procedures are only possible with calm, cooperative subjects. The operators have to work quickly and be attentive to the patient's needs.

## Electroencephalography

The scalp EEG reflects the spontaneous electrical activity of the cerebral cortex but not of deeper structures. Eight, 12, or 16 scalp electrodes may be used. A reduction of cerebral blood flow from an adult normal value of 50 ml 100 $g^{-1}$ $min^{-1}$ to <22 ml 100 $g^{-1}$ $min^{-1}$ will cause neuronal dysfunction, with cerebral ischaemia seen as cerebral blood flow decreases further down to 7–15 ml 100 $g^{-1}$ $min^{-1}$.[21] Interpretation of the EEG involves visual inspection of the frequency content and distribution of activity across the cortex, in addition to the recognition of specific patterns of activity. There are many ways to aid this interpretation (e.g. using a cerebral function analysing monitor, compressed spectral array, density spectral array, and brain symmetry index). The cerebral function analysing monitor shows the mean amplitude of the EEG signal plotted in time and the relative power in the frequency band of relevance.[22] Compressed spectral array is a graphical representation of the amplitudes of the wavelengths of interest by a pseudo-three-dimensional topographic plot of power *vs* frequency *vs* time, making it easier to detect and interpret changes. Density spectral array conveys the same data but by a greyscale-shaded or coloured two-dimensional contour plot, with dominant frequencies depicted as warmer colours (red and orange) and minor frequencies shown as cooler colours (blue and green). The β band, corresponding to 13–30 Hz, is most sensitive to ischaemia, whereas the α band (8–12 Hz) is a poor indicator of stroke.[23] Various EEG changes can be considered significant. A decrease of more than 50% of fast background activity, reduction in amplitude of >60%, an increase in δ wave (0–4 Hz) activity, slowing of overall frequencies, and a complete loss of signal are some of the recognized ischaemic signs.[24 25] The brain symmetry index can be used to assist analysis of asymmetry between the two cerebral hemispheres (spatial brain symmetry index) or of changes over time compared with baseline (temporal brain symmetry index).[26] During open carotid endarterectomies, EEG changes associated with a critical reduction in cerebral blood flow frequently occur within 20–30 s after clamping.[25]

Some of the limitations of the EEG include the need for interpretation by experienced personnel because of the complex and continuous generation of raw data. Although the EEG measures activity of the cerebral cortex, which is more susceptible to hypoperfusion, it may lack sensitivity for subcortical structure ischaemia. Watershed and embolic infarcts may be missed. Interpretation of the EEG can also be complicated by administration of anaesthetic agents and coexisting hypothermia.[21] Its intraoperative interpretation may be difficult in patients with abnormal baseline; for example, in patients with pre-existing strokes.

Processed EEG monitors, such as the bispectral index (BIS), though initially designed to assess hypnotic level, have also been used to detect cerebral ischaemia in some small studies.[27 28] A reduction in BIS value by >10 or by 30–40% may correlate with ischaemia. However, BIS devices have a 30–60 s delay in reporting, and it is unknown whether the reduced BIS value reflects localized ischaemia or global cortical inactivity. Its use in this regard is still controversial.

## Evoked potentials: somatosensory, motor, and brainstem auditory evoked potentials

The integrity of the nervous system is examined by applying stimuli of known intensity, duration, and frequency at one end, and characterizing the triggered responses at the other end of the neural pathway. A reduction in response amplitude (e.g. by 50%), an increase in latency (e.g. by 10%), a total loss of signal, or the need to increase stimulation voltage are some of the signs that indicate possible ischaemia.

Recording of somatosensory evoked potentials (SSEPs) involves stimulation of a peripheral sensory nerve, such as the median, posterior tibial, or common peroneal nerve, and recording the signal transmission through the dorsal column in the spinal cord, medial lemniscus, thalamus, and finally, into the sensory cortex. In general, the brain structures most at risk during hypoperfusion include the cortical grey matter and the watershed areas. During carotid endarterectomy, median nerve signal abnormalities are indicative of hypoperfusion in the watershed of the middle cerebral artery, whereas tibial nerve signal abnormalities point to the anterior cerebral artery watershed.[29]

To interrogate the motor pathways, the motor cortex is transcranially stimulated through the scalp. The signal travels down the corticospinal tract in the anterior spinal cord, and the motor evoked potential (MEP) is recorded at the spinal cord level ('D' or direct waves), along peripheral motor nerves (neurogenic MEP), or over the muscles with good corticospinal innervation (e.g. abductor pollicis brevis and tibialis anterior) as compound muscle action potentials.

In the recording of brainstem auditory evoked potentials (BAEPs), stimulation of the usual hearing pathway is done by delivering sound via headphones, which in turn activates the cochlear nucleus, lateral lemniscus/inferior colliculus in bilateral pons, and then the auditory cortex. The resulting nerve impulse has seven peaks corresponding to different structures along the pathway, thereby enabling identification of the sites of any insults, including those that involve the posterior circulation of the brain.

Evoked potentials have the advantage of giving objective, quantitative information that can be compared over time. They are especially useful when the baseline EEG is abnormal. Unlike the EEG, which measures only cortical activities, evoked potentials provide information on the integrity of the whole neural pathway. The disadvantages include potential alterations by general anaesthetics, especially volatile agents. Propofol interferes with evoked potentials to a lesser degree, making total i.v. anaesthesia the technique of choice when evoked potentials are used, especially for MEP measurement. Each type of evoked potential recording monitors a specific neural pathway and provides information only on that part of the neurological system. Therefore, a combination of different evoked potential measurements is often needed to cover the numerous pathways at risk during surgery. The evoked potentials of interest are very small in voltage and are susceptible to interference from other electrical apparatus in the operating theatres. During SSEP and BAEP recording, extra time is needed for signal averaging to improve the signal-to-noise ratio, and this small delay in data acquisition is necessary to allow accurate interpretation. Subdermal needle electrodes used can potentially cause needle stick injuries or transmit infection, and can be inserted only after anaesthesia. For MEPs, corkscrew electrodes used for scalp attachment may

cause local bleeding. Bite blocks are necessary because tongue and lip lacerations from MEP stimulation have been reported.[30–32]

## Transcranial Doppler

Transcranial Doppler uses a 2 MHz focused, pulsed Doppler ultrasound transducer to measure local blood flow velocity and can present the data graphically as velocity over time. Usually, the proximal portions of large intracranial arteries, such as the middle or anterior cerebral artery, are used. As these vessels often have fixed diameters, the measured maximal velocity corresponds well to blood flow. The angle of insonation between the ultrasound beam and the direction of arterial flow needs to be <30° to produce reasonably accurate measurements.[33]

The velocity profile measured by TCD changes significantly during pathological processes. If the total volume flow is maintained, isolated arterial stenosis causes focal velocity increase and local turbulence at the stenotic site and a reduction in velocity distal to stenosis. If volume flow is compromised, such as during proximal carotid cross-clamping, velocity reduces when collateral flow is inadequate. Emboli appear within the Doppler spectral waveform as characteristic high-intensity transient signals, which can be readily identified.

The clinical applications of TCD in vascular surgery include monitoring of arterial and shunt flow levels, enabling diagnosis of hypoperfusion, thrombosis, or hyperperfusion. The TCD is also the only monitor that can identify embolic load, providing semi-quantitative information as feedback to the surgeon regarding dissection technique and effects of vascular manipulations.

Transcranial Doppler is an operator-dependent technique. It cannot be used in 10–15% of patients because of the absence of an acoustic transtemporal window from temporal bone hyperostosis, a phenomenon more common in those who are older, females, and African-Americans. Dislodgement of TCD probes and signal interference are possible, especially if the probes are close to the surgical site.

A baseline TCD evaluation should preferably be done before surgery to document the presence of a transtemporal window, to obtain baseline velocity values, and to familiarize the operator with the patient's arterial anatomy and collateral flow patterns. During surgery, the transducer can be mounted on a headpiece and placed around the patient's head for continuous monitoring, and headphones may be used to block out background noise. Bilateral middle cerebral artery insonation may be used to allow comparison between hemispheres.

## Near-infrared spectroscopy

The aim of NIRS is to measure regional cerebral oxygen saturation ($rS_{O_2}$). Adhesive pads placed over the patient's forehead emit and capture reflected near-infrared light passing through the cranial bone to and from the underlying cerebral tissue. The amount of light reaching the photodetector is inversely proportional to the amount absorbed by oxyhaemoglobin and deoxyhaemoglobin at specific wavelengths. Commercial NIRS devices usually have two light detectors to allow the subtraction of extracranial tissue signals. The values obtained reflect primarily cerebral venous saturation, and pulsatility is not a requirement for valid readings.

Near-infrared spectroscopy provides non-invasive, continuous monitoring even in the absence of flow. The sensors are easy to apply, the machine is portable, and the measured saturations are displayed as percentages. It can be used to identify both hypo- and hyperperfusion. The sensors are designed to be applied to the forehead and thus measure oxygen saturation only at the frontal areas, which some consider to include the watershed area between the anterior and middle cerebral artery territories. The measured values can be affected by extracranial blood flow and ambient light. Measured baseline $rS_{O_2}$ may be low in an area of previous infarction. There is no recognized normal $rS_{O_2}$ range and considerable inter-individual variations exist, making relative changes in NIRS more useful than absolute values.[29]

## Stump pressure

During carotid endarterectomy, when the proximal common carotid and external carotid arteries are clamped, the pressure measured at the internal carotid artery distal to the clamp site is the stump pressure. It reflects the back pressure on the internal carotid artery, supplied by the collaterals from the circle of Willis. It is considered to be a surrogate marker of perfusion in the ipsilateral cerebral hemisphere. A pressure below 40–55 mm Hg is often used as a threshold for intervention.

## Effects of general anaesthesia

Ideally, any change in the measured neuromonitoring variables should reflect either mechanical or metabolic stress to the neural tissue of interest. In real life, anaesthetic agents can exert direct effects on neural tissues and have significant influence on neuromonitoring variables, clouding their interpretation. In this regard, the EEG and MEP are most susceptible. The EEG can be depressed by both inhalational and i.v. anaesthetics in a dose-related manner, ultimately resulting in burst suppression and electrical silence. Volatile anaesthetics cause significant dose-dependent depression of myogenic MEP signals, possibly by inhibiting pyramidal activation of spinal motor neurones. I.V. agents, such as propofol, when carefully titrated, usually do not affect MEP signals significantly. Although a large propofol bolus can cause a reduction or loss of MEP, signals return within minutes because of rapid redistribution and metabolism. Neuromuscular block will inevitably abolish compound muscle action potentials of the MEP by blocking signal transduction at the neuromuscular junction. Opioid infusions, ketamine, and dexmedetomidine in low-dose infusions may all be useful anaesthetic adjuncts that permit MEP recording.

Cortical SSEPs also exhibit increase in latency and decrease in amplitude under the influence of volatile anaesthetics, but to a lesser degree than MEPs. I.V. agents often cause less signal suppression. Brainstem auditory evoked potentials are resistant to anaesthetic effects.

Transcranial Doppler and NIRS are also relatively resistant to the effects of anaesthetic agents, with indirect changes observed because of blood flow changes reflecting physiological changes in response to the drugs. For volatile agents, the net effect seen depends on the balance between direct vasodilation *vs* flow–metabolism coupling-mediated vasoconstriction, with cerebral autoregulation often impaired at doses 1.5–2 times the minimal alveolar concentration. I.V. agents essentially cause a dose-dependent decrease in cerebral blood flow, keeping flow–metabolism coupling mostly intact.

To allow meaningful interpretation of neuromonitoring results, an anaesthetic technique that minimizes interference with the IONM being used should be chosen. Steady-state anaesthetic depth should be achieved and maintained soon after induction, with continuous infusions preferred over bolus administrations. Physiological variables, such as blood pressure, temperature, and patient position, should be kept stable to minimize their effect on signal integrity.

Table 2 Sensitivity, specificity, and diagnostic odds ratio reported by Guay and Kopp[35]

| Monitor (number of studies) | Sensitivity (95% CI) | Specificity (95% CI) | Diagnostic odds ratio (95% CI) | Cut-off points |
|---|---|---|---|---|
| EEG (*n*=5) | 0.70 (0.58–0.80) | 0.96 (0.94–0.97) | 65.3 (20.51–207.71) | |
| Evoked potentials (*n*=3) | 0.84 (0.66–0.95) | 0.78 (0.69–0.86) | 17.7 (2.38–123.85) | Response amplitude 0–50% of baseline |
| Transcranial Doppler (*n*=8) | 0.81 (0.69–0.91) | 0.92 (0.89–0.94) | 58.1 (23.0–146.3) | 48–70% reduction |
| Near-infrared spectroscopy (*n*=5) | 0.74 (0.54–0.89) | 0.82 (0.76–0.88) | 12.1 (3.52–41.24) | 15–20% reduction |
| Stump pressure (*n*=15) | 0.75 (0.69–0.81) | 0.88 (0.86–0.89) | 27.84 (13.38–57.94) | 25–50 mm Hg |

## Application in carotid surgery

The potential benefits of using neuromonitoring in carotid surgery include the following: (i) detection of intraoperative cerebral ischaemia caused by hypoperfusion during cross-clamping, guiding the decision on shunt placement or activation of a stroke protocol; (ii) provision of real-time feedback to surgeons regarding surgical technique and shunt function by detecting cerebral ischaemia and emboli; and (iii) detection of postoperative cerebral ischaemia or cerebral hyperperfusion syndrome (CHS).

### Intraoperative monitoring

A large body of literature in the last 30 yr has been dedicated to finding the most appropriate neuromonitoring technique to detect cerebral ischaemia during carotid surgery. Each of the techniques examined has its shortcomings. Criticisms include EEG being overly sensitive in estimating shunt requirement,[24] false negatives associated with SSEP use, stump pressure not being proved as a standardized or reliable method for detecting cerebral ischaemia, and the lack of a validated NIRS cut-off for hypoperfusion.[34]

In their meta-analysis, Guay and Kopp[35] compared the efficacy of different modalities in detecting cerebral ischaemia. They included 29 prospective trials comparing clinical monitoring with neuromonitoring in carotid endarterectomies performed under regional anaesthesia and estimated the diagnostic odds ratio for each of the five IONM modalities (Table 2). The diagnostic odds ratio is the ratio of the odds of positivity in disease relative to the non-diseased and therefore reflects the strength of relationship between test result and disease. An EEG with a high number of channels had the highest diagnostic odds ratio, followed by TCD and stump pressure. Sequential testing showed that a combination of stump pressure cut-off value of 25 mm Hg together with either TCD or EEG delivered the most promising results for detecting brain ischaemia.

However, there are inherent shortcomings in such a meta-analysis, such as the heterogeneity of patients and the wide range of cut-off points for diagnosis of ischaemia in different studies. Moritz and colleagues[36] tried to overcome these problems by performing four of the IONM modalities in all 48 patients of their prospective trial. Awake clinical monitoring was the gold standard against which SSEP, TCD, NIRS, and stump pressure were compared. Neurological deterioration occurred in 12 patients. They found that none of the monitoring modalities was equal to awake clinical monitoring. The percentage change in blood flow velocity measured by TCD (TCD%), percentage change in cerebral oxygenation measured by NIRS (NIRS%), and stump pressure all provided similar accuracy, but results were worse for SSEPs. They also calculated the best-fit cut-offs for each monitoring modality (Table 3).

However, given that neuromonitoring is usually used in patients under general anaesthesia instead of in the awake state, are these results transferable? In another study, Moritz and colleagues[37] compared various neuromonitoring variables in a randomized trial of 96 patients undergoing carotid endarterectomy under regional anaesthesia *vs* sevoflurane–fentanyl general anaesthesia. They found the results transferable, because values of mean stump pressure, percentage change in cerebral blood flow velocity measured by TCD, percentage change in regional cerebral oxygen saturation measured by NIRS ($rS_{O_2}$%), and the amplitude of SSEPs were not different between the two groups. However, it was noted that further studies are needed to determine the threshold for the diagnosis of cerebral ischaemia under general anaesthesia necessitating shunt placement.

Table 3 Best-fit cut-offs, sensitivity, and specificity reported by Moritz and colleagues.[36] NIRS, near-infrared spectroscopy; NIRS min, minimal cerebral oxygenation measured by NIRS during clamping; NIRS%, relative reduction (compared with baseline) in cerebral oxygenation measured by NIRS; SSEP, somatosensory evoked potential; TCD, transcranial Doppler; TCD min, minimal blood flow velocity measured by TCD during clamping; TCD%, relative reduction (compared with baseline) in blood flow velocity measured by TCD

| Parameter | Cut-off | Sensitivity (%) | Specificity (%) |
|---|---|---|---|
| SSEP | 50% | 82 | 57 |
| TCD min | 25 cm $s^{-1}$ | 100 | 69 |
| TCD% | 48% | 100 | 86 |
| NIRS min | 59 | 100 | 47 |
| NIRS% | 20% | 83 | 83 |
| Stump pressure | 40 mm Hg | 100 | 75 |

Given that the ultimate value of neuromonitoring in carotid surgery would be in the detection of cerebral ischaemia in time for intervention, the appropriate outcome measure should be the incidence of perioperative stroke and death. However, very few randomized controlled trials have been conducted in this regard. A recent update of the Cochrane Review looked at randomized controlled trials that compared routine shunting with no shunting or selective shunting, as well as trials that compared different shunting policies in patients undergoing carotid endarterectomy.[38] The authors included six trials, involving 1270 participants. Two of these trials looked at selective shunting guided by neuromonitoring modalities. The first one, involving 253 participants, showed no significant difference in postoperative neurological deficit between selective shunting with or without NIRS monitoring.[39] The second one, involving 131 participants, showed no significant difference in the risk of ipsilateral stroke between those using EEG and stump pressure *vs* stump pressure alone.[40] It concluded that no method of monitoring in selective shunting produced better outcomes.

In his systemic review, Aburahma[41] studied more than 100 carotid endarterectomy procedures between 1990 and 2010 and analysed the outcome of routine shunting, routine

Table 4 Perioperative stroke rate with different surgical approaches (routine shunting *vs* selective shunting *vs* routine non-shunting) reported by Aburahma and colleagues.[41] SSEP, somatosensory evoked potential; TCD transcranial Doppler

| Surgical approach | Perioperative stroke rate (%) | Perioperative stroke and death rate (%) |
|---|---|---|
| Routine shunting | 1.4 | 2 |
| Routine non-shunting | 2 | 2.2 |
| Selective shunting guided by EEG | 1.6 | 1.8 |
| Selective shunting guided by SSEP | 1.8 | 1.9 |
| Selective shunting guided by TCD | 4.8 | 4.8 |
| Selective shunting guided by stump pressure | 1.6 | 1.7 |
| Selective shunting guided by awake testing | 1.1 | 1.7 |

non-shunting, and selective shunting based on neuromonitoring. He concluded that there was a low perioperative stroke and death rate with the use of routine shunting and with selective shunting guided by EEG, SSEP, stump pressure, and clinical monitoring by awake testing. Routine non-shunting and TCD-guided selective shunting produced worse results (Table 4).

### Postoperative monitoring

Transcranial Doppler and NIRS may be used for the prediction and diagnosis of CHS after surgery. Cerebral hyperperfusion syndrome can occur any time up to 4 weeks after carotid endarterectomy, with the onset usually within hours to days.[42] Patients nearly always have more than a 100% increase in perfusion compared with baseline, which correlates with corresponding changes in the mean blood velocity at the ipsilateral middle cerebral artery measured by TCD. In one study with 184 patients, TCD had a positive predictive value of 41% and a negative predictive value of 99% for CHS when measured within the first 2 h after surgery.[43] In patients who have insufficient temporal bone windows for TCD measurement, there is some evidence that NIRS may be helpful. An increase in $rS_{O_2}$ after revascularization can be a sign of hyperperfusion, provided that cerebral oxygen consumption and arterial oxygen saturation are stable.[42] In a study of 151 patients, a 3% increase in $rS_{O_2}$ had a positive predictive value of 11% and a negative predictive value of 100% for CHS when measured within 1 h after surgery.[44] These studies show that TCD and NIRS are more useful in identifying patients with a low chance of developing CHS.

Apart from hyperperfusion, another mechanism for continued neural injury after carotid revascularizations in the postoperative period is cerebral embolism. The clinical significance of this phenomenon, the relationship between embolic load and symptom manifestation, and the optimal strategies for monitoring, treatment, and prevention are still to be elucidated.

In conclusion, no neuromonitoring modality has been conclusively proved to be superior when used in carotid surgery. Combining different monitors, such as EEG, TCD%, NIRS%, and stump pressure, may increase accuracy. Monitoring of SSEP seems to produce less convincing results. Transcranial Doppler has the added advantage of detecting emboli. Both TCD and NIRS may also have a place in postoperative monitoring.

## Application in aortic surgery

Aortic surgeries carry significant perioperative risk of neurological injury. Endovascular interventions, especially for pathologies involving the aortic arch and thoracic aorta, are less invasive, with decreased blood loss and improved haemodynamic stability compared with open surgical approaches. However, there is a trend towards performing these procedures of considerable complexity on patients with multiple co-morbidities. The perioperative challenges should not be underestimated.

The blood supply to the spinal cord, although complex and variable, has unique anatomical properties that determine its susceptibility to ischaemia during vascular surgery. The blood supply is dependent on three vessels, the single anterior spinal artery and a pair of posterior spinal arteries. The paired posterior spinal arteries, arising from vertebral arteries or posterior inferior cerebellar arteries, run longitudinally along the posterolateral surface of the spinal cord and are supplemented by small radicular arteries at various spinal levels. They largely supply the dorsal white matter tracts. The anterior spinal artery perfuses the anterior two-thirds of the spinal cord, including the anterior grey matter, with cell bodies of the motor neurones, which have a higher metabolic demand. It arises from the vertebral arteries and is augmented by segmental vessels, which can be branches of cervical arteries, intercostal arteries, lumbar arteries, and lateral sacral arteries. The arteria radicularis magna, also known as the great radicular artery or artery of Adamkiewicz, is the largest of such segmental arteries and provides vascular reinforcement for the lower thoracic and lumbar region. It travels with the T9–T12 roots in the majority of instances, but can occasionally follow roots L1 or L2 or have a high origin at T5–T8.[45] The heavy reliance of the anterior spinal artery on segmental radicular supply makes this region vulnerable to ischaemia during surgeries involving the thoracic and thoracoabdominal aorta.

In general, the distribution of segmental arteries divides the spinal cord functionally into three perfusion areas: cervicothoracic, midthoracic, and thoracolumbar regions. Haemodynamic watershed areas occur at the borders of neighbouring regions, where collateral circulation can be inadequate. The cervicothoracic area receives rich vascularization from vertebral arteries and costocervical trunks. The midthoracic area, corresponding to T4–T8 segments, comprises the biggest distance between radicular arteries because it usually receives vascular supply from only a single radiculomedullary artery. This is also the region where the anterior spinal artery is usually at its narrowest, explaining the ischaemic vulnerability of this area during systemic hypotension or feeding vessel occlusion. The thoracolumbar area, extending from around the T8 segment to the conus medullaris, receives support from the artery of Adamkiewicz. Distal spinal cord perfusion is supplied in part by the sacral and pelvic arteries, including branches from the internal iliac arteries.

Several surgical centres have identified patient and procedural factors associated with periprocedural stroke; these include

advanced age, presence of coronary artery disease,[46] severe aortic atheromatous disease,[10] chronic renal insufficiency, previous stroke history, the location and length of aorta involved, proximal graft landing zone '0–2',[1 47 48] and the presence of intraoperative hypotension.[47] It is controversial whether procedures involving the distal aortic arch that require occlusion or surgical bypass of the left subclavian artery may increase the stroke risk.[1 7 8 49–51]

Besides the location and type of aortic procedure, patient factors thought to be predictive of spinal cord ischaemia after thoracic aortic repair[52] include advanced age, chronic obstructive airway disease, renal insufficiency,[3] and hypertension. Perioperative blood loss and hypotension may play a role. Involvement of the thoracic aorta, increase in aortic coverage length, and the number of stent grafts deployed may also increase the risk of paraplegia because of the higher number of intercostals sacrificed during open surgery or excluded from aortic flow by the stent.[53 54] Spinal cord ischaemia after left subclavian artery coverage during thoracic aortic stenting is thought to be secondary to impaired anterior spinal and costocervical arterial blood flow.[49 50] Aortic procedures with the above features constitute higher risk of perioperative spinal cord ischaemia and may benefit from IONM.

## Spinal cord monitoring

The potential benefits of using intraoperative neuromonitoring in high-risk aortic surgery include the following: (i) detection of intraoperative cerebral and spinal cord ischaemia, which can assist in optimization of perfusion [such as fine-tuning haemodynamic targets for controlled hypertension, providing an indication for cerebrospinal fluid (CSF) drainage etc.]; and (ii) real-time feedback to the surgeon regarding surgical technique and need for surgical salvage (such as selective intercostal artery reimplantation,[55] ligation of back-bleeding arteries to prevent steal phenomenon, etc.).

## Intraoperative monitoring

### Evoked potentials

Many case reports and series have reported outcomes related to use of neurophysiological techniques for guided therapy in aortic surgery, but there is a lack of randomized controlled trials (Table 5). One reason for this is that it would be seen as unethical to perform a trial withholding monitoring from patients. Another reason is the difficulty in determining efficacy.

Somatosensory evoked potentials have been criticized as having a high false-positive (40–67%) and false-negative (13%) rate and a slow response (7–30 min) to spinal cord ischaemia.[65] False positives attributable to technical error in the delivery of stimulation and in recording are not uncommon and highlight the importance of the expertise required in its use. As a monitoring modality aimed to provide early warning on organ dysfunction, false negatives may be particularly concerning and their postulated reasons include the following: (i) the limited ability of SSEPs to determine whether ischaemia involves motor function, because isolated injuries in the spinal motor pathways are not always reflected in the sensory pathways of SSEPs; (ii) aortic surgery being more likely to compromise blood flow in the anterior spinal artery (which supplies the motor tracts) than the posterior spinal artery (which supplies the sensory dorsal column);[66] and (iii) posterior column axonal conduction occurs non-synaptically and requires little energy expenditure, which may render tissue in the somatosensory pathways more resistant to ischaemia than the anterior horn grey matter motor neurones in the motor pathways.[55 56]

In comparison, MEPs tended to have better clinical correlation, and low false negatives have been reported.[65] Both clinical and experimental studies have shown a very rapid response to ischaemic conditions, usually within 5 min. The rapid feedback is useful because it can trigger immediate efforts to improve spinal cord blood flow and, in turn, neurological outcome. This is supported by animal studies, which demonstrated that prolonged absence of MEP signals exceeding 1 h was consistently associated with spinal cord infarction and paraplegia, whereas signal recovery within 10 min after the initial decline corresponds to normal histopathology and motor function.[67]

In their series of 112 patients undergoing thoracoabdominal aneurysm repair, Jacobs and colleagues[57] used decreased MEP ratios (the ratio between the amplitude of the anterior tibial MEP to the abductor pollicis MEP) to qualify critical changes. A reproducible MEP ratio reduction consistently >50% is taken as the criterion to trigger spinal cord protection actions. In their study, MEPs decreased significantly in 19 patients (17%), of whom all but three responded to rescue measures. The three patients who had absent MEPs at the end of the procedure all had postoperative neurological deficits. Postoperative mean arterial pressures were maintained at the level required to maintain MEPs during surgery. There were no false-negative or false-positive results in the study.

Numerous studies have compared MEPs against SSEPs. Keyhani and colleagues[61] described 233 patients who received open thoracic and thoracoabdominal aortic aneurysm repair. An SSEP latency change >10%, amplitude reduction >50%, and absence of MEP were regarded as abnormal, which triggered spinal cord protective measures. Irreversible signal changes were significantly associated with immediate postoperative neurological deficits. Both methods had low sensitivity and positive predictive values (37 and 33% for SSEP; 22 and 45% for MEP), while both had >97% specificity and negative predictive values, indicating that patients with no signal loss were unlikely to suffer neurological deficits. Although Keyhani and colleagues[61] concluded that the MEP did not add further information compared with SSEP, it was noted that the sensitivity for permanent SSEP and MEP changes was 37.5 and 62.5%, respectively, with a respective odds ratio of 21.9 for SSEP and 60.8 for MEP in predicting irreversible change, giving MEP a potentially higher accuracy.[68]

Several studies showed better results with MEPs. Estrera and colleagues[62] looked at 105 patients with thoracic aorta repairs, 26% of whom experienced SSEP loss, but all recovered with intraoperative salvage measures. Among the 50% of patients who suffered MEP loss, all but one recovered. The patient whose MEP failed to recover was the only one who suffered from immediate spinal cord injury. Meylaerts and colleagues[56] compared MEPs and SSEPs in their prospective study of 38 patients undergoing thoracoabdominal aortic aneurysm repair. Ischaemic MEP changes (defined as MEP amplitudes <25% of baseline) occurred in 18 patients in relation to aortic clamping and blood pressure reduction. The changes responded to segmental artery reperfusion and blood pressure augmentation. No patients awoke paraplegic. However, significant SSEP changes accompanied the MEP changes in only five of these 18 patients, with a presentation delay of up to 34 min. In another 11 patients, isolated SSEP changes (amplitude reduction to <50% control) occurred without relation to MEP changes or surgical events. Given that no patients had paraplegia after the procedure, this gives SSEPs a possible false-positive rate of 39%. Weigang and colleagues[58] also noted that MEPs reacted earlier than SSEPs to intraoperative spinal cord ischaemia and treatment measures. In that study of 21 patients undergoing thoracoabdominal aortic endovascular

Table 5 Case series on the use of evoked potentials to monitor spinal cord in aortic surgery. MEP, motor evoked potential; SSEP, somatosensory evoked potential

| Study | Number of subjects | Monitoring modality studied | Findings | Conclusion |
|---|---|---|---|---|
| Meylaerts and colleagues[56] | 38 | SSEP *vs* MEP | Ischaemic MEP changes occurred in 18 patients, all correctable. SSEP changes occurred in five patients, with a delay of 2–34 min.<br>SSEPs decreased in 15 other patients without relation to intraoperative events or postoperative deficits | SSEPs showed delayed ischaemia detection and a high false-positive rate |
| Jacobs and colleagues[57] | 112 | MEP | Absent MEP signals (4.2% patients) at the end of the procedure correlated with acute paraplegia | The MEP was highly reliable in assessment of spinal cord ischaemia |
| Weigang and colleagues[58] | 21 | SSEP *vs* MEP | Three of 21 patients (14%) exhibited short-term MEP and SSEP loss, with intraoperative recovery.<br>SSEPs had delayed alterations in amplitude, latency, and recovery compared with MEPs | Changes in MEPs and SSEPs allow early detection of spinal malperfusion, resulting in spinal cord-protecting strategies to reduce the incidence of neurological complications. MEPs were considered superior to SSEPs because of their direct and rapid response to spinal malperfusion |
| Husain and colleagues[59] | 42 | SSEP *vs* MEP | Peripheral and cortical SSEPs and MEPs to all four limbs were used. Extremity ischaemia from femoral sheath and global cerebral ischaemia were identified as alternative causes for signal deterioration | Monitoring both peripheral and cortical SSEPs prevented false-positive results |
| Shine and colleagues[60] | 60 | SSEP *vs* MEP | MEPs had 88% sensitivity, 65% specificity, and 96% negative predictive value for spinal cord ischaemia. Earlier and longer absence of MEPs and SSEPs were associated with higher risk of paralysis | Rapid loss of MEP after aortic cross-clamp justifies aggressive anaesthetic and surgical techniques to increase spinal cord perfusion |
| Keyhani and colleagues[61] | 233 | SSEP *vs* MEP | Only irreversible changes are significantly associated with neurological outcome. Sensitivity and positive predictive value: SSEP 37% and 33%; MEP 22% and 45%, respectively. Negative predictive values >98% for both modalities | SSEPs and MEPs were highly correlated only when changes were irreversible. MEPs did not add further information to SSEPs |
| Estrera and colleagues[62] | 105 | SSEP *vs* MEP | Loss of SSEP in 26% of patients, all of which returned with intraoperative manoeuvres. Loss of MEP in 50% of patients, with return in all but one patient, who awoke with neurological deficits.<br>MEP changes occurred before SSEP changes and returned later | SSEPs and MEPs seem useful for guiding intraoperative manoeuvres |
| ter Wolbeek and colleagues[63] | 97 | SSEP *vs* MEP | Sensitivity of 93% and specificity of 96% for neurophysiological monitoring | Monitoring spinal cord function by neurophysiological monitoring is necessary |
| Horiuchi and colleagues[64] | 44 | MEP | The minimal MEP during surgery had 100% sensitivity and 64.9% specificity in predicting paraplegia. Only one patient who had borderline paraplegia showed a false-negative result. Adequate MEP cut-off points are 75–90% decrease during surgery and 64–75% decrease at the end of surgery | MEPs had relatively high sensitivity and acceptable specificity for predicting paraplegia and paraparesis |

stenting, three of the 21 patients (14%) exhibited short-term MEP and SSEP loss, with MEPs recovering after corrective measures and no patients suffered from any postoperative paralysis. The SSEPs tended to deteriorate gradually, with retarded restoration and impending long-term loss even after intervention, despite the absence of postoperative neurological deficits.

