The endothelial glycocalyx: the great luminal barrier

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In this issue of *Acta Anaesthesiologica Scandinavica*, Sun et al. present a study on the endothelial glycocalyx in dogs.[1] They conclude that administration of unfractionated heparin may protect the endothelial glycocalyx from shedding induced by Gram-negative sepsis. Is this an important finding? To answer this question, let us first take a closer look on the capillary wall. Traditionally, the endothelial cells of microvessels were regarded as the only barrier between the vascular lumen and the interstitial space. The net movement of fluid across the vessel wall was believed to be a result of an outward pressure in the vessel opposed by an inward-directed oncotic gradient generated by the circulating plasma proteins, mainly albumin.[2] As early as 1940, J. F. Danielli suggested that the polysaccharide layer covering the vascular lumen of healthy blood vessels served as an additional permeability barrier.[3] With improvements in histochemical analysis came a description of the constituents, and with better fixation and electron microscopic visualisation techniques came better pictures of this fragile luminal layer.[4–6] We now know that the entire vascular lumen of healthy blood vessels is covered with an up to 2-μm thick membrane-bound sponge-like mesh composed of proteins and sugars.[6] The basal skeleton of the layer is made of syndecans and glypicans with negatively charged side chains of mainly heparan sulphate.[7] In vivo, soluble components of the plasma, mainly albumin, are embedded within the pores of the meshwork.[8] It has been estimated that as much as 25% of the plasma volume is trapped in this way in a non-circulating part of the total intravascular space.[9] The combination of the meshwork and the trapped plasma proteins forms the biologically active barrier termed the endothelial glycocalyx. The constituents of the layer, e.g. syndecan-1 and heparan sulphate, can be found in the circulation in proportion to the degree of its degradation, and it appears that disease severity and even mortality correlate to the integrity of glycocalyx.[10,11]

What, then, are the physiologic functions of the endothelial glycocalyx?

Because plasma proteins are trapped within the endothelial glycocalyx, the inward-directed oncotic pressure gradient described by Starling[2] is dependent on an intact glycocalyx. In fact, there is a nanometer-thin zone with very low protein content below the glycocalyx next to the endothelial cells,[12] and degradation of the glycocalyx leads to the extravasation of protein rich exudate, which is seen during inflammatory states.[8] An intact endothelial glycocalyx with bound plasma proteins together with the endothelial cells is thus necessary for the integrity of peripheral vessels, a notion called the double layer concept.[13] Endothelial adhesion molecules for platelets and leucocytes, including selectins and integrins, do not extend beyond the normal glycocalyx and negative charges on the core proteins of the glycocalyx layer repel blood-borne cells. Shedding of the glycocalyx appears to be necessary for firm adhesion of blood leucocytes, platelets[8] and maybe even circulating tumour cells.[14] Furthermore, cytokines, chemokines and coagulations factors are found in the glycocalyx.[15]

Degradation or even destruction of the endothelial glycocalyx, called shedding, is seen in well-known causes of capillary leak, such as systemic inflammation, sepsis, ischaemia-reperfusion injury, haemorrhagic shock, trauma, and major abdominal surgery.[6,8] These are clinical scenarios where we, as anaesthesiologists will be inclined to load the patient with fluids in order to maintain the circulatory volume. Doing so, however, we risk stretching the atrial wall of the heart and cause the release of atrial natriuretic peptide, which by itself will cause shedding of the glycocalyx through a cyclic guanosine monophosphate-linked cascade. Thus, hypervolemia will lead to the degradation of the glycocalyx which in turn necessitates further volume substitution eventually causing oedema formation, accelerated inflammation, platelet hyperaggregation, and hypercoagulation. Inappropriate volume therapy may thus, especially during major surgery, increase the shedding of the endo-

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thelial glycocalyx and pave the road for postoperative complications. Unfortunately, the glycocalyx is destroyed within hours, whereas it takes days, 5 to 7 days in one study,[16] to restore the layer in vivo. To date, there are no known therapies that help rebuild the glycocalyx. It appears that the best strategy is to protect the glycocalyx from shedding in the first place.

So how can we protect this fragile structure in the daily anaesthesia clinic?

