Propofol Anesthesia and Remote Ischemic Preconditioning: An Unfortunate Relationship

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By nature, the human body is equipped with exceptional self-defensive mechanisms protecting it from possible detrimental threats. This includes active measures such as immune system activation to actively combat exogenous pathogens. In addition, it comprises certain feedback loops for the protection from possible internal threats, such as local tissue hypoxemia. This also includes adaptive processes, for instance the reduction of cellular energy metabolism and cessation of the cellular division and reproduction machinery to become less susceptible for suboptimal substrate supply. What makes these evolutionary inherited pathways so interesting for physicians is the possibility to harness their protective therapeutic potential by stimulating them before an expected harmful insult, for example, high-risk cardiac surgery. This is the general concept of preconditioning (Figure). Several reports in different organ systems have been published demonstrating that repetitive, short episodes of local ischemia (direct ischemic preconditioning) are able to "prime" the tissue, that is, to better withstand a consecutive, more severe ischemic insult.[1] However, direct ischemic preconditioning of an internal organ, such as the heart, is technically a challenging and potentially hazardous procedure. An elegant way to avoid this is remote ischemic preconditioning (RIPC). Here, temporary ischemia is not directly induced in the target organ, but by transient and repetitive occlusion of the blood supply in a body extremity, for example, by repetitive inflation of an external pressure cuff to cease arterial blood supply in an upper arm or in the leg. The effectiveness of RIPC on improving patient outcome, for example, organ function after high-risk cardiac surgery, has recently been a controversial matter of debate. Episodes of prolonged local tissue hypoxia in central organs are a frequent perioperative

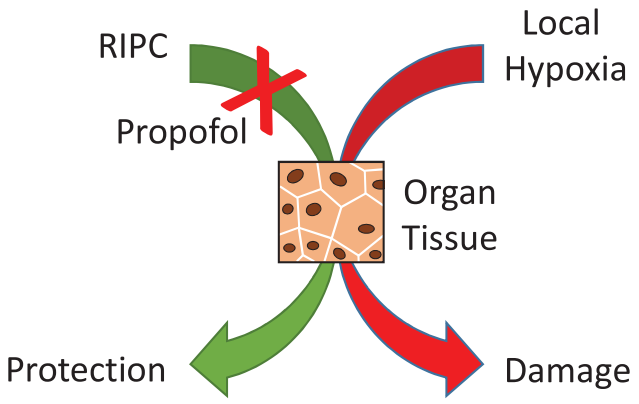

Figure. Propofol inhibits the protective effects of RIPC. RIPC indicates remote ischemic preconditioning.

threat to surgical patients. Cardiac surgery patients requiring coronary arterial bypass grafting (CABG) and/or cardiac valve repair are especially prone to local tissue hypoxia, for example, in the heart or the kidneys. This is predominantly explained by the necessity for cardioplegia and extracorporeal circulation, which is often accompanied by reduced systemic arterial perfusion pressures and immune system activation.

The protective effect of RIPC in the heart was first reported in 1994 by Whittaker and Przyklenk.[1] In this early report, dogs that were preconditioned by transient, repetitive occlusion of the antecedent circumflex coronary artery branch (ramus circumflexus [RCX]) showed smaller infarct sizes after left anterior descending coronary artery occlusion than control animals. This study demonstrated the concept of RIPC in the same organ, but different coronary vascular beds. With the start of the new millennium, reports on ischemic preconditioning increased in numbers. Subsequent studies showed that humoral factors in the blood are the mediators that convey the protective effect on the myocardium.[2–4] Moreover, further studies demonstrated that short, repetitive episodes of local ischemia in other organ tissues, for example, in the kidney, the mesentery, or skeletal muscle tissue, produced similar protective effects.[5,6]

The encouraging data from these animal studies gave rise to the hope that RIPC might also prove beneficial in patients. Several recently published clinical trials have investigated the effect of RIPC on organ protection, with partly very opposing and conflicting results; the Effect of Remote Ischemic Preconditioning on Clinical Outcomes in Patients Undergoing

