

REVIEW ARTICLE

Perioperative bradycardia and asystole: relationship to vasovagal syncope and the Bezold–Jarisch reflex

S. M. Kinsella^{1*} and J. P. Tuckey²

¹*Sir Humphry Davy Department of Anaesthesia, St Michael's Hospital, Southwell Street, Bristol BS2 8EG, UK.* ²*Department of Anaesthesia, Royal United Hospital, Combe Park, Bath BA1 3NG, UK*

*Corresponding author

Reflex cardiovascular depression with vasodilation and bradycardia has been variously termed vasovagal syncope, the Bezold–Jarisch reflex and neurocardiogenic syncope. The circulatory response changes from the normal maintenance of arterial pressure, to parasympathetic activation and sympathetic inhibition, causing hypotension. This change is triggered by reduced cardiac venous return as well as through affective mechanisms such as pain or fear. It is probably mediated in part via afferent nerves from the heart, but also by various non-cardiac baroreceptors which may become paradoxically active. This response may occur during regional anaesthesia, haemorrhage or supine inferior vena cava compression in pregnancy; these factors are additive when combined. In these circumstances hypotension may be more severe than that caused by bradycardia alone, because of unappreciated vasodilation. Treatment includes the restoration of venous return and correction of absolute blood volume deficits. Ephedrine is the most logical choice of single drug to correct the changes because of its combined action on the heart and peripheral blood vessels. Epinephrine must be used early in established cardiac arrest, especially after high regional anaesthesia.

Br J Anaesth 2001; **86**: 859–68

Keywords: anaesthesia; heart, arrhythmia, bradycardia; complications, cardiac arrest; complications, syncope; complications, Bezold–Jarisch reflex

Vasovagal syncope is loss of consciousness caused by reduced arterial pressure and blood supply to the brain, mediated through neural mechanisms rather than primary cardiac dysfunction. Bradycardia and vasodilation are the characteristic changes that cause systemic hypotension.⁴⁸ The trigger may be central, from psychic stress or pain, or may be initiated peripherally by a reduction in venous return to the heart.⁹⁴ In daily life this is commonest while the subject is standing. However, the anaesthetist may encounter these reactions during anaesthesia (especially regional), in hypovolaemia and in obstetrics.

The Bezold–Jarisch reflex overlaps with vasovagal syncope. It was initially described as a bradycardic response to injection of various alkaloid compounds, and later found to be mediated by chemoreceptors in the heart.⁹⁷ The term has now come to include reactions triggered by cardiac mechanoreceptor activation⁵⁸ and it has been used to describe perioperative bradycardia with hypotension.^{22 38 51 56 100} A further term in use is neurocardiogenic

syncope, which as well as vasovagal syncope includes micturition syncope and carotid sinus syndrome.⁹

Our understanding of these cardiovascular reflexes is fragmentary and complex. Information has been gained from patients and normal volunteers, humans and various other animal species, and using different mechanisms to reduce venous return and activate the reflex.^{9 33 58 74 82 86 94 95} This review summarizes present knowledge, emphasizing clinical aspects.

Cause

Haemorrhage

Vasovagal reactions from peripheral stimuli may occur when there is a decrease in venous return, from either hypovolaemia or a redistribution of blood volume. During the Second World War, cardiovascular responses to traumatic and experimental haemorrhage were observed.

Hypovolaemic hypotensive patients sometimes presented with a slow heart rate.³⁰ During progressive withdrawal of venous blood, blood pressure was initially maintained by vasoconstriction. With continuing blood loss, there might be a sudden fall in blood pressure, heart rate and peripheral resistance.⁶² Barcroft and colleagues found that the incidence of 'fainting' increased as blood loss increased, from 4% after loss of 440 ml to 50% after loss of 1000–1200 ml.⁶ An important later clinical finding was that, in cases where haemorrhage presented with relative bradycardia, transfusion alone would reliably increase the heart rate.^{47 78}

This pattern of cardiovascular change in response to haemorrhage is unfamiliar, as many textbooks describe a sustained tachycardia mediated via a withdrawal of afferent input from the arterial baroreceptors.⁸² This is probably because most hypovolaemic patients respond with a tachycardia, whereas the bradycardic response is noted in a minority only. Textbooks summarize information from a variety of sources, both human non-haemorrhagic models as well as animal experimental data, to produce a coherent picture. However, if the pattern of hypovolaemia presenting with bradycardia were not recognized, some patients may be treated inadequately or inappropriately.⁸²

Orthostasis

When a supine individual stands up, 300–800 ml of blood is redistributed from the intrathoracic capacitance vessels to the veins in the lower body. Compensation is needed to maintain venous return to the heart and systemic arterial pressure.⁹⁵ Turning a subject into the head-up position on a tilt table induces the change in blood distribution, but without muscle contraction in the legs which assists venous return during standing. Vasovagal syncope is more likely to occur in subjects with a smaller blood volume.^{10 25} If a standing subject faints, immediate collapse into the recumbent position will tend to increase venous return towards normal and thus limit the event. However, a severe response can occur if the tilt table is not flattened at the time of a faint.

Compression of inferior vena cava during pregnancy

In late pregnancy some women suffer an acute circulatory collapse, severe enough to mimic haemorrhagic shock, in the supine position.^{13 45} Hansen noted that orthostatic hypotension was less common as pregnancy progressed but that 12% of term women had severe hypotension and collapse while supine; this could be reversed by turning to the lateral recumbent position.³⁷ The cause was identified as compression of the inferior vena cava by the gravid uterus, reducing venous return and right atrial pressure.⁴⁷ Further reports of this phenomenon noted that sudden bradycardia occurred in some cases,^{45 47} and Lees and co-workers linked this 'supine hypotensive syndrome of pregnancy' with vasovagal fainting.⁴⁷

Regional anaesthesia

Spinal and epidural anaesthesia can prevent reflex vasoconstriction in the blocked segments. Although some hypotension is normal after high regional anaesthesia, if venous return is inadequate because of reduced blood volume or head-up tilting (reverse Trendelenberg), syncope and abrupt bradycardia or sinus arrest can occur.^{12 42 79}

Afferent pathways

Cardiac

Some chemical stimuli within the heart activate unmyelinated sensory nerve fibres that pass via the vagus nerve to the brainstem. This causes a vasodepressor response, the classical Bezold–Jarisch reflex.³³ The cardiac site of origin in humans was demonstrated in heart-transplant patients. Coronary artery angiography caused bradycardia in control subjects. On the other hand, the same stimulus resulted in a tachycardia in the residual sinus node tissue of subjects who had the afferent nerves from the heart interrupted by transplantation.⁴

