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A RANDOMIZED TRIAL OF REMOTE ISCHEMIC PRECONDITIONING AND CONTROL TREATMENT FOR CARDIOPROTECTION IN SEVOFLURANE-ANESTHETIZED CABG PATIENTS

Anaesthesiology

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ABSTRACT

Background: Remote ischemic preconditioning (RIPC) efficacy is debated. Possibly, because propofol, which has a RIPC-inhibiting action, is used in most RIPC trials. It has been suggested that clinical efficacy is, however, present with volatile anesthesia in the absence of propofol, although this is based on one phase 1 trial only. Therefore, in the present study we further explore the relation between RIPC and cardioprotection with perioperative anesthesia restricted to sevoflurane and fentanyl, in CABG patients without concomitant procedures.

Methods: In a single-center study, we aimed to randomize 46 patients to either RIPC (3x5 min inflation of a blood pressure cuff around the arm) or control treatment (deflated cuff around the arm). Blood samples were obtained before and after RIPC to evaluate potential RIPC-induced mediators (Interleukin (IL)-6, IL-10, Tumor Necrosis Factor-á, Macrophage Inhibitory Factor). An atrial tissue sample was obtained at cannulation of the appendix of the right atrium for determination of mitochondrial bound hexokinase II (mtHKII) and other survival proteins (Akt and AMP-activated protein kinase á). In blood samples taken before and 6, 12 and 24 h after surgery cardiac troponin T (cTnT) and C-reactive protein (CRP) were determined. Surgery was strictly performed under sevoflurane anesthesia (no propofol).

Results: We actually randomized 16 patients to control treatment and 13 patients to RIPC. The mean 24 h area under the curve (AUC) cTnT was 11.44 (standard deviation 4.66) in the control group and 10.90 (standard deviation 4.73) in the RIPC group (mean difference 0.54, 95% CI −3.06 to 4.13; p=0.76). The mean 24 h AUC CRP was 1319 (standard deviation 92) in the control group and 1273 (standard deviation 141) in the RIPC group (mean difference 46.2, 95% CI −288 to 380; p=0.78). RIPC was without effect on survival proteins in atrial tissue samples obtained before surgery (mitochondrial hexokinase, Akt and AMPK) and inflammatory mediators obtained before and immediately after RIPC (IL-6, IL-10, TNF-á, macrophage migration inhibitory factor).

Conclusion: Many factors can interfere with the outcome of RIPC. Trying to correct for this led to strict inclusion criteria, which, in combination with a decreased institutional frequency of CABG without concomitant procedures and a change in institutional anesthetic regimen away from volatile anesthetics towards total intravenous anesthesia, caused slow inclusion and halting of this trial after 3 years, before target inclusion could be reached. Therefore this study is underpowered to prove its primary goal that RIPC reduced AUC cTnT by <25%. Nevertheless, we have shown that the effect of RIPC on 24 h AUC cTnT, in cardiac surgery with anesthesia during surgery restricted to sevoflurane/fentanyl (no propofol), was between a decrease of 27% and an increase of 36%. These findings are not in line with previous studies in this field.

KEYWORDS

INTRODUCTION

Remote ischemic preconditioning (RIPC), the protection of an organ or tissue against infarction, induced by previous, repetitive short episodes of ischemia of a remote organ or tissue, was first discovered by Przyklenk et al. Short periods of ischemia and reperfusion in the circumflex coronary artery preconditioned myocardium outside of the occluded vasculature. Subsequently, short periods of ischemia/reperfusion (I/R) in other organs than the heart immediately prior to the sustained coronary artery occlusion could also induce preconditioning.

Type of anesthesia employed, comorbidities and co-medication are factors that have been found to influence the effect of RIPC. Propofol might counteract the protective effect of RIPC. In two recent large clinical trials, no protective effect of RIPC was found. Both these studies were mainly performed under propofol anesthesia. Although these studies have been criticized for their use of propofol in several commentaries and editorials, the establishment of RIPC efficacy with volatile anesthesia in the absence is not firmly based. For example, only one phase 1 trial demonstrated RIPC efficacy with the volatile anesthetic isoflurane as primary anesthetic agent (group size varied from 14 to 20 patients). However, it is well accepted that positive studies are prioritized for publication, thus it cannot be excluded that also for volatile anesthesia RIPC can be ineffective. Therefore, in the current study we aimed to randomize 46 patients to either RIPC (3×5 min inflation of a blood pressure cuff around the arm) or control treatment (deflated cuff around the arm) in coronary artery bypass graft (CABG) procedures with anesthesia restricted to the use of the volatile anesthetic sevoflurane as primary anesthetic agent in the absence of propofol. To this end, we evaluated the release of cardiac troponin T (cTnT) as primary outcome parameter of RIPC efficacy. As secondary read-out of cardiac damage and RIPC, we examined the development of systemic inflammation (C-reactive protein (CRP)). Additionally, it is established that when the heart is put into a cardioprotective state, this is often reflected by alteration of specific cardiac, so-called, survival proteins. Increases in mitochondrial hexokinase (mtHK) and in the phosphorylation status of Akt (p-Akt) or AMPK (p-AMPK) often associate with effective cardioprotective interventions. Therefore, as an additional secondary read-out of possible RIPC cardioprotective interference, we also examined whether RIPC affected mitochondrial HKII protein content (mtHKII) or HK activity, p-Akt or p-AMPK within the heart. Finally, it has been hypothesized that RIPC can be mediated through the immediate release of blood-borne factors mediating the cardioprotective signaling. To examine whether our RIPC maneuver was associated with increasing blood-borne factors, several inflammatory mediators (interleukin (IL)-6, IL-10, TNF-á, macrophage migration inhibitory factor (MIF)) were measured in blood obtained before and immediately after RIPC.