With the current knowledge, the best way to protect the glycocalyx is by avoiding hypervolemia, especially during major surgical procedures where degradation of the glycocalyx is anticipated, e.g. abdominal surgery. Interestingly, restrictive fluid regimens and individual goal-directed fluid strategies have benefitted patients in precisely these situations.[17,18] Animal experiments suggest that the choice of anaesthetics may also matter. Sevoflurane at 1 minimal alveolar concentration protected the glycocalyx from shedding in post-ischaemic guinea pig coronary vessels evidenced by syndecan-1, heparan sulphate, and electron microscopy. At the same time, endothelial adhesion of leucocytes and platelets was reduced to basal levels.[19] Propofol does not appear to provide the same protection.[20] Unfortunately, there are no clinical data, yet, to support these findings and the clinical consequence, if any, is unknown. Other potential strategies include maintaining a sufficiently high concentration of plasma albumin in order to fill out the pores, mechanically stabilise and complete the glycocalyx, but the minimal concentration of plasma albumin is unknown. Finally, hydrocortisone, antithrombin III, and nitric oxide have been shown to reduce shedding of the glycocalyx after ischaemia/reperfusion and tumour necrosis factor (TNF)-alpha-induced inflammation, but the clinical significance of this is also not known.[8]

In this issue of the journal, Sun et al. contributes to the rapidly expanding knowledge on the endothelial glycocalyx. The authors compare four groups of five beagle dogs: a sham group, a group with *Escherichia coli*-induced sepsis, a group with sepsis plus basic treatment consisting of crystalloid and antibiotics, and finally a group with sepsis plus basic treatment plus unfractionated heparin. They measured circulating markers of inflammation, i.e. interleukin-6 and TNF-alpha and markers of the glycocalyx degradation, i.e. syndecan-1 and heparan sulphate together with haemodynamic indices, lung function (oxygenation-index), and platelets. Infusion of *E. coli* induced a typical septic response in the animals including an increased TNF-alpha and IL-6, which correlated to an increase in syndecan-1 and heparan sulphate indicating degradation of the glycocalyx. Treatment with crystalloid and antibiotics partially reversed the changes, whereas treatment with crystalloids, antibiotics, and unfractionated heparin normalised the measurements to levels seen in sham group. This effect was mirrored in the survival of the animals. The study, however, was not powered to show a significant difference in mortality.

This is an animal experiment with a limited number of dogs far from the clinical practice. The study does not tell us whether the observed beneficial effects of heparin are due to a direct protective effect by heparin on the glycocalyx or due to an anti-inflammatory effect of heparin[21] that results in less organ dysfunction and hence decreased shedding. Nevertheless, the study shows that the endothelial glycocalyx is a highly dynamic structure that is amenable to therapeutic strategies well within the reach of the clinician. The importance of the study by Sun et al. lies not only in the acquired data, but as much in the inspiration that the study provides to the clinician and researcher that is looking for new ways to protect the glycocalyx.

It seems that the endothelial glycocalyx plays a fundamental role in the regulation of the microcirculation and in the initiation and control of inflammation and coagulation in ways that we have only recently begun to understand. New therapeutic strategies may protect the glycocalyx, and drugs may prevent shedding. Much more research is needed before we can safely apply such therapeutic strategies to the benefit of our patients. The study by Sun et al. is one small step in the right direction.

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REVIEW ARTICLE

Endothelial dysfunction after non-cardiac surgery: a systematic review

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Background: More than 50% of patients with increased troponin levels after non-cardiac surgery have an impaired endothelial function pre-operatively. Non-invasive markers of endothelial function have been developed for the assessment of endothelial dysfunction. The aim of this paper was to systematically review the literature to evaluate the association between non-cardiac surgery and non-invasive markers of endothelial function.
Methods: A systematic search was conducted in MEDLINE, EMBASE and Cochrane Library Database according to the PRISMA guidelines. Endothelial dysfunction was described only with non-invasive measurements done both pre- and post-operatively and published in English. All types of non-cardiac surgery and both men and women of all ages were included.
Results: We found 1722 eligible studies in our search, and of these, five studies fulfilled our inclusion and exclusion criteria. Endothelial function was disturbed in patients after non-cardiac surgery. Three studies found a significant decrease in the endothelial function immediately after surgery (2 and 24 h post-operatively). Two studies found that patients with previous endothelial dysfunction and scheduled for surgery (renal transplantation and vascular surgery respectively) had an improvement in endothelial dysfunction 1 month after surgery.
Conclusion: Endothelial function changes in relation to surgery. Assessment of endothelial function by non-invasive measures has the potential to guide clinicians in the prevention or treatment of post-operative myocardial damage.