In a prospective study of 97 thoracic and thoracoabdominal aortic open or endovascular repairs, ter Wolbeek and colleagues[63] looked at the efficacy of MEPs and SSEPs. Amplitude reduction of 50% or latency retardation of >10% were regarded as positive and triggered spinal cord protection strategies. Fourteen patients (14.4%) had closely correlated neurophysiological results and postoperative neurological status. Three patients had a false-positive result. One patient had a false-negative result and suffered paraplegia despite evoked potential recovery after initial depression. Sixteen patients (16.5%) had medication interaction or technical issues, and after discarding these patients with technical errors, the authors reported a 93% sensitivity and 96% specificity associated with the neurophysiological neuromonitoring method. Criticisms of this study included that it was unclear how well SSEPs and MEPs correlated, and whether those patients with transient neurophysiological changes who awoke with temporary neurological deficits should be regarded as true positives, false negatives or false positives.[69]

Some of the reasons for the variations in results include the following.

*Difficulty in defining efficacy.* To determine the true sensitivity of SSEPs and MEPs, one would need to avoid any corrective actions, which would be difficult to justify ethically.[62] If ischaemic evoked potential changes trigger corrective measures, which successfully reverse the neurophysiological warnings and the patient subsequently awakens with no deficits, it is unclear whether the monitoring represents false positives or simply reflects benefits of the interventions.[69]

*Variation in cut-off of a positive test.* Numerous cut-off points for a positive MEP test implying tissue ischaemia have been suggested, including a 50% loss of amplitude, a complete loss of MEP signal, or a need to increase the stimulation voltage required to obtain signals. In their retrospective review of 44 patients who received open aortic aneurysm repair, Horiuchi and colleagues[64] constructed receiver operating characteristic curves to determine the appropriate MEP cut-off points for detecting spinal cord injury. To achieve the best sensitivity and specificity, the cut-off for minimal MEP amplitude was 75–90% during surgery (100% sensitivity and 64% specificity) and 64–75% at the end of surgery after spinal cord protection measures (67% sensitivity and 78% specificity). However, the size of this case series was limited, and it is not clear whether the result can be applied to other types of aortic surgery.

*Influence of anaesthesia and hypothermia.* A variety of anaesthetic agents and neuromuscular blocking agents were used across the studies. Volatile anaesthetics are known to suppress MEPs significantly. Even with dosage half of the minimal alveolar concentration, volatile anaesthetics may not yield MEP signals comparable to those when i.v. agents are used. Infusion pumps for neuromuscular blocking agents and nerve stimulators can malfunction, and the clamping and unclamping of vessels can affect peripheral delivery of neuromuscular blocking agents, potentially confounding results. Likewise, regional epidural cooling and moderate hypothermia can suppress evoked potentials.

*Neurophysiological changes from causes other than spinal cord ischaemia.* In SSEP recording, loss of all cortical potentials with intact subcortical or peripheral signals in all extremities implies global cerebral ischaemia. Unilateral cortical potential loss with preserved peripheral potentials implies cerebral hemispheric ischaemia or lateralized spinal cord dysfunction. Loss of cortical potentials from tibial nerve stimulation but not median nerve implies spinal cord ischaemia.[59 70] Asymmetric single limb peripheral loss implies limb ischaemia (from femoral artery bypass cannulation, arterial lines, or vascular access for endovascular grafts) or peripheral nerve ischaemia, with SSEP changes more dramatic than MEP changes.[70] Thus, in order to establish the cause of injury, it is important to exclude misleading technical errors and to compare monitoring results from various sites along different parts of the neural pathway. It is not always clear in the methodology of different studies whether this was done.

It should be noted that while false-negative results reflect genuine failure of IONM potentially leading to devastating consequences, false-positive results could trigger unnecessary spinal cord protection interventions, which might carry risks themselves,[69 71] including induced hypertension, which might increase bleeding or cause rupture of anastomoses, spinal CSF drainage leading to subdural haematomas, unnecessary segmental artery implantations, and increased operating time. Complications from MEP monitoring are rare but should be taken into consideration. In a summary of >15 000 patients, MacDonald[30] reported five patients with seizures and five patients with cardiac arrhythmia. Twenty-nine instances of lip and tongue lacerations and one instance of mandibular fracture could have been prevented by soft bite blocks.

In summary, IONM is useful in detecting spinal cord ischaemia during aortic surgery, even though randomized controlled trials are lacking and multiple factors affect their interpretation as described above. Motor evoked potentials have quicker responses than SSEPs, and with lower false-negative rates. Use of IONM as a strategy to manage haemodynamic optimization, to detect spinal cord ischaemia, and to guide reimplantation of intercostal arteries is considered to be supported by class IIb evidence.[69 72 73]

## Near-infrared spectroscopy

Near-infrared spectroscopy is potentially an attractive alternative modality for spinal cord monitoring, because of its relative ease of use and good temporal resolution. A number of case reports and a pilot study have illustrated its use. Epidural and translaminar measurements are reported but are probably impractical in the vascular surgery setting with the current equipment. Owing to the small spinal neuronal tissue-to-bone ratio in humans and the variable skin-to-spinal cord distances, a transcutaneously placed probe is likely to record data from only a small amount of neural tissue, if any. Interpretation of results from transcutaneous probes requires the assumption that the spinal cord is perfused by a collateral network that also supplies the surrounding tissue structures.

Etz and colleagues[74] conducted a pilot study of 20 patients undergoing open and endovascular thoracoabdominal aortic repair, using NIRS probes placed transcutaneously over the upper thoracic (T5–T7) and lumbar (L1–L3) paraspinous vasculature before, during, and after surgical repair, until 48 h after surgery. Mean thoracic spinal NIRS readings did not vary during the procedure, but lumbar spinal NIRS saturations decreased significantly after proximal aortic cross-clamping, which then returned to normal after restoration of distal pulsatile flow. In those who developed spinal cord injury, lumbar spinal NIRS saturations were significantly lower (<75% of baseline for 15 min) than those who did not.

Case reports by Badner and colleagues,[75] Demir and colleagues,[76] and Moerman and colleagues[77] describe NIRS probes placed transcutaneously over the spinous processes in the midline. Spinal NIRS readings decreased with cross-clamping and hypotension, which prompted intercostal artery reimplantation or blood pressure augmentation. These changes correlated with MEP measurements and postoperative clinical neurological deficits. Spinal NIRS values were blood pressure dependent, and although changes occurred later than MEP changes, they were still rapid enough to guide therapy. These studies demonstrate a probable correlation between spinal NIRS saturations and spinal cord ischaemia.

Several issues remain unresolved. The optimal spinal cord-to-sensor distances and the correct location of the emitter and detector need to be studied. A direct correlation between regional NIRS monitoring and spinal cord perfusion is yet to be demonstrated, and comparison studies for its efficacy against other modalities are necessary. Nonetheless, application of NIRS in spinal cord monitoring represents a new direction in IONM.

### Postoperative monitoring

Delayed paraplegia and paraparesis after aortic surgery can happen despite the absence of immediate postoperative deficits. After surgery, spinal cord perfusion can be critically endangered but still sufficient to allow adequate function, as shown by leg movement in an awake patient. However, postoperative arterial hypotension, thromboembolism in crucial vessels, and cord oedema can provoke eventual spinal cord infarction.[57 65] Intraoperative ischaemia triggering postoperative apoptosis has also been postulated as one of the mechanisms of continued neural injuries.[65] If performed in a timely fashion, controlled hypertension and CSF drainage, titrating perfusion pressure to the level at which MEPs were maintained during surgery, may increase spinal cord blood flow and limit neural tissue loss. Early emergence and extubation are valuable in facilitating postoperative clinical evaluation. Nevertheless, for those who are too sedated or drowsy to participate in neurological examinations after surgery, there may be a place for neuromonitoring. Although MEPs are too painful to be used on unanaesthetized patients, SSEPs and NIRS may be feasible. Further studies are needed.

### Brain monitoring

Studies looking at the use of neuromonitoring for brain protection in thoracic aortic surgery are mostly performed in relation to open repair rather than endovascular repair. In open repair, possible uses of neuromonitoring[78 79] include the following: (i) provision of baseline preoperative assessment of the nervous system; (ii) detection of cerebral ischaemia during cardiopulmonary bypass, which may guide cannula positioning, flow optimization, and decisions for supplementary cerebral perfusion (EEG, SSEP, NIRS, or TCD); (iii) assurance on adequate physiological or pharmacological cerebral protection; (iv) identification of cerebral emboli and hyperperfusion (TCD); and (v) prognostication of patients after circulatory arrest (pace of signal recovery).

Use of neuromonitoring for the purpose of brain protection in endovascular thoracic aortic surgery is less well studied. Advancing and manipulating devices within the blood vessels, especially in the aortic arch curvature, may make cerebral embolization the predominant source of strokes complicating these interventions,[1 10 46 47] as suggested by clinical analysis, the pattern, and the timing of brain infarction.[1 9 38 39] As many IONM modalities may not readily pick up embolic events, this may be one reason why IONM use is not more widespread for brain monitoring in these procedures. Also, in the setting of established embolism, there is relatively little one can do to reverse the damage. However, in the presence of neural tissue already subjected to embolic insult, any concurrent inadvertent hypoperfusion is even more deleterious. One can therefore argue this warrants even closer monitoring.

Transcranial Doppler can be used to detect microembolic signals. In a study of 20 patients during TEVAR, Bismuth and colleagues[80] noted the highest microembolic signal counts during pigtail catheter placement in the diagnostic phase and device placement in the treatment phase. Device landing zones may also predict high microembolic signals. There was a significant association between the total number of microembolic signals and postoperative stroke, transient ischaemic attacks, and death. Some practical uses of this knowledge include using TCD for the systematic improvement of surgical techniques and evaluation of different vascular devices. Transcranial Doppler flow velocity changes could also be used to guide blood pressure management.

Brainstem auditory evoked potentials can potentially detect ischaemia and injury to the brainstem, and the use of this technique is routine in posterior fossa neurosurgery. It has also been used in endovascular procedures, such as cerebral aneurysm coiling and arteriovenous malformation embolization. In thoracic aortic procedures, particularly those involving the aortic arch, the blood supply to the vertebral arteries may be compromised if the stent covers the origin of the subclavian artery, leading to vertebrobasilar insufficency.[50 81] However, the use of BAEP in this setting has not been described. In one study of six patients in which BAEPs was used in vertebrobasilar stenting and angioplasty,[82] five patients had no BAEP changes or postprocedural neurological deficits, while one had an increase of latency in wave V of BAEP and suffered from severe left hemiparesis and seventh nerve paresis after the procedure. It is unknown whether BAEP can be similarly used in thoracic aortic surgery to detect vertebrobasilar ischaemia and to guide rescue manoeuvres, such as blood pressure augmentation, and surgical decisions, such as use of the 'chimney' technique or creation of a carotid–subclavian bypass.

## What if there is a signal change?

Besides the inherent limitation in the sensitivities and specificities of the above modalities, there are several other practical limitations to extensive neuromonitoring during major aortic and carotid surgeries. Many techniques require expertise and a dedicated team to extract meaningful information and react to rapidly changing conditions. It is not the modality itself, but the interpretation of the data provided and actions taken that are likely to improve outcomes. Close collaboration amongst anaesthetists, surgeons, and IONM service providers is of paramount importance in this regard. Before surgery, a coordinated and thorough treatment plan should be in place in the event of neuromonitoring signal changes, and possible surgical bail-out options should be discussed. Any suspicious signal change should alert the IONM service provider to exclude false-positive results and the anaesthetist to support neural tissues at risk and lessen secondary neurological injury. Possible actions may include measures to ensure adequate perfusion (such as augmenting the arterial blood pressure or reducing the CSF pressure), interventions to improve oxygenation (such as increasing the inspired oxygen fraction and blood transfusions), and methods to decrease tissue metabolism (by lowering body temperatures or by using pharmacological means). The surgeon may need to revise surgical plans (such as insertion of a carotid shunt, implantation

of segmental arteries, etc.) or hasten the procedure. This coordinated approach applies to both the intraoperative and postoperative periods.

In the long term, IONM can also facilitate the evolution of newer surgical techniques and guide treatment strategy development. Naylor and colleagues[83] described a 21 yr series of themed research and audit projects to develop strategies for preventing stroke and death after carotid endarterectomies. Three preventive strategies were identified, two of which involved IONM. Firstly, intraoperative TCD and completion angioscopy were most useful in virtually abolishing intraoperative stroke, by identifying and guiding the removal of intraluminal thrombus and large intimal flap repairs. Secondly, to almost abolish postoperative stroke, TCD was used to identify high-risk patients, to guide postoperative i.v. dextran use, and to prove treatment efficacy of preoperative dual antiplatelet therapy. These examples illustrate the potential role of IONM in treatment development.

## Conclusion

Procedural stroke and spinal cord ischaemia remain some of the most devastating complications of major vascular procedures for carotid and aortic diseases. Different neuromonitoring modalities have been used in attempts to ascertain the well-being of the nervous system during and after surgery. During carotid surgery, a combination of EEG, TCD%, NIRS%, or stump pressure may be useful, whereas TCD and NIRS may have a place after surgery. In aortic surgery, MEPs have quicker responses than SSEPs and lower false-negative rates in spinal cord monitoring, although further studies are needed to establish the appropriate method for brain monitoring in thoracic aortic endovascular surgery. These modalities heighten our awareness in preserving and protecting organ function in the nervous system. Equally important, real-time neuromonitoring provides us with information on the nature and timing of at-risk stages during vascular interventions, which, together with comprehensive careful preoperative planning, can help us to achieve systematic improvements in anaesthetic and surgical approaches. The current literature seems to suggest that IONM may indeed allow for the early detection of neurological injury and signal the need for various medical and surgical salvage strategies. Although formal cost–benefit analysis is still lacking, given the incidence of neurological complications in major vascular surgery and the potential cost of such injuries, it is likely that IONM will have an increasingly important role in the future. Anaesthesia providers should have a good understanding of these modalities to facilitate their use, appreciate their implications, and to use the information to guide timely implementation of appropriate neuroprotection measures for better patient outcome.

## Authors' contributions

Reviewed the literature and wrote the manuscript: V.C.S., C.C.M.P.

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None declared.

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Special Issue

# Spinal cord protection in aortic endovascular surgery

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## Abstract

A persistent neurological deficit, such as paraplegia or paraparesis, secondary to spinal cord injury remains one of the most feared complications of surgery on the descending thoracic or abdominal aorta. This is despite sophisticated advances in imaging and the use of less invasive endovascular procedures. Extensive fenestrated endovascular aortic graft prostheses still carry a risk of spinal cord injury of up to 10%; thus, this risk should be identified and strategies implemented to protect the spinal cord and maintain perfusion. The patients at highest risk are those undergoing extensive thoracic aortic stenting including thoracic, abdominal, and pelvic vessels. Although many techniques are available, lumbar cerebrospinal fluid drainage remains the most frequent intervention, along with maintenance of perfusion pressure and possibly staged procedures to allow collateral vessel stabilization. Many questions remain regarding other technical aspects, spinal cord monitoring and cooling, pharmacological protection, and the optimal duration of interventions into the postoperative period.

**Key words:** aortic aneurysm; cerebrospinal fluid; radiography; interventional; spinal cord injuries; vascular surgical procedures

**Editor's key points**

- Spinal cord injury occurs in 6.3% of patients undergoing repair of type II aortic aneuryms and 1–10% of patients undergoing endovascular repair of the thoracic aorta.
- The maintenance of an adequate blood pressure both during and after surgery is critical to maintaining spinal cord perfusion.
- Cerebrospinal fluid drainage to avoid pressures above 10 mm Hg is an effective strategy for preventing spinal cord injury but should be reserved for high-risk patients.

A persistent neurological deficit, such as paraplegia or paraparesis, secondary to spinal cord injury (SCI) remains one of the most feared complications of surgery on the descending thoracic or abdominal aorta. This is despite sophisticated advances in diagnostic and interventional strategies, including high-resolution three-dimensional imaging and a transition to less invasive endovascular procedures, including customized fenestrated endovascular aortic graft prostheses. The patients at highest risk are those undergoing extensive thoracic aortic repair for ruptured aneurysm or dissection. The broad class of aneurysm is often described by the Crawford classification, which relates to the origin and distal extent in the thoracoabdominal aorta, with type II being the most extensive (Table 1). In the past, estimates for the incidence of SCI were up to 31% of those undergoing open surgical repair of type II aneurysms, with rates even higher for those with aortic dissection.[1 2]

Specific strategies to protect the spinal cord focused on minimizing the cross-clamping time and the use of intercostal artery reimplantation. With a greater focus on spinal cord protection, including the use of cerebrospinal fluid (CSF) drainage and increased cardiopulmonary bypass, this rate has decreased to 6.3% for type II aneurysms in open surgery. Although arguably best practice, this figure is still significant, and it was hoped that endovascular techniques might provide some advantage by being less invasive. Ischaemic SCI with permanent dysfunction still occurs in 1–10% of patients in published series for thoracic endovascular aortic repair (TEVAR).[3] Endovascular aortic procedures are becoming increasingly common, replacing open surgical repair in the majority of instances involving aneurysm

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Table 1 Spinal cord ischaemia outcomes (percentage incidence) related to the Crawford classification of thoracoabdominal aneurysm extent for large series open procedures. *A Type V variant is also described (distal DTA to suprarenal). AA, abdominal aorta; DTA, descending thoracic aorta.

| Crawford classification* | Aneurysm alone (Svensson and colleagues)[1] (*n*=1234) | Dissection with or without aneurysm (Svensson and colleagues)[1] (*n*=276) | Aneurysm (dissection not specified) (Coselli and colleagues)[2] (*n*=2286) |
|---|---|---|---|
| Type I (proximal DTA to suprarenal AA; %) | 13 | 21 | 3.3 |
| Type II (proximal DTA to infrarenal AA; %) | 31 | 33 | 6.3 |
| Type III (distal DTA to infrarenal AA; %) | 6 | 13 | 2.6 |
| Type IV (suprarenal AA to distal AA; %) | 4 | 11 | 1.4 |

or dissection arising distal to the aortic arch. Paraplegia may also follow infrarenal abdominal aneurysm surgery, although for isolated open or endovascular aortic repair (EVAR) it is much less common (<0.25%).[4] Although surgery on the thoracoabdominal aorta is associated with a broad range of significant complications, this paper will focus on perioperative strategies for SCI prevention in TEVAR in particular, using a specific patient as an example.

## Spinal cord protection

Spinal cord ischaemia is clearly the result of a compromise of perfusion, with neurological injury occurring primarily because of profound acute ischaemia or as a consequence of more prolonged insufficiency with or without reperfusion injury. Perfusion insufficiency may be secondary to restriction of segmental arterial inflow during and after surgery, increased tissue pressure attributable to oedema or elevated CSF pressure, or increased venous pressure limiting outflow. The extent of endograft coverage gives an indication of risk, and extensive covered stent placement from the thoracic aorta to the iliac arteries is a risk factor (Fig. 1).[5] Many strategies have been described either to maintain spinal cord perfusion during and after the procedure or to protect the spinal cord against ischaemic or reperfusion injury. Some methods apply to open repair only (e.g. selective intercostal reimplantation) and others are applicable to closed (endovascular) repair. Not all are consistently effective, and most rely on 'bridging' a period of ischaemic risk until adequate native perfusion can resume. Staged repairs have been reported to be of benefit in some retrospective series, presumably because this allows time for collateral blood vessels to develop and stabilize over smaller regions of the cord at risk of ischaemia.[3 6 7] For detailed recommendations that have recently been published, the reader is directed to a Position Statement by the European Association for Cardio-Thoracic Surgery after a wide review of the literature.[3] Identification of the at-risk patient is an inexact science because of variability in individual anatomy, the extent of endograft coverage, and the location and complexity of endograft placement,[5] in addition to the risk of compromise of spinal cord perfusion by blood pressure variability.

The following sections provide an overview of the various perioperative protective strategies, spinal cord anatomy and physiology. The risks of the individual protective strategies also need to be considered.

### Minimizing the anatomical disruption of blood supply

It has become evident that the blood supply to the spinal cord is not simply dependent on a few key feeding vessels. Recent reviews and studies have emphasized that there is a rich anastomotic network of small vessels surrounding the cord that

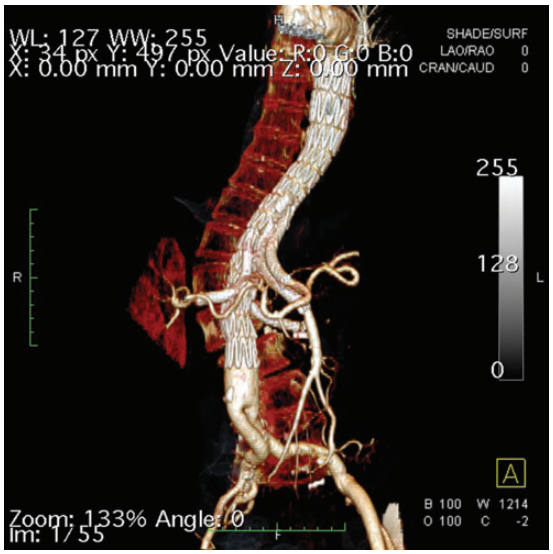


Fig 1 The postoperative computed tomography scan reconstruction of the thoracic endovascular aortic repair in the case study. Her initial woven Dacron infrarenal aorto-iliac graft can also be seen.

contributes to the usually single anterior and usually paired posterior spinal arteries.[8] The superior source vessels are branches from the left subclavian and vertebral arteries, which form the anterior and posterior spinal arteries. Throughout its length the anterior spinal arteries receive supply from the paired intercostal and lumbar segmental arteries and then caudally from branches of the inferior mesenteric, internal iliac, and sacral arteries. This rich network will be variably compromised by the anatomical disruption caused by the aortic pathology itself, by the operative ischaemic time, and by the persisting compromise after surgery. An additional concern is that reverse flow from spinal arteries may both contribute to extraprosthetic leaks after the placement of sealed or occlusive stent grafts (type II endoleaks) and 'shunt' blood from the spinal circulation by a low-resistance pathway. For these reasons, coiling of branch vessels is sometimes undertaken. Although this decreases the risk of an endoleak, the impact on SCI is less clear.

Preservation of vessels, selective re-anastomosis, or side-branch stenting of these larger supply vessels (including the artery of Adamkiewicz, an often large spinal artery in the lower thoracic to upper lumbar region) has controversial benefit.[3]

### Maintenance of perfusion pressure gradient

Probably the single most important strategy is the maintenance of an adequate perfusion pressure gradient to the spinal cord. This involves three elements: (i) maintaining an adequate mean systemic pressure; (ii) decreasing systemic venous pressure; and (iii) avoiding increases in CSF pressure surrounding the spinal cord. The patient we describe predominantly demonstrates the influence of these factors. It is important to realize that vulnerability to perfusion inadequacy persists into the postoperative period.[9] Dependence on an adequate systemic perfusion pressure may last for much longer, and well after hospital discharge, depending on the nature of the collateral circulation, although factors other than relative hypotension may be involved.[10] Overall, maintenance of an adequate blood pressure during the procedure and into the recovery period is critically important.[3]

Cerebrospinal fluid drainage is effective because acute changes in the spinal cord in response to ischaemia or reperfusion may result in oedema and increased CSF pressures during the procedure and for 48–72 h (or even longer) afterwards. The effectiveness of CSF drainage in reversing SCI signs and reducing SCI overall has been demonstrated both anecdotally and in a randomized trial.[11] It has been recommended that CSF pressures >10 mm Hg be avoided for at least 48 h after the procedure, that CSF drainage should occur if signs of SCI develop, and that excessive drainage be avoided.[3] It should be remembered that lumbar CSF drainage catheters carry their own risks; therefore, this intervention should be reserved for patients judged to be at high risk or in whom symptoms or signs develop.[12]

### Protection of the spinal cord against ischaemia or reperfusion injury

Hypothermia has been advocated to provide some degree of acute tolerance of the spinal cord to interruption of blood flow during surgery, especially during open procedures. Hypothermia may be achieved systemically (e.g. using the cardiopulmonary bypass pump) or by epidural perfusion with cold fluids. Although hypothermia is demonstratively effective in enabling the brain and spinal cord to tolerate ischaemia,[13] its role in the postoperative period is less clear. Systemic hypothermia also carries with it a number of risks, including dysrhythmia, coagulopathy, and metabolic disturbances, which must be balanced against potential benefits,[14] although these effects are minimal with moderate (34°C) systemic hypothermia.[5]

The use of selective spinal cord hypothermia using epidural cooling techniques has also been advocated. Limited published data in TEVAR are available, although case series in open procedures suggest a possible benefit;[15 16] these studies also often combine other protective techniques. The efficacy of cooling can be monitored by CSF temperature. It is, however, an invasive technique, applicable for a limited duration, and concerns regarding contamination and rebound spinal cord oedema have been raised.[3]

Pharmacological interventions aim to decrease the metabolic requirements of the spinal cord or to decrease the inflammatory or neurochemical responses to ischaemia or reperfusion. Steroids and naloxone have shown benefits in animal studies in reducing the effects of SCI and are reported in some series as components of multimodal therapies.[5] Intrathecal papaverine has been associated with decreased adverse SCI outcomes as part of a multifaceted approach to protection,[17] but awaits prospective trials. Other interventions, such as remote ischaemic preconditioning, may show promise in the future.[18]

### Monitoring for spinal cord ischaemia

Monitoring of spinal cord function is of primary relevance in the anaesthetized patient during surgery. Monitoring may be functional (e.g. somatosensory or motor-evoked potentials), metabolic (CSF analysis), or physiological (lumbar CSF pressure and paravertebral muscle oximetry). The purpose of monitoring is to enable an intervention to occur that would improve outcomes. The use of somatosensory and motor-evoked potentials may identify a need during open procedures to reimplant significant spinal arteries, although the sensitivity and specificity of abnormal evoked potential findings is not clearly established because they assess different aspects of spinal cord function and may be affected by lower limb ischaemia.[3] During TEVAR procedures, the options in response to somatosensory or motor-evoked potential changes are more limited and mostly confined to increasing systemic perfusion pressure or drainage of CSF.

The nature of perfusion via an anastomotic network of vessels that also supply the paravertebral muscles has led to an interest in near-infrared spectrometry as a means of monitoring the adequacy of spinal cord perfusion during and after surgery.[7 18]

After surgery, clinical monitoring of lower limb motor and sensory function, in addition to bowel and bladder continence,[19] are important and may indicate a need for blood pressure support or lumbar CSF drainage depending on the circumstances.

## Case study

Mrs J.D. was 67-yr-old woman with severe vascular disease and new onset back pain presenting for a multibranch TEVAR for a symptomatic Crawford type IV thoracoabdominal aneurysm. Fifteen years earlier, she had undergone an open infrarenal abdominal aortic aneurysm repair with a bifurcated Dacron graft. This was complicated by bowel ischaemia requiring an ileostomy. She had also had a lumbar laminectomy in 1980. She was high cardiovascular risk, having had a myocardial infarction (ST-segment elevation) in 2006 followed by percutaneous coronary intervention with stent and a non-ST segment elevation myocardial infarction 6 yr later followed by another percutaneous coronary intervention with stent. She had ceased smoking in 2003. Her exercise tolerance was limited by dyspnoea at <4 metabolic equivalents, but she had no claudication and was still working. She also had hypertension, hypercholesterolaemia, and primary biliary cirrhosis. Her current medications included aspirin (100 mg $day^{-1}$), clopidogrel (75 mg $day^{-1}$, ceased 7 days before surgery), metoprolol (100 mg twice a day), irbesartan (300 mg $day^{-1}$), and prednisolone (5 mg $day^{-1}$).

Investigation revealed a 6.5 cm lower thoracic and suprarenal aortic aneurysm with computed tomography (CT) scan. Cardiac studies showed an ejection fraction of 40%, akinesis of the left ventricle posterior and inferior wall, but no reversible ischaemia with thallium scanning. Liver function was mildly impaired, but renal function and coagulation studies were normal. She had mild emphysematous changes on chest X-ray. On examination, she weighed 50 kg, with multiple abdominal scars and severe kyphoscoliosis. Her abdominal aneurysm was tender to palpation.

The plan was for her to have a two-piece endograft. The first piece lined the distal thoracic aorta and second piece consisted of a four-branch endograft (Cook Medical, Brisbane, Queensland, Australia) with branches to the coeliac axis, superior mesenteric artery, and both renal arteries. The graft also included a reperfusion branch, which was to remain patent for up to a month after surgery to allow perfusion of the aneurysm sac, hence the spinal arteries (especially T11–T12). Coverage was planned to extend from the mid-thoracic aorta to a distal seal zone in the aortic

component of the original infrarenal aortic graft. The postoperative CT result can be seen in Fig. 1.

In addition, Mrs J.D. had diffuse stenosis of her external iliac arteries that rendered the delivery and deployment of the endografts problematic. Therefore, a left iliofemoral Dacron graft was to be placed via open extraperitoneal exposure to facilitate introduction of the devices. Open exposure of the left axillary artery was necessary to allow branch cannulation, and right femoral arterial access by percutaneous sheath was required for preoperative angiography to place the endografts accurately. Owing to the extensive coverage of her mid- and distal thoracoabdominal aorta and coverage of the infrarenal aorta, she was deemed to be at high risk of spinal cord ischaemia; therefore, a lumbar CSF drain was planned.