MATERIAL AND METHODS

This study was a single-center, randomized controlled clinical trial in male patients (>18 years) undergoing elective first time on-pump isolated CABG surgery. Exclusion criteria were diabetes mellitus, instable angina pectoris, increased baseline troponin levels, concomitant procedures, severe COPD, ejection fraction <40%, myocardial infarction within 2 weeks before surgery, peripheral vascular disease affecting the upper limbs, women and nicorandil use. Ticagrelor use was stopped 5 days before surgery. Clopidogrel, carbasalatecalcium and aspirin were continued until surgery. In the operating room, patients were randomized in blocks of 6 to control or RIPC treatment using a computer program (ALEA) by the researcher. Patients, anesthetists, surgeons and Intensive Care Unit (ICU) staff were blinded to treatment allocation. Samples were in a blinded manner.

Study Protocol

Patients were pre-medicated with midazolam 7.5 mg per os. Induction of anesthesia was performed with intravenously (i.v.) applied midazolam 0.1–0.2 mg/kg, i.v. sufentanil 1.0–1.5 ìg/kg and i.v. rocuronium 0.6 mg/kg. Continuous infusion of sufentanil 0.3 ìg/kg/h and sevoflurane were used for maintenance of hypnosis. No propofol was given until transport to the ICU and during ICU stay. All patients received routine monitoring, including ECG, continuous measurement of hemodynamics, capnography, pulse oximetry, and temperature measurement. A blood pressure cuff was placed around the patients arm. Following induction of anesthesia, RIPC was started immediately

in the intervention group, by 3 times 5 min inflation of the blood pressure cuff to 200 mmHg. During the RIPC procedure the patient was prepped and the RIPC procedure was finished before the start of surgery. Surgery started 13±6 min after the end of the last cuff inflation. Routine surgical techniques were employed and blood or cold crystalloid cardioplegia were used. During cannulation of the vena cavae, a tissue probe from the right atrium was taken and immediately processed. Management of the cardiopulmonary bypass was performed according to standard procedures. Patients were transported to the ICU under propofol anesthesia and at the ICU propofol anesthesia was continued until the patient reached a core temperature of 36 °C. At the ICU patients started to received insulin when blood-glucose levels were between 8 and 10 mM for two consecutive measurements. Blood samples were taken before and 6, 12, 24 and 48 h following surgery to determine cTnT and CRP levels. In addition, blood samples were obtained before and 5 min after the last RIPC or comparable time points in the control group for determination of IL-6, IL-10, TNF-á and MIF.

Statistical Analysis

Data are represented as mean+/− SD or single values with mean or median. Statistics were performed using SPSS Version 21. Data was tested for normality. Differences between groups were tested with a Students' t-test (cTnT, CRP, HK activity, pAkt/Akt, MIF) or Mann-Whitney U test (the amount of mtHKII, pAMPK/AMPK), depending on normality. Categorical values were compared using the Chi Squared (two categories) or Fisher's exact (more than two categories) test. A Pearson correlation coefficient was computed to assess the relationship between cTnT levels and the amount of mtHKII. Missing values in AUC analysis were substituted by the group mean. This was the case for 1 value in the control group and 1 in the RIPC group (control group: t=6: 1, RIPC group: t=24: 1). For MIF ELISA, values below the detection limit were replaced by the detection limit (12.75 pg/mL). 25 values were replaced. Before RIPC 7 in the control group and 4 in the RIPC group. After RIPC 8 in the control group and 6 in the RIPC group.

RESULTS

A total of 663 patients were screened. 562 patients were excluded because they did not meet inclusion criteria, 6 patients declined to participate and 60 patients were not included because of other reasons. Other reasons were, amongst others, that it was not possible to use sevoflurane on the extracorporeal circulation, the patient was already included in another clinical trial or logistical reasons. 35 patients were randomized, of which 29 could be included. Patients were excluded because surgery was performed off-pump (2), propofol was used at induction of anesthesia (1), increased pre-operative levels of cTnT (1), concomitant procedures were performed (1) or it was unable to perform the protocol during surgery (1).

Patient characteristics are presented in Table 1. Intraoperative data is presented in Table 2. There was no difference in inotropic support between groups (data not shown).