More than one in 100 otherwise healthy patients undergoing non-cardiac surgery will die within 30 days post-operatively,[1] and of these patients, 45% will die from vascular causes such as myocardial infarction. If a patient has increased troponin levels within 3 days after non-cardiac surgery, the risk of 30-days post-operative mortality is more than 10%.[1] Endothelial dysfunction predisposes to atherosclerosis[2] and increases the risk of thromboembolic events. Almost 58% of patients with a pre-operatively impaired endothelial function will develop post-operative myocardial injury.[3] Understanding the pathogenesis of post-operative myocardial injury is crucial for optimized treatment of patients at risk.

The endothelial function is important in the regulation of the blood supply to every organ in the body, including the heart.[2,4–6] The endothelial cells are affected by changes in the cellular environment such as inflammation[4,7] and oxida-

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tive stress[8] which occurs in the perioperative period.[9–11] The endothelial cells produce nitric oxide (NO) from the amino acid L-arginine by the endothelial NO synthases (eNOS).[7,8,12] NO diffuses to the vascular smooth muscle cells and causes smooth muscle cell relaxation and an increased vessel diameter.[8,13] Shear stress of the vessel wall increases the expression of eNOS in the cell membrane and, thus, the NO production.[7] When the production of NO is compromised for a longer period, a cascade of events involved in the development of atherosclerosis occur, such as vasoconstriction, platelet aggregation, smooth muscle cell proliferation and migration, leukocyte adhesion and oxidative stress, and thereby increased risk of plaque formation.[7]

One way of testing NO's ability to cause vasodilation is after shorter periods of induced ischemia, where increased shear stress on the vessel wall during reperfusion causes hyperemia (reactive hyperemia).[5,8] Peripheral reactive hyperemia can be used as a non-invasive marker of endothelial function mediated by NO[14] and correlates to the endothelial function of the heart.[5,8,13]

Surgery induces a stress response[11,15,16] with increased catecholamine and glucocorticoid production, decreased insulin levels and a general inflammatory response.[15,17] In addition, there will also be sympathetic activation resulting in increased shear stress on the vessel wall.[9,15] There is a dose relationship with minimally invasive surgery resulting in reduced stress response compared with open surgery.[18] Endothelial dysfunction in the perioperative period can represent both a risk factor for post-operative cardiovascular outcome, but can also be viewed as an outcome parameter of the surgery itself resulting in improved systemic endothelial function. We aimed to systematically review studies that investigate endothelial dysfunction in the perioperative period using non-invasive methods to describe changes in the hyperemic response. Secondarily, we wanted to examine if endothelial dysfunction was associated with increased post-operative myocardial damage.

Methods

This systematic review was planned, conducted and reported according to PRISMA guidelines[19] whenever applicable. We included studies with patients (male/female) of all ages (P) who had non-cardiac surgery (I), and non-invasive endothelial function (excluding studies that only measured biomarkers in blood) measures done pre-operatively and within 30 days post-operatively (C). The primary outcome (O) was changes in endothelial function. We did not exclude patients with pre-operative comorbidities. Only English language observational studies were included.