Other unmyelinated afferents are activated via mechanoreceptors which are usually sensitive to left ventricular distension, but may also respond to hypovolaemia.⁵⁸ A response to hypovolaemia can occur because, if there is myocardial stimulation combined with underfilling, deformation of the cardiac wall triggers mechanically sensitive nerves in the same way as stretching. The origin of vasovagal responses from cardiac afferents was proposed by Oberg and Thoren.⁶⁹ They found that both cardiac afferents and arterial baroreceptors cause circulatory compensation during haemorrhage in cats, but only the cardiac afferents caused bradycardia during rapid haemorrhage, a 'vago-vagal reflex'.⁷⁰ Ludbrook and Ventura showed that when venous return was progressively reduced in rabbits by inflation of a cuff round the vena cava, arterial baroreceptors mediated the compensatory phase and cardiac afferents were usually involved in the depressor phase.⁵⁵

Non-cardiac

Other evidence, also from patients who have had heart transplants, seems to contradict this 'cardiac' theory of the vasodepressor response in humans. In a number of cases, syncopal reactions have been noted in spite of evidence that reinnervation had not occurred.^{27 49 80} Evidence for differences between species comes from experiments in dogs, where sympathetic withdrawal occurring during haemorrhagic hypotension was mediated neither by aortic baroreceptors nor by cardiac nerves.⁶⁵ Even in species with good evidence of a cardiac origin for the inhibitory response, the heart may not be the only source. Cardiac afferent nerve block in rabbits did not reliably inhibit the sympatho-inhibitory phase during constriction of the inferior vena

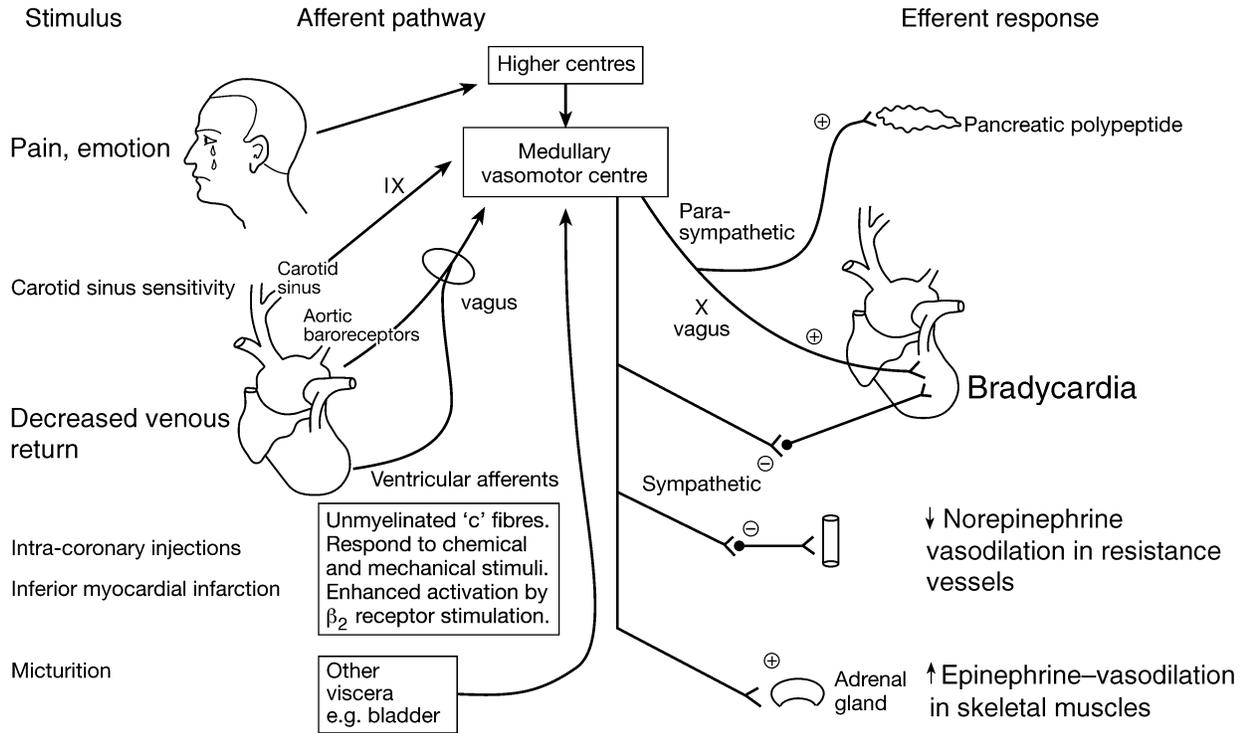


Fig 1 Neurally mediated syncope. IX, glossopharyngeal nerve; X, vagus nerve; ⊕, stimulates; ⊖, inhibits.

cava, indicating that there are sites of origin for this reflex other than the heart.⁵⁵

An alternative mechanism of triggering vasodepressor reflexes could be via arterial baroreceptors. Baroreceptor activation, secondary to increases in blood pressure, decreases sympathetic outflow and increases parasympathetic activity, leading to vasodilation and bradycardia. With a decrease in blood pressure, baroreceptor activity ceases, but with progressive hypovolaemia there may be paradoxical recurrence of baroreceptor discharge, so-called 'collapse firing' (Fig. 1).⁹⁵

Central transmission

Arterial baroreceptor and cardiac afferents enter the brain via the glossopharyngeal and vagus nerves, and synapse in the nucleus tractus solitarius and the ventrolateral medulla.⁶⁴ Arterial baroreceptor afferents may have a closer integration with mechanically sensitive than with chemosensitive cardiac afferents.⁷²⁻⁹⁶ Although there is some overlap, cardiac afferents that are mechanically sensitive may tend to be more concerned with circulatory homeostasis whereas chemosensitive afferents are activated by cardiac pathology.⁷²

Some syncopal reactions are initiated by emotional factors. It is known that the limbic system is concerned with emotions, and in some animal species stimulation of the limbic sympatho-inhibitory centre causes hypotension and bradycardia.⁹⁴ Once a reaction has started, orthostatic stress in the erect position will augment any central effects.

Strong emotions also cause sympathetic nervous system activation. The role of sympathetic stimulation in syncope, especially with regard to concentrations of circulating epinephrine, is noted in the next section.

There is evidence that endogenous opioids are important neurotransmitters in the nucleus tractus solitarius⁴⁶ and are involved in the syncopal response in animals.⁹³ This has generated particular interest because of the frequent clinical use of opioids and opioid antagonists and the hope that prevention or treatment strategies might be directed here.⁵⁴⁻⁹³ Blockade of cardiac afferent nerves prevented decompensation during simulated haemorrhage in rabbits; the same effect was also achieved by injecting extremely low doses of naloxone into the fourth ventricle.²⁶ However, in humans, intravenous naloxone pre-treatment did not alter vasovagal responses to lower-body negative pressure.²⁸⁻⁸⁵ The δ receptor subtype may be more important than the μ receptor, and therefore δ -specific antagonists may show more benefit.⁹³

Efferent responses

During vasovagal syncope, the efferent responses are increased vagal activity, especially to the heart, and decreased sympathetic activity. The resulting combination of bradycardia and vasodilation causes significant hypotension. Stroke volume and cardiac output generally decline further.⁹⁵ The vasovagal response with bradycardia and afterload reduction may protect the heart when the myocardial oxygen supply is compromised,⁹⁴ at the expense

of the overall need to maintain systemic arterial pressure and cardiac output. With tilt-induced vasovagal syncope, most cases show both cardiac and vascular components but a few may show either a predominantly bradycardic or vasodepressor response.⁸⁹

