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Clinical Practice

Endothelial dysfunction in the early postoperative period after major colon cancer surgery

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Abstract

Background. Evidence suggests that endothelial dysfunction in the early postoperative period promotes myocardial injury after non-cardiac surgery. The aim of this study was to investigate the impact of colon cancer surgery on endothelial function and the association with the l-arginine-nitric oxide pathway postoperatively.

Methods. Patients undergoing elective colon cancer surgery (n = 31) were included in this prospective observational cohort study. Endothelial function, as measured using the reactive hyperaemia index (RHI), was assessed non-invasively using digital pulse tonometry. RHI and plasma concentrations of L-arginine, asymmetric dimethylarginine (ADMA), dihydrobiopterin and biopterin metabolites, tetrahydrobiopterin (BH4) and total biopterin were measured before surgery, at four h after surgery and at postoperative day one and two. Cardiac troponin I was measured before surgery and once daily on postoperative days one to four.

Results. Preoperative RHI was 1.86 (1.64 – 2.11) and decreased significantly during the observation period (linear mixed effects model of serial measurements, $P = 0.015$). Both L-arginine ($P < 0.001$) and ADMA ($P = 0.024$) decreased during the postoperative period. All biopterin metabolites were significantly decreased after surgery. A significant positive correlation was found between logAUC(l-arginine/ADMA) and logAUC(RHI) ($P = 0.015$) and between logAUC(L-arginine/ADMA) and logAUC(BH4) ($P = 0.015$). None of the patients had cardiac troponin I elevations.

Conclusions. RHI was attenuated in the first days after colon cancer surgery indicating acute endothelial dysfunction. Endothelial dysfunction correlated with disturbances in the L-arginine – nitric oxide pathway. Our findings provide a rationale for investigating the hypothesized association between acute endothelial dysfunction and cardiovascular complications after non-cardiac surgery.

Clinical trial registration. NCT02344771.

Key words: cardiovascular optimisation; myocardial injury; non-cardiac surgery; perioperative complications

Myocardial infarction is the most frequent perioperative cardiovascular complication after non-cardiac surgery.[1] Myocardial injury that does not fulfil the universal definition of myocardial infarction is present in 8% of patients in the perioperative period and is associated with 30-days mortality.[2] Myocardial oxygen supply-demand mismatch is believed to be central in the

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Editor's Key Points

- The endothelium regulates vascular tone, modulates inflammation and has anti-thrombotic and anti-atherosclerotic properties.
- Endothelial dysfunction is commonly associated with cardiovascular disease.
- This study found that endothelial dysfunction was associated with disturbances in the L-arginine nitric oxide pathway.
- Interventions that could protect endothelial function may result in reductions in perioperative cardiovascular risk.

development of myocardial injury.[1] In the perioperative period, the cardiovascular system is challenged as a result of surgical stress and trauma, anaesthesia, pain, hypoxemia and hypovolaemia. These factors are likely to contribute to the development of oxygen supply-demand mismatch.[1] Moreover, the vascular integrity and homeostasis may be compromised postoperatively because of endothelial dysfunction.[3–5]

The endothelium regulates vascular tone, modulates inflammation and has anti-thrombotic and anti-atherosclerotic properties.[6] Endothelial dysfunction is largely characterized by decreased vascular bioavailability of nitric oxide (NO).[6] Vascular NO is produced by the endothelial NO synthase (eNOS), which generates NO from L-arginine and O_2 in response to receptor dependent agonists (bradykinin, acetylcholine, adenosine triphosphate) and shear stress of the vessel wall.[6] Studies have shown that NO bioavailability is highly sensitive to increased oxidative stress,[6] as both direct reaction between NO and reactive oxygen species and indirect redox-induced uncoupling of eNOS function may contribute to a rapidly declining NO concentration.[7]