Preparation for anaesthesia included radial arterial blood pressure monitoring, wide-bore i.v. access, and a central venous catheter. The lumbar CSF drainage catheter was inserted at L3–L4 (presumed) interspace using a 19 gauge multi-hole nylon epidural catheter via a 16 gauge Tuohy needle (Portex®; Smiths Medical Australasia Pty. Ltd, Brisbane, Queensland, Australia). This was placed successfully in one pass, with 10 cm of catheter threaded into the subarachnoid space. This was attached to a Codman drainage kit (EDS 3™ CSF External Drainage System; DePuy Synthes, North Ryde, NSW, Australia). Induction of anaesthesia was uneventful; she was intubated and ventilated throughout the procedure, and maintained on sevoflurane with a total of 600 μg of fentanyl during the 7 h procedure.

Spinal cord protection involved maintaining the CSF pressure at 12 cm $H_2O$, with the catheter on 'overflow' at this level. The slow free drainage of CSF could thus be observed, and any increase in CSF drainage would be detected by an increased rate of production, with the pressure self-regulating to the set height of overflow. Cerebrospinal fluid drained at ~8 ml $h^{-1}$ throughout the procedure. Blood pressure was supported throughout the procedure using a phenylephrine infusion, aiming for a mean arterial pressure >80 mm Hg. Heparin was administered intermittently to maintain the activated clotting time >200 s.

The procedure itself was technically challenging but achieved a satisfactory result, with all branch targets perfused. A small posterior perfusion branch was part of the graft design, effectively to create an endoleak to allow temporary perfusion of spinal artery branch vessels via the sac. The patient was extubated and transferred to the intensive care unit awake and alert, for ongoing observation and management.

During the next 14 h, she became haemodynamically unstable, requiring norepinephrine (up to 11 μg $min^{-1}$) and a total of 8 units of packed red cell transfusion. She was neurologically stable throughout. A CT scan identified a retroperitoneal haematoma around the site of the iliofemoral anastomosis, so she was returned to theatre for exploration, drainage, and oversewing of an anastomotic leak under GA. On return to the intensive care unit, she was extubated within 2 h and again neurologically intact. The CSF drain was kept at an overflow pressure of 12–15 cm $H_2O$ and drained <8 ml $h^{-1}$.

On transfer to the ward the next day, hourly neurological observations continued, and the CSF drain was clamped and released every 6 h for pressure checks. At 36 h after the procedure, her CSF pressure reading was 24 cm $H_2O$, with no neurological signs. Five millilitres of CSF was drained, and the pressure decreased to 16 cm $H_2O$. On review 6 h later, she complained of pain in her left groin and 'heaviness' in her left leg, although power and objective sensory assessment was normal. The CSF pressure was 11 cm $H_2O$. The CSF drain was removed uneventfully at 48 h after the procedure. Haemodynamics were normal. An increase in high-sensitivity Troponin-I (hs-TnI) had been noted as 230 ng $l^{-1}$ at 24 h, which decreased to 118 ng $l^{-1}$ by 48 h. The ECG was unchanged. She was mildly dyspnoeic, with a haemoglobin of 87 g $l^{-1}$, but otherwise able to mobilize.

During the next few days, she was assessed as mildly fluid overloaded and diuresed. Her left leg was persistently noted to be mildly weak. The patient was able to weight bear, but pain limited attempts at ambulation. A CT scan on postoperative day 6 showed no endoleak and all branch vessels patent. On recommencing irbesartan she became posturally hypotensive (90/60 mm Hg) and so this was ceased. Haemodynamics then stabilized and ambulation slowly improved. From day 8 to 10 she became progressively hypertensive, and her antihypertensive medications were adjusted accordingly. She also complained of back pain and left flank pain.

At 19.30 h, 11 days after the procedure, she became diaphoretic, light headed, hypotensive (80/40 mm Hg) and bradycardic (45 beats $min^{-1}$). Shortly after this she lost motor power in both legs and lost sensation below the umbilicus. She was commenced on i.v. epinephrine to support her circulation, and urgent magnetic resonance imaging was ordered to assess the spinal canal (for haematoma), which was not useful because of the metal stent material. A CT scan showed graft patency, with the exception of occlusion to the branch to the left kidney. There was no endoleak. The patient was transferred to the intensive care unit, where her troponin was 20 952 μg $l^{-1}$. The ECG was suggestive of anterior ischaemia. Discussion occurred between the vascular and cardiology teams regarding the need for anticoagulation, which would preclude the insertion of a new lumbar CSF drain. During this time, her haemodynamics had stabilized on the epinephrine infusion and her sensory and lower limb motor function was returning to normal. It was decided that her spinal cord perfusion was pressure dependent; thus, in light of an acute coronary syndrome, she would be anticoagulated with heparin and tirofiban. She was taken to the cardiac catheter laboratory, where her mid-right coronary stent was found to be thrombosed. This was reopened, and she was commenced on ticagrelor. Her hs-TnI peaked at 47 647 μg $ml^{-1}$. She was weaned of inotropic support during the next 24 h and discharged to the ward.

She remained in hospital for a further 10 days, which were relatively uneventful, before being discharged home neurologically intact.

## Case study discussion

The management of the patient described highlights several points regarding spinal cord protection in patients undergoing TEVAR procedures.

### Assessment of risk

The presence of a previous infrarenal surgical aortic bifurcation graft and iliac vascular disease meant that the distal cord perfusion was already compromised. Extensive coverage of spinal arteries by the proposed branched TEVAR meant that cord perfusion was dependent on proximal vessels and collateral systems distally. However, this was a 'staged' procedure; therefore, collateral vessels might have developed or enlarged since the original procedure.[6]

### Plan for protection

A lumbar CSF drain was placed, arterial pressure was supported throughout and into the first 24 h, the left subclavian artery was preserved, and finally, the graft itself contained a patent perfusion branch to maintain perfusion of the sac and intercostals in

the early postoperative phase until development of collaterals. This perfusion branch thrombosed within 2 weeks, so should not be considered as a long-term solution, especially as the overarching surgical aim was to depressurize and thrombose the aneurysm itself.

### Choice of lumbar drain type

A number of options exist for percutaneous lumbar CSF drains, although the most common choices are between silicone (silastic) catheters and epidural catheters. Either choice should involve a catheter with multiple distal orifices to minimize the risk of obstruction. The insertion depth is typically 8–10 cm.[12] There is no clear advantage to one over the other, with silastic catheters being softer and larger bore but also more prone to kinking, shearing, or breaking,[20] and requiring a larger (e.g. 14 gauge) insertion needle.

### Monitoring environment

During the procedure, our institution does not use evoked potential monitoring. The aim is for an alert, responsive patient immediately after surgery who can comply with early and frequent neurological assessment in a high-dependency unit environment. These patients should ideally be monitored closely in a high-dependency unit for 48 h or longer, but resource limitations often mean that a stable patient may be discharged to the ward after 24 h. Hourly neurological observations should continue, however.

### Duration of spinal cord drainage

This was continued for 48 h because she had been asymptomatic, although it could be be argued that continued drainage should be provided for a further 24 h, considering the one episode of (asymptomatic) elevated CSF pressure.

The subjective left leg 'heaviness' in the first postoperative week was of concern. However, there was clinically little to find, and the presumption at the time was that this was because of discomfort from the open iliac procedure and residual haematoma from the subsequent anastomotic leak.

### Risk of late cord ischaemia

This situation was contributed to by hypotension secondary to myocardial infarction and tachyarrhythmia and by thrombosis of the deliberate residual endoleak. An additional concern was late haemorrhage.

There are challenges with imaging the cord because although CT angiography can identify vessel blood flow, the most sensitive technique for spinal cord ischaemia is magnetic resonance imaging, which is made difficult if not impossible by the metallic stent skeleton components of the endograft, even though the device was magnetic resonance imaging 'compatible'.

For this patient, there was an additional difficult decision relating to the potential need for anticoagulation and antiplatelet therapy as after percutaneous coronary intervention for her myocardial infarction. This had to be balanced against the potential benefit of re-inserting a spinal cord drainage catheter. Fortunately, return of motor and sensory function in response to pressure support decreased the imperative for the CSF drain.

Overall, the description of management of this patient emphasizes how marginal the spinal cord blood supply can be, even in the absence of symptoms, and that this vulnerability may persist for some time.

## Conclusion

In TEVAR procedures, if spinal cord perfusion is severely compromised, recovery may not be possible. Planning is important, and reliance on staged grafts may not be sufficient. However, there is good evidence that short-term strategies that allow for recovery of adequate ongoing perfusion, presumably by the development of collateral blood vessels, are effective. Careful monitoring and assessment and prompt early intervention should symptoms or signs of cord ischaemia develop is critical. Perfusion compromise may occur *de novo* even weeks after the procedure.

## Authors' contributions

Patient procedural management and perioperative care: D.A.S., M.J.D.
Manuscript preparation, editing and review: D.A.S., M.J.D.

## Declaration of interests

None declared.

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Special Issue

# Vascular surgery-related organ injury and protective strategies: update and future prospects

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## Abstract

Whilst there has been a reduction in the prevalence of peripheral vascular disease worldwide, a significant proportion of the world's growing population is still affected by disease of the aorta, carotid, iliac and lower limb arteries. These if left untreated can result in severe morbidity and mortality. However vascular surgery, the main definitive treatment for such conditions, is associated with subsequent injury to vital organs including the kidneys, heart, brain, intestines and lungs, with a consequent increase in both morbidity and mortality. The current thinking is that the underlying mechanism of injury is direct organ ischaemia and ischaemia induced formation of free radicals, cytokine release and mitochondrial failure. Various methods to alleviate such injuries have been investigated including pre- and postconditioning strategies, pharmacological therapies including volatile anaesthetic and alpha$_2$ adrenoceptor agonist drugs and more recently remote conditioning strategies. Although these interventions have demonstrated some reduction in the biomarkers for organ injury, attempts to translate these benefits into clinical practice have not been successful in terms of morbidity, mortality or length of hospital stay. For this reason, further research is needed in this area to facilitate the translation of the potential interventional benefits from bench to bedside.

**Key words:** mechanism of action; protective agents; surgical injuries; vascular surgery

**Editor's key points**

- Major vascular surgery often necessitates the cross clamping of blood vessels so exposing patients to the risk of ischaemia and reperfusion injury.
- The mechanisms of ischaemia –reperfusion injury include free radical formation, mitochondrial failure and systemic inflammation.
- Ischaemic preconditioning and postconditioning show benefit in reducing biomarkers of ischaemia reperfusion injury, but this has not been shown to translate into clinical benefit.
- Volatile anaesthetic agents also appear to have cytoprotective properties and may mask the benefits of ischaemic preconditioning strategies in clinical studies.

Disease of the aorta, carotid, iliac and lower limb arteries, which affect a significant proportion of the population, if left untreated can result in severe morbidity and mortality. Smoking, atherosclerosis, genetic makeup, uncontrolled hypertension, diabetes and increasing age are contributing factors to these diseases.[1 2]

The reported prevalence of abdominal aortic aneurysm (AAA) varies between studies.[3] It depends on many factors including environment, life style, genetic makeup, the diameter of the aorta taken as diagnostic of AAA, and the methods used to conduct the population survey. In a collaborative study conducted in England, Denmark and Western Australia in 2001, the observed overall incidence in the male population varied between 3.9 and 7.7% with the lowest incidence observed in Denmark and the highest in England.[3] The incidence is lower in the female population with

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an incidence of 0.2 and 3.1% in the 65–75 yr old and 85 yr age groups respectively.[4]

The overall prevalence of peripheral vascular disease (PVD) affecting the lower limbs is often determined from studies of ankle brachial index (ABI), defined as the ratio of the systolic arterial pressures in the lower limb to the average systolic pressure in the brachial arteries. An ABI of 0.9 or less is indicative of PVD. The prevalence of PVD was reported as being 19.1% (95% CI: 18.1–20.0%) in a prospective study Rotterdam population greater than the age of 55 yr in 1998.[5] In contrast, a population study of population based in cities and rural towns, aged between 35–79, in Spain showed a prevalence of 4.5% (95% CI: 4.0–5.0%) during the period 2005–2006.[2]

More recently in 2013, of 3.3 million participants in the United States suggested that the prevalence of arterial diseases is decreasing, with an observed prevalence of lower limb PVD of 3.56% (95% CI: 3.54–3.58%), carotid artery stenosis of 3.94% (95% CI: 3.92–3.96%) and AAA of 0.88% (95% CI: 0.86–0.89%).[6] Modifiable risk factors including diabetes, hypertension, current and previous smoking, hyperlipidaemia, and sedentary lifestyle were significantly associated with arterial disease.[6] The authors of this and previous studies[1 2] concluded that lifestyle changes are contributing to the reduction in the prevalence of vascular disease.[6]

Despite this reduction in the prevalence of arterial disease in recent years, there still remain a significant number of patients who require surgical intervention as definitive treatment to reduce the risks of serious morbidity and mortality. However, surgery is associated with other complications including ischaemia-reperfusion injury, and thus there is the need to minimize these complications where possible.

In this review, we shall discuss the incidence of ischaemic injury to end organs during vascular surgery and consider potential anaesthetic techniques that can be used to limit such injury. We performed a comprehensive literature review using PubMed.gov to access MEDLINE. Articles with the following terms were accessed: 'vascular surgery', 'preconditioning', 'postconditioning', 'organ injury' and 'protection'. Studies were selected for inclusion in the review based on their relevance to vascular surgery related organ injuries and potential protective strategies.

## Vascular surgery related organ injury

Organ injury is one of the major risks and complications of vascular surgery. It is associated with both increased morbidity and mortality. Whilst any surgical procedure can result in direct injury to organs and tissues, vascular surgery carries the added risk of injury as a result of changes in perfusion. Furthermore, vascular patients often have underlying co-morbidities increasing their operative morbidity and mortality risks.

### Kidneys

Postoperative renal dysfunction and failure is a major concern post vascular surgery. In 2007, the classification and diagnosis of acute kidney injury (AKI) was standardized via the Acute Kidney Injury Network (AKIN), a system based on changes in serum creatinine and urine output.[7] Unfortunately studies vary in their definition of postoperative renal dysfunction.

A study of 666 patients in 1989 showed a renal dysfunction incidence rate of 5.4% in elective non-ruptured aneurysm patients (as defined by a >20% increase of the preoperative creatinine).[8] Other studies have quoted the incidence of patients requiring dialysis as a result of acute renal failure post vascular aneurysm surgery at 5.5% for suprarenal patients (including thoracic/thoraco-abdominal aorta surgery) and 0.6% for infra-renal patients. The mortality for these groups were 63 and 69% respectively for supra and infra-renal patients.[9]

There are several possible mechanisms of kidney injury in aortic surgery. In AAA repair, aortic clamping may lead to ischaemic injury to the kidneys. Even in operations involving infra-renal clamping, renal blood flow is decreased by 38% and there is a concurrent 75% increase in renal vascular resistance.[10] Furthermore, aortic cross clamping and release can result in ischaemia-reperfusion injury in muscles, leading to renal failure as a result of nephrotoxin in release from rhabdomyolysis.[11]

There appears to be little evidence to suggest any increase in renal dysfunction in endovascular aortic repairs (EVAR) compared with open surgery.[12] As with open repairs, there may be a degree of lower limb ischaemia. However, in endovascular repairs, a large volume of contrast media is required with an associated risk of contrast nephropathy, whose effects may be clinical or sub-clinical.[13] Renal infarction and damage can also result from emboli and the occlusion of the renal arteries from misplaced grafts,[13] with a study showing 8.5% of patients who undergo an endovascular aneurysm repair experience unintentional renal ischaemia. Intentional covering of accessory renal arteries does occur and is reported in 3.4% of patients undergoing EVARs, leading to limited segmental infarctions in the kidneys.[14]

Revascularization in limb ischaemia can also lead to kidney injury, often thought to be via rhabdomyolysis from muscle injury and ischaemia-reperfusion injury inducing AKI. A study reported 14.9% of patients developed chronic kidney disease (CKD) post-surgical revascularization of lower extremities,[15] with the development of AKI (as defined by AKIN criteria) postoperatively, increasing the risk of CKD and mortality. Finally, the presence of the co-morbidity diabetes was found to be an independent risk factor for developing AKI post vascular surgery.[16]

### Brain

Carotid endarterectomy (CEA) is performed for treatment of significant stenosis of the carotid artery in asymptomatic and symptomatic patients[17] and is beneficial in preventing recurrent strokes if performed acutely in selected patients.[18] However, CEA is linked with a perioperative risk of developing or worsening a stroke, with urgent CEA being associated with higher rates of morbidity and mortality than elective procedures.[19] The incidences of perioperative stroke during CEA is 3.4 and 5.6% respectively for asymptomatic and symptomatic patients. There are two main mechanisms underlying stroke in CEA, cerebral ischaemia and embolization.[20] Cerebral ischaemia occurs during cross clamping of the internal carotid artery, leading to a drop in oxygenation.[21] Severe cerebral ischaemia is particularly problematic in patients with contralateral internal carotid artery stenosis.[22] However the most common cause of stroke in CEA has been repeatedly been shown to be technical error.[23]

As mentioned previously, vascular patients often have underlying co-morbidities, in particular impaired renal function. Data shows chronic renal insufficiency affects the outcomes of carotid endarterectomies; in particular moderate renal impairment (described as a GFR of 30–59 ml $min^{-1}$ 1.73 $m^{-2}$) is a significant negative independent risk factor for cardiac and pulmonary morbidity, and severe renal impairment (GFR of <30 ml $min^{-1}$ 1.73 $m^{-2}$) is associated with higher operative mortality as well.[24]

It is not just in CEAs that the brain can be affected. Thoracic aorta repairs using the thoracic endovascular aortic repair (TEVAR) method also runs a risk of stroke, in particular in patients with a large atheroma burden and prior strokes.[25 26]

Postoperative cognitive decline (POCD) is a major complication seen not just in vascular surgery.[27 28] POCD has been examined in detail in a recent review.[29] In brief, the decline in cognitive function post-surgery has been linked to the neuro-inflammatory response after surgical trauma.[30] This increase in inflammatory activity within the brain has subsequently been associated with cognitive decline, in both the short and long-term which we will review later.

### Heart

Myocardial infarction (MI) occurs in 1–11.6% of patients undergoing non-cardiac surgery.[31 32] Variable statistics are available regarding incidence rates, with the incidence of perioperative myocardial infarction at 1–26% and an incidence of myocardial ischaemia at 14–26%, in patients undergoing non-cardiac vascular surgery. Whilst some studies state that the presence of myocardial ischaemia in fact was a prognostic indicator for postoperative mortality,[32–34] the recent VISION study (Vascular Events in Noncardiac Surgery Patients Cohort Evaluation) found that irrespective of the presence of ischaemic features, the elevation of troponin after non-cardiac surgery was an independent predictor of 30-day mortality.

Damage to the myocardium (ischaemia and infarction) during surgery occurs because of the imbalance between oxygen supply and demand, a process that has two possible aetiologies. Type 1 (from the universal classification of myocardial infarction as defined by Thygesen and colleagues[35]) arises via plaque rupture and thrombosis formation, leading to reduced blood flow. The stress of surgery induces a change in morphology of the coronary plaques,[36] transforming the plaque into a more vulnerable state and increasing the risk of plaque rupture.[37] Plaque rupture leads to coronary thrombus formation, causing the eventual dynamic obstruction of coronary vessels, a process similar to non-operative myocardial infarctions and has been reported as being present in over 50% of perioperative MIs.[37]

Type 2 myocardial damage is linked with increased oxygen demand with insufficient coronary blood flow. Surgery induces an increased heart rate, contractility and sympathetic tone via the release of catecholamines.[36 38] In vascular patients, who often have underlying coronary artery disease and therefore poor coronary vasodilator reserve, the inability to appropriately compensate for this increase in oxygen further increases myocardial damage.[36] In addition, the release of catecholamines also further promotes coronary spasm and increased shear stress on the coronary vessels, further increasing the risk of plaque disruption and subsequent perioperative MIs.[37]

Studies have shown that patients suffering a fatal perioperative MI, usually harbour underlying multi-vessel coronary disease. Whilst severity is not predictive of potential territory for infarct, the underlying coronary disease and the high prevalence of cardiac risk factors (diabetes, cardiac history, gender, smoking) in vascular patients makes them high risk of suffering a perioperative MI.[37]

### Intestines

Intestinal ischaemia in abdominal aortic surgery can occur when flow through the superior or the inferior mesenteric artery is compromised. Patient undergoing infra-renal AAA repairs have a 1.1–1.4% incidence of intestinal ischaemia.[39] In emergency ruptured AAA repair the incidence of bowel infarction is three times higher than in elective aneurysm surgery.[40 41] In surgery for aorto-iliac occlusive disease the incidence of intestinal ischaemia is lower than that seen in ruptured and non-ruptured AAA repair.[39 42] The presence of intestinal infarction post abdominal aortic surgery, increased the 30-day mortality rate more than five-fold (67%) when compared with the overall rate of 13%,[42] with an increased overall mortality rate if bowel resection was required.[41]

Intestinal ischaemia in vascular surgery is multifactorial with causes including aortic cross clamping, thrombosis, embolization and retractor injury/poor surgical technique. Prolonged suprarenal aortic cross-clamping can lead to increased risk of embolization of the superior mesenteric artery and an increased risk of colonic necrosis.[40] When intestinal ischaemia does occur the presenting feature postoperatively is usually bloody diarrhoea, requiring a colonoscopy for accurate diagnosis.[41]

### Lung

Remote lung injury has been linked with vascular surgery via the process of ischaemia—reperfusion injury of distant organs. A previous study reported that 3% of patients who underwent a vascular or general surgical procedure developed respiratory failure postoperatively. The subsequent consequences of respiratory failure include poor perioperative outcomes,[43] increased mortality,[44] increased costs[45] and decreased long-term survival.[46]

A reason for the poor outcomes is the development of acute respiratory distress syndrome via the systemic inflammatory response. This is often caused by the process of ischaemic reperfusion injury (IRI) in the postoperative period, after aortic cross-clamping or re-vascularization of ischaemic limbs.[47] The mechanism by which IRI leads to distant organ injury is explored later.

Acute lung injury is a powerful demonstration of the ability of injury to one organ to cause remote injury to another organ[48–50] and how costs can rapidly spiral. It has even been reported that the impact and costs of postoperative complications, secondary to lung injury or lung infections, outweigh those of thromboembolic, cardiovascular and other infections combined.[45]

## Mechanisms of injury

The mechanism of injury in many of the above situations is ischaemia reperfusion injury (IRI).[51–53] This is as a result of the switch of the tissue from aerobic to anaerobic respiration. Tissues are able to fully recover from short periods of ischaemia. However, prolonged ischaemia can cause non-reversible damage to the tissue[54] and subsequent reperfusion only acts to exacerbate the injury.[55]

The underlying mechanisms of injury are thought to be because of free radical formation, mitochondrial failure, inflammation and beyond.

### Free radical formation

The process of ischaemia followed by reperfusion produces free radicals, molecules with unpaired electrons, which are readily reactive. These free radicals are named depending on the components, with most coming under the umbrella of either reactive oxygen species or reactive nitrogen species, examples include superoxide anion, hydroxyl radical and nitric oxide.[52] The release of these molecules is a result of a decrease in ATP generation as a result of ischaemia and consequent collateral mechanisms to compensate in maintaining energy production.

It has been suggested the reactive species are produced by the action of NADPH oxidase and xanthine oxidase enzymes[56] and the mitochondria in response to the reduced efficacy of respiratory complexes I and III.[57] This results in the production of superoxide ions ($O_2$) which are subsequently converted in to hydroxyl

(OH˙) radicals by superoxide dismutase. Xanthine oxidase can also act on the hypoxanthine produced by the breakdown of ATP to AMP after ischaemia, also leading to the production of $O_2^-$ ions.[58] It is important to note that these processes are minimal during the ischaemic period themselves, as a result of the reduced enzyme activity and the low availability of oxygen.

On reperfusion, these reactions return as enzyme activity increases leading to an increase in concentration of free radicals. These, despite their short half-lives, are thought to exert more distant effects through peroxidation and hydrogen atom removal on the constituent parts of the cell membrane[59 60] and the intercell transport of breakdown products such as aldehyde.[59] Furthermore, the generation of free radicals is thought to stimulate the release of IL-8, which activates neutrophils and contributes to the neutrophil sequestration in the pulmonary vasculature. This causes an increase in microvascular permeability in the lungs, resulting in pulmonary oedema and impaired gas exchange and the subsequent distant organ injury seen in IRI.[61]

During the ischaemic period, the shortage of ATP and reduction in enzyme activity also leads to an increase in intracellular calcium and sodium ions, in addition to the generation of lactate through glycolysis. This causes changes in intracellular pH and will likely increase the cellular osmotic pressure leading to the swelling and rupture of cells.[62–65]

### Mitochondrial failure

After reperfusion, the return of normal cellular pH in combination with the raised intracellular calcium and free radicals are believed to act together to produce an opening of the mitochondrial permeability transition pores (mPTP). The change in permeability of mitochondrial membrane is believed to cause leakage of cytosol from the mitochondria and the collapse of the mitochondrial potential.[65 66] This is thought to herald the beginning of the common cell death pathway producing necrosis and apoptosis during reperfusion after prolonged ischaemia.[67]

The breakdown of the mitochondrial membrane also releases cytochrome C which can subsequently activate apoptosis.[68] This, in addition to free radicals and other breakdown products such as aldehydes are able to inflict further direct tissue injury through protein fragmentation and modification, resulting in changed function and increased susceptibility to proteolytic degradation.[69] Some evidence also suggests that the combination of free radicals and aldehydes have also been shown to have intra-nuclear effects; leading to disruption of cytoprotective signals such as heat shock protein (HSP) 72.[69 70]

### Central and systemic inflammation

Cellular damage can lead to activation of local innate immunity mechanisms, which if severe enough can lead to central inflammation, as shown in models of acute hepatic, renal injury[71 72] and surgical trauma.[30] The presence of central inflammation has been linked with a decline in cognitive function.[30 71] The underlying mechanism of spread from peripheral to central inflammation still remains unclear. Mechanisms suggested have included stimulation of afferent pathways,[73 74] the interaction of proinflammatory cytokines and the Blood Brain Barrier (BBB) leading to increased permeability,[72] or direct action on the parts of the brain not protected by the BBB.[29 75]

As yet, none of the above mechanisms have been convincingly proved to be biologically important. Animal models of transection of the afferent nerves connecting the periphery to the central nervous system, have been mixed with only some studies showing a reduction in neuroinflammation on histology.[76 77] The BBB is thought to be reactive to pro-inflammatory cytokines including TNF receptors[72] and IL-1 receptors[78] which can subsequently act to induce Rho-associated kinases within the BBB, subsequently leading to increased leucocyte migration and subsequent inflammation.[79 80] Pro-inflammatory cytokines are also able to act on the parts of the brain not covered by the BBB and subsequently this is a way for inflammation to spread slowly through the brain.[81] Moreover, how neuroinflammation causes neuropathological changes at cellular level and in turn impaired cognition remains unknown, although such changes have been observed in animal models.[82–84]

## Strategies in prevention and treatment

Strategies in prevention can be divided into those involving ischaemic conditioning or choice of anaesthetics (summarized in Table 1).[52 53] Ischaemic conditioning can be applied either before or after the ischaemic insult, directly to the tissue or to other tissue beds.[85] An alternative approach is the choice of anaesthetic used during the operation be it inhalation such as isoflurane,[86] sevoflurane[87] or xenon[48 53] or i.v. such as dexmedetomidine.[88]

### Ischaemic conditioning

In ischaemic conditioning short non-lethal bursts of ischaemia are used to prepare target tissue for ischaemic insult and is thought to subsequently attenuate the IRI.[89] It can be applied either directly to the tissue before[89] or after the insult,[90] or through a remote vascular bed at any time.[89 91 92]

#### Ischaemic preconditioning

Preconditioning is where bursts of non-lethal ischaemia are applied before the insult. The bursts of ischaemia will then generate small amounts of free radical.[93 94] It has been suggested that these free radicals provide protection in a particular two peak pattern; a short phase starting immediately after the conditioning stimuli and lasting up to four hours and an extended phase starting after 24 hours and lasting a few days.[95 96] In the early phase, peaks of adenosine,[97] bradykinin[98] and opioid receptor agonists[99] have been noted, leading to phosphorylation and activation of matrix metalloproteinases[100–105] which induce the release of growth factors thought to produce cytoprotection.[104] It has been suggested that the underlying stimulus for this is the expression of hypoxic inducible factor (HIF)-1[106] which triggers breakdown of ATP to adenosine and consequent activation of the adenosine receptors.[107] This potentially leads to G-protein receptor activation and consequent activation of the reperfusion injury salvage kinase (RISK) pathways.[52] The RISK pathways include the ERK and phosphatidylinositol-3-kinase (PI3-K) pathway. The PI3-K pathway is thought to work through inhibition of glycogen synthase kinase-3beta (GSK-3β), via phosphorylation of the serine residues within the GSK-3β molecule, hence preventing opening of the mPTPs, crucial in triggering the apoptotic and necrotic processes within the cells.[108] The activation of both ERK and PI3-K have also been shown to inhibit the janus kinase (JAK) and signal transducer and activating factor of transcription (STAT3) pathway, leading to a reduction in pro-apoptotic proteins.[109]

Clinically, indirect ischaemic preconditioning has been explored in some small pilot studies which have proved equivocal in clinical benefit.[110] These studies typically use surrogate markers as end-points to suggest organ injury such as postoperative creatinine and troponin and are not powered to detect clinical differences. One randomized control trial (RCT), performed in

Table 1 Summary of animal models and clinical trials relating to treatment of ischaemia reperfusion injury encountered in vascular surgery

| Strategy | Pre-clinical | | | Clinical | | |
|---|---|---|---|---|---|---|
| | Author | Model | Finding | Author | Model | Finding |
| Ischaemic preconditioning | Wever and colleagues[89] | Rat | Improved renal biochemical markers of function | Loukogeorgakis and colleagues[96] | Remote ischaemic conditioning | Reduced flow mediated vasodilation suggestive of protection at 4, 24 and 48 h |
| | Yamaki and colleagues[91] | Rat | Improved renal histology and biochemical makers of function | Ali and colleagues[111] | Remote ischaemic conditioning in abdominal aortic aneurysm (AAA) repair | Protective effect on myocardial injury, myocardial infarct and renal impairment |
| | Kharbanda and colleagues[95] | Porcine | Reduced infarct size and better left ventricular function | Walsh and colleagues[115] | Remote ischaemic conditioning in AAA repair | Non-significant postoperative renal function |
| | Liu and colleagues[97] | Rabbit | Reduced infarct size | Walsh and colleagues[113] | Remote ischaemic conditioning in endovascular AAA repair | Improvement in urinary biomarkers but no effect on clinical end-point |
| | Schoemaker and colleagues[98] | Rat | Reduced infarct size | Li and colleagues[112] | Remote ischaemic conditioning in AAA repair | Attenuates intestinal and pulmonary injury |
| | Patel and colleagues[99] | Rat | Reduced infarct size | Walsh and colleagues[116] | Remote ischaemic conditioning in carotid endarterectomy | Trend towards improvement in neurological outcome |
| Ischaemic postconditioning | Miklos and colleagues[90] | Rat | Improvement in renal biochemical markers and reduction in pro-inflammatory cytokine release | | | |
| | Liang and colleagues[106] | Rabbit | Reduced release of markers of muscle cell stress | | | |
| | Gyurkovics and colleagues[126] | Rat | Improved histology biochemical markers of renal function and serum inflammatory markers | | | |
| | Tsubota and colleagues[127] | Mice | Reduced muscle necrosis and reduced inflammation in the affected tissue | | | |
| | Aranyi and colleagues[128] | Rat | Improved distant organ microcirculation, no difference in muscle outcome | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Inhalation anaesthetics | Kim and colleagues[130] | Mice isoflurane postconditioning | Attenuates renal, hepatic and intestinal IRI | Beck-Schimmer and colleagues[134] | Prospective randomized control trial comparing preconditioning using sevoflurane alone against propofol alone | Helped to attenuate postoperative liver injury |
| | Annecke and colleagues[131] | Porcine intra-operative sevoflurane | Attenuates endothelial glycocalyx shedding | Slankamenac and colleagues[135] | Retrospective sevoflurane intra-operatively during hepatic in-flow occlusion in hepatic resection | No difference in outcome compared with i.v. anaesthesia |
| | Ma and colleagues[132] | Mice xenon pre-conditioning | Attenuates renal IRI and stimulates cytoprotective factors | | | |
| | Zhang and colleagues[133] | Mice isoflurane preconditioning | Attenuates renal IRI and improves histology through cytoprotective factor release | | | |
| | Zhao and colleagues[49] | Rat xenon post-conditioning | Attenuates distant lung IRI and reduces pro-inflammatory pathways | | | |
| I.V. Anaesthetics | Cho and colleagues[117] | Rat remifentanil pre-treatment | Attenuates intestinal IRI and pro-inflammatory response | Wang and colleagues[88] | Dexmedetomidine intra-operatively during hepatic in-flow occlusion in hepatic resection | Attenuates intestinal and hepatic IRI |
| | Gu and colleagues[136] | Rat dexmedetomidine pre and post treatment | Attenuates lung IRI and pro-inflammatory response | Powell and colleagues[138] | Randomized control trial of patients undergoing emergency repair of AAA | Reduced mortality in patients receiving only local anaesthetic when compared receiving general anaesthesia |
| | Gu and colleagues[137] | Rat dexmedetomidine pre and post treatment | Attenuates renal IRI and increases survival | | | |

the UK, into ischaemic preconditioning showed a reduction in incidence of myocardial injury by 27% (39% *vs* 12%; *P*=0.005), myocardial infarction by 22% (27% *vs* 5%; *P*=0.006) and renal impairment by 23% (30% *vs* 7%; *P*=0.009).[111] A further RCT, in a Chinese population, has demonstrated that ischaemic preconditioning improved markers of lung function as represented by alveolar/arterial gradient, up to 24 h postoperatively (*P*=0.039). The study also showed improved serum intestinal fatty acid binding protein (a marker of villi degradation and used as a surrogate marker for intestinal injury) at 24 h, compared with the control group (*P*=0.003).[112] A pilot RCT exploring preconditioning effect in endovascular AAA repair, in the UK, has also shown some protective effect towards renal function.[113] By measuring urinary retinol binding protein (RBP), a surrogate marker that increases in renal injury, the study found a significantly lower increase in RBP in the preconditioned group at 24 h (*P*=0.04).