Increased parasympathetic activity is not selective for the heart, as pancreatic polypeptide titres increase during haemorrhage⁷⁸ and presyncope^{42,79} indicating a more general parasympathetic activation. The gastrointestinal effects probably account for the nausea accompanying vasovagal syncope and possibly an increase in splanchnic blood flow.³

Lewis postulated that there was a vascular component to fainting reactions, as the associated hypotension was not reversed when atropine was administered to correct the bradycardia.⁴⁸ Studies of forearm blood flow using venous occlusion plethysmography and cardiac output^{6,13} confirmed this. An increase in forearm blood flow was found at the time of fainting induced by table tilting, the exaggerated lordotic posture and spinal anaesthesia.¹³

The vasodilation is caused by sympathetic inhibition. During haemodialysis, presyncope was associated with increased sympathetic nerve activity and calf vascular resistance and decreased calf blood flow. Syncope with hypotension and bradycardia came with decreased sympathetic nerve activity and vascular resistance. Calf blood flow did not change because of the simultaneous reduction in blood pressure and resistance.¹⁹

The importance of the vascular component was shown during near-syncope in a heart-transplanted patient. Although the contraction frequency of the transplanted ventricle increased, hypotension occurred associated with decreased sympathetic nerve activity.⁸⁰ It has been suggested that sympathetic 'switch-off' with reduced systemic vascular resistance and hypotension may normally precede the change in heart rate at syncope.⁷⁴

The decrease in sympathetic nerve activity before or during syncope is followed by decreased concentrations of norepinephrine.^{94,101} However epinephrine concentrations increase, causing muscle vasodilation and tending to reduce systemic vascular resistance further.^{94,101} Exogenous β -agonists may also increase the tendency to vasovagal reactions.¹ At the same time as most tissues show a decrease in vascular resistance, there is evidence of cerebral vasoconstriction in presyncope and syncope.^{9,34,41} The significance of this is unclear.⁹

Anaesthesia

General anaesthesia

Modern anaesthetic agents do not have anticholinergic or sympathomimetic side effects. Simple 'vagal' (as opposed to vasovagal) reflexes with bradycardia and transient asystole are more common, especially during ophthalmic or pelvic surgery. Bradycardia characteristically resolves

quickly when the stimulus ceases. Generally, hypotension will only occur if bradycardia is extreme. It is presumed that there is no component of vascular dilation.⁸⁴

True vasovagal reactions have been described around the time of induction of general anaesthesia,^{24,35,36,38,44} associated with anxiety and pain of venepuncture. When full cardiovascular monitoring has preceded venous cannulation, asystole has been noted of several minutes' duration, requiring cardiopulmonary resuscitation.^{36,38,44} The patient may give a history of syncopal attacks during venepuncture or minor surgery.^{36,38} If the syncopal reaction is delayed for a short time, then anaesthetic drugs may also be given, which will complicate the diagnosis considerably.^{24,35} Compensated hypovolaemia may become evident after induction of anaesthesia.⁷⁷

Spinal and epidural anaesthesia

Pain and anxiety may cause fainting during induction of regional anaesthesia as with general anaesthesia.^{61,87} Case reports note a history of fainting, as well as the added influence of orthostatic stress from the sitting position used for needle insertion.^{61,87}

Haemodynamic instability is expected with the onset of the block, but delayed bradycardia or asystole may be more sinister. Although fatalities associated with regional anaesthesia are usually found in the elderly and those with co-morbidity,^{5,71} the landmark report by Caplan and colleagues¹⁶ indicated a risk even in healthy patients. These authors reviewed 14 cases of cardiac arrest leading to death or severe brain damage in patients having spinal anaesthesia. Cases were identified from a database of over 900 closed insurance claims during 1978–1986. All but one case occurred during surgery after the block had been established for some time. The average upper limit of sensory block was T4.

In the time leading up to the arrest, heart rate and blood pressure showed a gradual decline. The last assessment of apparently adequate ventilation and circulation was followed, on average in <2 min, by the first clue of problems. This 'first clue' was bradycardia, hypotension, cyanosis or loss of consciousness, in descending order of frequency. Cardiac arrest comprised either asystole or severe bradycardia with loss of output.

Caplan and colleagues¹⁶ suspected two aspects of management which might have been responsible for these devastating outcomes. The first was the use of central depressant drugs in addition to the regional anaesthesia. Twelve patients had had at least one but usually more than one intravenous opioid or sedative, including fentanyl, diazepam, droperidol and thiopentone. Half the patients were in a sleep-like state. Besides a contribution from unappreciated respiratory depression, the authors 'speculated that circulatory changes related to high sympathetic block' were an important factor. The authors also highlighted possible deficiencies in the treatment of the cardiac

arrest. On average, epinephrine was not given until 6 min after the start of cardiopulmonary resuscitation and 8 min after the first clue of impending arrest.

These descriptions suggest vasovagal reactions after a critical reduction in venous return. Regional anaesthesia may have affected the physiological responses so that cardiac arrest was sustained. Hypertension and tachycardia in response to hypoxia do not occur during epidural anaesthesia in dogs, probably because of sympathetic block.⁷³ Furthermore, coronary perfusion pressure gradient (which indicates the likelihood of successful resuscitation attempts) during ventricular fibrillation in dogs was significantly reduced after high spinal anaesthesia.⁷⁶

Caplan and colleagues¹⁶ acknowledged that these cases were likely to be a biased sample of all those patients who develop cardiac arrest during spinal anaesthesia, as they came from medicolegal sources. This is borne out by the subsequent publication of cases of bradycardia or brief asystole in association with epidural or spinal anaesthesia, which seemed to start in the same way but have successful outcomes.^{14 29 50 56} Spinal block height was often at the upper thoracic level,^{14 29} whereas epidural analgesia was induced with large doses of local anaesthetic.^{29 50} Deep sedation was not used.^{29 50} Although some episodes occurred soon after induction of anaesthesia, most started during the operation and two developed only in the post-operative recovery ward.^{29 50}

The 'event' that was noted was a sudden decrease in heart rate, although often a gradual decline in heart rate during stable anaesthesia had preceded this.⁵⁶ Bradycardia was reversed with atropine initially in all subjects, but ephedrine, epinephrine and external cardiac massage were also needed in some cases. None of these patients suffered morbidity after the event, reinforcing Caplan and colleagues' suggestion¹⁶ that immediate treatment of bradycardia or asystole under these circumstances is crucial.

An aspect of management that may have contributed to the event in some cases was the use of infusions of epinephrine to maintain cardiac output and sodium nitroprusside to induce hypotension.⁵⁰ Decreases in cardiac filling pressure were recorded or surmised in several cases. Both β -stimulants¹ and nitroprusside⁹⁹ have been implicated in inducing vasovagal reactions.