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Coronary Artery Bypass Graft Surgery (ERICCA) trial is a multicenter phase III trial that included 1612 patients who underwent CABG and/or cardiac valve surgery.[7] The patients underwent 4 cycles of 5-minute upper arm ischemia with 5-minute intervals after the induction of general anesthesia and before skin incision (RIPC group) or sham procedure without inflation of the cuff. More than 90% of the patients included in the ERICCA trial were treated with propofol. Both groups did not show significant differences in the primary outcome parameter, which was a composite of cardiovascular death, myocardial infarction, coronary revascularization, and stroke after 12 months, or with respect to postoperative myocardial injury, as measured by the release of high-sensitivity troponin T. However, the perioperative anesthetic regimen was not defined in this study and also included numerous cases in which propofol was used as the hypnotic agent in combination with opioids. The second big multicenter trial investigating the effect of RIPC in cardiac surgery, the Remote Ischemic Preconditioning for Heart Surgery (RIPHeart) study, was published back to back with the ERRICA trial in the same volume of the *New England Journal of Medicine*.[8] The RIPHeart trial included 1403 patients who underwent cardiac surgery. Interestingly, the RIPHeart study design specifically included the use of propofol as the only allowed narcotic agent, completely excluding the use of volatile anesthetics. Very similar to the ERICCA trial, RIPHeart used 4 cycles of 5-minute upper arm ischemia interrupted by 5-minute reperfusion intervals after induction of general anesthesia before skin incision. And also similar to the ERICCA trial, RIPHeart yielded only negative results, that is, no differences between the RIPC and the control group with respect to mortality, myocardial infarction, perioperative myocardial injury (measured by high-sensitivity troponin T), and stroke.

In contrast to the aforementioned trials, Zarbock et al[9] found in a multicenter trial in 240 patients undergoing cardiac surgery that the use of RIPC led to a significantly decreased incidence of acute kidney injury (AKI) and a lower frequency for renal replacement therapies. Notably, the anesthetic regimen in this study excluded the use of propofol. Here, thiopental was used for induction and sevoflurane for maintenance of general anesthesia. Furthermore, patients scheduled for cardiac surgery were only enrolled in this study if they had a high risk for the development of postoperative AKI, as reflected by a Cleveland Clinic Foundation score of 6 or higher. Thus, the study by Zarbock et al[9] (Effect of Remote Ischemic Preconditioning on Kidney Injury among High-risk Patients Undergoing Cardiac Surgery [RIPCRenal] trial) investigated high-risk patients, whereas the ERICCA and the RIPCHeart trials did not focus on this patient collective. Of note, ERICCA and RIPHeart both used composite (cardiac) primary outcome parameters and were both not designed to specifically detect the effect or RIPC on renal function. In fact, AKI was a secondary outcome parameter in the ERICCA and RIPHeart trials, but both studies were not powered to detect a difference regarding the AKI incidence. The results of the study by Zarbock et al[9] have since been further supported by a recently published meta-analysis of studies on RIPC in cardiac surgery patients. This meta-analysis detected a statistically significant effect of RIPC in reducing the incidence of AKI after cardiac surgery only in the subgroup of patients in studies in which propofol was not used in the anesthetic regimen and found this effect to be absent when propofol was used.[10] Another recently published meta-analysis of human trials using RIPC in cardiac surgery patients demonstrated similar results. Here, the subgroup analysis also demonstrated a significant reduction in AKI incidence, composite end points, and myocardial injury in patients who were treated without propofol.[11]

Direct evidence on the effect of propofol on RIPC in human trial is rare. In 2012, Kottenberg et al[12] published results from a smaller single-center trial investigating the effect of RIPC on cardiac troponin I serum level kinetics in cardiac surgery patients undergoing CABG surgery. In this report, RIPC induced a reduction in postoperative cardiac troponin I levels only when the patients received an anesthetic regimen without the use of propofol.[12] Furthermore, RIPC induced the activation of the intracellular signal transducer and activator of transcription 5 (STAT5) signaling pathway in the myocardial tissue.[13] The same group later on demonstrated that these alterations in STAT5 signaling were nearly completely absent when RIPC was performed in patients receiving propofol, indicating that propofol reverses the organ-protective effects of RIPC.[14]