Interestingly, the anaesthetic techniques used in these studies differ. The Chinese study used a completely i.v. regimen of remifentanil and propofol, whilst the other two RCTs utilized volatile anaesthetics.[111–113] Of note though is the fact that all three studies have shown that the improved biomarkers did not translate into actual clinical benefit in patient outcome including morbidity, mortality or length of stay.[114] Furthermore, there is also one pilot study demonstrating no effect on either renal biomarkers or clinical outcome.[115]

Studies in other forms of vascular surgery such as carotid endarterectomy have not shown any benefit from ischaemic preconditioning against the outcomes of saccadic latency or cognitive function testing.[116] A possible explanation for these equivocal results is the effect of anaesthetics as a potential protective agent mitigating any perceived effect the preconditioning may have had on the tissue beds.[117 118]

### Ischaemic postconditioning

Ischaemic postconditioning was first explored in a canine model of myocardial ischaemia, whereupon it was shown to be significantly protective against ischaemic changes by demonstrating smaller infarct size, lower creatine kinase release and reduced pro-inflammatory cell adhesion.[119] It has subsequently been explored thoroughly with relation to cardiac surgery.[120] In the setting of vascular surgery, it remains a relatively unexplored intervention. It is thought that postconditioning can act on the same receptors triggered by preconditioning including adenosine,[121] bradykinin[122] and opioid receptor activation.[123] Activation of these receptors leads to a downward cascade of PI3K,[124] which has been associated with the cytoprotective stabilization of mitochondrial membranes on reperfusion[125] as discussed above.

In animal models, postconditioning has been explored with respect to abdominal aortic surgery looking at the reaction of skeletal muscle, systemic inflammatory reaction and renal function.[126–128] One study in rats, cross-clamped the aorta to induce lower limb ischaemia and initiated postconditioning at the start of reperfusion by declamping the aorta for 10 s, then reapplying the clamp for 10 s. This cycle was repeated six times in total.[126] A different study in mice included right hindlimb ischaemia via a tourniquet, then applied two cycles of remote postconditioning by inducing twice five min of ischaemia followed by five min of reperfusion in the left hindlimb, immediately before reperfusion and subsequent analysis on the right leg.[127]

These two rodent models have shown an improvement in muscle necrosis (*P*<0.001), myeloperoxidase activity (*P*<0.001), systemic inflammatory reaction as marked by TNF-$\alpha$ (*P*<0.01) and creatinine (*P*<0.05) compared with the non-postconditioning group.[126 127] Although there is some promise in the pre-clinical phase, no clinical data is currently available for postconditioning in vascular surgery.

### Inhalation anaesthesia

As mentioned above, the choice of anaesthesia may have an effect on the outcomes within vascular surgery. Inhalation anaesthetics have been shown to work through the RISK pathways, as identified in ischaemic conditioning and also the JAK-STAT3 pathways as recently reviewed in-depth by Kunst and Klein.[129]

In pre-clinical studies, multiple inhaled anaesthetic agents have been cited as having organo-protective effects after IRI post vascular surgery. These include isoflurane,[130] sevoflurane[131] and xenon.[132] In addition, isoflurane and sevoflurane have both been proved as organo-protective in the pre and postconditioning model.[48 130–133] It is important, to note that these studies were performed on animal models of kidney IRI. A variety of different measures for renal function were used including glycocalyx shedding,[131] cell morphology and biochemical markers of renal function.[132]

It remains unclear, however, if these benefits will lead to any clinical benefit. Currently there are only two RCTs, both for hepatic surgery. The first RCT used sevoflurane preconditioning on top of propofol and showed an improvement in ALT (*P*=0.01) and AST levels (*P*=0.05) and also a reduction in significant complications postoperatively (*P*=0.05) compared with propofol along. However there was no difference in overall length of hospital stay.[134] The second RCT differed in that it used sevoflurane as the sole anaesthetic agent. This RCT found no difference in liver markers AST and ALT and also no clinical difference in overall length of stay or postoperative complications, when compared with using propofol as the sole anaesthetic agent.[135]

### Non-inhalation anaesthesia

The effects of continuous i.v. anaesthesia warrant separate discussion. We discussed above a study comparing sevoflurane against a particular i.v. anaesthesia regimen in the form of propofol.[135] A number of other i.v. anaesthetic regimens have shown benefits. Dexmedetomidine, an alpha$_2$ adrenergic receptor agonist, has been shown to have both local and systemic effects reducing IRI and subsequent systemic inflammatory response leading to insult to distant organs.[136 137] Although the exact underlying molecular mechanism remains unclear, there is already some evidence that dexmedetomidine has some clinical benefit as a preconditioning agent.[88] It is interesting that in this study, Wang and colleagues[88] chose to use a continuous i.v. anaesthetic protocol, removing any volatile anaesthetic as a potential confounder in the experiment. Furthermore, in addition to the reduction in the marker of bowel injury, preconditioning with dexmedetomidine also led to an improvement in liver function and its reaction to direct IRI when compared with the group that received no preconditioning.[88] An alternative i.v. anaesthetic regimen investigated is remifentanil, which has been shown in a rat model to attenuate IRI within bowel.[117]

Clinically, there has only been some incidental data suggesting the anaesthetic approach can affect outcome. In the setting of emergency AAA repair using EVAR, local anaesthesia only has been shown to have a four-fold improvement in 30 day mortality rates compared with patients who received general anaesthesia in the recent IMPROVE trial.[138]

## Summary

In recent years, there has been a reduction in the prevalence of peripheral vascular disease worldwide; however, there still

remains a significant population suffering from the disease requiring surgical intervention. These patients are at higher risk of serious perioperative morbidity and mortality, compared with the general population. In particular, abdominal aneurysm and limb revascularization surgery is associated with a higher risk of developing myocardial infarction, acute kidney injury, ischaemic bowel injury and lung injury. These occur as a result of tissue ischaemia and or reperfusion injury, or as a consequence of the huge release of inflammatory cytokines perioperatively and also as a result of surgical mishap. Carotid endarterectomy surgery is particularly associated with an increased risk of perioperative stroke, or worsening stroke in patients undergoing urgent revascularization.

Attempts have been made to reduce the injury sustained during vascular surgery. The application of both ischaemic and pharmacological therapies, including volatile anaesthetic and alpha$_2$ agonist drugs, pre- and postconditioning strategies and recently remote conditioning strategies have been investigated. Although these interventions produce some reduction in the biomarkers of organ injury in many clinical studies, they have not resulted in significant reduction in length of hospital stay, in morbidity or in mortality. However, a confounding factor in the studies evaluating the organ protective effects of ischaemic conditioning strategies perioperatively are that volatile anaesthetics, used to maintain general anaesthesia during surgery, are known to have cyto-protective properties. Therefore the use of volatile anaesthetics may possibly mask the protective properties provided by the ischaemic conditioning strategies. However, there may be occasions where these agents used for general anaesthesia, may be associated with an increased mortality compared with local anaesthetic alone in specific clinical situations.

## Conclusion

The current anaesthetic techniques used in vascular surgery are relatively safe and furthermore are associated with a reduced mortality in particular clinical settings. Conditioning strategies when applied in experimental models of ischaemia and reperfusion injury showed significant organ protection but these have not been translated into significant clinical benefits. It could be that we have not yet found the best way to apply them clinically, however till then, the search towards reducing morbidity and mortality after vascular surgery continues.

## Authors' contributions

D.M. developed the concept and all authors participated to write the work.

## Declaration of interest

D.M. is a board member of BJA.

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Review Article

# Myocardial ischaemia reperfusion injury: the challenge of translating ischaemic and anaesthetic protection from animal models to humans

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## Abstract

Myocardial ischaemia reperfusion injury is the leading cause of death in patients with cardiovascular disease. Interventions such as ischaemic pre and postconditioning protect against myocardial ischaemia reperfusion injury. Certain anaesthesia drugs and opioids can produce the same effects, which led to an initial flurry of excitement given the extensive use of these drugs in surgery. The underlying mechanisms have since been extensively studied in experimental animal models but attempts to translate these findings to clinical settings have resulted in contradictory results. There are a number of reasons for this such as dose response, the intensity of the ischaemic stimulus applied, the duration of ischaemia and lost or diminished cardioprotection in common co-morbidities such as diabetes and senescence. This review focuses on current knowledge regarding myocardial ischaemia reperfusion injury and cardioprotective interventions both in experimental animal studies and in clinical trials.

**Key words:** anaesthetic conditioning; diabetes; ischaemic conditioning; ischaemia-reperfusion injury

The recent VISION (The Vascular events In non-cardiac Surgery patIents cOhort evaluatioN) study[1] found that 8% of patients more than 45 yr of age suffered myocardial injury, based on troponin assay, after non-cardiac surgery, of which 84.2% were asymptomatic. This finding was significant because, amongst these, one in 10 died within 30 days. Ischaemic heart disease (IHD) is also one of the leading causes of death in economically developed countries worldwide. Increasing attention has been paid to the development of interventions to re-establish blood perfusion to ischaemic myocardium, to salvage tissue and protect against paradoxical reperfusion injury.[2] This also decreases the risk of post-ischaemic complications such as heart failure and arrhythmia.[2] Despite improvements in therapeutic strategies such as angioplasty, thrombolysis, percutaneous coronary intervention and coronary artery bypass surgery, recent studies indicate that post-ischaemic 30 day mortality and morbidity (about 8.5% after angioplasty and about 14% with thrombolysis) remains significant.[3] The incident rate of IHD and post-ischaemic complications are significantly increased in patients with co-morbidities such as diabetes[4] and/or hypertension. To make things worse, patients with diabetes are not responsive to cardioprotective strategies such as ischaemic preconditioning (IPC),[5 6] postconditioning (IPo),[7] and anaesthetic conditioning (APC)[8] that are otherwise effective in non-diabetic subjects. This highlights the need to determine why hearts in patients with co-morbidities, in particular those with diabetes are susceptible to ischaemia and yet not sensitive to cardioprotective interventions. The answer to this question may facilitate the development of novel cardioprotective strategies that may also be applicable in other patients, such as the elderly.

## Mechanism of ischaemia reperfusion injury

Myocardial infarction is usually caused by rupture of an atheromatous plaque in a coronary artery. Re-establishment of coronary blood flow (reperfusion) is mandatory to salvage the ischaemic myocardium but this is accompanied by dramatic changes in mitochondrial permeability transition pore (mPTP) opening, generation of reactive oxygen species (ROS), bioavailability of nitric oxide (NO), intracellular distribution of $Ca^{2+}$ and $Na^+$, and pH. Paradoxically, reperfusion itself can actually cause cardiomyocyte death and subsequent irreversible myocardial injury, a phenomenon termed 'ischaemia reperfusion injury (IRI)'.[9] (Fig. 1).

### Mitochondrial dysfunction during myocardial ischaemia reperfusion

In order to meet the high energy demand for both contractility and diastolic relaxation, the heart needs a continuous energy supply, which depends on the synthesis of adenosine triphosphate (ATP). Approximately 95% of this ATP comes from mitochondrial oxidative phosphorylation.[10] Thus, mitochondrial function has been considered as a key factor in the aetiology of myocardial ischaemia, a state of energy deficit in the heart. Mitochondrial dysfunction affects cell viability through a wide array of events including reduction or loss of ATP synthesis, increase in ATP hydrolysis,[11] impairment in ionic homeostasis,[12] and formation of ROS.[13] All these suggest a critical role of mitochondria in myocardial IRI and, as such, mitochondria may act as critical triggers, mediators and effectors for protective strategies directed against myocardial IRI.

Under physiological conditions, the mitochondrial inner membrane is impermeable (except for a few selected metabolites and ions). However, under pathological conditions such as myocardial ischaemia, oxygen and nutrient deprivation causes a non-selective opening of the inner mPTP, resulting in depolarization and uncoupling/impairment of oxidative phosphorylation.[14] This not only leads to ATP depletion but also causes the breakdown of any available ATP, which subsequently induces the hydrolysis of ATP and the enhancement of mitochondrial inorganic phosphate.[12] On the other hand, during ischaemia (in the absence of oxygen) cellular metabolism switches to anaerobic glycolysis and the subsequent accumulation of lactate reduces intracellular pH (lower than 7.0).[15] Depletion of ATP and acidosis impede the ability of the $Na^+/K^+$ antiporter to remove excess $Na^+$ caused by the increase of intracellular proton accumulation-induced activation of $Na^+/H^+$ ion exchanger, resulting in intracellular $Ca^{2+}$ overload and mitochondrial swelling.[11] Influx of $Ca^{2+}$ into the mitochondria and an increase in ROS production both favour mPTP opening, but the associated acidosis obstructs its opening. After reperfusion, a quick pH correction exacerbates the opening of the mPTP within a few min.[16 17] This, in turn, leads to an abrupt increase in flow of accumulated electrons and an associated increase in electron leak which, together with the damaged electron transport chain, not only damages mitochondria but also promotes a burst production of superoxide anion and other ROS,[18 19] eventually causing cell death (Fig. 1). Therefore, preventing mPTP opening at the time of reperfusion (mPTP remains closed during ischaemia) or timely removal of damaged mitochondria would serve as promising therapeutic avenues to protect the heart from myocardial IRI.

It has been shown that direct inhibition of mPTP opening by cyclosporine A, attenuated myocardial injury after reperfusion both in experimental studies in small[20] and large animals[21] and in patients with acute ST-elevation myocardial infarction.[22] Treatments targeting inhibition of mPTP have been proved to be cardioprotective and are currently being evaluated for clinical use.[23 24] As such, the mPTP provides an important therapeutic target for preventing lethal myocardial IRI. However, because of the complexity of mitochondrial metabolism and the fact that most experimental studies have been performed on isolated mitochondria which lack cellular context, further investigation

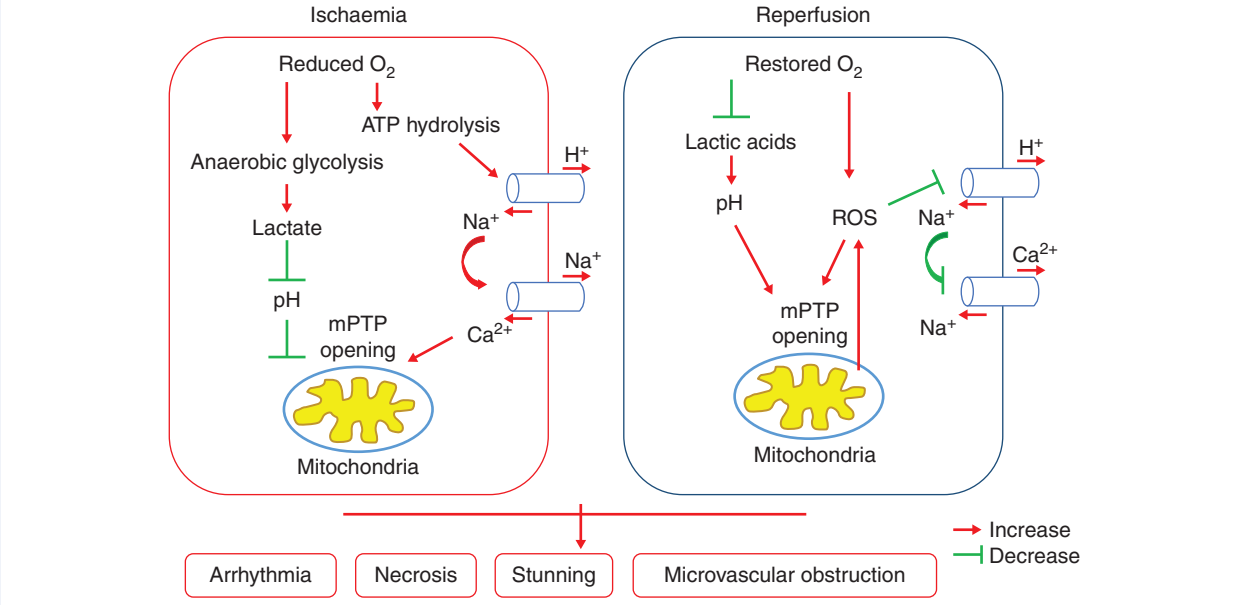


Fig 1 Schematic of proposed mechanism of myocardial ischaemia reperfusion injury. Myocardial ischaemia reperfusion increases mitochondrial permeability transition pore (mPTP) opening which elevates reactive oxygen species (ROS) generation, decreases nitric oxide (NO) bioavailability, and disrupts intracellular distribution of $Ca^{2+}$, $Na^+$ and pH, resulting in cardiomyocyte death and subsequent irreversible myocardial injury.

is needed to reveal the whole picture of the role and mechanisms of mPTP in myocardial IRI and its application as a therapeutic target for cardioprotection.

### Overproduction of reactive oxygen species during myocardial ischaemia reperfusion

ROS such as superoxide anion, hydrogen peroxide, and hydroxyl radicals are generated as by-products of cellular metabolism. Under physiological conditions, small amounts of ROS are beneficial as they participate in normal cellular signaling[18] and serve as an important mediator in the cardioprotection of IPC.[25] However, under stress conditions such as myocardial ischaemia reperfusion, after prolonged ischaemia, re-introduction of blood flow (reperfusion) leads to a massive burst of ROS production from damaged mitochondria.[11] This exceeds the defensive capacity of the cells (e.g. catalase, glutathione peroxidase, and superoxide dismutase) and is detrimental to cardiomyocytes. Production of large quantities of ROS results in overloading of $Ca^{2+}$,[2,10] breakdown of critical proteins as a result of protein oxidation,[26] generation of peroxynitrite (ONOO-),[27] disruption of cholesterol containing membranes as a result of lipid peroxidation,[28] opening of the mPTP,[29] and reduction of nitric oxide availability.[30] This phenomenon is termed oxidative stress and ultimately causes cell death.

As increased generation of ROS during the first min of reperfusion is a major contributor to the pathogenic mechanisms underlying myocardial IRI, antioxidant therapy has been considered an appropriate option of preventive treatment. However, results from experimental and clinical studies are inconsistent. We and others have shown that antioxidant treatment with N-acetylcysteine and/or allopurinol, attenuates post-ischaemic myocardial injury in a rat model of myocardial IRI[27 31] and in patients undergoing coronary artery bypass surgery.[32] However, others did not observe a beneficial antioxidant effect in patients with vascular disease,[33 34] and long-term antioxidant (vitamin E) supplementation does not prevent major cardiovascular events and may even increase the risk of heart failure.[35] A possible explanation for this contradiction may be the difference in timing and the choice of an antioxidant that targets specific ROS. It may also be because of the inability of the antioxidant to actually enter the cell.[36] Given that mitochondria are considered as the primary site of ROS generation, discovery of mitochondrial-specific antioxidants[37 38] may provide more effective therapy in combating myocardial IRI.

### Reduction of nitric oxide bioavailable during myocardial ischaemia reperfusion

Nitric oxide (NO) is produced by NO synthases [NOS, with three isoforms respectively called endothelial (eNOS), neuronal (nNOS), and inducible NOS (iNOS)] through converting L-arginine to L-citruline in the presence of oxygen. NO is a critical signalling molecule in the cardiovascular system, acting as one of the most important defence mechanisms against myocardial IRI and as a mediator of cardioprotective interventions such as IPC and IPo. NO exerts its cardioprotective effect via distinct mechanisms: (1) activation of NO-sensitive guanylyl cyclase,[39] (2) inhibition of mitochondrial $Ca^{2+}$ influx[40 41] and activation of the mitochondrial $K_{ATP}$ channel,[42] (3) activation of cGMP,[43] (4) enhancement of cyclooxygenase-2,[44] and (5) abrogation of ONOO- mediated lipid radical chain propagation.[45] In the setting of prolonged myocardial ischaemia, the activity/activation of NOS (primarily eNOS and nNOS) is reduced concomitant with the reduced supply of oxygen that is required for the synthesis of NO from NOS. Thus, deprivation of oxygen during ischaemia leads to reduced or diminished NO release. Hence, enhancement of NOS activity/activation and NO bioavailability has been shown to be cardioprotective. Indeed, eNOS knockout exacerbates post-ischaemic myocardial injury in mice subjected to myocardial IRI,[46] while overexpression of eNOS improves post-ischaemia cardiac functional recovery.[47] Also, enhancing NO bioavailability by exogenous application of NOS and L-arginine, attenuates ischaemia reperfusion-induced microcirculatory alterations[48] and post-ischaemic infarction.[49] However, high concentration of NO in the presence of increased superoxide anion production may be detrimental as a consequence of increased formation of peroxynitrite (ONOO-), which exacerbates post-ischaemic myocardial injury. Interestingly, treatment with a NO donor in combination with an antioxidant, has been shown to reduce post-ischaemic myocardial infarct size and improve contractile function in the isolated rat heart model,[49] indicating that maintaining a physiological concentration of NO is important for NO to confer its cardioprotective effects. Taken together, the cardioprotective effects of NO depend on its concentration/production, subcellular localization, and its bioavailability. Thus, further studies are needed to better understand the metabolism and dynamics of NO during myocardial IRI, in order to liberate the correct amount of NO in the correct place and at the correct time, under varying pathological conditions.

### Other mechanisms of pre- and post-conditioning cardioprotection

Many of the endogenous signalling pathways that participate in anaesthetic-mediated cardioprotection have been identified. Mitochondrial oxidative phosphorylation is the main source of ATP production in the heart, providing the steady supply of ATP required to sustain cardiac contraction, and, as such, mitochondria have been the main focus in cardioprotection. Indeed, signalling pathways targeting cell factions other than mitochondria, such as the nucleus and membrane, also play important roles. For instance, sevoflurane postconditioning by activating Nrf2, upregulated antioxidant genes in the nucleus, resulting in attenuation of myocardial IRI.[50] The integrity and functionality of the cell membrane has also been proposed[51] to mediate the cardioprotection of anaesthetics such as sevoflurane[52] and isoflurane.[53] Sevoflurane preconditioning has also been shown to confer delayed cardioprotection via inhibiting Beclin 1-mediated autophagic cell death, in cardiac myocytes subjected to hypoxia/reoxygenation injury after brief exposure to sevoflurane 24 h before inducing hypoxia,[54] and is likely to involve both mitochondrial and non-mitochondrial mechanisms. Further in-depth investigation is needed to decipher their relative importance, timing of activation, and interactions, and to provide more insight into the mechanisms of volatile anaesthetic cardioprotection.

## Protection against myocardial ischaemia reperfusion injury

### Ischaemic conditioning

Ischaemic conditioning is achieved by intermittent occlusion of a coronary vessel either locally or remotely, by inducing reversible ischaemia of a distant organ (remote ischaemic conditioning), and limits myocardial infarct size. Ischaemic conditioning can be applied at different time points: before the induction of a period of prolonged ischaemia (IPC, ischaemic preconditioning) or immediately at the onset of reperfusion after prolonged ischaemia (IPo, ischaemic postconditioning). All these cardioprotective

strategies confer their effects by activating endogenous pro-survival signalling pathways.

## Ischaemic preconditioning

Ischaemic preconditioning (IPC) was first described by Murry and co-workers in a dog model.[55] The first clinical evidence was provided by inducing several cycles of transient non-lethal ischaemia, using an aortic cross-clamp interspersed with reperfusion. This reduced post-ischaemic myocardial troponin T release and ATP depletion in patients undergoing cardiac bypass surgery.[56] The protective effect of IPC is biphasic. The 'first window' or early phase arises immediately after ischaemic stress and lasts for 2–3 h. The 'second window' or late phase cardioprotection occurs 12–24 h after initial preconditioning and lasts for up to 48–72 h.[57–59] Ischaemic preconditioning confers its early phase protection through the modification of existing prosurvival proteins in the heart, to protect against myocardial infarction, but it has no significant effect on limiting the degree of contractile dysfunction. The late phase of IPC protection, is a result of the production of cytoprotective proteins in the myocardium and protects the heart from cardiomyocyte death while improving post-ischaemic cardiac functional recovery.[57] Thus, the late phase of IPC cardioprotection is more clinically applicable for its more significant protection and longer duration.

IPC confers cardioprotection by creating a cardiac 'memory' between the triggers and end-effectors in the signalling pathways in order to keep the heart in a 'preconditioned' state.[60] Three major endogenous triggers of IPC are adenosine,[61] bradykinin,[62] and opioids,[63] all of them are classified as G coupled protein receptor dependent triggers. There are others including ROS, the mitochondrial $K_{ATP}$ channel and NO, which probably trigger IPC through the activation of G coupled proteins[64] and protein kinases.[65] After being stimulated by IPC, these triggers activate their downstream mediators, among which are mainly protein kinases, such as protein kinase C (PKC), Akt, tyrosine kinase, and the mitogen activated protein kinase (MAPK). PKC was one of the first mediators of IPC to be identified.[66 67] Gene knockout of PKC-ε cancels the cardioprotective effects of IPC in mice.[68] However, in isolated ischaemic reperfused rat hearts, PKC-δ inhibition attenuates myocardial IRI, while PKC-ε activator (but not PKC-δ activator) mimics IPC,[69] supporting the notion that PKC activation-mediated cardioprotection in IPC is isoform-specific. Further investigation is needed to provide a full picture of the beneficial or detrimental role of specific isoforms of PKC activation in the process of IPC. Numerous upstream activators (e.g. PI3K-Akt,[70] NO,[71] and mitochondrial $K_{ATP}$ channel[72]) or downstream targets (Sarcolemmal $K_{ATP}$ channel,[73] mitochondrial $K_{ATP}$ channel,[74] and p38 MAPK[75]) of PKC have also been suggested as IPC mediators. There are others that work in parallel with the PKC pathway in IPC, including receptor tyrosine kinase, MEK1/2-Erk1/2, the Jak-STAT pathways, GSK-3β, and ROS[25 76] (Fig. 2).

The ultimate end-effector of IPC has not been determined, despite extensive research. The mitochondria is where most signalling pathways governing IPC cardioprotection converge. The opening of the mitochondrial $K_{ATP}$ channel by IPC inhibits mitochondrial $Ca^{2+}$ overload[77 78] and attenuates myocardial IRI. Other studies have shown that opening of the mitochondrial $K_{ATP}$ channel facilitates the generation of small amounts of ROS and activates PKC, which in turn phosphorylates the mitochondrial $K_{ATP}$ channel and keeps it in the opened state.[79] Inhibition of mPTP opening has also been considered as the final step in the process of IPC. It has been shown that IPC may inhibit mPTP opening through GSK-3β, eNOS, or via the reperfusion injury salvage kinase (RISK) pathway[80 81] (Fig. 2). Of note, there are also other components that have been suggested as the end-effectors of IPC, for instance, the cytoskeleton, gap-junctions, and the $Na^+/H^+$ exchanger.[80] Although IPC has been reported to be effective in both experimental and clinical studies, it needs to be performed before the onset of prolonged myocardial ischaemia [i.e. acute myocardial infarction (AMI)], which is neither predictable nor feasible in most clinical situations. Therefore, the majority of clinical investigations of IPC have been restricted to various cardiovascular surgical procedures, including both vascular and cardiac operations in which the ischaemia is predictable.

## Ischaemic postconditioning

Recently, effort has focused on modifying events occurring at the time of myocardial reperfusion (ischaemic postconditioning, IPo). Applying transient brief interruptions of reperfusion by ischaemic episodes to reduce myocardial injury, has higher clinical potential than IPC as, for example, it can be performed after myocardial infarction. IPo was first demonstrated by Zhao and his co-workers, in a rabbit model in which the investigators showed that three repeated cycles of 30 s reperfusion followed by 30 s of occlusion, after a prior 60 min of coronary occlusion, markedly reduced post-ischaemic myocardial infarct size and improved cardiac functional recovery.[82] IPo has also shown considerable promise in clinical settings. In children undergoing corrective surgery for tetralogy of fallot, IPo, achieved by two cycles of unclamping the aorta for 30 s and then re-clamping the aorta for 30 s, reduced the concentrations of creatine kinase (CK-MB) and troponin T (two reliable markers of myocardial injury) 2 h after surgery.[83] This has also been confirmed in a number of clinical studies including cardiac surgery for congenital heart disease,[84] aortic valve replacement,[85] and percutaneous coronary intervention.[86]

It is now widely accepted that IPo confers its cardioprotective effects via two intracellular pathways, the RISK pathway which involves PI3K/Akt[87] and the survival activating factor enhancement pathway (SAFE), which involves Jak/signal transducer and activator of transcription 3 (STAT3).[88] These pathways converge in the mitochondria which is, obviously, an integration point that is decisive for cardiomyocyte survival.[14]

As the experimental design of IPo mimics IPC and their cardioprotective effects are similar, it is not surprising that IPo and IPC share related cardioprotective signalling pathways. Indeed, elements of the RISK pathway, including PI3K, Akt, eNOS, and adenosine receptors have also been shown to be involved in IPo (Fig. 3). In isolated rat hearts, IPo stimulation reduced post-ischaemic infarct size with associated elevations in Akt, eNOS, and p70S6K, while these beneficial effects of IPo were abolished by PI3K inhibition (either by LY294002 or wortmannin), indicating the involvement of PI3K-Akt in IPo.[89] In addition, pharmacological inhibition of MEK1/2 abrogated IPo cardioprotection.[90] Furthermore, other components of the RISK pathway, such as PKC, Protein G, and p38 MAPK, are implicated in IPo cardioprotection.[91] All these not only support the concept that cardioprotection of IPo shares a similar pathway (RISK) with IPC, but also suggest that the RISK pathway could be a common pathway mediating cardioprotection. However, the involvement of the RISK pathway in IPo has also been questioned. It was reported that Erk1/2 but not PI3K-Akt was involved in IPo cardioprotection in isolated rabbit hearts.[92] Similarly, in *in vivo* porcine hearts, IPo significantly increased Akt and Erk1/2 phosphorylation but failed to reduce post-ischaemic infarct size.[93] The reason for these controversial results is not clear, but a possible explanation would be the difference of the models and the protocols used in each experiment. However, this may also suggest that IPo may confer cardioprotective effects through RISK-independent pathways.