Two prospective studies examined the prevalence and risk factors for bradycardia and other intraoperative complications during spinal anaesthesia, in a total of 2700 patients.^{17 90} Bradycardia occurred in 10%, hypotension in 22% and nausea in 10%. No patients developed asystole. The most important factor implicated in all of these complications was dermatomal block to T5/6 or higher. Bradycardia was more likely with young age or ASA 1 physical status, in contrast to hypotension found more frequently in the elderly. Bradycardia defined as a decrease below a threshold (heart rate <50 beats min^{-1}) is consistent with cardiac sympathetic nerve inhibition associated with mid-thoracic block level.³² However, the development of

sudden bradycardia over a few heartbeats, and the potential for the reversal of bradycardia by postural changes that increase venous return, can only be explained by a vasovagal reaction.³²

In summary, spinal and epidural anaesthesia are not infrequently associated with bradycardia or hypotension defined by crossing a particular threshold level for rate or arterial pressure.^{17 90} Less frequently, vasovagal reactions with sudden bradycardia or asystole occur, initiated by reduced venous return and therefore more likely with high block level and hypovolaemia. Outcomes are usually good, but delays in instituting corrective treatment and resuscitation may cause permanent cerebral damage or death.¹⁶ The risk of asystole extends into the post-operative phase.⁵⁰ The risk of life-threatening vasovagal reactions during regional anaesthesia may be in the order of three per 1000,²⁹ compared with 5% of patients who have both bradycardia and hypotension during spinal anaesthesia.¹⁷

Obstetric anaesthesia

An early report of supine hypotensive syndrome in pregnancy describes a woman who had a Caesarean section because it was thought that she was hypovolaemic secondary to a ruptured uterus.⁶³ The syndrome is not usually of serious consequence in isolation, because once recognized it is rapidly relieved by a change in position. However, regional anaesthesia combined with inferior vena cava compression introduces significant risk because of interference with cardiovascular control, and the inability of the patient to move herself. Holmes reviewed the literature from the 1930s to the 1950s on maternal mortality during Caesarean section with spinal anaesthesia. Problems occurred soon after the patient was moved into the supine position, as the sympathetic block developed. Sudden bradycardia was found in cases when heart rate was recorded.^{39 40} Holmes suggested that unappreciated compression of the vena cava was the likely cause, rather than other possibilities such as respiratory insufficiency.³⁹ The risk is present even without the sympathetic block induced by regional anaesthesia: a patient with severe pre-operative supine hypotension died after induction of general anaesthesia.²⁰ These life-threatening reactions are now rare since the introduction of lateral tilt during Caesarean section, but cases still occur despite these precautions.^{2 60 81 100}

Interscalene block for shoulder surgery

New surgical techniques present new anaesthetic problems and challenges. A recent development is the practice of shoulder arthroscopy in the sitting position, using interscalene block for anaesthesia.^{22 43 51} D'Alessio and colleagues²² reported vasovagal events, defined as hypotension or bradycardia requiring treatment, in 20 of 116 patients who had surgery in this way. Epinephrine was used for the interscalene block as well as for injection into the surgical

incision sites and joint irrigation. Patients who received higher doses of epinephrine were more likely to belong either to the vasovagal group or to a subset of the non-vasovagal group who were given β -adrenergic blockers for treatment of tachycardia or hypertension ($n=18$). Intraoperative peak heart rate was higher in these two groups than in those without problems. The authors suggested that the Bezold–Jarisch reflex resulted from a combination of awake surgery in the sitting position with augmentation of the cardiovascular stress as a result of the β -agonist effects of epinephrine reducing systemic vascular resistance and stimulating the myocardium. The patients who received β -antagonist treatment for tachycardia or hypertension were protected from this. This finding was supported by a randomized study comparing treatment with metoprolol, glycopyrrolate or placebo after surgical positioning.⁵¹ Hypotensive or bradycardic events, or both, were found in only 5% of the group treated with metoprolol; this was significantly lower than the incidences in the placebo and glycopyrrolate groups (28% and 22%, respectively).

Expression of syncopal reactions

The identification of a minority of patients who demonstrate vasovagal responses during haemorrhage or regional anaesthesia might suggest that these individuals are qualitatively different. Development of the tilt table and lower-body negative pressure devices allowed standardized and repeatable testing, with the hope of distinguishing ‘normal’ and ‘abnormal’ individuals. Although syncope thresholds vary among individuals,^{10,66} a number of factors prevent a simple division of the population into two groups. Tilt-table testing may provoke syncope in otherwise asymptomatic subjects. On the other hand, patients with a clinical history may not demonstrate problems even with provocative testing such as isoprenaline infusions in addition to head-up tilt. Besides this, syncope in a given subject may be expressed to a different degree when tested using the same method on different occasions,⁹ and may be provoked by one stressor but not another.¹⁹

The amount by which cardiac output is reduced at the time of vasovagal syncope depends on experimental design and the method by which it is induced.⁹⁵ At one time the trigger for syncope was believed to be ‘contractions of an almost empty ventricle’ causing stimulation of left ventricular mechanoreceptors.⁶⁹ This has not been studied during clinical blood loss, but the bulk of evidence from experimental syncope does not support this suggestion. Although one study found that baseline left ventricular fractional shortening during systole increased from 23% in the supine position to 51% at the onset of syncope during head-up tilt,⁸³ another found no difference in cardiac volume preceding tilt-induced syncope.⁶⁸ Two studies of the effects of epidural anaesthesia also did not demonstrate significant cardiac underfilling: Sander-Jensen and col-

leagues found a 25% reduction in end-systolic volume at bradycardia,⁷⁹ while Jacobsen and co-workers found only a 13% reduction in left ventricular diameters at the onset of presyncopal symptoms.⁴²

Does an explanation lie in the experimental design? Hypovolaemia and the standing position may be counted as ‘natural’ stresses which the circulatory reflexes are designed to counteract, but head-up tilt and epidurals affect the integrated cardiovascular response to reduced venous return. During head-up tilt the leg muscles do not contract and therefore the ‘muscle pump’ that augments venous return is inactive, so that vasovagal reactions can occur in subjects who do not give a clinical history.⁹⁴ Epidural anaesthesia inhibits not only the muscle pump but also compensatory veno- and arterioconstriction.

We conclude that there is no true separation between normal and abnormal, but a range of individual susceptibility to vasovagal reactions from those who may have life-threatening problems during their daily life⁵⁷ to those who do not respond to provocative testing. A patient may show syncope in some circumstances but not in others.

Implications for anaesthetic management

We consider that a pragmatic approach in clinical practice is to separate patients on the basis of whether or not they have a history of syncopal episodes.

Anaesthetic management of the patient with known syncope

A detailed history may provide a pattern to the attacks, precipitating factors, the severity and any previous medical investigations. Sometimes syncopal episodes are specifically related to venepuncture and general anaesthetic induction.^{36,38} Cardiological investigation may be appropriate, although prophylactic treatment in general is not very effective.