Table 1 Patient Characteristics

	All patients		Patients with mitochondria samples	
	Control (n=16)	RIPC n=13)	Control (n=14)	RIPC (n=10)
Age	66±9.6	70±7.5	67±9.7	71±7.3
Body mass index	27.5±4.1	25.6±2.9	26.9±3.6	25.5±2.6
Euroscore, mean	3.1±1.9	3.8±2.0	3.1±1.4	3.8±2.1
Angina pectoris	15 (94)	10 (77)	13 (93)	9 (90)
Grade 1	0 (0)	1 (8)	0 (0)	1 (10)
Grade 2	5 (31)	4 (31)	5 (36)	4 (40)
Grade 3	6 (38)	4 (31)	6 (43)	3 (30)
unknown	4 (25)	1 (8)	2 (14)	1 (10)
Previous myocardial infarction	7 (44)	8 (62)	5 (36)	6 (60)
Previous PCI	2 (13)	5 (39)	2 (14)	4 (40)
Hypertension	11 (69)	8 (62)	9 (64)	5 (50)
Hypercholesterolaemia	7 (44)	4 (31)	6 (43)	4 (40)
Ever smoked	11 (69)	9 (69)	11 (79)	7 (70)
Pack-year, mean (SD)	29±14	34±19	29±14	39±15
Family history IHD	6 (38)	6 (46)	6 (43)	4 (40)
COPD	2 (13)	1 (8)	2 (13)	1 (10)
Peripheral vascular disease	1 (6)	1 (8)	1 (7)	0 (0)
Cerebrovascular accident	0 (0)	1 (8)	0 (0)	1 (10)
Medication				
Statins	16 (100)	13 (100)	14 (100)	10 (100)
β-blocker	13 (81)	11 (85)	11 (79)	8 (80)
ACE inhibitor	7 (44)	4 (31)	6 (43)	4 (40)
Diuretics	4 (25)	1 (8)	4 (29)	1 (10)
Nitrate	7 (44)	5 (39)	6 (43)	4 (40)
Coumarin derivatives	1 (6)	0 (0)	1 (7)	0 (0)
Clopidogrel	2 (13)	5 (39)	0 (0)	4 (40)
Carbasalate calcium/aspirin	16 (100)	11 (85)	14 (100)	9 (90)

PCI: Percutaneous Coronary Intervention; IHD: Ischaemic Heart Disease; COPD: Chronic Obstructive Pulmonary Disease. Values are presented as mean±SD or number (%)

Table 2 Intraoperative Data

	All patients		Patients With Mitochondria Samples	
	Control (n=16)	RIPC (n=13)	Control (n=14)	RIPC (n=10)
Bypass time (min)	109±22	114±42	110±22	107±17
Total cross-clamp time (min)	71±17	72±26	71±17	67±15
Number of grafts				
One	1 (6)	0 (0)	1 (7)	0 (0)
Two	0 (0)	0 (0)	0 (0)	0 (0)
Three	7 (44)	5 (39)	7 (50)	4 (40)
Four	6 (38)	6 (46)	5 (36)	4 (40)
Five	2 (13)	2 (15)	1 (7)	2 (20)

Values are presented as mean±SD or number (%)

DISCUSSION

Due to slow inclusion, resulting from strict inclusion criteria, a change in patient population in our hospital (much less surgeries without concomitant procedures were performed than expected) and a change in institutional anesthetic regimen away from volatile anesthetics towards total intravenous anesthesia (TIVA), this trial was stopped after 3 years, but before target inclusion was reached. We have shown that the effect of RIPC on 24 h AUC cTnT was between a decrease of 27% and an increase of 36%. We cannot exclude that the clinically significant difference of 25% in our sample size calculation exists in cardiac surgery with anesthesia restricted to sevoflurane/fentanyl (no propofol).

Concerning the secondary outcome parameters, we were unable to show a cardioprotective effect of RIPC in CABG patients under sevoflurane anesthesia in 24 h cTnT or CRP release. In addition, no differences in cardiac mtHKII protein content or mitochondrial HK activity before bypass were observed between control and RIPC. RIPC was also without effects on the survival proteins Akt and AMPK. Finally, in this study the RIPC intervention was not associated with detectable changes in the plasma cytokines IL-6, IL-10, TNF-á or MIF, immediately following the RIPC protocol, making it unlikely that these factors are affected by the RIPC maneuver.

CONCLUSION

Due to the fact that the number of patients needed was not reached within 3 years, the study was too underpowered to draw any clear conclusion out of it. Nevertheless, the results are not in line with previous studies in that field, which makes it interesting and worth being discussed, but the small number of patients being included makes the study itself failed for its primary goal, i.e. testing whether RIPC decrease AUC cTnT by 25% in propofol-anesthetized patients. In our explorative study with limited number of patients, it is indicated that RIPC under sevoflurane anesthesia does not reduce cTnT release by more than 27%. Together with our findings that RIPC was without any effect on our secondary outcome parameters reflecting possible cardioprotection, our findings suggest that the absence of propofol is no guarantee for RIPC to result in more than 27% reduction in cardiac damage, and that other factors than anesthesia contribute to RIPC effectiveness.

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