A systematic literature search was done in March 2014 in MEDLINE, EMBASE and The Cochrane Library Database. We used the following search strategy: *(((((Perioperative Period[MESH]) OR (((perioperative) OR preoperative) OR postoperative))) AND ((((((Endothelial) OR Endothelium) OR Endothelium, Vascular[MESH]) OR Endothelial Cells[MESH])) AND dysfunction))) AND human*. We restricted the search to 'journal articles' in EMBASE. When all studies were identified, two researchers independently screened titles and abstracts. Duplicates and non-English language papers were excluded and only original papers were included. The same two researchers reviewed all relevant articles in a full-text screening independently. Articles were considered eligible when non-invasive measurements of endothelial function were used and pre-and post-operative values were stated. When the two researchers failed to reach an agreement, the authors reached an agreement after discussion by all authors. Measures registered were type of surgery, number of subjects, demographical values and measures of change between post-operative and baseline measurements. All data were handled and combined using the Microsoft Office Excel 2007 (Microsoft, Seattle, WA, USA). All included articles were evaluated by both reviewers for bias assessment using the Newcastle–Ottawa Scale (NOS).[20] NOS are used for assessing the quality of non-randomized trials evaluating the level of selection bias, comparability and ascertainment of the outcome in each trial.

Results

We found 1722 (Fig. 1) possibly relevant articles in MEDLINE, EMBASE and The Cochrane Library Database. No additional records were identified through other sources. We removed 203 duplicates and 150 non-English language papers. After the title and abstract screening, 47 articles were full text assessed for eligibility. A total of

five manuscripts[21–25] (Table 1) were found eligible. The mean NOS value was 5, range 4–6.

Characteristics of patients in the included studies are seen in Table 1. A total of 49% of the patients were women, and the mean age ranged from 38 to 71 years. Only one article[24] included patients without any comorbidities, the remaining four studies[21–23,25] described at least one severe coexisting disease. Four studies[22–25] described changes in endothelial function in the perioperative period using flow-mediated dilation (FMD) measurements (Table 2), one paper[21] used forearm plethysmography.

Four studies[21–23,25] found significant changes in the endothelial function post-operatively when compared with baseline measures. Because of

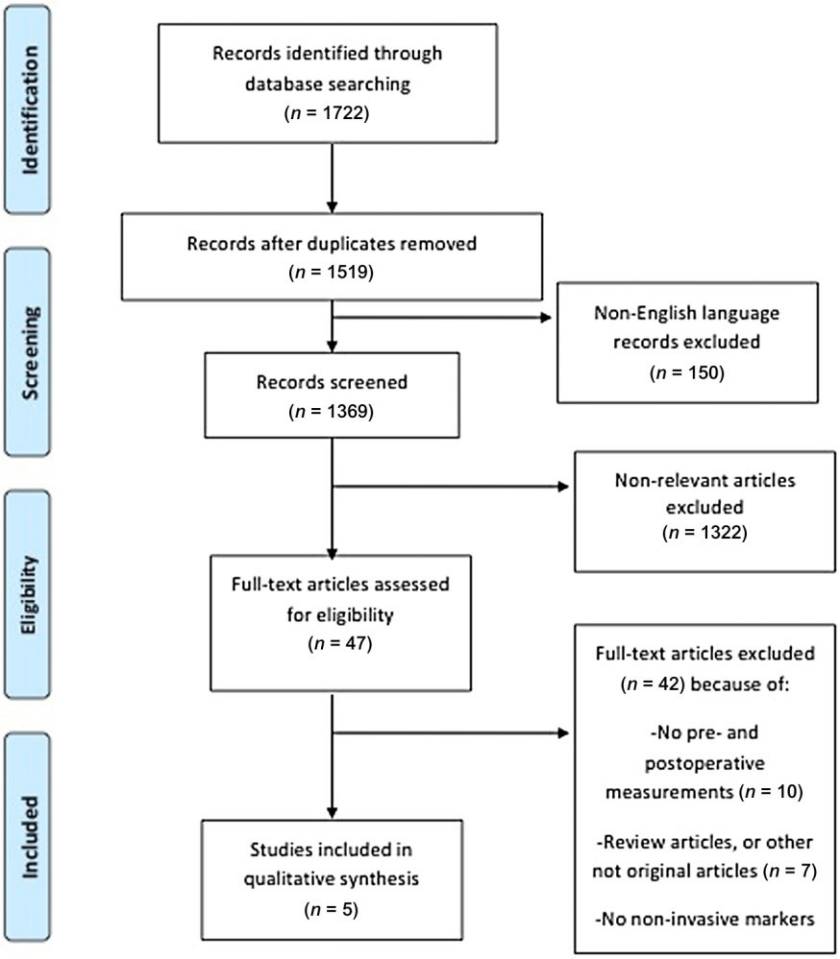

Fig. 1. Flow chart according to PRISMA guidelines.