In mild cases it is probably appropriate merely to apply full non-invasive cardiovascular monitoring before doing anything painful. However, management of severe cases must be planned carefully. We would consider oral premedication with a sedative and an anticholinergic.⁴⁴ Topical local anaesthetic cream for the venepuncture site⁴⁴ may be used before intravenous induction, or an inhalational induction of anaesthesia.³⁸ Drugs implicated in the genesis of asystole include propofol, fentanyl, suxamethonium and vecuronium.

During the maintenance of general anaesthesia, vasovagal syncope does not occur.⁸⁴ However bradycardia in response to perioperative bleeding has been noted during neurolept anaesthesia.⁷⁵

If regional anaesthesia is being performed, similar considerations apply as for induction of general anaesthesia. The lateral position for insertion of a spinal or epidural is preferable to the sitting position.^{61,87}

Management of spinal and epidural anaesthesia in patients with no history of syncope

Block height

The incidence of baseline bradycardia is greater if the block extends above the mid-thoracic region.^{17,90} A high block may increase the risk of a vasovagal reaction in several ways. There may be direct cardiac sympathetic inhibition and decreased territory for compensatory vasoconstriction.¹¹ Indirect effects include deafferentation (see below) and ventilatory impairment. Although block height cannot be precisely controlled, especially with a single-shot technique, important factors during spinal administration that are within the control of the anaesthetist include drug dose, baricity and patient positioning.^{31,88}

Sedation and breathing

Although episodes of bradycardia may occur during regional anaesthesia in the absence of sedation,^{16,50} oversedation may increase the risk.^{16,73} Hypnotic drugs should be given to obtain anxiolysis rather than deep sedation. The patient who is able to communicate symptoms may give an early warning of the development of a vasovagal reaction. The effective dose of midazolam, propofol and thiopentone is reduced by 40–75% during spinal anaesthesia, possibly as a result of deafferentation caused by the regional block.^{8,91,92} Opioids should be reserved for intraoperative discomfort or pain.

Hypoxaemia may occur during high regional anaesthesia because of hypoventilation, or a reduction in cardiac output causing 'shunt effect'. Prophylactic oxygen administration should be considered. Pulse oximetry is helpful, and end-tidal carbon dioxide can be monitored even in unintubated patients using a sidestream capnograph.

Circulating volume status and body position

Pre-existing hypovolaemia before induction of regional anaesthesia may lead to cardiovascular collapse.¹² Compensatory vasoconstriction in unblocked regions of the body maintains peripheral resistance with epidural blocks up to the T5 level,¹¹ but passive venous return is crucial in this situation. Intraoperative blood loss must be meticulously replaced.

Changing from a head-down position to horizontal can precipitate cardiac arrest,⁶⁷ whereas asystole⁶¹ may be reversed by lowering the heart relative to the lower body. Greene and Brull³² emphasize the necessity of using a slight head-down position during spinal-induced hypotension.

Pharmacological prophylaxis

The treatment of bradycardia of gradual onset during regional anaesthesia will depend on the associated blood pressure as well as the clinical and surgical situation. However, it is not possible reliably to prevent a vasovagal reaction by keeping above a particular heart-rate threshold, as such a reaction may occur after a period of normal heart rate or tachycardia.⁵⁰

Treatment

During general anaesthesia, simple vagal reactions will usually respond to stopping the stimulus. However, when a vasovagal reaction is suspected during regional anaesthesia, then the cardiovascular change is augmented by vasodilation and is likely to lead to significant hypotension. Restoration of venous return is urgent as spontaneous recovery from asystole may occur if this is achieved,⁶¹ although drug treatment must not be delayed. Head-down tilt or leg elevation should be used,¹⁶ and compression of the vena cava should be relieved in obstetric cases.^{39,40} Intravenous fluids must be considered if there is any suspicion of hypovolaemia; a rapidly running infusion will hasten the transit of drugs into the central circulation. However, it is essential to distinguish between true hypovolaemia resulting from blood or fluid loss and a shift of blood from central to peripheral compartments. Vasovagal syncope may occur after a relatively small reduction in cardiac volume during epidural anaesthesia.^{42,79}

Anticholinergic drugs are often the first treatment for slow heart rate during anaesthesia, especially general anaesthesia. Although atropine has been used as the only agent to treat asystole during regional anaesthesia,⁵⁶ it may not be the best single agent if bradycardia is suspected to be accompanied by vasodilation. Hypotension during vasovagal syncope may persist after the relief of bradycardia by atropine.⁴⁸

Sympathomimetic drugs, by contrast, will counteract the vasodilation in both the arterial and venous circulations. Commonly used agents are either ephedrine or various selective α -agonists. Most assessments have been in the context of prophylaxis and treatment of hypotension during regional anaesthesia, with the authors drawing different conclusions. One study found that ephedrine was less effective than metaraminol at reversing hypotension and decreases in central venous pressure and systemic vascular resistance index. Metaraminol, on the other hand, decreased the heart rate.²¹ However, Butterworth and colleagues showed that both ephedrine and phenylephrine increased blood pressure effectively, but only ephedrine decreased venous capacitance.¹⁵ Starting with a low heart rate, the direct sympathetic effects on the heart rate of ephedrine are advantageous, whereas, if baroreceptor function remains active,⁵⁹ an α -agonist might reduce it further. However if hypotension persists after adequate doses of ephedrine, or epinephrine-containing epidural solutions, an α -agonist might be considered.

Successful use of thump pacing for asystole during regional anaesthesia has been described.⁵⁰ However, once persisting cardiac arrest occurs, external cardiac massage must be started to ensure circulation of resuscitation drugs and perfusion of vital organs. Prompt treatment with epinephrine has been emphasized as crucial for successful recovery.^{14,16,50} A study in dogs has suggested that above-

normal doses of epinephrine may be necessary during cardiac arrest in association with high spinal anaesthesia.⁷⁶

A standard sequence using atropine, ephedrine and then epinephrine to treat bradycardia during spinal anaesthesia has been advocated.¹⁴ Although flexibility is necessary, we suggest that ephedrine is the most logical choice for a single agent to treat profound bradycardia or asystole during regional anaesthesia, given the lack of vasoconstrictor effect of atropine and the potential for heart rate reduction with α -agonists. For asystole or persistent severe bradycardia, epinephrine should be used early.