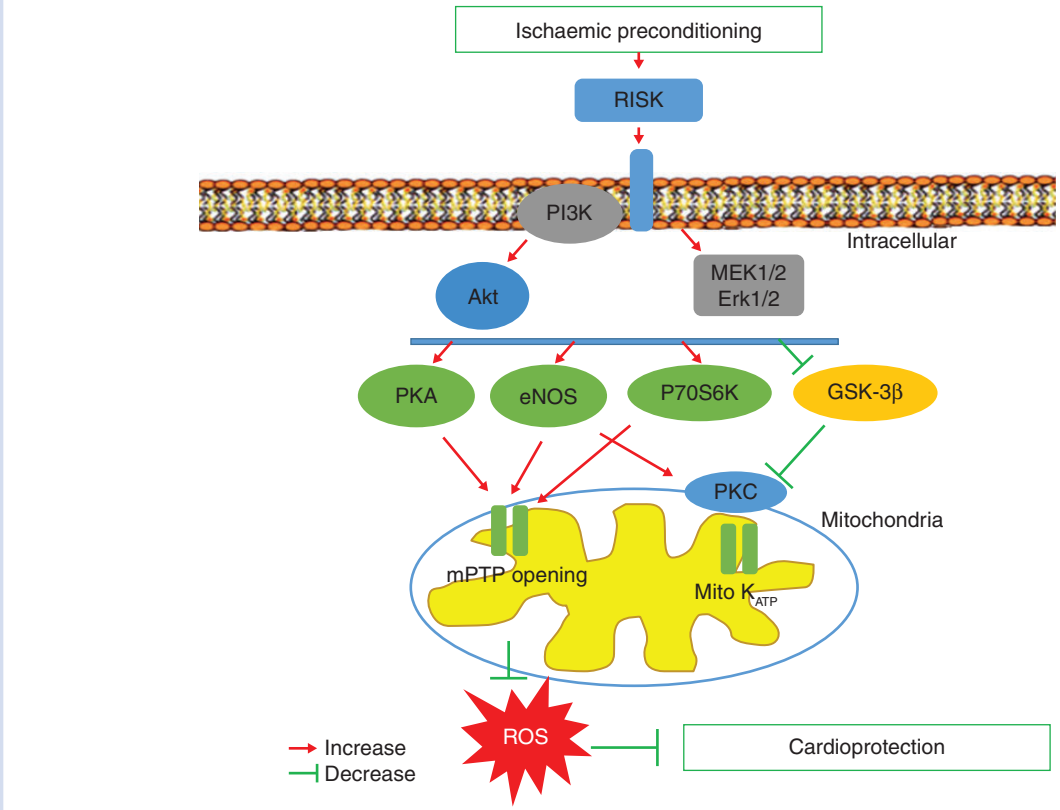


Fig 2 Schematic of proposed mechanism of ischaemic preconditioning cardioprotection. Ischaemic preconditioning exerts its cardioprotection through the reperfusion injury salvage kinase (RISK) pathway that involves the activation of PI3K/Akt and MEK1/2 and, subsequently, activates PKA, eNOS, P70S6K and GSK-3β, leading to a decrease in mitochondrial permeability transition pore (mPTP) opening and increase in the mitochondrial $K_{ATP}$ (Mito $K_{ATP}$) channel opening which attenuates myocardial ischaemia reperfusion injury.

Indeed, the more recently identified SAFE pathway has been shown to be essential and can be activated independent of the RISK pathway during IPo.[88]

The SAFE pathway is initiated by moderate elevation of tumour necrosis factor (TNF)-α (a pro-inflammatory cytokine). The cardioprotective effects of IPo were lost in TNF-α knockout mice[94] and exogenous TNF-α given at the onset of reperfusion at a relative low dose can mimic the protective effects of IPo,[94] indicating that low doses of TNF-α might serve as a trigger of IPo cardioprotection. Interestingly, administration of TNF-α to mimic the protective effects of IPo did not lead to the activation of Akt or Erk1/2,[95] while inhibition of Erk1/2 (by PD98059) or PI3K (by wortmannin) aborted the protective effects mediated by TNF-α when applied at moderate dosage.[94] These findings together with the fact that Akt and Erk1/2 are components of the RISK pathway, provide evidence that downstream signalling of the SAFE pathway is different from that of RISK and that the SAFE pathway can be activated independently in the setting of IPo. This concept has been further supported by a study showing that neither Akt nor Erk1/2 inhibition had significant impact on IPo-induced reduction of post-ischaemic infarct size in an *in vivo* pig myocardial IRI model.[88]

After initiation by IPo, TNF-α binds to its receptor (TNFR2 in myocardial IRI) and subsequently activates/phosphorylates STAT3, a transcription factor that has been shown to be an essential component of the SAFE pathway in IPo. Once phosphorylated/activated, tyrosine-phosphorylated STAT3 shuttles into the nucleus and initiates stress-responsive gene transcription,[96 97] serine-phosphorylated STAT3 moves to mitochondria to regulate the mitochondrial respiratory chain[97 98] (Fig. 3). The importance of STAT3 activation in the context of IPo has been demonstrated by both pharmacological inhibition[99] and genetic deletion of STAT3.[100] However, information regarding how IPo activates STAT3 is lacking. Moreover, although STAT3 is recognized as a transcription factor, its activation during myocardial IRI is much too rapid to assume that it works by modulating gene transcription. Of note, it has been shown that the RISK pathway is involved (but not essential) in IPo cardioprotection and cross-talk exists between the RISK and SAFE pathways.[94] As Akt cannot be phosphorylated in STAT3 knockout mice subjected to IPC,[101] it suggests that IPo may activate Akt via STAT3. IPo also activates STAT3 and increases its mitochondrial expression which subsequently improves mitochondrial function in pig hearts.[99] Given that mitochondrial STAT3 co-localises with cyclophilin D, the target of the mPTP inhibitor,[102] and that mPTP also works as the end-effector of the RISK pathway, it follows that the SAFE and RISK pathways may converge at the mitochondria.

## Remote ischaemic conditioning

Remote conditioning is a strategy whereby application of one or more cycles of non-lethal ischaemia reperfusion to an organ or tissue, distant from the heart either before inducing prolonged

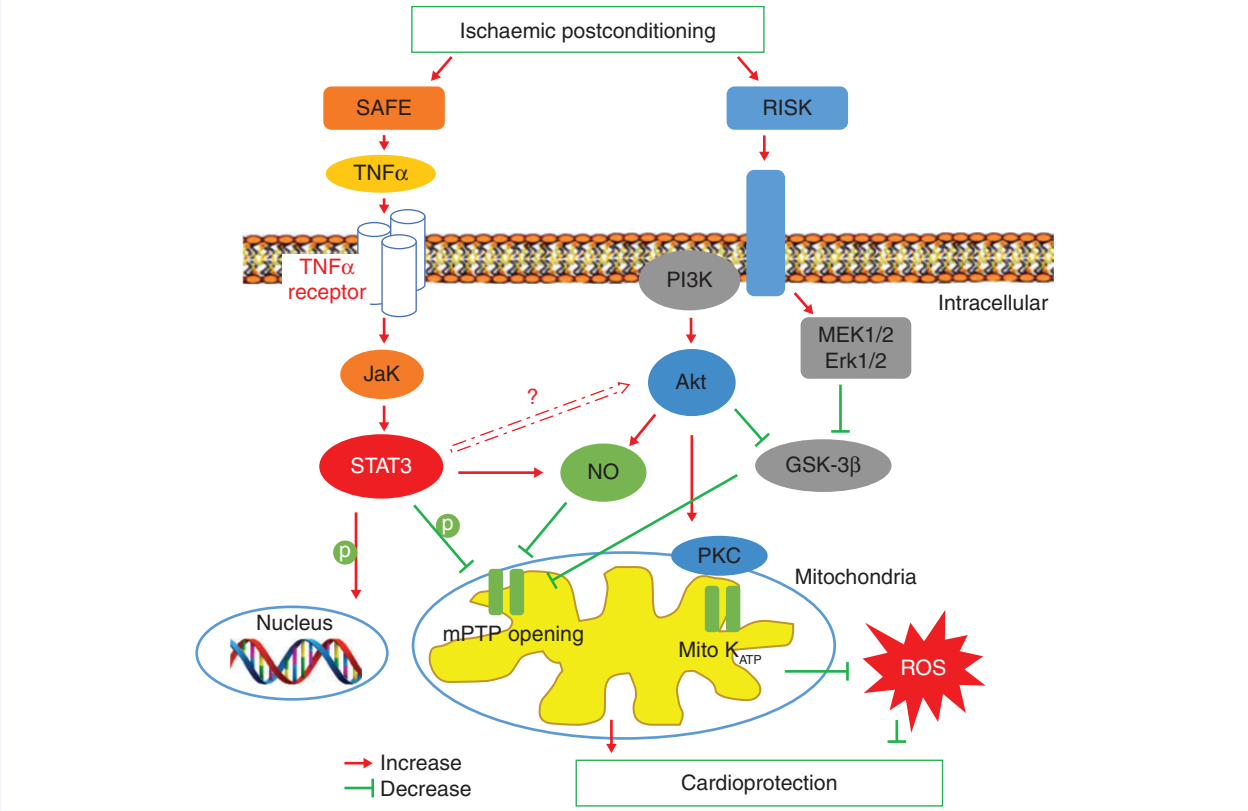


Fig 3 Schematic of proposed mechanism of myocardial ischaemic postconditioning cardioprotection. Ischaemic postconditioning confers cardioprotection through the survivor activating factor enhancement (SAFE) and reperfusion injury salvage kinase (RISK) pathways. These involve the activation of Jak/STAT3 and PI3K/Akt, which subsequently decreases mitochondrial permeability transition pore (mPTP) opening and increases mitochondrial $K_{ATP}$ (Mito $K_{ATP}$) channel opening, which attenuates myocardial ischaemia reperfusion injury.

ischaemia (remote ischaemic preconditioning, RIPC),[103] or at the onset of reperfusion (remote ischaemic postconditioning)[104] protects against myocardial IRI. It was first discovered in 1997 when it was shown that repeated occlusions to a lower limb of rabbits could attenuate myocardial infarct size after myocardial IRI, and it was initially called 'ischaemic preconditioning at a distance'.[105] This simple and effective technique has subsequently been translated into clinical use. The first clinical application of RIPC in humans was in 2006 in children undergoing cardiac surgery, where RIPC (four 5 min cycles of lower limb ischaemia and reperfusion using a blood pressure cuff) significantly reduced postoperative troponin I release and inotrope requirement.[106] However, negative results have also been reported in cardiac bypass surgery.[107 108] The possible explanation for this contradiction is not clear but may be as a result of: (1) the use of anaesthetics such as sevoflurane, opioids and propofol, which can exert cardioprotective effects themselves during cardiac bypass surgery; (2) differences in protocol and the timing of RIPC application; and (3) differences in patient population and type of cardiac surgery. Thus, large multi-centre, randomized, controlled clinical trials are needed to confirm the cardioprotective effects of RIPC. Indeed, a recent large-scale trial has shown that RIPC is cardioprotective in patients undergoing elective coronary artery bypass graft (CABG) under ischaemic cardioplegic arrest, in which medication with β-blockers, statins, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) was not interrupted for the CABG,[109] while the use of propofol was discontinued and diabetes was an exclusion criterion.[110] The efficacy of RIPC mediated cardioprotection was reflected in a reduction in serum troponin release, assessed by the area under the curve values for serum troponin I from baseline to 72 h after surgery. Aortic cross-clamp time was the major independent variable that impacted efficacy of RIPC.[109] However, two recent large-scale, prospective, randomized, sham-controlled trials of RIPC in cardiac surgery with cardiopulmonary bypass, have shown that RIPC was not effective when utilized in anaesthetised patients immediately before surgery.[111 112] This may be related to the use of propofol, which induces cardioprotection via different mitochondrially related molecular mechanisms.[113] In contrast, RIPC applied some time before surgery, increases myocardial salvage-index in patients with acute myocardial infarction.[114] Experimentally, we and others have demonstrated that RIPC repeated for three consecutive days, reduced myocardial infarction in rats with chronic heart failure after myocardial infarction[115] and in rats with diabetes,[116 117] two main co-founders that impact the efficacy of RIPC cardioprotection. These suggest that RIPC initiated at a remote time may allow the second-window of cardioprotection to develop and, thereby, improve tolerance to ischaemia during cardiac surgery. Thus, RIPC should not be abandoned but merits further clinical trials concerning optimal timing of application.

Although RIPC currently has been extensively investigated, the underlying mechanism remains unclear. Three inter-related

events have been proposed: (1) RIPC-induced generation of endogenous autocoids (e.g. encephalin, endorphin) in the remote organ; (2) transmission of the protective signal from the remote organ to the target organ; (3) events occurring in the target organ which ultimately confer the protective effect. Several signalling mediators have been proposed to be involved in RIPC including PKC, ROS, NO, Akt, Erk1/2, p38 MAPK, and STAT3,[118] which are also the mediators of IPC and IPo. Further studies are needed to identify potential triggers, clarify the downstream targets, and explore the end-effectors of RIPC.

## Cardioprotection by anaesthetics

Application of certain drugs used in anaesthesia (e.g. isoflurane, sevoflurane, propofol, and opioids) before or during the early phase of reperfusion can also reduce myocardial IRI, a phenomenon that is termed anaesthetic preconditioning (APreC) and postconditioning (APoC), or collectively referred to as anaesthetic pre- or post-conditioning (APC).

## Mechanisms of APoC cardioprotection conferred by volatile anaesthetics, propofol or opioids

Similar to ischaemic preconditioning, volatile anaesthetics and opioids provide protection against myocardial IRI by stimulating the generation of a small amount of ROS, which triggers and enhances the production of endogenous antioxidant enzymes and activates mitochondrial $K_{ATP}$ channels, limiting myocardial infarction.[119] In contrast, propofol protects against myocardial IRI mainly via its ROS scavenging properties, which enhances endogenous cardiac antioxidant capacity and ultimately attenuates myocardial IRI.[120] Opioids play an important role in mammalian hibernation. Endogenous and exogenous (e.g. remifentanil and morphine) opioid agonists reduce myocardial oxidative stress and $Ca^{2+}$ overload and attenuate myocardial IRI both in animal models and in patients undergoing cardiac surgery .[121–124] Our most recent study shows that remifentanil preconditioning confers cardioprotection in rats, primarily via activation of JAK2/STAT3 signalling, that can function independent of PI3K/Akt activation.[125] However, it should be noted that application of high doses of opioid receptor agonists such as morphine[126] and remifentanil[127] may cause significant increases in ROS production in the vascular endothelium and myocardium and subsequently impair vascular endothelial function and exacerbate myocardial ischaemia-reperfusion injury, although the doses of remifentanil required to do this are much higher than those used clinically.

Major randomized clinical trials of anaesthetic conditioning are listed in Table 1 which includes cardiac surgeries conducted under either on-pump or off-pump conditions. It should be mentioned that only the on-pump surgery provides typical ischaemia-reperfusion injury and that the duration of ischaemia time may be one of the determinants of the effectiveness of conditioning protection.

## Similarity in mechanism and potential advantages of APC *vs* ischaemic conditioning

The concept of APC was evolved from IPC and IPo, and the mechanisms governing their cardioprotective effects are similar. APC confers cardioprotection mainly via the RISK and SAFE pathways (Fig. 4). APC activates the RISK pathway via a G-protein-coupled cell surface receptor[128] and activates the SAFE pathway through the TNFα receptor,[8 129] which all inhibit IRI-induced mPTP opening and activate the opening of the $K_{ATP}$ channel, thereby protecting cardiomyocytes from IRI-induced cell death. However, unlike IPC and IPo, anaesthetic application during APC is to the whole body and it is possible, therefore, that APC may also exert protection to other organs and other types of cells rather than just cardiomyocytes. We have recently shown that sevoflurane pre-treatment protects against TNF-α-induced vascular endothelial dysfunction, through activation of the eNOS/NO pathway and inhibition of NF-κB.[130] Sevoflurane may also protect against liver injury in patients undergoing cardiac surgery.[131–134] Exogenous opioids have also been shown to confer systemic multi-organ protection. Remifentanil pre-treatment ameliorated liver injury in rats subjected to hepatic ischaemia reperfusion[135] and attenuated intestinal IRI in mice.[136]

Compared with IPC and IPo, APC is more clinical feasible as anaesthetic agents are being used in surgery anyway. The beneficial effects of APC in a clinical setting was first demonstrated by Belhomme and colleagues[137], who reported that isoflurane preconditioning (5 min isoflurane exposure followed by 10 min washout) reduced the release of cardiac troponin I (TnI) and CK-MB, markers of cardiac injury, in patients undergoing CABG surgery. Subsequently, the effects of APC in patients undergoing on-pump and off-pump CABG surgery have been examined with conflicting results. Exposure to isoflurane at 1–1.5 MAC end-tidal throughout surgery, reduced postoperative plasma TnI and CK-MB release in patients undergoing CABG surgery with cardiopulmonary bypass.[138] While in patients undergoing off-pump CABG surgery, sevoflurane at 1 MAC provided optimal myocardial protection as increasing sevoflurane concentration to 1.5 MAC did not further attenuate myocardial injury and sevoflurane did not confer cardioprotection when being used at 0.75 MAC.[139] We also showed that treatment with propofol (120 mcg $kg^{-1}$ $min^{-1}$ for 10 min before the onset of cardiopulmonary bypass (CPB) until 15 min after aortic unclamping and then decreased to 60 mcg $kg^{-1}$ $min^{-1}$ until the end of surgery) significantly attenuated cardiac injury in patients undergoing CABG, as compared with isoflurane or low dose propofol.[140] Continuous administration of 1 MAC desflurane induced cardioprotection in patients undergoing CABG surgery evidenced as reduced cardiac TnI release.[141] However, administration of isoflurane 1 MAC for 5 min followed by a 5 min washout before CPB, did not reduce troponin I concentrations in patients undergoing CABG with CPB.[142] Similarly, a double-blind trial showed that there was no difference among patients receiving propofol or sevoflurane during surgery in terms of postoperative recovery in the cardiac intensive care unit.[143] Thus, currently it is premature to draw a firm conclusion as to whether APC is beneficial in the clinical settings of CABG surgery, when patients are elderly with co-morbidities such as diabetes and hypertension.

A recent meta-analysis of 2578 patients where on pump and off pump patients were analysed separately, compared peak postoperative cardiac TnI between volatile and i.v. anaesthesia. Volatiles reduced postoperative peak serum cardiac TnI enzyme concentrations by ~8% on-pump with no difference seen in off pump cardiac surgery.[144] An accompanying editorial stated 'So how much longer do we need to keep repeating that the use of a volatile anaesthetic regimen during on-pump coronary artery surgery is associated with a lower post-operative cardiac troponin release compared with an intravenous anaesthetic regimen?' and suggested that 'authors must stop designing and performing this type of study; ethical committees must stop approving such trials and editors must stop publishing over and over again data that simply confirm what is already known'.[145] However, all we can discern from such data is that, although volatile anaesthetics do seem to reduce cTnI concentrations in IRI, the clinical

Table 1 Major randomized clinical trials of anaesthetics in patients undergoing coronary artery surgery. CABG: coronary artery bypass surgery; CPB: cardiopulmonary bypass; AVR: aortic valve replacement; MAC: minimum alveolar concentration; BNP: brain natriuretic peptide; cTnI: cardiac troponin I; cTnT: cardiac troponin T; CK-MB: creatine kinase-MB; LDH: lactate dehydrogenase

| Author | No. | Background anaesthesia | Anaesthetic | Control | Surgery | Endpoint |
|---|---|---|---|---|---|---|
| Liu[169] | 36 | Institutional standard general anaesthesia | Sevoflurane, 1–8% | Propofol, 2–4 mg $kg^{-1}$ | Off-pump CABG | Reduced cTnI, CK-MB, and LDH |
| Bulow[170] | 30 | Induction: Sufentanil 0.5–1 μg $kg^{-1}$, pancuronium 0.1 mg $kg^{-1}$; Maintain: Sufentanil 0.5–1 μg $kg^{-1}$ $h^{-1}$ | Dexmedetomidine 0.3 μg $kg^{-1}$ $h^{-1}$ | Propofol 4 μg $ml^{-1}$ | On-pump CABG surgery under mini-CPB | Reduced oxidative stress and inflammation markers |
| Rogers[171] | 101 | Institutional standard general anaesthesia | Propofol in cardioplegia solution 6 μg $ml^{-1}$ | Intralipid in cardioplegia solution | On-pump CABG or AVR surgery | Reduced cTnI |
| Jia[172] | 105 | Induction: Midazolam (2 mg), propofol (2 mg $kg^{-1}$), and fentanyl (2–3 μg $kg^{-1}$). | Propofol 3–4 μg $ml^{-1}$, or Sevoflurane 0.7 MAC + propofol 1 μg $ml^{-1}$ | Sevoflurane 1–1.3 MAC | Off-pump CABG | Reduced postoperative lymphopenia |
| Sirvinskas[173] | 72 | Induction: A bolus injection of 20 mg of etomidate and 0.2–0.3 μg $kg^{-1}$ of fentanyl; 1 mg $kg^{-1}$ of rocuronium | Sevoflurane 2–3 vol% | Propofol 2–3 mg $kg^{-1}$ | On-pump CABG | Protected the mitochondrial outer membrane, reduced cTnI |
| Jerath[174] | 141 | Induction: 5 μg $kg^{-1}$ fentanyl, 0.05–0.1 mg $kg^{-1}$ midazolam, 1 mg $kg^{-1}$ propofol, and 0.5 mg $kg^{-1}$ rocuronium. Maintain: volatile group using isoflurane or sevoflurane. | Isoflurane or sevoflurane. The choice of volatile agent was left to the discretion of the attending anaesthetist | Propofol 50–75 μg $kg^{-1}$ $min^{-1}$ | On-pump CABG | Faster extubation times, higher prevalence of vasodilation with hypotension and higher cardiac outputs necessitating greater use of vasoconstrictors |
| Landoni[175] | 200 | Induction: Midazolam (0.15–0.25 mg $kg^{-1}$) or thiopental (3–6 mg $kg^{-1}$), opioid (fentanyl 5–10 μg $kg^{-1}$), and rocuronium (0.6–1.2 mg $kg^{-1}$). Maintain: fentanyl (3–5 μg $kg^{-1}$ $h^{-1}$), rocuronium (10 μg $kg^{-1}$ $min^{-1}$) | Sevoflurane 0.5–2 MAC, 4–6 h, from induction of anaesthesia to transport to ICU and including cardiopulmonary bypass-CPB | Propofol 2–3 mg $kg^{-1}$ $h^{-1}$ for the same 4–6 h period | Combined valvular and coronary surgery | No difference in composite of death, prolonged intensive care unit stay, and mortality |
| Kim[176] | 153 | Institutional standard general anaesthesia | Lidocaine 2 mg $kg^{-1}$ $h^{-1}$ after bolus 1.5 mg $kg^{-1}$, or Dexmedetomidine 0.3–0.7 μg $kg^{-1}$ $h^{-1}$, or Lidocaine+ dexmedetomidine | Isoflurane 0.8–1.0 MAC | Off-pump CABG | Lower cTnI and CK-MB in lidocaine and the combination group |
| Yilmaz[177] | 86 | Institutional standard general anaesthesia | Lidocaine 1.5 mg $kg^{-1}$, 2 min before aortic declamping, Amiodarone 300 mg, intravenously 15 min before release of the aortic cross clamp | Placebo | CABG (On-pump or off-pump not stated) | Lower incident rate of ventricular fibrillation |
| Mrozinski[178] | 60 | Fentanyl 0.2 mg, etomidate 0.3 mg $kg^{-1}$, vecuronium bromide 0.1 mg $kg^{-1}$ | Desflurane 3–9% throughout the procedure, 1 MAC for at least 15 min before coronary artery clamping | Propofol, continuous infusion 2–4 mg $kg^{-1}$ $h^{-1}$ | Off-pump CABG | No difference in cardiac function, CK-MB, and cTnI. Desflurane demonstrated improved stability in haemodynamic profile |

*Continued*

Table 1 *Continued*

| Author | No. | Background anaesthesia | Anaesthetic | Control | Surgery | Endpoint |
|---|---|---|---|---|---|---|
| Guerrero[179] | 60 | Etomidate 0.2 mg $kg^{-1}$, fentanyl 4 μg $kg^{-1}$, cisatracurium 0.15 mg $kg^{-1}$ | Sevoflurane-sevoflurane, 0.7–1 MAC | Sevoflurane-propofol Propofol-propofol 2–4 μg $ml^{-1}$ | Off-pump CABG | Lower N-terminal pro-BNP and cTnI and lower number of inotropic drugs |
| Wang[139] | 48 | Midazolam 0.05–0.1 mg $kg^{-1}$, fentanyl 15 μg $kg^{-1}$, vecuronium 0.1 mg $kg^{-1}$ | Sevoflurane 0.75, 1, or 1.5 MAC | Midazolam 0.1–0.15 mg $kg^{-1}$ $h^{-1}$, fentanyl <= 30 μg $kg^{-1}$, 0.1 mg $kg^{-1}$ $h^{-1}$ vecuronium | Off-pump CABG | Sevoflurane 1.0 MAC decreased cTnI |
| Suryaprakash[180] | 139 | Induction: Fentanyl 5–10 μg $kg^{-1}$, midazolam 0.02 mg $kg^{-1}$, and rocuronium 1 mg $kg^{-1}$. Maintain: fentanyl 1 μg $kg^{-1}$ $h^{-1}$ and atracurium 7.5 μg $kg^{-1}$ $min^{-1}$ | Sevoflurane 1–2% or Desflurane 4–6% in a mixture of air and oxygen | Propofol 2–4 mg $kg^{-1}$ $h^{-1}$ | Off-pump CABG | No difference in cTnI |
| Soro[143] | 73 | Midazolam 0.1–0.3 mg $kg^{-1}$, etomidate 0.2–0.4 mg $kg^{-1}$, fentanyl 2–40 μg $kg^{-1}$, cisatracurium 0.1 mg $kg^{-1}$ | Sevoflurane 0.7–1.5% | Propofol 1–4 mg $kg^{-1}$ $h^{-1}$ | On-pump CABG | No difference in cTnI, CK-MB, NT-proBNP, haemodynamic events and lengths of stay in the intensive care unit and hospital |
| Bassuoni[181] | 126 | Fentanyl 0.5 μg $kg^{-1}$, rocuronium 0.2 μg $kg^{-1}$ | Induction with sevoflurane 8% and maintained with sevoflurane 1–1.5 MAC | Induced by 1–2 mg $kg^{-1}$ and maintained with continuous infusion of 2–3 mg $kg^{-1}$ $h^{-1}$ of propofol | Off-pump CABG | Reduced cTnI, less in duration, cumulative duration, and magnitude of ST-segment depression of ischaemic events |
| Imantalab[182] | 60 | Sufentanil 1 μg $kg^{-1}$, etomidate 0.2 mg $kg^{-1}$, cisatracurium 0.15 mg $kg^{-1}$ | Propofol 6–8 mg $kg^{-1}$ $h^{-1}$, isoflurane | Midazolam 0.2 μg $kg^{-1}$ $h^{-1}$ | CABG (On-pump or off-pump not stated) | Lowest cTnI in isoflurane groups and highest in midazolam group |
| Riha[183] | 38 | Institutional standard general anaesthesia | Induction: midazolam 0.1 mg $kg^{-1}$, Dexmedetomidine 1 μg $kg^{-1}$, ketamine 1 μg $kg^{-1}$. Maintain: ketamine 2–4 mg $kg^{-1}$ $h^{-1}$, dexmedetomidine 0.5–1.5 μg $kg^{-1}$ $h^{-1}$, midazolam 0.1 mg $kg^{-1}$ | Induction: midazolam 0.05 mg $kg^{-1}$, sufentanil 0.5 μg $kg^{-1}$, etomidate 0.2 mg $kg^{-1}$. Maintain: 1–1.5 MAC sevoflurane | On-pump CABG | Reduced cTnI and CK-MB |
| Ceyhan[184] | 40 | Etomidate 0.3 mg $kg^{-1}$, pancuronium 0.1 mg $kg^{-1}$, remifentanil 1 mcg $kg^{-1}$ | Sevoflurane 2–4% | Isoflurane 1–2% | On-pump CABG | Lower cTnI and CK-MB |
| Lee[185] | 99 | Induced with a bolus of 0.2 mg $kg^{-1}$ etomidate followed by 0.8 mg $kg^{-1}$ rocuronium and a continuous infusion of remifentanil and propofol using a target-controlled infusion pump | 1.5 mg $kg^{-1}$ bolus at induction of lidocaine followed by a 2.0 mg $kg^{-1}$ $h^{-1}$ infusion intraoperatively | An equal volume of saline | Off-pump CABG | Reduced cTnI and CK-MB |
| Tempe[186] | 45 | Fentanyl, 5–10 μg $kg^{-1}$, along with thiopental, 1–2 mg $kg^{-1}$, and pancuronium, 0.1 mg $kg^{-1}$ | Isoflurane 1.0–2.5% | Propofol 1.5–3.5 mg $kg^{-1}$ $h^{-1}$ | Off-pump CABG | Lower cTnT and CK-MB |

| | | | | | | |
|---|---|---|---|---|---|---|
| Wong[122] | 40 | Induction: Fentanyl 5 μg $kg^{-1}$, pancuronium 0.15 mg $kg^{-1}$. Maintain: Propofol 60 μg $kg^{-1}$ $min^{-1}$ | Remifentanil 1 μg $kg^{-1}$ followed by a 0.5 μg $kg^{-1}$ $min^{-1}$ infusion for 30 min after induction but before sternotomy | Normal saline | On-pump CABG | Lower CK-MB, cTnI, h-FABP |
| Arm[187] | 45 | Sufentanil 1.0 μg $kg^{-1}$ $h^{-1}$, midazolam 0.12 mg $kg^{-1}$ $h^{-1}$, pancuronium 0.01 mg $kg^{-1}$ every 30 min | A 10-min exposure to isoflurane 2.5% followed by 5 min of washout | No isoflurane | On-pump CABG | Improvement of haemodynamic data, less need for inotropic support and lower CK-MB and cTnI |
| Frassdorf[188] | 30 | Sufentanil 0.3 mg $kg^{-1}$ $h^{-1}$ and propofol as target controlled infusion 2.5 mg $ml^{-1}$ | 10 min before establishing the extracorporeal circulation, patients of the sevoflurane I group received 1 MAC of sevoflurane for 5 min. Patients of the sevoflurane-II group received (2 times) 5 min of sevoflurane, interspersed by 5-min washout 10 min before extracorporeal circulation | No further intervention | On-pump CABG | Two periods of sevoflurane preconditioning reduced cTnI |
| Cho[189] | 50 | Induction: Midazolam 0.03–0.05 mg $kg^{-1}$ after ketamine 1% (0.5 mg $kg^{-1}$) or the same volume of normal saline. Sufentanil 1.5–2.0 μg $kg^{-1}$ and rocuronium bromide 50 mg were administered and tracheal intubation was performed. Maintain: Sevoflurane 1.5–2.5%, and continuous infusion of sufentanil 0.2–0.3 μg $kg^{-1}$ $h^{-1}$ and vecuronium 1–2 μg $kg^{-1}$ $min^{-1}$ | ketamine 0.5 mg $kg^{-1}$ during induction of anaesthesia | Normal saline | Off-pump CABG | No effect on pro-inflammatory cytokines release |
| Winterhalter[190] | 42 | Institutional standard general anaesthesia | Remifentanil infusion rate 0.25 mg $kg^{-1}$ $min^{-1}$ | Fentanyl total fentanyl dose 2.6 (0.3) mg | CABG (On-pump or off-pump not stated) | Reduced pro-inflammatory cytokines release |
| Piriou[191] | 72 | Anaesthesia was induced and maintained with propofol, cisatracurium, and sufentanil. Before the CPB, anaesthesia was maintained with a continuous infusion of propofol and boluses or infusion of sufentanil as clinically indicated. | Sevoflurane 1 MAC administrated via the ventilator for 15 min followed by a 15 min washout before CPB | No sevoflurane | On-pump CABG | No benefit |
| Meco[192] | 28 | A combination of fentanyl, midazolam, propofol and pancuronium | Desflurane preconditioning was elicited after the onset of cardiopulmonary bypass via a 5 min exposure to desflurane 2.5 MAC, followed by a 10 min washout before aortic cross-clamping and cardioplegic arrest. | An equivalent period (15 min) of pre-arrest desflurane-free bypass | On-pump CABG | Reduced cTnI and NT-proBNP |