Endothelial function can be estimated by measuring the peripheral vasodilation in response to a stimulus that increases the vascular NO production.[8] Digital pulse amplitude tonometry is a non-invasive and operator-independent method, that measures the peripheral vasodilation in response to reactive hyperaemia.[8] The endothelial function is expressed as a reactive hyperaemia index (RHI), where a low RHI indicates worse endothelial function.[8] For patients undergoing non-cardiac surgery, preoperative endothelial dysfunction predicted myocardial injury within the first three postoperative days, with an odds ratio of 10.1 (95% confidence interval 3.3-30.9),[9] and an impaired preoperative endothelial function predicted major adverse cardiac events within 30 days of vascular surgery.[10] Moreover, sudden changes of the endothelial function have been observed in patients suffering from acute brain dysfunction,[11] aneurysmal subarachnoid haemorrhage[12] and acute myocardial infarction.[13] Thus, sudden postoperative endothelial dysfunction may influence the risk of postoperative myocardial injury. The effect of surgery on postoperative endothelial function measured by digital pulse amplitude tonometry has not been investigated before.

We conducted a prospective cohort study on patients undergoing major colon cancer surgery in order to investigate the impact of surgery on the RHI response and its relation to the NO pathway in the early postoperative period.

Methods

The study was approved by the Regional Ethic Committee of Region Zealand (SJ-429) and the Danish Data Protection Agency (REG-116-2014). The study was reported on clinicaltrials.gov (NCT-02344771). All included patients signed a written informed consent before participation. The study was a prospective cohort study and was performed between March and June 2015 at Zealand University Hospital. Patients referred to elective colon cancer surgery at the Department of Surgery were consecutively screened and included in the study. Exclusion criteria: not capable of giving informed consent after oral and written information, previously included in the study, surgery within seven days of the study. Patients were consecutively screened for inclusion. After withdrawal and exclusion, 31 patients completed the study. The attending surgeon and anaesthetist did a routine preoperative evaluation of the patient. In addition, data were collected on cardiovascular risk factors and the revised cardiac risk (Lee) index was calculated.[14] Colon cancer was staged according to the Union Internationale Contre le Cancer staging system. We classified postoperative surgical complications according to the Clavien-Dindo Classification.[15]

Endothelial function

The primary outcome was endothelial function assessed by non-invasive digital pulse amplitude tonometry by the use of an EndoPat2000 (Itamar Medical Ltd., Caesarea, Israel). We measured the endothelial function preoperatively, four h postoperatively and on days one and two postoperatively. All measurements were performed at the same h (plus or minus two h). An EndoPat endothelial function measurement consists of three phases: baseline, occlusion, and hyperaemia.[6] An EndoPat probe is placed on the index finger of each hand. Recordings are done simultaneously from both fingers throughout the study to adjust for any systemic effects.[6] After baseline data acquisition, a bp cuff is inflated on one arm to 200 mm Hg (suprasystolic pressure) for five min. During the occlusion period, signals are absent from the hyperaemic finger but continue from the control finger. After cuff release, pulse amplitude increases in the hyperaemic finger. The EndoPat system collects data digitally and performs automatic calculations of the post-occlusion (hyperaemia)/pre-occlusion (baseline) ratio, the reactive hyperaemia index (RHI).

Laboratory assays

NO bioavailability was indirectly measured by plasma L-arginine, plasma asymmetric dimethylarginine (ADMA), plasma tetrahydrobiopterin (BH4), plasma dihydrobiopterin (BH2) including biopterin metabolites and total plasma biopterin concentration preoperatively, four h postoperatively and on days one and two postoperatively. Blood samples were drawn into EDTA tubes just before the endothelial function measurement. For analysis of biopterins, 1ml blood was drawn into a vacutainer containing 1 mg of dithioerythritol dissolved in 25μL H_2O. The sample was gently mixed to avoid haemolysis and centrifuged at 2000g for five min. Plasma was immediately snap-frozen and stored at -80°C until analysis. Biopterins were analysed using HPLC with fluorescence detection as described previously.[16] For arginine and ADMA, blood samples were centrifuged at 3000g for 10 min and the plasma snap-frozen and stored at -80°C until analysis. Quantification of L-arginine and ADMA was achieved by HPLC with fluorescence detection using