Future research

Ideally patients who are likely to have vasovagal reactions during anaesthesia could be identified before surgery, but this is unlikely for several reasons. It has been noted that many subjects who develop vasovagal reactions in daily life are at merely one end of a spectrum of cardiovascular control,⁹ with a minority suffering life-threatening events.⁵⁷ Provocation tests such as the tilt table give variable results on repeated testing.⁹ Prophylactic treatment is unreliable, although recent advances in pacemaker technology are promising.¹⁸

The extent of the problem needs clearer definition.²⁹ General risk factors for bradycardia during spinal anaesthesia, such as block height and young age, have been elucidated,^{17,90} but the identification of severe bradycardic-hypotensive events may need a different approach, such as critical incident reporting.⁶⁰

Analysis of heart-rate variability, which gives a measure of the absolute and relative activity of the sympathetic and parasympathetic systems, has shown differences in syncopal and non-syncopal subjects.⁵² The drawback is that several minutes of recording are needed for analysis. However, recent approaches such as complex demodulation, which allow pattern recognition over a much shorter time-scale, might be more applicable to clinical practice.⁵³ If a pre-syncopal state could be reliably identified, this might allow monitoring not only perioperatively but also into the recovery period.⁵⁰

The assumption that there is a vascular component to sudden hypotension and bradycardia during anaesthesia and with tilt-table testing has often been made, whereas the use of direct measurements has been limited to experimental situations.^{6,13,19} It has been noted that the efferent expression of vasovagal reactions may include primarily cardiac slowing, vasodilation or a mixed pattern. To identify the haemodynamic changes occurring during bradycardic episodes, it is essential to monitor whether there is accompanying vasodilation. This is only likely to be feasible during clinical practice if non-invasive methods are used. In the past, monitoring of vasoconstrictor tone has been performed, albeit crudely, with photoelectric plethysmography.²³ Experimentally, plethysmographic amplitude increases markedly at the time that sympathetic nerve

activity decreases during syncope.⁹⁸ The principle of photoelectric plethysmography is used as the basis of pulse oximetry.

References

- 1 Almqvist A, Goldenberg IF, Milstein S. et al. Provocation of bradycardia and hypotension by isoprotenerol and upright posture in patients with unexplained syncope. *New Engl J Med* 1989; **320**: 346–51
- 2 Anon. *Why Mothers Die: Report on Confidential Enquiries into Maternal Deaths in the United Kingdom 1994–1996*. Norwich: HMSO, 1998
- 3 Arndt JO, Hock A, Stanton-Hicks M, Stuhmeier K-D. Peridural anesthesia and the distribution of blood in supine humans. *Anesthesiology* 1985; **63**: 616–23
- 4 Arrowood JA, Mohanty PK, Hodgson JM, Dibner-Dunlap ME, Thames MD. Ventricular sensory endings mediate reflex bradycardia during coronary arteriography in humans. *Circulation* 1989; **80**: 1293–300
- 5 Auroy Y, Narchi P, Messiah A, Litt L, Rouvieu B, Samii K. Serious complications related to regional anesthesia. Results of a prospective survey in France. *Anesthesiology* 1997; **87**: 479–86
- 6 Barcroft H, Edholm OG, McMichael J, Sharpey-Schafer EP. Post haemorrhagic fainting. Study by cardiac output and forearm flow. *Lancet* 1944; **i**: 489–91
- 7 Barriot P, Riou B. Hemorrhagic shock with paradoxical bradycardia. *Intensive Care Med* 1987; **13**: 203–7
- 8 Ben-David B, Vaida S, Gaitini L. The influence of high spinal anesthesia on sensitivity to midazolam sedation. *Anesth Analg* 1995; **81**: 525–8
- 9 Benditt DG, Erickson M, Gammage MD, Markowitz T, Sutton R. A synopsis: neurocardiogenic syncope, an international symposium, 1996. *Pacing Clin Electrophysiol* 1997; **20**: 851–60
- 10 Bergenwald L, Freyschuss U, Sjostrand T. The mechanism of orthostatic and haemorrhage fainting. *Scand J Clin Lab Invest* 1977; **37**: 209–16
- 11 Bonica JJ, Berges PU, Morikawa K. Circulatory effects of peridural block: I. Effects of level of analgesia and dose of lidocaine. *Anesthesiology* 1970; **33**: 619–26
- 12 Bonica JJ, Kennedy WF, Akamatsu TJ, Gerbershagen HU. Circulatory effects of peridural block: III. Effects of acute blood loss. *Anesthesiology* 1972; **36**: 219–27
- 13 Bridgen W, Howarth S, Sharpey-Schafer EP. Postural changes in the peripheral blood-flow of normal subjects with observations on vasovagal fainting reactions as a result of tilting, the lordotic posture, pregnancy and spinal anaesthesia. *Clin Sci* 1950; **9**: 79–91
- 14 Brown DL, Carpenter RL, Moore DC et al. Cardiac arrest during spinal anesthesia. *Anesthesiology* 1988; **68**: 971–2
- 15 Butterworth JF, Piccione W, Berrizbeitia LD, Dance G, Shemin RJ, Cohn LH. Augmentation of venous return by adrenergic agonists during spinal anesthesia. *Anesth Analg* 1986; **65**: 612–6
- 16 Caplan RA, Ward RJ, Posner K, Cheney FW. Unexpected cardiac arrest during spinal anesthesia: a closed claims analysis of predisposing factors. *Anesthesiology* 1988; **68**: 5–11
- 17 Carpenter RL, Caplan RA, Brown DL, Stephenson C, Wu R. Incidence and risk factors for side effects of spinal anesthesia. *Anesthesiology* 1992; **76**: 906–16
- 18 Connolly SJ, Sheldon R, Roberts RS, Gent M. The North American Vasovagal Pacemaker Study (VPS). A randomized trial of permanent cardiac pacing for the prevention of vasovagal syncope. *J Am Coll Cardiol* 1999; **33**: 16–20
- 19 Converse RL, Jacobsen TN, Jost CMT et al. Paradoxical