*Continued*

Table 1 *Continued*

| Author | No. | Background anaesthesia | Anaesthetic | Control | Surgery | Endpoint |
|---|---|---|---|---|---|---|
| Murphy[193] | 30 | Standardized opioid-isoflurane anaesthetic | Morphine (40 mg) | Fentanyl (1000 microg) | On-pump CABG | Reduced inflammatory response |
| Corcoran[194] | 27 | Fentanyl 15 μg $kg^{-1}$ and inhalation of isoflurane 0.5%, with pancuronium 0.1 mg $kg^{-1}$ | Target-controlled infusion propofol immediately before aortic cross-clamp release until 4 h after reperfusion | Saline | Impaired left ventricular function undergoing CABG | Attenuated free-radical-mediated lipid peroxidation and systemic inflammation |
| Lee[195] | 40 | Institutional standard general anaesthesia | Isoflurane 2.5 MAC was administered for 15 min followed by a 5 min washout period before aortic cross-clamping | A time-matched period of isoflurane-free cardiopulmonary bypass | On-pump CABG | Improved cardiac index and stroke volume index, lower cTnI |
| Xia[140] | 44 | Midazolam 0.1 mg $kg^{-1}$, fentanyl 15 μg $kg^{-1}$, pancuronium 0.1 mg $kg^{-1}$ | Propofol 60 mg $kg^{-1}$ $min^{-1}$; or dose of propofol was increased to 120 mg $kg^{-1}$ $min^{-1}$ for 10 min before the onset of CPB until 15 min after aortic unclamping and then decreased to 60 mg $kg^{-1}$ $min^{-1}$ until the end of surgery | Isoflurane 1%–3.5% | On-pump CABG | Reduced cTnI and oxidative stress markers |
| Cromheecke[196] | 30 | Induction: Remifentanil 0.4 μg $kg^{-1}$ $min^{-1}$ | Sevoflurane 0.5–1% | Target-controlled infusion of propofol 2 μg $ml^{-1}$ | On-pump AVR | Improved cardiac function and lower cTnI |
| Garcia[197] | 72 | Propofol or etomidate, opioids and neuromuscular blocking agents and maintained with a target-controlled infusion of propofol 2–5 μg $ml^{-1}$ to stabilize mean arterial pressure and heart rate within 20% of baseline values, with opioids, and neuromuscular blocking agents, as required | Sevoflurane (10 min at 4 vol%) during CPB | Placebo | On-pump CABG | Reduced the incidence of late cardiac events during the first year after CABG. Lower NT-proBNP, cTnT |
| Conzen[198] | 20 | Sufentanil 0.025 μg $kg^{-1}$ $min^{-1}$ | Sevoflurane 1 MAC | Propofol 2–3 μg $ml^{-1}$ | Off-pump CABG | Lower cTnI |
| Julier[199] | 72 | Maintain: propofol infusion, continuous infusion or repeated doses of opioids, and pancuronium or vecuronium administration as required. | First 10 min of complete CPB with sevoflurane 4 vol% (2 MAC) | First 10 min of complete CPB with placebo (oxygen-air mixture only) | CABG under cardioplegic arrest | Reduced BNP, No difference in ST-segment changes, arrhythmias, CK-MB, and cTnT |

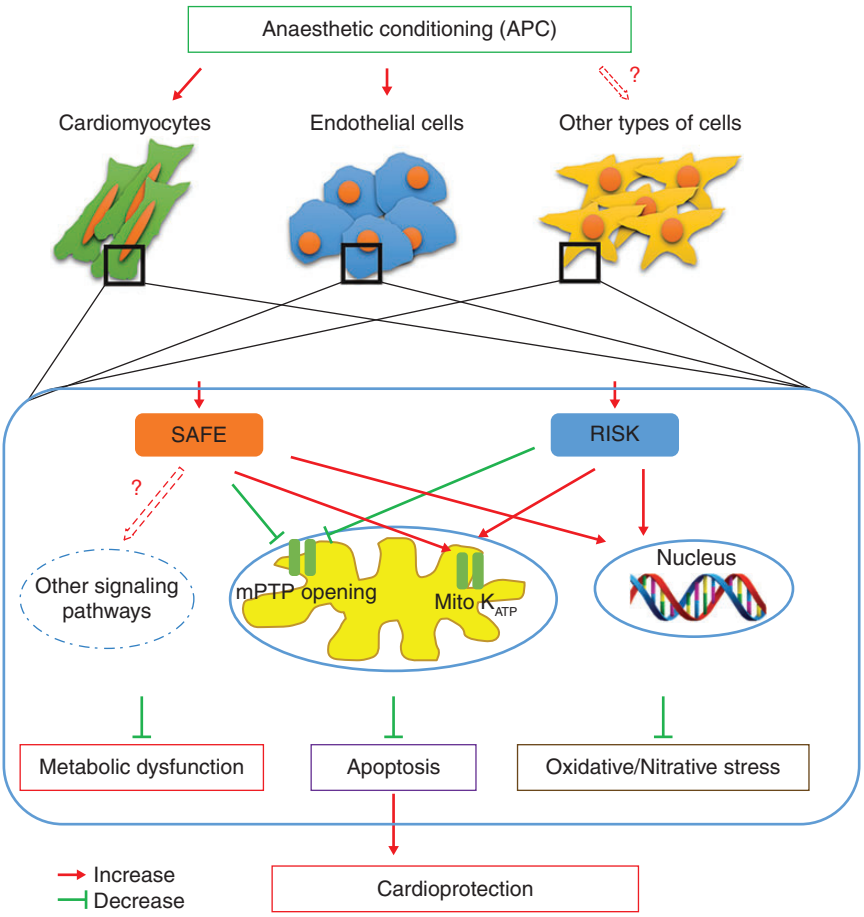


Fig 4 Schematic of proposed mechanism of myocardial anaesthetic conditioning cardioprotection. Anaesthetic conditioning protects the heart and other organs against ischaemia reperfusion injury through the survivor activating factor enhancement (SAFE) and reperfusion injury salvage kinase (RISK) pathways, which, subsequently, through mitochondrial-dependent and non-mitochondrial-dependent (nuclear or other) signalling pathways, decrease mitochondrial permeability transition pore (mPTP) opening and increase mitochondrial $K_{ATP}$ (Mito $K_{ATP}$) channel opening which attenuates ischaemia reperfusion injury.

significance of cTnI reduction is unclear (although *likely* to be good). I.V. anaesthesia in the above meta-analysis was not homogeneous, with midazolam and even etomidate included in that cohort, and, in our opinion, this does not mean that volatiles are preferable to propofol in patients with cardiovascular disease as both possess some, although different, cardioprotective properties. For example a large trial suggested that sevoflurane appears to be superior to propofol in patients with little or no ischaemic heart disease, such as non-CABG surgery and CABG surgery without severe preoperative ischaemia, whereas propofol seems superior in patients with severe ischaemia, and/or cardiovascular instability, possibly because myocardial ischaemia has already preconditioned the heart and propofol exerts it's protection differently.[146]

Although experimental animal studies have consistently shown effective cardioprotection and have identified the specific cellular signalling involved, only a few studies have attempted to identify and confirm the specific cellular signalling of IPC, IPo, and APC in humans. More importantly, attempts to translate the findings regarding the mechanism and effectiveness of IPC, IPo, and APC from experimental animals into the clinical setting have largely failed. The reason for these failures might be: (1) many of the patients have comorbidities such as diabetes, aging, dyslipidemia, and hypertension which have been shown to influence the protective effects of IPC, IPo, and APC; (2) poor experimental design and no allowance for the use of concomitant medication such as anaesthetics. Some of the confounding factors such as age, diabetes and myocardial remodelling that may cause conflicting results in clinical trials have been discussed elsewhere[147 148] and summarized below.

## Cardioprotection in diabetes and the impact of diabetes on anaesthetic cardioprotection

Higher rates of cardiovascular disease and mortality after AMI are observed in patients with diabetes. These patients are not only vulnerable to myocardial IRI but also not sensitive to cardioprotective strategies such as ischaemic conditioning and anaesthetic conditioning, that are effective in non-diabetic animal models of myocardial ischaemia/reperfusion or in non-diabetic patients undergoing CABG surgery. Clinically, diabetes is considered as an independent risk factor for cardiac injury during and after cardiac surgery.[149] Poorer recovery and higher mortality rates (two to four-fold higher than in non-diabetic subjects) after acute

myocardial ischaemia/infarction (AMI) have also been reported.[150] Infarct size was 30–70% larger after reperfusion therapy (either thrombolytic therapy or percutaneous coronary intervention) in diabetic than in non-diabetic patients,[151 152] and worse short and long-term progression after AMI was observed.[153 154]

Multiple factors have been proposed to contribute to the disparate outcomes regarding the susceptibility of diabetic hearts to myocardial IRI including: (1) the duration and the severity of the diabetic status; (2) the experimental protocols (e.g. type of animal species, severity of ischaemia and reperfusion); (3) the metabolic profiles of diabetic subjects at the time the experiment was conducted. Enhanced oxidative stress, which is mainly because of the burst production of ROS and/or depleted endogenous antioxidant system in diabetes, has been suggested as a major factor.[155] Increased oxidative stress has been shown to increase mPTP opening[156] and induce $Ca^{2+}$ overload,[157] factors that are attributable to myocardial IRI as discussed earlier. More importantly, enhanced oxidative stress may also impair endogenous cardioprotective signalling, which not only increases post-ischaemic myocardial injury in diabetic hearts but also diminishes or abolishes the protective effects of cardioprotective interventions such as ischaemic conditioning.

With a few exceptions, the cardioprotection of IPC, IPo, and APC has been shown to be compromised or even abolished in the hearts of diabetics. The effectiveness of sevoflurane postconditioning in reducing post-ischaemic myocardial infarct size and apoptosis in non-diabetic rats, was completely abrogated in streptozotocin-induced diabetic rats and diabetes blockade of sevoflurane postconditioning could not be restored by insulin,[8] although it could be restored by treatment with the antioxidant N-Acetylcysteine, which attenuated or restored diabetes induced reductions in cardiac p-STAT3 and adiponectin.[158] Defects in the RISK and SAFE pathways in diabetes have also been considered as a reason.[159 160] However, the exact role and the mechanism of reduced cardiac STAT3 activation in diabetes is not clear and needs further investigation, in order to facilitate the development of novel interventions to restore myocardial sensitivity to IPo in diabetes.

### Major cardiovascular co-morbidities that may affect ischaemic or anaesthetic conditioning effects

Ischaemic, anaesthetic preconditioning and postconditioning, trigger endogenous cardioprotective mechanisms that render the heart more resistant to lethal IRI. However, in addition to diabetes and senescence as aforementioned, certain major cardiovascular co-morbidities such as hyperlipidemia,[161 162] cardiomyocyte hypertrophy,[163] hypertension,[164 165] and myocardial remodelling,[166] and many of their associated medications (e.g. β-blockers, glibenclamide, glicazide) may interfere with the mechanisms of conditioning cardioprotection, thereby limiting the efficacy of ischaemic or anaesthetic conditioning in clinical settings. The exact mechanisms by which these co-morbidities and medications interfere with conditioning cardioprotection are not well understood. Glibenclamide abolishes the protective effect of mitochondrial $K_{ATP}$ channel opening[167] and is one of the worst drugs in this regard. Statins may actually increase the effect of remote ischaemic conditioning[168] (interestingly, in this trial, smokers were more resistant to remote ischaemic conditioning). A recent analysis of patients undergoing elective CABG with/without remote ischaemic preconditioning found that β-blockers, statins, ACE inhibitors, ARBs and intraoperative nitroglycerine had no significant impact on remote ischaemic conditioning-induced cardioprotection.[109] Further comprehensive analysis of the cardioprotective genetic profile in normal, protected, and in comorbid conditions in the context of conditioning stimuli, may lead to identification of novel molecular targets for cardioprotection and facilitation of clinical translation.

## Summary and future perspectives

Anaesthetic and ischaemia-induced myocardial protective effects are fascinating phenomena that have been extensively studied in various animal models with several mechanisms now elucidated. Clinically, beneficial effects, in terms of reduction in markers of cardiac injury, have also been demonstrated in patients undergoing heart surgery. Remote ischaemic conditioning, as a relatively simple and safe technique, may have particular clinical application (not only in protecting the heart but many other organs), however, many studies have been hampered by small sample sizes and lack of hard and more long-term clinical outcome data, with many relying on surrogate markers of cardiac injury. Certain patients that are particularly vulnerable to vascular complications (e.g. those with diabetes, hypertension and senescence), are particularly resistant to cardiac conditioning of all forms and this may be further complicated by adjuvant pharmacotherapy. Despite some 'proof of concept', large randomized clinical trials are still needed to determine whether this is just a healthy heart phenomenon or whether it's something that we can routinely use to protect our increasingly high-risk patients undergoing cardiac and vascular surgery.

## Authors' contributions

Writing paper: all authors
Revising paper: all authors

## Declaration of interest

None declared.

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Special Issue

# Contrast induced nephropathy in vascular surgery

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## Abstract

Contrast induced nephropathy (CIN) is traditionally associated with outpatient imaging studies. More recently, patients afflicted with vascular pathologies are increasingly undergoing endovascular treatments that require the use of iodinated contrast media (CM) agents, thus placing them as risk of developing CIN. As perioperative physicians, anaesthetists should be aware of the risk factors and measures that might minimize acute kidney injury caused by CM. This review evaluates recent data regarding preventive measures against CIN and where possible, places the evidence in the context of the patient receiving endovascular surgical treatment. Measures including the use of peri-procedural hydration, N-acetylcysteine, statins, remote ischaemic preconditioning, renal vasodilators and renal replacement therapy and the use of alternatives to iodinated contrast agents are discussed. It should be noted that most of the available data regarding CIN are from non-surgical patients.

**Key words:** acute kidney injury; contrast media; endovascular procedures

**Editor's key points**

- A systematic review estimated the overall frequency of CIN in vascular surgery patients exposed to angiography to be 9.2%.
- Patients who develop CIN suffer an increased burden of in hospital and longer term morbidity.
- Maintaining adequate hydration remains a cornerstone of preventing CIN but evidence to support a particular hydration strategy is lacking.
- There is no evidence to support the routine use of NAC in prophylactic protocols for surgical patients at risk of CIN.

Despite efforts to prevent it, contrast induced nephropathy (CIN) remains a significant cause of iatrogenic acute kidney injury (AKI). With the increasing use of endovascular procedures requiring iodine containing contrast media (CM) in older patients and those with significant co-morbidities, the prevention of AKI is assuming greater importance. This narrative review will serve as an update to one previously published in this journal[1] and will concentrate on areas where there have been noteworthy changes, with a focus on patients undergoing vascular surgery where such data are available. Readers are referred to the previous review for more in depth discussion on the risk factors (Table 1),[2–4] the pathophysiology of CIN and renal handling of CM, the details of which remain largely unchanged, and will be mentioned only in brief here.

## Definitions

The widely accepted definition for contrast induced nephropathy is a deterioration of renal function, indicated by either an increase in serum creatinine concentration of 25% from baseline, or an absolute increase of 26–44 μmol litre$^{-1}$ (0.3–0.5 mg dl$^{-1}$) within 48–72 h of i.v. contrast administration.[5] In order to standardize the definition of acute kidney injury from different aetiologies, two groups, the Acute Dialysis Quality Initiative (ADQI) and Acute Kidney Injury Network (AKIN) have separately proposed a system of defining and staging AKI, regardless of the likely cause. These include the RIFLE (Risk, Injury, Failure, Loss, End-stage kidney disease) and the AKIN systems respectively, the latter being a modification of the former, which should theoretically improve sensitivity and specificity.[6]

Table 1 Risk factors for CIN

| |
|---|
| Pre-existing renal impairment[2–4] |
| Diabetes mellitus |
| Peri-procedural intravascular depletion |
| Congestive heart failure |
| Volume and type of contrast administered |
| Concomitant use of other nephrotoxic drugs |

According to the AKIN criteria, stage 1 AKI may be diagnosed if one of the following occurs within 48 h:

- An absolute serum creatinine increase >26.4 μmol litre$^{-1}$ (≥0.3 mg dl$^{-1}$).
- An increase in serum creatinine ≥50% (≥1.5-fold) above baseline.
- Urine output reduced to ≤0.5 ml kg$^{-1}$ h$^{-1}$ for at least 6 h.

These are not specific to suspected contrast-induced AKI and differ from the previously used definitions of CIN. These criteria may be seen more frequently in future studies of CIN, which will aid the comparison of different studies.

## Incidence of CIN in patients with vascular disease

In the Manual on Contrast Media by the American College of Radiology,[7] the authors made a distinction in terminology between the diagnoses of post-contrast acute kidney injury and contrast induced nephropathy. In the latter CM is considered to be the cause of the renal injury. Be that as it may, very few studies have adequate controls to separate between the two entities and quoted incidences are likely to include a combination of both.[8] Furthermore, the reported incidences of CIN after cardiology and radiology procedures vary widely, owing to variation in the definitions used in earlier studies and the inclusion of patients with different numbers of known risk factors.[9] The aetiology of AKI in patients undergoing endovascular aneurysm repair (EVAR) in the perioperative period is multifactorial, with the kidneys being potentially subjected to a variety of haemodynamic, mechanical and pharmacological insults. Hence it is difficult to attribute AKI after EVAR solely to the adverse effects of CM and data are relatively scarce. An earlier study in patients undergoing EVAR showed that 24% of patients with baseline renal insufficiency had a creatinine increase postoperatively, with this being permanent in around two thirds of patients.[10] More recent data may be found in a multivariate analysis of the American College of Surgeons National Surgical Quality Improvement Program, where 13191 patients were identified as having undergone AAA repairs, 9877 of who had EVAR.[11] The investigators divided these patients as having moderate baseline renal impairment if their eGFR was between 30–60 ml min$^{-1}$, and severe impairment if their eGFR was <30 ml min$^{-1}$. Patients with moderate baseline renal impairment had an AKI rate of 1% and a dialysis rate of 1.1%. This compares with an AKI rate of 4.1 and 6.3% respectively in those with severely impaired baseline renal function. However, the definition of AKI used was a creatinine increase of 2 mg dl$^{-1}$ (176 μmol litre$^{-1}$), a standard that is much higher than that used for the definition of CIN (0.5 mg dl$^{-1}$ /44 μmol litre$^{-1}$). Interestingly, the odds of developing renal impairment were higher in the open repair group (OR=3, 95% CI 2.2–4.0). This was borne out in another systematic review of open vs EVAR in patients more than 80 yr old, where the relative risk for renal failure was close to three in the open procedure group.[12] Other studies investigating various preventative measures for AKI have shown incidences of CIN between 3–8% of vulnerable patients undergoing angiography in the vascular surgical setting.[13–15] In a systematic review by Zaraca and colleagues[16] the overall frequency of CIN from six eligible studies was 9.2% (79 out of 862 patients).

## Clinical consequences of CIN

The sequelae of CIN are variable and difficult to quantify, as there is not a well-demarcated pathophysiological pathway to account for the morbidity and mortality in patients who develop CIN. For the most part, AKI associated with CIN is asymptomatic and transient; like other mild forms of AKI, it requires only observation and supportive management, and rarely requires renal replacement. However, observational studies consistently point to a greater chance of death in those who develop CIN, compared with those who do not, with the odds lasting beyond one yr after detection. Furthermore, data gleaned from randomized trials of therapeutic interventional measures also indicate an added morbidity attributable to the occurrence of CIN.[17] Earlier data indicated an in-hospital mortality rate of up to 30% and a two yr mortality rate of 80%.[2 18] In a prospective cohort analysis, the development of CIN after contrast-enhancing CT scan was shown to be associated with a similar risk of death in one yr as coronary artery disease, heart failure or advanced age.[19] In a prospective study of 9877 subjects with a median follow up of 42 months, the rate of CIN was 11% in those with chronic kidney disease (CKD) and 2% in those without CKD, calculated after adjusting for known confounders of death and excluding patients who had died in hospital (24), had surgery (2999), were on dialysis (250) and had incomplete laboratory data (2233). CIN was associated with long-term mortality for the entire cohort (HR=2.26, CI=1.62 to 2.29, $P$<0.0001). Subgroup analysis showed that patients with CKD also had a higher long-term mortality if they developed CIN (HR 2.62, CI=1.91 to3.57, $P$<0.0001) but CIN had no effect on mortality in patients without CKD (HR=1.23, CI 0.47=2.62, $P$=0.6).[20]

## Pharmacology of iodinated contrast media (CM)

Commercially available CM are based on either one (monomers) or two (dimers) tri-iodinated benzene rings. They are further classified according to their ionization and osmolarity. CM vary in their chemical and physical properties but the imaging efficacy is solely based on their ability to attenuate x-rays, which is dependent on the number of iodine molecules present.[21] The ionic form affects the electrical potential of the cell membranes, which accounts for an increased toxicity.[22]

The improved safety profiles of the non-ionic low-osmolar or iso-osmolar CM (osmolality equal to that of blood) have resulted in universal uptake in clinical practice.[23–25] Osmolality was thought to play an important role in the pathogenesis of CIN, but the anticipated benefit of lower incidence of CIN by reducing osmolality has not been borne out in meta-analyses that compared the risks of CIN between high-osmolar and low-osmolar CM; and between low-osmolar and iso-osmolar CM regardless of the routes of administration.[25 26]

There has been a shift in thinking that suggests viscosity may be a particularly important contributing factor in the development of CIN, especially with low-osmolar CM having up to a 50-fold increase in viscosity.[27–29] The complex interaction of

osmolality and viscosity in the development of CIN, may explain the mixed results with iso-osmolar CM in reducing CIN.[30–32] All CM are similar, essentially having low lipophilicity, low protein binding and undergoing renal excretion without significant metabolism.[33] CM are distributed from the intravascular compartment to highly perfused organs, such as the liver and kidney with the exception of the brain parenchyma when there is an intact blood-brain barrier.[34 35] CM elimination half-life is between 90–120 min with normal excretory function, but is delayed in the presence of renal insufficiency.[35]

A number of earlier studies pointed to the association of volume of contrast used with the development of CIN such that it has been incorporated as a component of a proposed risk scoring system.[3] It has to be stressed however that there are no randomized trials designed to evaluate this issue specifically, as it may be considered unethical to expose patients to unnecessary amounts of contrast. As the volume of CM used may reflect the complexity of the pathology or required procedure, it may be argued that observational studies could be biased towards selecting out a subset of patients at higher risk of developing CIN. Some are of the opinion that limiting the volume of CM may in fact negatively impact upon the evaluation of patients undergoing diagnostic procedures and have produced retrospective data refuting the association between CM dose and rate of CIN.[36] Yet others are still producing observational evidence, indicating that exceeding the maximal allowable dose still adversely affects patient outcome.[36] On balance, irrespective of the type of contrast used, judiciously limiting the contrast load should still form an essential part of CIN prophylaxis until more convincing data suggest otherwise.

## Preventative measures

### Hydration

Although there are no direct trials comparing hydration to placebo, hydration remains the foundation of preventative strategies against the development of CIN. Many of the studies evaluating potential benefits of other strategies have incorporated hydration for both the control and intervention groups. Consensus, however, has not yet been achieved with respect to the optimal volume, composition and regime of fluid administration. A meta-analysis suggested that there is minimal difference in efficacy between oral and i.v. hydration.[37] However, it may be difficult to coordinate oral hydration with fasting time in the immediate preoperative period and some will favour i.v. hydration for high risk patients shortly before surgery.[38] Hydration with 0.9% saline may be superior to hypotonic saline, as is the administration of fluids over a longer period compared with a shorter time.[39]

Based on the premise that alkalinization of the urine may decrease the generation of hydroxyl free radicals that can harm the renal tubules, several studies have been performed to evaluate the use of isotonic bicarbonate rather than isotonic 0.9% saline as the hydration agent. Many of these have similar deficiencies in methodology such as small sample sizes and lack of power. Meta-analyses have also found a moderate to high degree of heterogeneity, publication bias and different treatment effect, thus resulting in different overall effects. On the whole, some of the studies suggest bicarbonate is not inferior to 0.9% saline, while others show some benefits. Nevertheless, not many international organizations have recommended choosing bicarbonate over 0.9% saline, but have suggested hydration with either solution over no hydration. However, physicochemical drug compatibilities are a concern and concomitant drug administration through the i.v. line used for isotonic bicarbonate, should be avoided.

There is a body of evidence around forced diuresis with matching fluid replacement. This was studied in the REMEDIAL II[40] and MYTHOS[41] trials. Where forced diuresis was achieved using diuretics or osmotic agents alone and without adequate fluid replacement, the treatment was ineffective or even detrimental.[42–44] In comparison using an automated fluid delivery system that matches fluid administration to urine output, investigators from both these trials were able to achieve urine output in the range of 300 ml $h^{-1}$ in some of their patients and were able to reduce the event rate of CIN to roughly half that of their comparator arms respectively. The event rate for pulmonary oedema in the REMEDIAL II trial was 2.1% in the hydration group compared with 0.7% in the control group ($P$=0.62). This compares with rates of 6 and 12% in the treatment and control groups respectively ($P$=0.15) in the MYTHOS trial.

In the absence of this fluid delivery device, or a clinical environment where a regimen of high volume forced diuresis can be safely delivered, a practical protocol for elective patients undergoing procedures involving CM, may be the administration of either isotonic 0.9% saline, or sodium bicarbonate, at a rate of 1 ml $kg^{-1}$ $h^{-1}$ for 12 h before and 12 h after the anticipated contrast administration, and for more emergent procedures a regime of 3 ml $kg^{-1}$ $h^{-1}$ for 1 h before and 1 ml $kg^{-1}$ $h^{-1}$ for 6 h after is appropriate. The abbreviated regime may also be indicated for those in whom sustained volume expansion is not feasible.[39] The Prevention of Serious Adverse Events following Angiography (PRESERVE) trial is in the pipeline (NCT01467466). This study aims to enrol 8680 patients, and to evaluate the effectiveness of isotonic sodium bicarbonate compared with isotonic saline and oral N-acetyl cysteine vs oral placebo.