However, no clinical trial has been conducted that was specifically designed to investigate the influence of an anesthetic regimen with propofol on the effectiveness of RIPC. Thus, in the absence of these trials, the evidence from animal studies remains the closest estimation. In this volume of *Anesthesia & Analgesia*, Behmenburg et al[15] present data from an animal trial using a rat model of RIPC and myocardial infarction. The authors demonstrate that the use of propofol for general anesthesia reverses the protective effect of RIPC on myocardial injury. Male Wistar rats received 4 cycles of 5-minute bilateral hind limb ischemia at 5-minute intervals before left anterior descending coronary artery ligation for 25 minutes. After 120 minutes of reperfusion, the animals were killed and the myocardial infarct size was analyzed. RIPC led to a reduced infarct sizes in animal groups receiving pentobarbital or sevoflurane/remifentanil for the induction and maintenance of anesthesia. In sharp contrast, the use of propofol in combination with remifentanil completely abolished the protective effect of RIPC on the myocardial infarct size. This is the first report from a study directly designed to investigate the adverse effects of propofol on RIPC and the results fit very well to the observations from previously published reports, which indicated possible adverse effects of propofol on the effectiveness of RIPC (Figure).

Another important aspect regarding the research on RIPC is the lack of mechanistic understanding of the mode-of-action of RIPC. Here, several important questions remain open. First, the optimal RIPC modality remains unclear. To date, no study has addressed the optimal site and duration of the RIPC stimulus as well as the optimal number of repetitions. Furthermore, the temporal aspect of RIPC effectiveness has not been addressed. It is unclear as to how effectively RIPC might convey renal or myocardial protection with increasing time periods between preconditioning and insult, with the strength of the insult and optionally with nontransient ischemic insults. Also, the effect on the long-term outcome has not been addressed so far. Last but not least, the mediator(s) conveying the organ protection have not been identified, nor is it clear whether the same

mediator is involved in affecting organ protection in different organs. These questions have to be addressed by future studies.

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DISCLOSURES

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Impact of Anesthetic Regimen on Remote Ischemic Preconditioning in the Rat Heart In Vivo

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Remote ischemic preconditioning (RIPC) seems to be a promising cardioprotective strategy with contradictive clinical data suggesting the anesthetic regimen influencing the favorable impact of RIPC. This study aimed to investigate whether cardio protection by RIPC is abolished by anesthetic regimens. Male Wistar rats were randomized to 6 groups. Anesthesia was either maintained by pentobarbital (Pento) alone or a combination of sevoflurane (Sevo) and remifentanil or propofol (Prop) and remifentanil in combination with and without RIPC. RIPC reduced infarct size in Pento- and Sevo-anesthetized rats (Pento-RIPC: 30% ± 9% versus Pento-control [Con]: 65% ± 6%, $P < .001$; Sevo-RIPC: 31% ± 6% versus Sevo-Con: 61% ± 8%, $P < .001$), but RIPC did not initiate cardio protection in Prop-anesthetized animals (Prop-RIPC: 59% ± 6% versus Prop-Con: 59% ± 8%, $P = 1.000$). Cardio protection by RIPC is abolished by Prop. (Anesth Analg 2018;126:1377–80)

Cardiovascular disease is the main cause of death worldwide.[1] Therefore, it should be of tremendous socioeconomic interest to reduce its fatal consequences, that is, myocardial infarction. Remote ischemic preconditioning (RIPC) seems to be a promising option to promote cardio protection after myocardial ischemia/reperfusion injury. In contrast to direct ischemic preconditioning, RIPC confers cardio protection at a distance, that is, with transient ischemic periods of a limb induced with a tourniquet. Therefore, RIPC is a noninvasive and easy-to-use technique with low risk for the patients. Various animal studies confirmed the infarct-limiting effect of RIPC within the past years,[2] and even some proof-of-concept studies demonstrated the protective effects of RIPC in cardiovascular surgery.[3] However, clinical data are not consistent. Two recent multicenter trials (RIPHeart[4] and ERICCA[5]) with >1300 patients each did not show any beneficial effects of RIPC in cardiac surgery. Possibly, differences in protective impact of RIPC in clinical studies are caused by different anesthetic regimes. Almost all patients in ERICCA and RIPHeart trials were operated using propofol (Prop) anesthesia. Results from a single-center trial with only few patients suggest that RIPC does induce cardio protection with isoflurane anesthesia, but does not with Prop anesthesia.[6] It is known that various confounding factors influence the effect of cardioprotective strategies, that is, comorbidities, comedication, and aging.[7] All of these confounding factors apply to cardiac surgical patients, and subsequently, the exclusive influence of the anesthetic regime on cardio protection by RIPC in clinical studies cannot be precisely identified.