- withdrawal of reflex vasoconstriction as a cause of hemodialysis-induced hypotension. *J Clin Invest* 1992; **90**: 1657–65
- 20 Courtney L. Supine hypotensive syndrome during Caesarean section. *Br Med J* 1970; **i**: 797–8
 - 21 Critchley LAH, Short TG, Gin T. Hypotension during subarachnoid anaesthesia: haemodynamic analysis of three treatments. *Br J Anaesth* 1994; **72**: 151–5
 - 22 D'Alessio JG, Weller RS, Rosenblum M. Activation of the Bezold-Jarisch reflex in the sitting position for shoulder arthroscopy using interscalene block. *Anesth Analg* 1995; **80**: 1158–62
 - 23 Dorlas JC, Nijboer JA. Photo-electric plethysmography as a monitoring device in anaesthesia. Application and interpretation. *Br J Anaesth* 1985; **57**: 524–30
 - 24 Dorrington KL. Asystole with convulsion following a subanaesthetic dose of propofol plus fentanyl. *Anaesthesia* 1989; **44**: 658–9
 - 25 El-Sayed H, Hainsworth R. Relationship between plasma volume, carotid baroreceptor sensitivity and orthostatic tolerance. *Clin Sci* 1995; **88**: 463–70
 - 26 Evans RG, Ludbrook J, Potocnik SJ. Intracisternal naloxone and cardiac nerve blockade prevent vasodilatation during simulated haemorrhage in awake rabbits. *J Physiol* 1989; **409**: 1–14
 - 27 Fitzpatrick AP, Banner N, Cheng A, Yacoub M, Sutton R. Vasovagal reactions may occur after orthotopic heart transplantation. *J Am Coll Cardiol* 1993; **21**: 1132–7
 - 28 Foldager N, Bonde-Petersen F. Human cardiovascular reactions to simulated hypovolaemia, modified by the opiate antagonist naloxone. *Eur J Appl Physiol* 1988; **57**: 507–13
 - 29 Geffin B, Shapiro L. Sinus bradycardia and asystole during spinal and epidural anesthesia: a report of 13 cases. *J Clin Anesth* 1998; **10**: 278–85
 - 30 Grant RT, Reeve EB. Clinical observations on air-raid casualties. *Br Med J* 1941; **ii**: 293–7
 - 31 Greene NM. Distribution of local anesthetic solutions within the subarachnoid space. *Anesth Analg* 1985; **64**: 715–30
 - 32 Greene NM, Brull SJ. *Physiology of Spinal Anesthesia*, 4th edn. Baltimore, MD: Williams and Wilkins, 1994
 - 33 Grimm DR. Neurally mediated syncope: a review of cardiac and arterial receptors. *J Clin Neurophysiol* 1997; **14**: 170–82
 - 34 Grubb BP, Gerard G, Roush K *et al*. Cerebral vasoconstriction during head-upright tilt-induced vasovagal syncope. A paradoxical and unexpected response. *Circulation* 1991; **84**: 1157–64
 - 35 Guise PA. Asystole following propofol and fentanyl in an anxious patient. *Anaesth Intensive Care* 1991; **19**: 116–18
 - 36 Hampl KF, Schneider MC. Vasovagal asystole before induction of general anaesthesia. *Eur J Anaesth* 1994; **11**: 131–3
 - 37 Hansen R. Ohnmacht und Schwangerschaft. *Klin Wochenschr* 1942; **21**: 241–5
 - 38 Hart PS, Yanny W. Needle phobia and malignant vasovagal syndrome. *Anaesthesia* 1998; **53**: 1002–4.
 - 39 Holmes F. Spinal analgesia and Caesarean section. Maternal mortality. *J Obstet Gynaecol Br Emp* 1957; **64**: 229–32
 - 40 Holmes F. The supine hypotensive syndrome. Its importance to the anaesthetist. *Anaesthesia* 1960; **15**: 298–306
 - 41 Ikeda T, Ohbuchi H, Ikenoue T, Mori N. Maternal cerebral hemodynamics in the supine hypotensive syndrome. *Obstet Gynecol* 1992; **79**: 27–31
 - 42 Jacobsen J, Sofelt S, Brocks V, Fernandes A, Warberg J, Secher NH. Reduced left ventricular diameters at onset of bradycardia during epidural anaesthesia. *Acta Anaesthesiol Scand* 1992; **36**: 831–6
 - 43 Kahn RL, Hargett MJ. β -Adrenergic blockers and vasovagal episodes during shoulder surgery in the sitting position under interscalene block. *Anesth Analg* 1999; **88**: 378–81
 - 44 Keane TK, Hennis PJ, Bink-Boelkens MTE. Non-drug related asystole associated with anaesthetic induction. *Anaesthesia* 1991; **46**: 38–9
 - 45 Kinsella SM, Lohmann G. Supine hypotensive syndrome. *Obstet Gynecol* 1994; **83**: 774–88
 - 46 Lawrence AJ, Jarrott B. Neurochemical modulation of cardiovascular control in the nucleus tractus solitarius. *Prog Neurobiol* 1996; **48**: 21–53
 - 47 Lees MM, Scott DB, Kerr MG, Taylor SH. The circulatory effects of recumbent postural change in late pregnancy. *Clin Sci* 1967; **32**: 453–65
 - 48 Lewis T. Vasovagal syncope and the carotid sinus mechanism with comments on Gowers's and Nothnagel's syndrome. *Br Med J* 1932; **i**: 873–6
 - 49 Lightfoot JT, Rowe SA, Fortney SM. Occurrence of presyncope in subjects without ventricular innervation. *Clin Sci* 1993; **85**: 695–700
 - 50 Liguori GA, Sharrock NE. Asystole and severe bradycardia during epidural anesthesia in orthopedic patients. *Anesthesiology* 1997; **86**: 250–7
 - 51 Liguori GA, Kahn RL, Gordon J, Gordon MA, Urban MK. The use of metoprolol and glycopyrrolate to prevent hypotensive/bradycardic events during shoulder arthroscopy in the sitting position under interscalene block. *Anesth Analg* 1998; **87**: 1320–5
 - 52 Lipsitz LA, Mietus J, Moody GB, Goldberger AL. Spectral characteristics of heart rate variability before and during postural tilt. Relations to aging and risk of syncope. *Circulation* 1990; **81**: 1803–10
 - 53 Lipsitz LA, Hayano J, Sakata S, Okada A, Morin RJ. Complex demodulation of cardiorespiratory dynamics preceding vasovagal syncope. *Circulation* 1998; **98**: 977–83
 - 54 Ludbrook J. Faint heart. *Br Med J* 1989; **298**: 1054–5
 - 55 Ludbrook J, Ventura S. Roles of carotid baroreceptor and cardiac afferents in hemodynamic responses to acute central hypovolaemia. *Am J Physiol* 1996; **270**: H1538–48
 - 56 Mackey DC, Carpenter RL, Thompson GE, Brown DL, Bodily MN. Bradycardia and asystole during spinal anesthesia: a report of three cases without morbidity. *Anesthesiology* 1989; **70**: 866–8
 - 57 Maloney JD, Jaeger FJ, Fouad-Tarazi FM, Morris HH. Malignant vasovagal syncope: prolonged asystole provoked by head-up tilt. *Cleveland Clin J Med* 1988; **55**: 542–8
 - 58 Mark AL. The Bezold Jarisch reflex revisited: clinical implications of inhibitory reflexes originating in the heart. *J Am Coll Cardiol* 1983; **1**: 90–102
 - 59 Mark AL. Cardiopulmonary baroreflexes in humans. In: Shepherd JT, Abboud FM, eds. *Handbook of Physiology*, Section 2: *The Cardiovascular System*, Vol. III. Bethesda, MD: American Physiological Society, 1983: 795–813
 - 60 McBrien ME, Bali IM. Untoward incident reporting in obstetric anaesthesia: a 6-month prospective study in Northern Ireland. *Int J Obstet Anesth* 1996; **5**: 225–8
 - 61 McConachie I. Vasovagal asystole during spinal anaesthesia. *Anaesthesia* 1991; **46**: 281–2
 - 62 McMichael J. Clinical aspects of shock. *J Am Med Assoc* 1944; **124**: 275–81
 - 63 McRoberts WA. Postural shock in pregnancy. *Am J Obstet Gynecol* 1951; **62**: 627–32
 - 64 Morillo CA, Ellenbogen KA, Pava LF. Pathophysiologic basis for vasodepressor syncope. *Syncope* 1997; **15**: 233–49
 - 65 Morita H, Vatner SF. Effects of hemorrhage on renal nerve activity in conscious dogs. *Circ Res* 1985; **57**: 788–93
 - 66 Murray RH, Thompson LJ, Bowers JA, Albright CD.