### N-acetylcysteine

As far as pharmacological prophylaxis is concerned, N-acetylcysteine (NAC) is probably the most widely studied pharmacological agent for the prevention of CIN. NAC is inexpensive, easy to administer and has a favourable safety profile (although not totally harmless, as anaphylactoid reactions have been reported when used via the i.v. route in other clinical contexts[45]); it also may have free radical scavenging and organ protective effects.[46] However the results regarding its efficacy are equivocal and to date no firm recommendations can be given for its routine use, especially in light of the ACT trial (see Table 2).[13 14 47–69] This is probably attributable to heterogeneity in the design of the studies, ranging from definition of CIN, types of CM used, co-morbidities of patients, dose of NAC, routes of administration and of the co-interventions used, most notably that of hydration protocols. The disparity in study designs is reflected in differences in rates of baseline events and effect sizes reported. To complicate matters, NAC has been shown to decrease serum creatinine, an effect that is likely to be independent of changes in glomerular filtration rate (GFR).[70] Direct comparison studies suggest that the higher dose oral regimen of 1200 mg twice daily, may be more beneficial than 600 mg twice daily.[71 72] More relevant to the perioperative setting, Lawlor and colleagues[15] could find no additional benefit of NAC over hydration alone in patients undergoing vascular procedures in a small ($n$=78), single centre trial. It is of interest that NAC at high doses was not reno-protective in patients undergoing cardiac bypass and abdominal aortic aneurysm repair.[73 74]

In the largest and most methodologically rigorous trial to date, the Acetylcysteine for Contrast-Induced Nephropathy

Table 2 Summary of evidence for N-Acetylcysteine from clinical trials comparing NAC with control. This table contains randomized trials involving patients undergoing either coronary or peripheral angiography, with a primary outcome that measures the incidence of CIN as defined as a 25% increase in serum creatinine from baseline or a 0.5 mg $dl^{-1}$ (44 μmol $litre^{-1}$) increase in the absolute value, within 48-72 h of i.v. contrast administration. C, coronary angiography; P, peripheral angiography; PO, per oral; RR, relative risk; CI, 95% confidence interval

| Study | NAC (N) (dose in mg) | Control (N) | Procedure | PO or i.v. | Incidence NAC vs Control | Comments |
|---|---|---|---|---|---|---|
| Investigators ACT (2011)[14] | 1172 (1200) | 1136 | P,C | PO | 12.7 vs 12.7% | RR=1 (0.81-1.25) P=0.97 |
| Amini et al. (2009)[47] | 45 (600) | 45 | C | PO | 11.1 vs 14.3% (P=0.656) | |
| Azmus et al. (2005)[48] | 196 (600) | 201 | C | PO | 7.1 vs 8.4% (P=0.62) | |
| Briguori et al. (2004)[49] | 92 (600) | 91 | P,C | PO | 4.1 vs 13.7% (P=0.019) | Fenoldopam in control group |
| Carbonell et al. (2007)[50] | 107 (600) | 109 | C | i.v. | 10.2 vs 10.1% | Normal renal function |
| Carbonell et al. (2010)[51] | 39 (600) | 42 | C | i.v. | 5.1 vs 23.8% | Chronic renal failure OR=0.17; CI=0.03-0.84; (P=.027) |
| Coyle et al. (2006)[52] | 68 (600) | 69 | C | PO | 9.2 vs 1.4% (P=0.043) | |
| Diaz-Sandoval et al. (2002)[53] | 25 (600) | 29 | C | PO | 8 vs 45% (P=0.005) | RR=0.21 CI=0.06 to 0.8 |
| Ferrario et al. (2009)[54] | 99 (600) | 101 | P,C | PO | 8.1 vs 5.9% (P=0.6) | |
| Fung et al. (2004)[55] | 46 (400) | 45 | C | PO | 17.4 vs 13.3% (P=0.8) | |
| Goldenberg et al. (2004)[56] | 41 (600) | 39 | C | PO | 10 vs 8% (P=0.52) | |
| Gomes et al. (2005)[57] | 77 (600) | 79 | C | PO | 10.4 vs 10.1% (P=1) | |
| Gulel et al. (2005)[58] | 25 (600) | 25 | C | PO | 12 vs 8% | |
| Kay et al. (2003)[59] | 102 (600) | 98 | C | PO | 4 vs 12% | RR=0.32 CI=0.10-0.96; P=0.03 |
| Kim et al. (2010)[60] | 80 (600) | 86 | C | PO | 5 vs 15.1% (P<0.05) | |
| MacNeill et al. (2003)[61] | 21 (600) | 22 | C | PO | 5 vs 32% (P=0.046) | |
| Miner et al. (2004)[62] | 95 (2000) | 85 | C | PO | 9.6 vs 22.2% (P=0.04) | |
| Ochoa et al. (2004)[63] | 36 (1000) | 44 | C | PO | 8 vs 25% (P=0.051) | OR=3.7 CI=0.94-14.4 |
| Oldemeyer et al. (2003)[64] | 49 (1500) | 47 | C | PO | 8.2 vs 6.4% (P=0.74) | |
| Rashid et al. (2004)[13] | 46 (1000) | 48 | P | i.v. | 17.6 vs 14.3% (P>0.05) | |
| Sadat et al. (2011)[65] | 21 (600) | 19 | P | PO | 1/21 vs 3/19 (P=0.33) | |
| Sandhu et al. (2006)[66] | 53 (600) | 53 | P | PO | 2.8 vs 0% | |
| Seyon et al. (2007)[67] | 20 (600) | 20 | C | PO | 2.5 vs 7.5% | |
| Shyu et al. (2002)[68] | 60 (400) | 61 | C | PO | 3.3 vs 24.6% (P<0.001) | |
| Thiele et al. (2010)[69] | 126 (1200) | 125 | C | i.v. | 14 vs 20% (P=0.28) | |

(ACT) Trial Investigators, have convincingly demonstrated a lack of efficacy for NAC in reducing the incidence of CIN, mortality or need for dialysis at 30 days, a finding that was observed in all subgroups analysed, including those with renal impairment.[14] This was a multicentre trial involving 46 different sites and 2308 patients with at least one risk factor for the development of CIN, randomized to receive either 1200 mg of NAC or placebo. The usual definition of CIN (see above) was used as the primary endpoint and an intention to treat analysis was used. The event rate for both groups was 12.7% (RR=1, CI=0.81 to 1.25, P=0.97). There was also no difference in the combined end point of 30 day mortality or need for dialysis (2.2% in treatment vs 2.3% in the control group, HR 0.97, CI=0.56 to 1.69, P=0.92). These effects were consistent across all subgroup analyses. Hence there is no evidence of overall benefit to support the routine use of NAC in prophylactic protocols for surgical patients at risk of CIN.

## Statins

Evidence for possible perioperative benefit from the pleiotropic effects of hydroxymethylglutaryl coenzyme A reductase inhibitors (statins), has continued to emerge over the past decade.[75] With respect to CIN, initial retrospective analysis pointed to an association with pre-procedural statin use and a reduction in the incidence of CIN.[76] In a follow-up study of 434 patients undergoing PCI, statin-treated patients had a lower incidence of CIN (3 vs 27%, $p<0.0001$) and a superior post-procedural creatinine clearance (80 (20) vs 65 (16) ml $min^{-1}$, $p<0.0001$). These benefits were seen across all subgroups except those with a pre-existing creatinine clearance <40 ml $min^{-1}$.[77] Prospective, randomized trials involving large numbers are difficult because of the ubiquitous use of statins in patients with cardiovascular co-morbidities. However, the randomized trials in patients undergoing coronary angiography, using high dose statins seem beneficial.[78–81]

In a trial involving 241 statin-naive patients with acute coronary syndrome undergoing PCI, 120 patients were randomized to receive atorvastatin (80 mg+40-mg) before the procedure, compared with 121 placebo controls, with all patients receiving atorvastatin 40 mg daily post-procedure. The treatment group had a significantly lower rate of CIN compared with placebo (5 vs 13.2%, P=0.046) and were independently associated with a decreased risk of CIN (OR=0.34, CI=0.12 to 0.97, P=0.043) and a shorter hospital stay ($p$=0.007).[79] Similar results were reported by the Protective Effect of Rosuvastatin and Antiplatelet Therapy on Contrast-Induce Acute Kidney Injury and Myocardial Damage in Patients With Acute Coronary Syndrome (PRATO-ACS) Study. In this study, consecutive statin-naive patients with non-ST elevation ACS undergoing early invasive intervention, were randomly assigned to receive rosuvastatin (40+20 mg per day; $n$=252) or no statin treatment control group ($n$=252). The results showed a beneficial effect of statins on CIN (6.7 vs. 15.1%; adjusted OR=0.38; CI=0.20 to 0.71, P=0.003). There was also a lower 30-day

incidence of adverse cardiovascular and persistent renal damage (3.6 vs. 7.9%, $P$=0.036).[80] Conversely, there is contrary evidence in one single-centre prospective study enrolling patients with chronic renal disease, where statins did not confer additional benefits over standard preventative measures.[82] On balance, although the data are promising, it would be premature to recommend high dose statins for the sole purpose of preventing CIN. However, given the favourable side-effect profile, it may be argued that escalation of dose in those already on statins and starting statin-naïve patients on the medication (if it is otherwise indicated) for the perioperative period, is a reasonable approach for reducing CIN. Table 3 summarize the trials involving statins in the prevention of CIN.

### Remote ischaemic preconditioning

Remote ischaemic preconditioning (RIPC) involves the application of series of intermittent non-lethal ischaemic stimuli, to a particular region of the body (often a limb), in order to mitigate ischaemic damage to an organ in another region. In practice the preconditioning stimulus may be applied to either an upper or lower limb, using a non-invasive BP cuff. Recent clinical trials have shown a potential beneficial renal effect from this technique when used in cardiac surgery.[83 84] Several small single-centre prospective trials showed a reduced rate of CIN in patients undergoing coronary angiography or percutaneous interventions,[85–87] with further research in progress (Table 4[88]). However, patients in the control groups of these studies had unusually high event rates, which raises concerns over the generalizability of the results to other lower risk patient groups. Nevertheless, when the preconditioning stimulus is being applied to upper or lower limbs using non invasive BP cuffs, the reported complication rates are very low to nil in the vast majority of studies, and the potential protection may spread beyond the kidneys.[89] Thus there appears to be little downside to using RIPC and this technique warrants further study in patients at risk of CIN.

### Renal replacement therapy (RRT)

As CM can be effectively removed by haemodialysis (HD) or haemofiltration (HF), these interventions have been proposed as a means of preventing CIN. Although earlier trials on high risk patients using HF held promise, there were some methodological weaknesses that may have influenced the results, such as differential medical management in the intervention group.[90 91] In a meta-analysis that examined the use of HD or HF, RRT vs standard medical therapy was shown not to affect the incidence of CIN. This meta-analysis suffered from significant heterogeneity in terms of patient background, treatment protocols and types of contrast used. Interestingly, in a subgroup analysis that examined only HD ($n$=6 trials), where the heterogeneity was significantly reduced, the relative risk of developing CIN was actually higher in HD than in the comparator groups.[92] This was similar to the findings of an earlier meta-analysis.[93] A trend towards a reduction in temporary rescue RRT in the HD/HF groups was reported, but again heterogeneity between the included trials was significant. When limited to only the HF studies ($n$=3 trials), the heterogeneity was substantially reduced and the difference in temporary RRT requirements was significantly less in the treatment groups. Looking at individual trials, it would appear that HD might have more benefit in those with a lower baseline renal function[94] than in those with slightly more reserve.[95] On balance, given the resource implications, risks associated with RRT and the marginal benefits over less invasive measures, the prophylactic use of RRT cannot be recommended.

### Agents acting on the renal circulation

Renal vasoconstriction has been implicated in the pathogenesis of CIN[29] although much of the evidence comes from animal studies. As such, agents with renal vasodilating effects have been investigated and, disappointingly, there is no strong evidence for their efficacy in CIN prophylaxis across several classes of agents tested. Trials involving dopamine mostly did not demonstrate any benefit with its use.[96–99] Similarly patients given fenoldopam also did not experience any benefits in terms of reduction in CIN.[100 101] Calcium channel antagonists did not fare any better, with only one small trial showing some benefits[102] whilst others showed less favourable results.[103 104] Owing to both its renal vasodilatory and diuretic effects, the adenosine antagonist theophylline and, to a lesser degree, aminophylline have also been investigated for protective effects. Dai and colleagues[105] systematically analysed 13 prospective, randomized trials involving theophylline and three involving aminophylline and showed an overall odds ratios of 0.48 in reducing the incidence of CIN in favour of theophylline, but with moderate statistical heterogeneity.[105] There was also no impact on mortality or need for dialysis. There were also no benefits seen in subgroup analyses of patients with poorer baseline renal function or of trials of higher quality.

A relative newcomer to the family of renal vasodilators to be tested for the prevention of CIN is the prostacyclin analogue iloprost. To date there is a single-centre randomized, double-blind, placebo-controlled study of iloprost involving 208 patients. The drug was well tolerated and resulted in a reduction of CIN from 22% in the control group to 8% in the treatment group, with the latter demonstrating a slight increase in eGFR. Further larger confirmatory trials are required before a recommendation can be given for the use of iloprost.

## Peri-procedural management

The cornerstone of successful prevention and management of CIN is vigilance of the clinical team; the first step is to identify patients at risk. These comprise patients who have received CM in the days leading up to surgery and those having known risk factors, which include increased serum creatinine, diabetes mellitus, dehydration, congestive heart failure, age more than 70 yr and concurrent administration of nephrotoxic drugs.[26] The limitations of serum creatinine in reflecting renal function are well known and, therefore, estimation of GFR using one of the established formulas would be preferable in identifying those with reduced renal reserve,[29] and an eGFR of <60 mls $min^{-1}$ 1.73 $m^{-2}$ should raise concern.[26]

As the vast majority of the trials on preventative measures for CIN have been performed during diagnostic or minimally invasive procedures, we have concentrated on a small number of interventions to maintain academic rigour. However, the kidneys of surgical patients may face several concurrent or sequential insults in the perioperative period and minimizing the occurrence of CIN is just one part of management aimed at preventing AKI. Close communication within the operating team is essential and concerns regarding any potential nephrotoxic drugs or interventions (such as manipulations likely to compromise renal blood flow) should be discussed.

Given the recent evidence regarding forced diuresis, it is inappropriate to expose dehydrated patients to contrast in the

Table 3 Summary of the effect of statins on contrast induced nephropathy. Adj OR, Adjusted odds ratio; CKD, chronic kidney disease; CI, 95% confidence interval; Cr, creatinine; NAC, N acetylcysteine; NS, normal saline; NTSE-ACS, non ST elevation acute coronary syndrome; PRCT, Prospective Randomized Control Trial

| Author & Yr | Study Type & Number of patients | Procedure | Primary Outcome | Treatment & Incidence | Comparator & Incidence | Statistical Significance | Effect size | Comments |
|---|---|---|---|---|---|---|---|---|
| Khanal *et al.* (2005)[76] | Prospective multicentre audit (*n*=29409) | PCI | Cr ↑ 0.5 mg $dl^{-1}$ | Pre - procedural statins (*n*=10831); 4.37% | Statin naïve patients (*n*=18040); 5.93% | P<0.0001 | Adj. OR 0.87 (0.77-0.99, P=0.03) | Preprocedural renal failure patients excluded |
| Patti *et al.* (2008)[77] | Prospective cohort study; (*n*=434) | PCI | Cr ↑ 0.5 mg $dl^{-1}$ or 25% from baseline | Pre - procedural statins (*n*=260); 3% | Statin naïve patients (*n*=174); 27% | P<0.0001 | 90% risk decrease | 4 year follow up |
| Xinwei *et al.* (2009)[78] | RCT (*n*=228) | ACS patients PCI | Cr ↑ 0.5 mg $dl^{-1}$ or 25% from baseline | Simvastatin 80 mg (S80) (*n*=113) | Simvastatin 20 mg (S20) (*n*=115) | CIN incidence not stated<br>Cr returned to normal in S80 but not S20 | Not given | Cotreatment NS hydration |
| Toso *et al.* (2010)[82] | Single centre PRCT (*n*=304) | Patients with pre-existing CKD for PCI | Cr ↑ 0.5 mg $dl^{-1}$ within 5 days | Atorvastatin 80 mg $day^{-1}$ *n*=151; 10% | Placebo (*n*=152); 11% | P=0.86 | | Cotreatment NS hydration plus NAC |
| Patti *et al.* (2011)[79] | Multi-centre PRCT (*n*=241) | ACS patients PCI | Cr ↑ 0.5 mg $dl^{-1}$ within 5 days | Atorvastatin 80 mg then 40 mg $day^{-1}$ (*n*=120); 5% | Placebo (*n*=121); 13.2% | P=0.046 | OR=0.34 CI=0.12 to 0.97, P=0.043 | |
| Han *et al.* (2014)[81] | Multi-centre PRCT (*n*=2998) | DM and CKD patients for PCI, peripheral angiography | Cr ↑ 0.5 mg $dl^{-1}$ or 25% from baseline at 72h | Rosuvastatin10 mg $day^{-1}$ for 5 days (*n*=1,498); 2.3% | Standard care (*n*=1,500); 3.9% | P=0.01 | | NS hydration for both groups |
| Leoncini *et al.* (2014)[80] | Single centre PRCT | NSTE-ACS patients | Cr ↑ 0.5 mg $dl^{-1}$ or 25% from baseline within 72h | Rosuvastatin 40+20 mg $day^{-1}$ (*n*=252); 6.7% | Standard care (*n*=252); 15.1% | | Adj OR=0.38 CI=0.2 to 0.71, P=0.003 | |

Table 4 Summary of evidence for remote ischaemic preconditioning and renal protection. AKI, Acute Kidney Injury; CABG, Coronary Artery Bypass Graft; CI, 95% confidence interval; KDIGO, Kidney Disease Improving Global Outcome; MCRCT, Multi-Centre Randomized Control Trial; OR, Odds Ratio; PCI, Percutaneous Coronary Intervention; PRCT, Prospective Randomized Control Trial; RCT, Randomized Control Trial; RIPC, Remote ischaemic preconditioning

| Study | Type | Procedure | RIPC (N) | Control (N) | Outcome (RIPC vs CON) | Effect size | Comments |
|---|---|---|---|---|---|---|---|
| Venugopal *et al.* (2010)[83] | Secondary analysis | CABG* | 38 | 40 | AKI stages:<br>I: 3 vs 25%<br>II: 3 vs 0%<br>III: 0 vs 0% | P=0.005 | data from 2 prospective trials |
| Zarbock *et al.* (2015)[8] | MCRCT | Cardiac surgery* | 120 | 120 | KDIGO AKI<br>37.5 vs 52.5% | ARR, 15%; CI=2.56-27.44%; P=0.02 | |
| Er *et al.* (2012)[85] | PRCT | Coronary angiography | 50 | 50 | 12 vs 40% | OR=0.21<br>CI=0.07 – 0.57 P=0.002 | |
| Deftereos *et al.* (2013)[86] | PRCT | PCI | 113 | 112 | 12.4 vs 29.5% | *p*=0.002; OR=0.34; CI=0.16 to 0.71 | |
| Yamanaka *et al.* (2014)[87] | RCT | PCI | 63 | 62 | 10 vs 36% | P=0.003<br>OR=0.18 CI 0.05-0.64; P=0.008 | |

elective setting. At a minimum the patient should receive pre hydration either with 0.9% saline or isotonic bicarbonate.

Where patients are admitted on the day of surgery they should be instructed to drink oral fluids liberally the night before. Preoperative anaemia should be sought and treated where time permits, as anaemia is correlated with the incidence of CIN.[106–108] One should be aware that patients taking beta blockers are more likely to develop anaphylactoid reactions to CM and are, in turn, potentially more resistant to treatment.[109]

Apart from incorporating measures that are directed specifically at minimizing CIN, one must not forget other common sense measures to preserve renal function. These include maintenance of renal blood flow and renal perfusion pressure, avoidance of nephrotoxic agents, judicious glycaemic control, and the appropriate management of any postoperative complications.[110] With respect to perioperative management of medications, one must not overlook the potential for a postoperative decrease in renal clearance of drugs such as metformin, with the potential to cause lactic acidosis. Other drugs that undergo renal excretion may also need closer monitoring.

There is a scarcity of robust data regarding the influence of anaesthetic technique on CIN/AKI incidence. Multivariate analyses of patients from the EUROSTAR data in 2007, indicated a lower incidence of systemic complications, including renal outcomes, from the use of loco-regional techniques compared with general anaesthesia in EVAR, especially in the higher risk patients.[111] However in another single centre retrospective analysis of 302 patients undergoing EVAR, there was no statistically significance difference between the two techniques in terms of all complications and all-cause mortality.[112]

## Alternatives to iodinated contrast media

For those who are allergic or at very high risk of developing CIN, alternatives may be considered. The most practical alternative in endovascular surgery is carbon dioxide ($CO_2$) but because of its cumbersome delivery, inferior image quality and potential for embolism, it has not gained popularity. Carbon dioxide is a highly soluble gas that briefly displaces the blood, before being rapidly dissolved and excreted through exhalation.[113] Being non-allergenic, non-nephrotoxic and of low viscosity relative to blood, makes $CO_2$ a safe contrast medium.[114 115] Even though $CO_2$ possesses these favourable characteristics, the risk of neurotoxicity, limiting its use to infra-diaphragmatic arteriography has been recommended.[116 117] Other limitations include being less user-friendly and the complication of vapour lock that may risk impeding blood flow and result in tissue ischaemia.[117 118] Notwithstanding these limitations, practitioners have successfully used $CO_2$ digital subtraction angiography ($CO_2$ -DSA) either to assist or as an alternative to CM for EVAR in high-risk patients, with similar results.[119–121] It has also been investigated for the detection of endoleaks post graft placement, where it has shown moderate sensitivity and specificity for type I but not type 2 endoleaks and the authors have suggested that it may have a potential for initial evaluation of endoleak in order to minimize CM exposure.[122] Therefore, this technique is gaining acceptance as a credible alternative to CM in endovascular procedures. Needless to say, its use requires careful planning and good communication between members of the operating team.

### Gadolinium

Gadolinium was once thought to be a suitable alternative to CM. This was disproved after the report of its association with nephrogenic systemic sclerosis (NSF).[123] NSF is a serious fibrosing dermatopathy associated with hardened skin nodules, joint contractures and multi-organ involvement in its severe form, but no effective treatment is currently available.[124] Furthermore, gadolinium is more nephrotoxic than CM in equivalent doses that produce the same x-ray attenuating function.[125] Therefore, the European Society of Urogenital Radiology (ESUR) does not recommend its use for angiography and CT.[26]

## Concluding remarks

CIN prevention is continually evolving. The data regarding N-acetyl cysteine, and to lesser extent, bicarbonate, theophylline and renal replacement therapy, is illustrative of the problems that physicians face in their endeavour to minimize patient harm. Multiple small trials with different designs and co-treatments, spanning over a long time have predominated in the literature and limited interpretation of the efficacy of

treatments, even with meta-analysis. Thankfully, some better quality evidence, especially with regards to hydration and NAC, is beginning to emerge attributable, in part, to standardization of definitions and more rigorous study design. Maintaining a high urinary flow rate around the time of contrast exposure is pivotal in minimizing harm from the CM. However, evidence is equivocal at best for the strategy of reducing oxidative damage, by either antioxidants or urinary alkalinization. The renal vasodilator iloprost is promising but further data are awaited. Patients taking statins should be maintained on therapy and there is evidence that initiation of treatment may have other benefits also.[75] Intraoperative remote ischaemic preconditioning is simple and safe but requires further validation before it can be recommended as a prophylaxis.

## Authors' contributions

Writing paper: G.T.C.W., E.Y.P.L.
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## Declaration of interest

None declared.

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Special Issue

# New antiplatelet drugs and new oral anticoagulants

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## Abstract

In our daily anaesthetic practice, we are confronted with an increasing number of patients treated with either antiplatelet or anticoagulant agents. During the last decade, changes have occurred that make the handling of antithrombotic medication a challenging part of anaesthetic perioperative management. In this review, the authors discuss the most important antiplatelet and anticoagulant drugs, the perioperative management, the handling of bleeding complications, and the interpretation of some laboratory analyses related to these agents.

**Key words:** antiplatelet agents; anticoagulants and haemorrhage; blood coagulation tests

**Editor's key points**

- Antiplatelet agents significantly increase the risk of bleeding in high-risk surgery.
- A number of anticoagulant drugs that either inactivate factor Xa or directly inhibit thrombin have become available in recent years.
- Current data do not support the use of periperative bridging therapy to cover the withdrawal of oral anticoagulants in patients at low risk of thromboembolism.
- Standard coagulation tests together with assay of factor Xa activity can be used to guide the managment of new anticoagulant drugs in the perioperative setting.

Arterial and venous thrombosis have an important impact on worldwide morbidity and mortality. Worldwide, >10 million deaths per annum are caused by arterial thrombotic events (ischaemic stroke, heart disease, and peripheral gangrene).[1 2] Platelets are the key prothrombotic element in arterial thrombosis, forming aggregates interconnected by fibrin. Antiplatelet treatment can counteract this process. For decades, aspirin has been the first-line antiplatelet drug of choice; recently, however, alternative antiplatelet substances have been introduced.

Half a million deaths related to venous thromboembolism occur in the European Union per year.[1] Venous thrombi consist primarily of fibrin with some cells trapped in between. Anticoagulants are the drugs of choice to prevent or treat these conditions. For decades, warfarin and heparin were the mainstay of treatment, but the development of new anticoagulant drugs is constantly enlarging the pharmaceutical armamentarium.

In this review, the pharmacological properties of the new antiplatelet and new oral anticoagulant drugs, their usage in the perioperative setting, and the management of bleeding complications are discussed.

## Antiplatelet agents (Table 1)

Platelet adhesion, activation, and aggregation are mediated by numerous adhesive proteins. The reactions of these proteins underpin the physiological responses to endothelial damage or rupture of atherosclerotic plaques. Amplification of these mechanisms and excessive thrombus formation endanger vascular flow, leading to occlusion of arteries and temporary or persistent ischaemia.[3] Blocking such thrombus formation can prevent ischaemic events.

Treatment strategies for prevention or therapy of arterial thrombosis are changing constantly. The duration of treatment,

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Table 1 Summary of the characteristics of currently available antiplatelet drugs

| Characteristic | Aspirin | Clopidogrel | Prasugrel | Ticagrelor | Cangrelor | Abciximab | Eptifibatide | Tirofiban |
|---|---|---|---|---|---|---|---|---|
| Route of administration | Oral once daily, (i.v.) | Oral once daily, (i.v. under investigation) | Oral once daily | Oral twice daily | i.v. | i.v. | i.v. | i.v. |
| Bioavailability | 68% | 50% | 80% | 36% | | | | |
| Plasma peak concentration | 30–40 min | 1 h | 30 min | 1.5 h | Seconds | Dose dependent | Dose dependent | Dose dependent |
| Time to plasma steady state | | 2–8 h | 30 min to 4 h | 30 min to 2 h | Seconds | Initial bolus and continuous application | Initial bolus and continuous application 4–6 h | Initial bolus and continuous application 10 min |
| Plasma half-life | 15–30 min | 8 h | 7 h | 7 h | 2–5 min | 10–15 min | 2.5 h | 2 h |
| Plasma protein binding | Strong | Strong | Strong | Strong | | | | |
| Time from last dose to offset | 7–10 days | 7–10 days | 7–10 days | 5 days | 60 min | 12 h | 2–4 h | 2–4 h |
| Reversibility of platelet inhibition | No | No | No | Yes | Yes | Yes | Yes | Yes |
| Recommended period of discontinuation before surgical intervention (see Fig. 2) | 0–5 days | 7 days | 10 days | 7 days | 1–6 h | 48 h | 8 h | 8 h |

especially of dual or triple antiplatelet therapy, is highly dependent on the indication for treatment and, for percutaneous coronary intervention, the chemical constitution of any coronary stents (Table 2).[4–6]

## Acetylsalicylic acid (aspirin)

For >50 yr, aspirin has been known to have antithrombotic and anti-inflammatory properties.[7] Aspirin is a cyclooxygenase (COX) inhibitor that irreversibly inhibits COX1 and, in higher doses, COX2. Inhibition of COX1 is the main antithrombotic mechanism; the formation of prostaglandin $H_2$ is blocked, thus thromboxane A2 cannot be synthesized. Thromboxane A2 activates platelets and stimulates their aggregation.[8] The irreversibility of the effect of aspirin causes inhibition for the lifespan of a platelet (7–10 days). After the discontinuation of aspirin intake by a patient, their platelet function can be expected to increase by 10–15% per day as a result of new platelet formation.[8 9] Aspirin is a key component of antiplatelet treatment to reduce death attributable to myocardial infarction or stroke.[10] Bleeding risk is smaller with low doses (75–100 mg), which deliver an equivalent antithrombotic impact to higher doses (300 mg).[11] Drug interactions with aspirin are scarce, but co-administration of non-selective COX1 inhibitors may impair its efficacy. Owing to potential aggravation of ischaemic heart diseases attributable to selective COX2 inhibitors, these drugs should be avoided in patients with coronary artery disease. About one-third of patients receiving aspirin manifest treatment failure (thrombotic complication or death). Non-compliance is a substantial problem but difficult to quantify, with estimates ranging between 3 and 40%. Adverse events resulting from rebound thrombocyte activation after aspirin withdrawal are frequent. Some patients show biochemical resistance or high platelet reactivity, detected by platelet function assays. Diabetes, cardiac surgery, or acute coronary syndromes, all of which are associated with an inflammatory response, are associated with high platelet reactivity. In addition, genetic polymorphisms (COX1, COX2 alleles, platelet glycoprotein receptors), or increased platelet turnover (bone marrow diseases) can reduce the effect of aspirin. The fact that aspirin has only a single binding site and does not influence

Table 2 Treatment recommendations for antiplatelet agents.[4–6] BMS, bare metal stent; DES, drug-eluting stent; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease

| Condition | Treatment recommendations |
|---|---|
| Primary prevention | Aspirin<br>Risk *vs* benefit evaluation |
| Acute coronary syndrome | PCI: aspirin lifelong plus ticagrelor, prasugrel, or clopidogrel ≥12 months<br>Non-PCI: aspirin lifelong plus clopidogrel or ticagrelor ≥12 months |
| Stable angina or former myocardial infarction | Aspirin lifelong plus clopidogrel<br>BMS ≥1 month<br>DES ≥6 months |
| Recent stroke | Aspirin in high-risk situation plus clopidogrel 90 days |
| Past stroke | Aspirin or clopidogrel |
| PVD | Aspirin or clopidogrel |

other thrombocyte receptors results in aspirin having less antithrombotic effect than many other agents.[9 12 13]

## $P2Y_{12}$ receptor antagonists

$P2Y_{12}$ receptors are adenosine diphosphate (ADP) receptors expressed on the surface of thrombocytes, which can be blocked chemically. The overall effect of ADP on platelets, the change of conformation, emergence of pseudopodia, platelet aggregation, and interaction with other cellular or plasma components to promote coagulation, is reduced.[14] Currently, clopidogrel, prasugrel, and ticagrelor are in use, and cangrelor has recently been licensed. Those substances are often prescribed in conjunction with aspirin, i.e. dual antiplatelet therapy (DAPT).[15]

### Clopidogrel

Clopidogrel is a thienopyridine and a prodrug, of which 85% is hydrolysed to an inactive metabolite. The remaining part is activated via cytochromes P3A4/3A5 and P2B6/1A2/2C9/2C19.6. The active metabolite binds irreversibly to $P2Y_{12}$. For rapid onset of platelet inhibition, an initial loading dose is necessary.[8 16] The pharmacological effect lasts for the lifespan of the affected thrombocytes.[15] The CYP450 dependency makes clopidogrel susceptible to drug interactions. Proton-pump inhibitors can also reduce its effect. No studies have been published proving sufficient evidence that any other drug interactions have any impact on its therapeutic effect.[17] Thirty per cent of patients treated with clopidogrel do not show adequate platelet inhibition. Genetic polymorphisms (CYP2C19, $P2Y_{12}$ receptor) or altered intracellular signal pathways seem to be causative. Patients, especially if diabetic, may show high platelet reactivity even when receiving dual antiplatelet therapy. However, non-compliance, discontinuation of drug intake, or lack of access to clopidogrel are more frequent causes of inadequate platelet inhibition than pharmacological high platelet reactivity.[15]

### Prasugrel

Prasugrel, a third-generation oral thienopyridine, is a prodrug, converted by CYP450 enzymes to its active metabolite. It binds irreversibly to $P2Y_{12}$, inhibiting platelet function for the lifespan of the affected platelets. Prasugrel shows a more reliable conversion to the active drug and more rapid onset of action than clopidogrel. Prasugrel produces more effective platelet inhibition than clopidogrel. Genetic polymorphisms (CYP2C9, CYP2C19) do not influence the metabolism of prasugrel. Drug interactions attributable to CYP-dependent conversion have not been described.[9]

### Ticagrelor

Ticagrelor is an oral non-thienopyridine reversible $P2Y_{12}$-blocking agent. CYP3A4 and CYP3A5 are the enzymes involved in the hepatic metabolism of ticagrelor. One of its active metabolites also has an important platelet-inhibiting effect. Twenty-four hours after the last intake, the antiplatelet effect of ticagrelor has declined by 50%, and 20% of the antiplatelet activity remains after 3 days. CYP3A4, CYP3A5, and CYP2D6 are moderately inhibited by ticagrelor, and drug interactions associated with this effect have been reported. Digoxin concentrations should be monitored in the event of concomitant use. Serum concentrations of some statins (lovastatin and simvastatin) are increased. Concomitant use of CYP3A4 inhibitors (ketoconazole, ritonavir, and clarithromycin) or inducers (rifampicin, phenytoin, carbamazepine, and dexamethasone) should be avoided.[18]

### Cangrelor

Cangrelor is the most recently (June 2015) approved i.v. non-thienopyridine, reversible $P2Y_{12}$-blocking agent. Steady-state concentrations are achieved after 18–24 h of i.v. infusion without a loading dose or a preliminary bolus being recommended. Platelet inhibition is >90%. Cangrelor is inactivated by plasma enzymes, and within 60 min of stopping the infusion the platelet function has recovered to normal.[19] These favourable pharmacokinetic properties make cangrelor a promising agent for bridging of high-risk patients in the perioperative setting.[20]

## Glycoprotein IIb/IIIa inhibitors

Glycoprotein IIb/IIIa (GpIIb/IIIa) receptors are the most numerous proteins on the platelet surface. Glycoprotein IIb/IIIa inhibitors block the adhesion of fibrinogen to the activated platelet, preventing the building of interplatelet bridges. Adhesion of fibronectin, von Willebrand factor, and vitronectin are inhibited. The activation of the GpIIb/IIIa receptor is one of the final steps in platelet activation, building cross-linked platelet–fibrinogen complexes. Glycoprotein IIb/IIIa receptors also contribute to a positive feedback mechanism with thrombin and collagen, producing a sustained prothrombotic effect.[21 22] Abciximab, tirofiban, and eptifibatide are i.v. GpIIb/IIIa inhibitors that are currently in use.