Therefore, the aim of the study was to investigate the influence of anesthetic regimes used in daily clinical routine, that is, a combination of sevoflurane (Sevo) and remifentanil or Prop and remifentanil on cardio protection by RIPC in the rat heart in vivo. The results of this study might help to understand and explain the inconsistent data in cardiac surgery.

METHODS

In this study, an in vivo model of regional myocardial ischemia/reperfusion injury in male Wistar rats was used to evaluate the cardioprotective impact of RIPC with regard to anesthetic management.

The current investigation was conducted in accordance with the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health (Publication number 85-23, revised 1996) and was performed after obtaining approval from the Animal Ethics Committee of the University of Duesseldorf, Germany.

Surgical Preparation

Surgical preparation was performed as described previously.[8] In brief, male Wistar rats (2–3 months), weighing 301 ± 17 g, were anesthetized by intraperitoneal pentobarbital (Pento) injection (80 mg/kg). After tracheal intubation, mechanical ventilation was performed with 30% oxygen/70% nitrogen and monitored by blood gas analysis throughout the experiments to keep acid–base state in physiologic limits. The right jugular vein was cannulated for saline and drug infusion, and the left carotid artery was cannulated for measurement of aortic pressure. A lateral left-sided thoracotomy was performed, and a ligature (5-0 Prolene; Ethicon, Somerville, NJ) was passed below the left anterior descending coronary artery. All animals underwent 25 minutes of regional myocardial ischemia and 120 minutes of reperfusion. At the end of experiments, the hearts were excised and infarct size measurement was performed using triphenyltetrazolium chloride staining as described previously.[8] In brief, hearts were

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excised and mounted on a modified Langendorff apparatus for perfusion with ice cold normal saline via the aortic root at a perfusion pressure of 80 cm H_2O to washout intravascular blood. Subsequently, the coronary artery was reoccluded, and the heart was perfused with 0.2% Evans blue in normal saline for 10 minutes. Intravascular Evans blue was then washed out by perfusion with normal saline for 10 minutes. This treatment identified the area at risk as unstained. Afterward, the heart was cut into transverse slices, which were stained with 0.75% triphenyltetrazolium chloride solution and fixed in formalin solution. The area at risk and the infarct size were determined using planimetry by using SigmaScan Pro5 (SPSS Science Software, Chicago, IL).

Experimental Protocol

Rats were randomly assigned to one of the experimental groups (6 groups, each n = 6, Figure A). According to the group, anesthesia was maintained with either Pento (40 mg/kg/h) or Sevo (1 minimal alveolar concentration) combined with remifentanil (0.5 µg/kg/min) or Prop (12 mg/kg/h) combined with remifentanil (0.5 µg/kg/min).