Table 1 Baseline characteristics of studies included in the systematic review.

Study	Year	Type of surgery	Subjects (n)	Male/female	Age (mean)	Comorbidity
Onizuka et al.[21]	1992	Pulmonary operation (lobectomy/pneumonectomy)	12	8/4	68 years	Lung cancer
Kocak et al.[22]	2005	Renal transplantation	50	27/23	38 years	Chronic kidney disease
Unal et al.[23]	2011	Femoropopliteal bypass surgery	54	32/22	47 years	Multiple*
Bukal et al.[24]	2012	Total knee replacement surgery	39	13/26	71 years	No
Hu et al.[25]	2013	Non-cardiac surgery (laparotomy/laparoscopy)	106	53/53	60 years	Multiple†

*Diabetes (33%), ischemic cardiac pathology (65%), chronic renal failure (20%), Behcet's disease (4%). †Hypertension (10.4%), diabetes (6.6%), coronary artery disease (1.9%), stroke (0.9%).

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Table 2 Changes in flow-mediated dilation after non-cardiac surgery.

		FMD						
	Type of surgery	l/2 h	1 d	2 d	3 d	7 d	14 d	28 d
Hu et al.[25]	Non-cardiac surgery (Laparotomy/Laparoscopy)	↓	↓	–				
Unal et al.[23]	Femoropopliteal bypass surgery		–					↑
Kocak et al.[22]	Renal transplantation						↑*	
Bukal et al.[24]	Total knee replacement surgery	–		–	–	–		

*FMD was significantly increased in hemodialysis patients after transplantation, but was significantly decreased when compared with healthy controls. ↑/↓/–, Significant increase/decrease/no changes in endothelial function after surgery compared with baseline measures. h, hours; d, day/days; FMD, flow-mediated dilatation of the brachial artery.

considerable heterogeneity between each trial, it was not possible to perform meta-analysis.[8] Primary causes of heterogeneity were clinical diversity with different types of surgery and subjects with considerable comorbidities, and methodological diversity due to low NOS scores.

Immediate post-operative changes in endothelial function

Low FMD measures indicate a reduced reactive hyperemia and generalized endothelial dysfunction, which is either transient or permanent. Two studies (Table 2) reported FMD measurements within the first seven post-operative days and they found a decreased FMD level in the first 24 h post-operatively.[24,25] A significant decrease was found in FMD after laparotomy or laparoscopy in 106 patients undergoing non-cardiac surgery.[25] FMD measures were significantly lower in the laparotomy group 2 h, 1 day and 7 days after the operation compared with patients who underwent laparoscopic procedures, indicating a dose–response correlation. Bukal et al.[24] also found a decreased FMD level within the first 24 h post-operatively in patients with no comorbidities, who underwent knee replacement surgery. However, both studies[24,25] found that FMD had normalized again 7 days after the operation, when compared with baseline measurements. Onizuka et al.[21] found a significant increased forearm vascular resistance in 12 patients immediately after pulmonary surgery and until 24 h post-operatively when compared with baseline measures. After 24 h, vascular resistance measurements were nearly normalized.

Late post-operative changes in endothelial function

A study of 30 patients in need of chronic hemodialysis[22] reported changes in endothelial function 14 days after renal transplant surgery. All patients significantly improved their endothelial function 2 weeks post-operatively; however, none of them gained the same function as the healthy controls in the study. No measurements were done between the surgical intervention and 14 days post-operatively. Unal et al.[23] also measured changes in endothelial function 28 days after femoro-popliteal bypass surgery in 54 patients with several comorbidities. Post-operative FMD measurements improved significantly, but no comparison was made with healthy controls.

Other post-operative cardiovascular changes

None of the included studies investigated post-operative myocardial damage in the patients. Therefore, the relation between post-operative changed endothelial function and myocardial damage could not be assessed in this systematic review.