### Abciximab

Abciximab is a humanized monoclonal mouse antibody. It reversibly binds to thrombocytes within 1 min of adminstration. A loading dose is necessary to achieve a >80% receptor blockage. It shows the highest affinity to the GpIIb/IIIa receptor of the three licensed drugs.[23] It has a short plasma half-life, but a long biological activity.

### Tirofiban and eptifibatide

Tirofiban and eptifibatide are synthetic GpIIb/IIIa inhibitors that reversibly bind and rapidly dissociate (10–15 s) from the GpIIb/IIIa receptor. The plasma concentration of these drugs determines the receptor occupancy and extent of platelet inhibition. Both molecules compete with fibrinogen for the binding of the GpIIb/IIIa receptor. The affinity for the receptor is greater for tirofiban than for eptifibatide.[23]

## Other antiplatelet agents

Cilostazol and dipyridamole are phosphodiesterase inhibitors that interfere with degradation of cyclic adenosine monophosphate and cyclic guanosine monophosphate. In addition to their antiplatelet action, they cause vasodilation because of an effect on vascular smooth muscle.

The protease-activated receptor-1 antagonists, agents such as vorapaxar and atopaxar, inhibit platelet activation through alternative routes, including thrombin-mediated platelet aggregation. Numerous other platelet surface proteins (glycoprotein VI, glycoprotein Ib, prostaglandin E, nitrous oxid, and thromboxane A) are potential targets for inhibitory drugs currently under investigation.[3 8]

# Management of antiplatelet therapy in the perioperative setting (Fig. 1)[24 25]

Dual antiplatelet therapy is known to reduce significantly the number of arterial thrombotic events in the perioperative period. Discontinuation of antiplatelet agents is associated with a risk of myocardial infarction, stent thrombosis, and death attributable

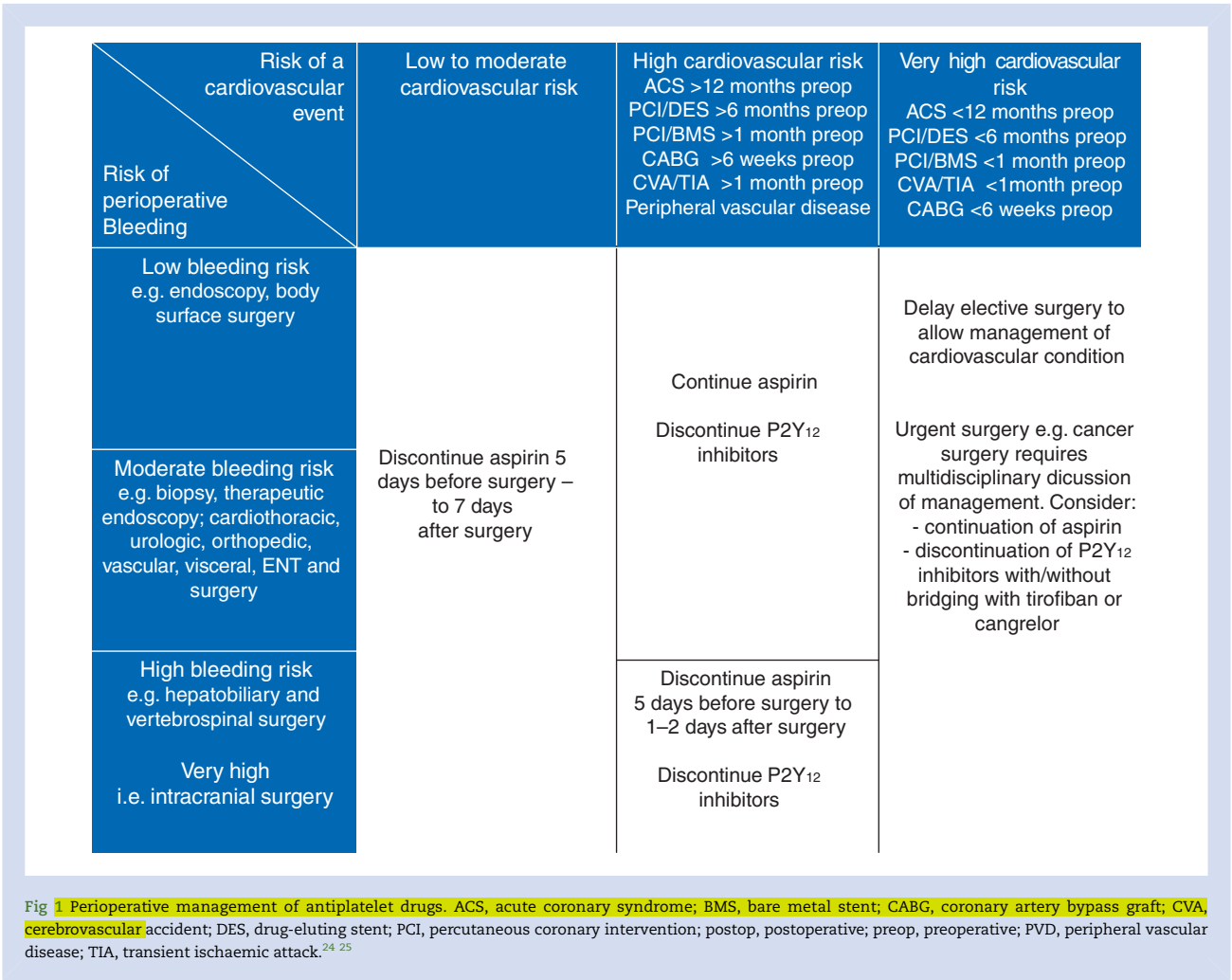


Fig 1 Perioperative management of antiplatelet drugs. ACS, acute coronary syndrome; BMS, bare metal stent; CABG, coronary artery bypass graft; CVA, cerebrovascular accident; DES, drug-eluting stent; PCI, percutaneous coronary intervention; postop, postoperative; preop, preoperative; PVD, peripheral vascular disease; TIA, transient ischaemic attack.[24 25]

to inflammatory-mediated rebound effects of platelet adhesion. Persistent perioperative application is associated with higher risk of bleeding (2.5–20 *vs* 30–50%) and a 30% higher rate of blood cell transfusion; however, mortality linked to these circumstances is hardly increased. The necessity of elective surgery should be assessed on a patient-by-patient basis. Antiplatelet therapy and treatment for other co-morbidities should be optimized. The relative risks of a thromboembolic event and of bleeding should be weighed. Postoperative restarting of antiplatelet therapy depends on the individual patient's cardiovascular risk profile, the bleeding risks associated with the particular operation, and the pharmacokinetics of each drug. The aim should be to re-establish the antiplatelet regimen as early as is reasonably possible. Hospital discharge without restarting treatment carries substantial risks.[19 26]

For operations with a low bleeding risk, antiplatelet therapy does not need to be interrupted. In procedures with a high risk of bleeding, aspirin should be maintained and other antiplatelet substances discontinued long enough before surgery to allow the antiplatelet effect to have waned. If possible, for example after percutaneous coronary angioplasty, the operation should be delayed until the patient has a lower risk of cardiovascular complications. In patients with a low risk of thromboembolic events who require surgery that carries a high risk of haemorrhage, antiplatelet therapy should be interrupted in the perioperative period. The continuous evaluation of the bleeding should guide intra- and postoperative therapeutic strategies.[8 9 27] The management of bleeding is discussed below.

In situations where there is a high chance of bleeding and withdrawal of antiplatelet therapy carries a high risk of cardiovascular events, bridging of antiplatelet therapy can be considered. Bridging therapies involve replacing antiplatelet therapy using long-acting $P2Y_{12}$ antagonists with a short-acting anticoagulant or antiplatelet agent that can be discontinued shortly before surgery. The use of tirofiban and eptifibate has been described. More recently, cangrelor has become available and is recommended as a suitable drug because of its pharmacokinetic profile. In the situation of bridging, treatment with aspirin should be continued and the other oral agent stopped 5–7 days before surgery. A short-acting i.v. agent should be started no more than 72 h after the discontinuation of DAPT. Four to six hours (or 1 h for cangrelor) before surgery, the i.v. drug is discontinued and is restarted 6 h after surgery. The patient's usual DAPT is restarted as soon as the risk of perioperative haemorrhage is negligible.[28–32]

Heparinoids are sometimes used for bridging. This is based on their known effect in unstable angina and Non-ST-elevation myocardial infarction (NSTEMI); they do not have any protective effect against coronary or stent thrombosis. Heparin is not an appropriate substitute for antiplatelet agents. Non-steroidal

anti-inflammatory agents and, in particular, reversible COX1 inhibitors can be considered as short-term substitutes.[8 26 27]

## The management of bleeding

Antiplatelet drugs have haemorrhage as a common side-effect. Several factors associated with a higher risk of bleeding have been identified, including female sex, advanced aged (>75 yr), impaired renal function, anaemia, low body weight (<60 kg), and a history of transient ischaemic attack or stroke. In a surgical context, complex or urgent operations are considered as high-risk situations for bleeding.

Major surgical bleeding in patients treated with antiplatelet agents increases perioperative morbidity and mortality, as do blood transfusions. A restrictive transfusion management strategy is widely recommended, with transfusion thresholds of the order of a haemoglobin <80 g litre$^{-1}$ or a haematocrit <25%.[33] No antagonists for antiplatelet agents are available. Management of significant haemorrhage is based on the administration of tranexamic acid, fibrinogen, factor XIII, desmopressin, platelets, and activated factor VIIa. The prothrombotic properties of these agents may pose a risk of major thrombotic complications.[8 9 34]

## Drug monitoring and laboratory tests

Numerous platelet function tests are available (e.g. turbidometric light transmittance, VerifyNow, Thrombelastogram, Multiplate, or Platelet Function Analyser-100). These were often initially designed to identify platelet function disorders (either dysfunction or hyperactivity). With the increasing armamentarium of platelet-inhibiting drugs, many of which display significant intra-individual variation in their efficacy, these assays have become more relevant to drug monitoring, the design of individualized pharmacotherapy, perioperative evaluation, and the planning of surgery. The results of platelet function tests vary between assays and depend on the cut-off values used to define a normal test. A further limitation is the dependency of these assays on haematocrit and platelet count.[35–37]

## Anticoagulant agents (Table 3)

Anticoagulants inhibit the initiation and progress of coagulation and fibrin-clot formation and propagation. Their uses include the treatment or prevention of venous thromboembolism and atrial fibrillation. For acute treatment of venous thromboembolism and during revascularization therapy, immediately acting parenteral anticoagulants are used. Low molecular weight heparins and, recently, parenteral anti-factor Xa agents (fondaparinux) have widely replaced unfractionated heparin.[38 39] Oral anticoagulants are indicated for long-term treatment or prevention of thromboembolic complications of different cardiovascular diseases, such as venous thromboembolism, myocardial infarction, or atrial fibrillation, and after implantation of mechanical valves.[38]

### Parenteral anticoagulants

#### Unfractionated heparin and low molecular weight heparin

Heparins are indirectly acting anticoagulants that bind to and activate antithrombin. After inducing a conformational change in antithrombin, the heparins dissociate and bind to further antithrombin molecules. Activated antithrombin accelerates the inactivation of coagulation factors IIa, IXa, Xa, Xia, and XIIa. Unfractionated heparin dosing depends on the indication for its

**Table 3** Summary of the characteristics of currently available anticoagulant drugs

| Characteristic | Warfarin | Oral | | | | Parental | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Dabigatran | Apixaban | Edoxaban | Rivaroxaban | Unfractionated heparin (s.c./i.v.) | Low molecular weight heparins (s.c.) | Fondaparinux (s.c.) | Argatroban (i.v.) | Bivalirudin (i.v.) |
| Mechanism of action | Vitamin K antagonist | Direct inhibition IIa | Direct inhibition Xa | Direct inhibition Xa | Direct inhibition Xa | Direct inhibition Xa=IIa | Direct inhibition Xa>IIa | Direct inhibition Xa | Direct inhibition IIa | Direct inhibition IIa |
| Bioavailability (%) | 80 | 6 | 66 | 62 | 80 | 30 | 90 | 100 | 100 | 100 |
| Plasma half-life | 20–60 h | 12–14 h | 8–15 h | 10–14 h | 7–10 h | 1 h | 4 h | 17 h | 50 min | 24 min |
| Duration of action from last dose | 48–96 h | 48 h | 24 h | 24 h | 24 h | Dose dependent (s.c.) | Dose dependent | 48–96 h | 2–4 h | 1 h |
| Peak plasma concentration | Variable | 2 h | 2.5–4 h | 1–2 h | 1–3 h | 4 h (s.c.) | 3 h | 2 h | | 0.25–2 h |
| Elimination | Metabolism | 80% renal | 25% renal | 50% renal | 50% renal, 50% hepatic | Reticulo-endothelial system | Hepatic metabolism, renal excretion 10% | Renal | 65% faeces, 22% urine | 20% renal |
| Drug interaction | CYP2C9, CYP3A4, CYP1A2 | P-glycoprotein inhibitors | CYP3Y4, P-glycoprotein inhibitors | P-glycoprotein inhibitors | Strong CYP3A4 inhibitors or inducers and P-glycoprotein inhibitors | | | | | |

use and is highly variable. Low molecular weight heparins can be used at a fixed dose for prophylaxis and in a weight-adjusted dose for therapeutic anticoagulation.[40]

### Fondaparinux

Fondaparinux selectively and irreversibly binds to antithrombin III, thus inactivating factor Xa and, in turn, interrupting thrombin formation and thrombus propagation.[40]

### Direct thrombin inhibitors

Parenteral direct thrombin inhibitors bind directly, selectively, and reversibly to the active site of thrombin. Fibrin formation and propagation of clot formation are inhibited. Currently, desirudin, argatroban, and bivalirudin are licensed direct thrombin inhibitors. They are the main alternative therapeutic agents in heparin-induced thrombocytopenia.[40 41]

## Oral anticoagulants

### Vitamin K antagonists

For more than 80 yr, vitamin K antagonists have been known to have anticoagulant properties and were the most frequently used oral anticoagulant drugs. After the identification of dicoumarol warfarin, phenprocoumon and acenocoumarol were synthesized.[42] These drugs, the latter mainly used in Europe, hinder the synthesis of vitamin K-dependent clotting factors; vitamin K reductase is blocked, causing a depletion of reduced vitamin K. This is needed for the γ-carboxylation and activation of vitamin K-dependent clotting factors II, VII, IX, and X. Additionally, they inhibit the carboxylation of the anticoagulant proteins C, S, and Z, causing a transient procoagulant state.[43 44]

Although vitamin K antagonists are highly effective agents they do have numerous limitations.

1. Genetic polymorphisms producing variation in patients' sensitivity.
   - Drugs such as warfarin act on the vitamin K epoxide reductase complex 1 (VKORC1). People with the A allele of VKORC1 produce less VKORC1 subunit than those with the more common G allele and require less VKA to produce an anticoagulant effect.
   - Warfarin is metabolized in the liver by CYP2C9. People with the CPY2C9*2 and CPY2C9*3 variants metabolize warfarin less effectively than those with wild-type CPY2C9*1 and require a lower dose to warfarin to achieve effective anticoagulation.
2. Non-genetic factors, including age, body weight, dietary vitamin K intake, concomitant diseases, and alcohol consumption, modulate the required dose.
3. Vitamin K antagonist drugs show variable pharmacodynamic properties, with slow onset and slow offset of action.
4. Vitamin K antagonists are subject to interactions with drugs metabolized by CYP2C9, CYP3A4, and CYP1A2.
5. They have a narrow therapeutic window, with the need for constant monitoring.

A >10-fold interpatient variation in the dose necessary to reach the desired anticoagulant effect is observed, leading to a risk of under- or overdosing and causing haemorrhage or thromboembolism. This made the development of alternative drugs attractive.[38 42 45]

## New oral anticoagulants

In 2004, ximelagatran was licensed by the European Medical Agency, thus becoming the first oral thrombin inhibitor to reach the market. As a result of potential hepatotoxicity, it was withdrawn soon after.[46] Since 2008, further new oral anticoagulants have been introduced. These include the direct thrombin inhibitor, dabigatran, and the direct factor X inhibitors, such as rivaroxaban, apixaban, and edoxaban. Other new oral antiocoagulants (NOACs) are currently being tested in clinical trials.

### Dabigatran etexilate

Dabigatran etexilate, a low molecular weight prodrug, is a direct thrombin inhibitor. It is converted to its active form, dabigatran, by non-specific esterases in the liver and plasma. It binds directly to the active site of thrombin via ionic interactions. Fibrin-bound thrombin and free thrombin are inactivated competitively and reversibly. Unlike heparins, which cannot inhibit clot-bound factor II, dabigatran can inhibit thrombus expansion triggered by thrombin. The following events in the coagulation cascade are prevented by dabigatran: conversion of fibrinogen into fibrin, positive feedback amplification of coagulation activation, cross-linking of fibrin monomers, platelet activation, and inhibition of fibrinolysis. Co-medication with P-glycoprotein inhibitors, including ketoconazole, amiodarone, verapamil, or quinidine, may increase its plasma concentration. Rifampicin may reduce the plasma concentration because of induction of P-glycoprotein.[47 48]

### Apixaban

Apixaban is a direct, selective factor Xa inhibitor that inhibits free and prothrombinase complex-bound factor Xa. It is rapidly absorbed in the stomach and small bowel, independently of food intake. Absorption is mediated by P-glycoprotein, and P-glycoprotein inhibitors can increase absorption. Metabolism is mediated by CYP3A4, and concomitant use of CYP3A4 and P-glycoprotein inducers (carbamazepine, phenobarbital, phenytoin, St John's wort, and rifampicin) cause a decreased concentration of apixaban.[42 48 49]

### Rivaroxaban

Rivaroxaban is a direct, highly selective, reversible, competitive inhibitor of free and complex-bound factor Xa. The bioavailability of this lipophilic drug is increased by concomitant food intake, causing more predictable plasma concentrations. Co-treatment with CYP3A4 inhibitors or inducers and P-glycoprotein inhibitors is (relatively) contraindicated, because it may lead to altered plasma concentrations of rivaroxaban.[42 48 50]

### Edoxaban

Edoxaban is a direct, highly selective and competitive inhibitor of factor Xa. It has a bioavailability of 62%. Co-administration of strong P-glycoprotein inhibitors (e.g. ketoconazole, amiodarone, verapamil, or quinidine) cause an increased effect of edoxaban, necessitating a dose reduction of 50%. Dose adjustment in patients with low body weight (<60 kg) or moderate renal impairment is also necessary.[51]

## The perioperative setting (Table 4)

Of all patients receiving oral anticoagulant treatment, 10% have to interrupt it for invasive procedures at some point.[52] In current clinical practice, bridging therapy is widely used to cover the temporary withdrawal of oral anticoagulation. Recent data (e.g. BRIDGE Trial, ORBIT-AF) suggest that this approach increases

Table 4 Recommendations for perioperative omission or new oral antiocoagulants

| Drug | Glomerular filtration rate (ml min$^{-1}$) | Bleeding risk | Duration of omission before surgery (h) | Recommendations for restarting |
|---|---|---|---|---|
| Dabigatran | >50 | Moderate | 36 | Decisions on restarting these agents depend on surgical bleeding risk (see Fig. 1), renal function, the indication for anticoagulation, and the presence or otherwise of a neuroaxial catheter. A pause of at least 6 h after the surgical intervention is recommended |
| | 50–30 | | 48–72 | |
| | <30 | | Minimum 72 | |
| | >50 | High | 48–72 | |
| | 50–30 | | 96 | |
| | <30 | | Minimum 120 | |
| Rivaroxaban | | Moderate | 18 | |
| <10 mg | | High | 24 | |
| Rivaroxaban | >50 | Moderate | 24 | |
| >15 mg | 50–30 | | 48 | |
| | <30 | | Minimum 72 | |
| | >50 | High | 36 | |
| | 50–30 | | 48 | |
| | <30 | | Minimum 72 | |
| Apixaban | >50 | Moderate | 24 | |
| | 50–30 | | 48 | |
| | <30 | | Minimum 72 | |
| | >50 | High | 48 | |
| | 50–30 | | 72 | |
| | <30 | | Minimum 72 | |
| Edoxaban | >50 | Moderate | 24 | |
| | 50–30 | | 48 | |
| | <30 | | Minimum 72 | |
| | >50 | High | 48 | |
| | 50–30 | | 72 | |
| | <30 | | Minimum 72 | |

the risk of perioperative haemorrhage but with little beneficial effect on thromboembolic complications in patients with atrial fibrillation.[53 54] Most importantly, two major aspects need to be considered, as follows: (i) the risk of intervention related haemorrhage (as subdivided in Fig. 1); and (ii) the risk of perioperative thromboembolism, classified as low, medium, or high (as in Table 5).[55]

A low-risk procedure in a low-risk patient does not require discontinuation of oral anticoagulation. In patients with lone atrial fibrillation or a $CHA_2DS_2$-VASc ≤4 ($CHADS_2$, $CHADS_2$ risk score for stroke in atrial fibrillation based on congestive heart failure, hypertension, age >75 yr, diabetes, and stroke or transient ischaemic attack; $CHA_2DS_2$- VASc, updated risk score for stroke in atrial fibrillation including $CHADS_2$ risk factors plus vascular disease age 65–75 yr and female sex), bridging is of questionable value because haemorrhagic risks exceed the risk of thromboembolic complications in these patients. High-risk procedures or high-risk patients do need bridging therapy to cover withdrawal of vitamin K antagonists. All intermediate-risk patients ($CHA_2DS_2$-VASc >4) and interventions carrying an intermediate risk of bleeding are likely to require patient-by-patient estimation of the individual bleeding and thromboembolic risk.[56]

In contrast to the periopertive management of vitamin K antagonists, current data do not support preoperative bridging therapy to cover the perioperative withdrawal of NOACs.[28 29 57 58] The advice for interruption of NOACs depends on their plasma half-life and the patient's co-morbidities, especially renal function. Two half-lives (remaining drug concentration <25%) are considered as an adequate compromise between the reduction of bleeding risk and the prevention of a thromboembolic event. If there is reduced elimination or a high risk of perioperative haemorrhage, the time of discontinuation should be increased. For minor surgical procedures, treatment with NOACs can be continued without interruption. Usual haemostatic measures are undertaken, and an awareness of the risk of bleeding is important. For major surgical procedures that carry a high bleeding risk and interventions near delicate structures or in enclosed spaces (e.g. neurosurgery), NOACs should be discontinued.[59 60]

If emergency surgery is needed, an evaluation of the indication for treatment with a NOAC, and the daily dose, last intake, and renal function allows a rough estimation of the pharmacological activity at the time of planned surgery. If feasible, a delay for at least 24 h from the last dose is advisable. New oral antiocoagulant ingestion less than 2–6 h previously may be treated with activated charcoal. Haemodialysis may be used for dabigatran elimination. The treatment of bleeding is discussed in the next section.[59 60]

Postoperative resumption depends on the risk of bleeding, the renal function, and the presence of neuroaxial catheters.

## Management of bleeding

Bleeding risk is increased in patients aged >75 yr, with concomitant aspirin intake, diabetes mellitus, low body weight (<50 kg), or an elevated plasma concentration of the anticoagulant.[61] Minor bleeding can be treated with basic measures, including compression, sclerotherapy, blood-pressure regulation, and so forth. It usually does not require pharmacological correction of coagulation. Anticoagulation should be interrupted until no further bleeding is detected.[58]

In the event of major bleeding (>20% of patient's blood volume), potential causes should be identified without delay. General measures should be undertaken, including the avoidance

Table 5 An approach to classifying arterial and venous thromboembolic risk in surgical patients. $CHADS_2$, $CHADS_2$ risk score for stroke in atrial fibrillation based on congestive heart failure, hypertension, age >75 yr, diabetes, and stroke or transient ischaemic attack; CHA2DS2-VASc, updated risk score for stroke in atrial fibrillation including $CHADS_2$ risk factors plus vascular disease age 65–75 yr and female sex;[55] VTE, venous thromboembolic event

| Thromboembolic risk | Risk factors |
|---|---|
| Low risk | VTE >12 months previously without risk factors for further event |
| | $CHADS_2$ ≤2 without cerebrovascular disease |
| | $CHA_2DS_2$-VASc <4 |
| | Bileaflet aortic valve without further risk factors (e.g. diabetes, atrial fibrillation, or congestive heart failure) |
| Intermediate risk | Recurrent VTE |
| | Active cancer |
| | VTE 3–12 months |
| | Factor V Leiden carrier |
| | Prothrombin mutation carrier |
| | $CHADS_2$ score 3–4 |
| | $CHA_2DS_2$-VASc score 4–5 |
| | Bileaflet aortic valve disease with further risk factors |
| High risk | VTE <3 months, severe thrombophilia |
| | Cerebrovascular accident <6 months previously |
| | $CHADS_2$ score 5–6 |
| | $CHA_2DS_2$-VASc score >5 |
| | Prosthetic cardiac valve |
| | Aortic valve replacement with cage ball valve |

and correction of acidosis, hypothermia, and hypocalcaemia. Specific reversal agents for NOACs are not yet available. Research on the development of specific reversal agents is in progress (e.g. idarucizumab for dabigatran, andexanet alfa for factor Xa inhibitors, and PER977 for factor Xa and thrombin inhibitors).[62]

Procoagulant agents may be required. Options include prothrombin complex concentrate (25–50 U $kg^{-1}$) or activated prothrombin complex concentrate (50–100 U $kg^{-1}$); the latter is more efficient but also more likely to cause thromboembolic complications. Recombinant factor VIIa may be used as rescue medication, but carries a high risk of thromboembolism. Adjuncts such as tranexamic acid or desmopressin may be considered, but there are few clinical data regarding their efficacy.[59 60 63]

## Drug monitoring and laboratory tests (Fig. 2)[64]

One advantage of NOACs over vitamin K antagonists is the avoidance of the necessity of routine laboratory monitoring. The most frequently used coagulation tests (activated partial thromboplastin time and international normalized ratio) are influenced by NOACs, because they directly inhibit factor IIa or Xa, the end points of these assays. The degree of alteration of clotting assays depends on the plasma concentration of the NOAC. Moreover, normal test results indicate a lack of a significant NOAC effect. This is particularly true for the activated partial thromboplastin time test in patients taking dabigatran.[65–67] Interpretation of drug plasma concentration is difficult because there is no defined range that reflects optimal treatment levels or bleeding risk. In daily clinical practice, routine laboratory testing during NOAC treatment is currently not recommended. A better understanding of their influence on laboratory coagulation tests might allow optimization and individualization of treatment in the future.[68] Laboratory testing is advisable in patients requiring urgent surgery, those with a rapid decline in renal function, or in bleeding patients. Test results should be interpreted in the context of the time of last drug administration. At present, our ability to state that there is no NOAC effect is probably greater than our ability to quantify any NOAC effect.

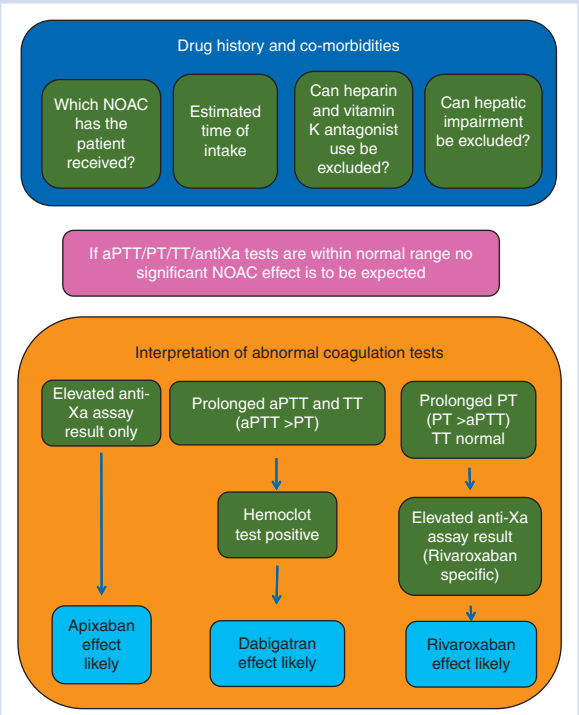


Fig 2 Interpretation of laboratory coagulation tests in patients with suspected new oral antiocoagulant treatment. anti-Xa, anti-Xa assay; aPTT, activated partial thromboplastin time; Hemoclot test, Hemoclot® thrombin inhibitor assay; PT, prothrombin time; TT, thrombin time.[64]

## Concomitant use of antiplatelet agents and new oral antiocoagulants

In clinical routine, the number of patients receiving antiplatelet therapy and NOAC therapy is increasing. Data suggest that

NOACs offer benefit in ischaemic events when used concomitantly with a single antiplatelet regimen. Patients on DAPT (aspirin and clopidogrel) who additionally receive a NOAC show a 3-fold increase in the risk of haemorrhage without further reduction of adverse cardiac events. Potentially, the bleeding risk is higher with more potent antiplatelet agents (ticagrelor and prasugrel), although data to confirm this are lacking. An individualized approach is necessary in patients who might be favourably treated with a combination of DAPT (including prasugrel and ticagrelor) and NOACs, balancing the potential benefit against the increased risk of haemorrhage. A dose reduction may be a potential strategy, but research to confirm this is required. The indication for long-term use of NOACs and DAPT in an individual patient should be re-evaluated regularly.[69]

## Conclusion

It is essential for anaesthetists to know the properties of new antiplatelet agents and NOACs because their management in the perioperative period or the bleeding patient is crucial. The perioperative period is associated with significant prothrombotic risk because of the inflammatory response to surgery. This risk must be balanced with the likelihood of haemorrhage in patients treated with antiplatelet or anticoagulant drugs. Both situations carry a significant burden of morbidity and mortality. With the increasing use of a broad range of antiplatelet and anticoagulant drugs, most anaesthetists face these dilemmas on a regular basis.

Guidelines are published and updated regularly to enable appropriate, up-to-date treatment, and the anaesthetist should ensure that they are familiar with relevant local and national guidance.[28 29 67]

Sophisticated laboratory assays are unevenly accessible in emergency situations, but standard laboratory tests, such as activated partial thromboplastin time, international normalized ratio, or basic platelet function tests, are not. These allow adaptation and guidance of treatment strategies (Fig. 2). Multidisciplinary discussion to plan the best treatment in high-risk patients undergoing surgery is essential.

## Authors' contributions

The review was conceived by V.K.-O. and M.F.

## Declaration of interest

None declared.

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