- Hemodynamic effects of graded hypovolemia and vasodepressor syncope induced by lower body negative pressure. *Am Heart J* 1968; **76**: 799–811
- 67 Nishikawa T, Anzai Y, Namiki A. Asystole during spinal anaesthesia after change from Trendelenburg to horizontal position. *Can J Anaesth* 1988; **35**: 406–8
- 68 Novak V, Honos G, Schondorf R. Is the heart 'empty' at syncope? *J Auton Nerv Syst* 1996; **60**: 83–92
- 69 Oberg B, Thoren P. Increased activity in left ventricular receptors during hemorrhage or occlusion of caval veins in the cat—a possible cause of the vaso-vagal reaction. *Acta Physiol Scand* 1972; **85**: 164–73
- 70 Oberg B, White S. The role of vagal cardiac nerves and arterial baroreceptors in the circulatory adjustments to hemorrhage in the cat. *Acta Physiol Scand* 1970; **80**: 395–403
- 71 Olsson GL, Hallen B. Cardiac arrest during anaesthesia. A computer-aided study in 250,543 anaesthetics. *Acta Anaesthesiol Scand* 1988; **32**: 653–64
- 72 Paton JFR. Convergence properties of solitary tract neurones driven synaptically by cardiac vagal afferents in the mouse. *J Physiol* 1998; **508**: 237–52
- 73 Peters J, Kutkuhn B, Medert HA, Schlaghecke R, Schuttler J, Arndt JO. Sympathetic blockade by epidural anesthesia attenuates the cardiovascular response to severe hypoxemia. *Anesthesiology* 1990; **72**: 134–44
- 74 Quan KJ, Carlson MD, Thames MD. Mechanisms of heart rate and arterial blood pressure control: implications for the pathophysiology of neurocardiogenic syncope. *Pacing Clin Electrophysiol* 1997; **20**: 764–74
- 75 Rorsgaard S, Secher NH. Slowing of the heart during hypotension in major abdominal surgery. *Acta Anaesthesiol Scand* 1986; **30**: 507–10
- 76 Rosenberg JM, Wahr JA, Sung CH, Oh YS, Gilligan LJ. Coronary perfusion pressure during cardiopulmonary resuscitation after spinal anesthesia in dogs. *Anesth Analg* 1996; **82**: 84–7
- 77 Ruiz K. Asystole on induction. *Anaesthesia* 1989; **44**: 698–9
- 78 Sander-Jensen K, Secher NH, Bie P, Warberg J, Schwartz TW. Vagal slowing of the heart during haemorrhage: observations from 20 consecutive hypotensive patients. *Br Med J* 1986; **292**: 364–6
- 79 Sander-Jensen K, Marving J, Secher NH et al. Does the decrease in heart rate prevent a detrimental decrease of the end-systolic volume during central hypovolaemia in man? *Angiology* 1990; **41**: 687–95
- 80 Scherrer U, Vissing S, Morgan BJ, Hanson P, Victor RG. Vasovagal syncope after infusion of a vasodilator in a heart transplant recipient. *New Engl J Med* 1990; **322**: 602–4
- 81 Scull TJ, Carli F. Cardiac arrest after Caesarean section under subarachnoid block. *Br J Anaesth* 1996; **77**: 274–6
- 82 Secher NH, Bie P. Bradycardia during reversible haemorrhagic shock—a forgotten observation? *Clin Physiol* 1985; **5**: 315–23
- 83 Shalev Y, Gal R, Tchou PJ et al. Echocardiographic demonstration of decreased left ventricular dimensions and vigorous myocardial contraction during syncope induced by head-up tilt. *J Am Coll Cardiol* 1991; **18**: 746–51
- 84 Sharpey-Schafer EP. Syncope. *Br Med J* 1956; **iii**: 506–9
- 85 Smith ML, Carlson MD, Thames MD. Nalaxone does not prevent vasovagal syncope during simulated orthostasis in humans. *J Auton Nerv Syst* 1993; **45**: 1–9
- 86 Somers VK, Abboud FM. Neurocardiogenic syncope. *Adv Intern Med* 1996; **41**: 399–435
- 87 Sprung J, Abdelmalak B, Schoenwald PK. Vasovagal cardiac arrest during the insertion of an epidural catheter and before the administration of epidural medication. *Anesth Analg* 1998; **86**: 1263–5
- 88 Stienstra R, Veering BT. Intrathecal drug spread: is it controllable? *Reg Anesth Pain Med* 1998; **23**: 347–51
- 89 Sutton R, Petersen M, Brignole M, Raviele A, Menozzi C, Giani P. Proposed classification for tilt induced vasovagal syncope. *Eur J Card Pacing Electrophysiol* 1992; **3**: 180–3
- 90 Tarkkila P, Isola J. A regression model for identifying patients at high risk of hypotension, bradycardia and nausea during spinal anesthesia. *Acta Anaesthesiol Scand* 1992; **36**: 554–8
- 91 Tverskoy M, Shagal M, Finger J, Kissin I. Subarachnoid bupivacaine blockade decreases midazolam and thiopental hypnotic requirements. *J Clin Anesth* 1994; **6**: 487–90
- 92 Tverskoy M, Fleishman G, Bachrak L, Ben-Shlomo I. Effect of bupivacaine-induced spinal block on the hypnotic requirement of propofol. *Anaesthesia* 1996; **51**: 652–3
- 93 Van Leeuwen AF, Evans RG, Ludbrook J. Haemodynamic responses to acute blood loss: new roles for the heart, brain and endogenous opioids. *Anaesth Intensive Care* 1989; **17**: 312–9
- 94 Van Lieshout JJ, Wieling W, Karemaker JM, Eckberg DL. The vasovagal response. *Clin Sci* 1991; **81**: 575–86
- 95 Van Lieshout JJ, Wieling W, Karemaker JM. Neural circulatory control in vasovagal syncope. *Pacing Clin Electrophysiol* 1997; **20**: 753–63
- 96 Verberne AJM, Guyenet PG. Medullary pathway of the Bezold-Jarisch reflex in the rat. *Am J Physiol* 1992; **263**: R1195–202
- 97 von Bezold A, Hirt L. Über die physiologischen Wirkungen des essigsäuren Veratrin. *Untersuchungen aus dem physiologischen Laboratorium Wurzburg* 1867; **1**: 75–156
- 98 Wallin BG, Sundlof G. Sympathetic outflow to muscles during vasovagal syncope. *J Auton Nerv Syst* 1982; **6**: 287–91
- 99 Wasserstrum N. Nitroprusside in preeclampsia. Circulatory distress and paradoxical bradycardia. *Hypertension* 1991; **18**: 79–84.
- 100 Watkins EJ, Dresner M, Calow CE. Severe vasovagal attack during regional anaesthesia for Caesarean section. *Br J Anaesth* 2000; **84**: 118–20.
- 101 Ziegler MG, Echon C, Wilner KD, Specho P, Lake CR, McCutchen JA. Sympathetic nervous withdrawal in the vasodepressor (vasovagal) reaction. *J Auton Nerv Syst* 1986; **17**: 273–8.