Discussion

In this systematic review, we found five studies which fulfilled all our inclusion and exclusion criteria regarding the effect of surgery on the endothelial function. The endothelial function was significantly decreased in two studies[21,25] while two other studies[23,24] did not find any immediate changes in the endothelial function within the first 24 h after surgery. In two studies

including patients in need of chronic hemodialysis and patients with peripheral arterial disease improved their endothelial function 14 and 28 days post-operatively; however, no measurements of the immediate post-operative changes in these patients were done, and when compared with healthy controls, the endothelial function was still reduced.

Pre-operatively endothelial dysfunction has previously been shown to be a predictor of post-operative myocardial damage. A multicenter trial including 238 patients undergoing intermediate or high-risk non-cardiac surgery had their endothelial function assessed by the non-invasive EndoPat device (Itamar Medical Ltd, Caesarea, Israel).[14] EndoPat measures changes in reactive hyperemia in the finger tip, as a measure of endothelial function, which is similar, but not interchangeable,[26] to the FMD method. In the following 3 days post-operatively, all patients had daily troponin levels measured, no EndoPat measurements were done post-operatively. The authors found that 57.9% of patients with pre-operative endothelial dysfunction had post-operative myocardial damage compared with 11.0% of the subjects without pre-operative endothelial dysfunction. Furthermore, the pre-operative assessment of endothelial dysfunction identified post-operative myocardial damage with a sensitivity of 31% and a specificity of 96%.

The long-term effect of surgery on the endothelial function was found to be two sided. If subjects had a known impaired endothelial function and were having an operation in order to better the condition, i.e. revascularization[23] or renal transplant,[22] an improved endothelial function was found 28 days after the operation. However, no FMD measurements were done in the first 24 h post-operatively, even though patients, who suffer myocardial injury after non-cardiac surgery, will have increased troponin levels within the first 3 days post-operatively.[1] An impaired endothelial function before surgery might predict the risk of myocardial injury after surgery and therefore measurements of the endothelial function in the first 24 h post-operatively would have been highly relevant. However, if the patients with increased risk of perioperative myocardial injury avoid myocardial injury, they will improve their baseline endothelial function due to the improved vascular flow or renal function provided by the operation. Thus, endothelial dysfunction may be a way to describe the systemic effects of surgical stress on the body. This should be investigated further in the future.

The primary non-invasive methods used for assessing the endothelial function in this systematic review were FMD. The endothelial function is reflected by measurements of the dilation of the brachial artery diameter after induced ischemia using a high-resolution ultrasound device.[8] If post-ischemic dilation is below 8%, the endothelium is considered dysfunctional.[27] However, it has been suggested that this method is associated with considerable interobserver variability.[8] Some authors recommend 6–9 months of training, before an observer would be able to do valid measurements.[8] Forearm strain gauge plethysmography was used by Onizuka et al.[21] This method describes the volume changes in the forearm after induced ischemia.[28] The method is also non-invasive, and does not require the same amount of observer training. However, the equipment is less portable and therefore not ideal for the clinical setting. In the resent years, a new method for the diagnosis of endothelial dysfunction called EndotPat has been introduced.[8,14] The EndoPat is easy to use, free of inter-observer variability[8] and suitable for the clinical setting as it is portable.[8]

This study has several limitations. Only five articles were included despite a thorough search. Furthermore, the articles differed in design, population, size and outcomes making our findings heterogenic. Therefore, it is not possible to make general conclusions for patients undergoing other procedures, than the ones described in this review. None of the included articles scored maximum rating in the NOS, which again reduce the validity of our study. Four[21–25] of five articles described the changes in the endothelial function in patients with at least one comorbidity. It was unclear if the changes in endothelial function was caused by the comorbidities or due to the surgery in the four studies,[21–25] and this might confound the results.

With this systematic review, we have found that non-cardiac surgery both improves and decreases endothelial function depending on the purpose of the operation and the primary disease. Further studies are needed in order to examine, if assessment of endothelial function can help predict post-

operative cardiovascular complications, and ultimately, can be used for optimization of perioperative medical care. It should also be examined if assessment of endothelial dysfunction can be used as a surrogate marker of surgical stress response.

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