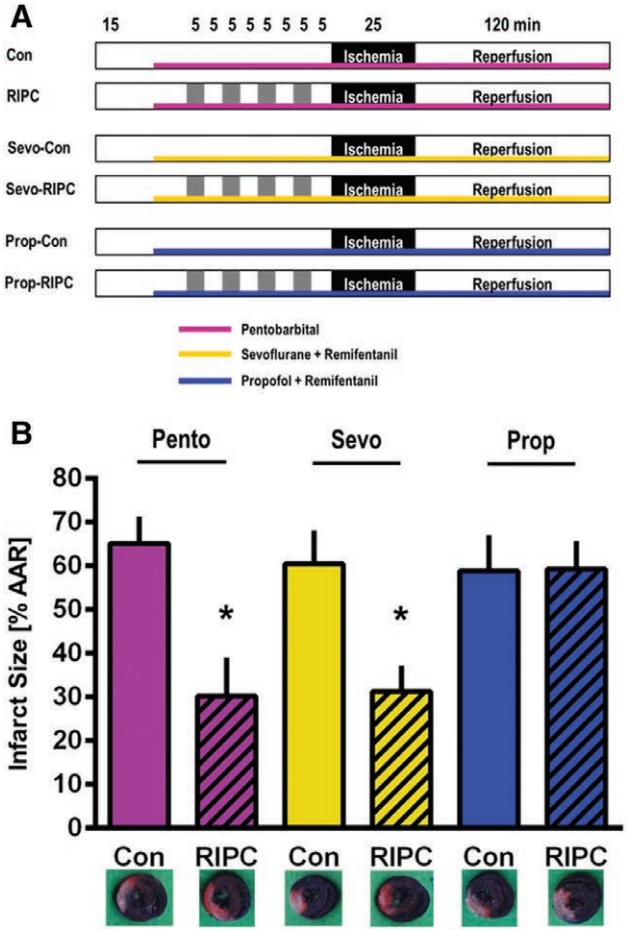

Figure. A, Experimental design. Four cycles of 5-min bilateral hind limb ischemia interspersed with 5 min of reperfusion before ischemia (25 min) and reperfusion (120 min). B, Infarct size measurement. Histogram shows the infarct size (percent of area at risk) of Cons and RIPC. Data are presented as mean ± SD, *P < .05 versus Pento-Con and Sevo-Con, respectively. AAR indicates area at risk; Con, control; Prop, propofol; RIPC, remote ischemic preconditioning; Sevo, sevoflurane; SD, standard deviation.

Control Groups (Pento-Control, Sevo-Control, and Pro-Control). After surgical preparation, rats received the corresponding anesthesia continuously.

RIPC Groups (Pento-RIPC, Sevo-RIPC, and Pro-RIPC). In addition to the respective control (Con) group, rats received 4 cycles of 5-minute bilateral hind limb ischemia interspersed with 5 minutes of reperfusion before myocardial ischemia and reperfusion. Ischemia was induced by inflating 2 modified blood pressure cuffs to 200 mm Hg and reperfusion started by deflating the cuff.

Statistical Analysis

Infarct sizes were determined by a researcher blinded to the experimental groups and analyzed by 1-way analysis of variance followed by Tukey post hoc test (GraphPad Software, San Diego, CA). Comparisons of infarct size among different Con groups (Pento-Con, Sevo-Con, and Prop-Con) were of special interest and furthermore difference in infarct size between Con and RIPC of each anesthetic regimen (ie, Pento-Con versus Pento-RIPC, Sevo-Con versus Sevo-RIPC, and Prop-Con versus Prop-RIPC). Comparisons of hemodynamics between groups or between different time points within a group were performed with a 2-way analysis of variance followed by Tukey post hoc test. Hemodynamics for statistical analysis were recorded at baseline, last washout (4 minutes), ischemia (15 minutes), and reperfusion (30 and 120 minutes). Data are expressed as mean ± standard deviation. Confidence intervals (CIs) are shown for the difference in means between treatment and Con group. Differences were considered statistically significant when P values were <.05.

Sample size was calculated using GraphPad StatMate Version 1.01 (GraphPad Software, San Diego, CA) and yielded a group size of n = 6 as necessary to detect a difference in infarct size of 25% with a power of 80% and an $\alpha < .05$. The estimations of the mean difference of 25% and the standard deviation of 10% were based on previous own data.[9]

RESULTS

Infarct Size

In the Con group of Pento-anesthetized rats, 25 minutes of regional myocardial ischemia and 120 minutes of reperfusion caused an infarct size of 65% ± 6% of the area at risk (Figure B). RIPC in Pento rats strongly reduced infarct size to 30% ± 9% of the area at risk (mean difference versus Pento-Con: 35%, 95% CI, 22–48, $P < .0001$). Balanced anesthesia with Sevo/remifentanil and Prop/remifentanil alone did not influence infarct size (Sevo-Con: 61% ± 8%, mean difference versus Pento-Con: 5%, 95% CI, −8 to 17, $P = .878$; Prop-Con: 59% ± 8%, mean difference versus Pento-Con: 6%, 95% CI, −7 to 19, $P = .671$). RIPC reduced infarct size in Sevo/remifentanil-anesthetized rats (Sevo-RIPC: 31% ± 6%; mean difference versus Sevo-Con: 29%, 95% CI, 17–42, $P < .0001$), but cardio protection by RIPC was completely abolished in Prop/remifentanil-anesthetized rats (Prop-RIPC: 59% ± 6%; mean difference versus Prop-Con: −0.4, 95% CI, −13 to 12, $P = 1.000$). The estimated treatment effect was an infarct size reduction of 25%.

Hemodynamic Variables

Hemodynamic variables are summarized in the Table. No significant differences in heart rate and aortic pressure were observed between the experimental groups during baseline, ischemia, or reperfusion. Heart rate decreased during reperfusion compared to baseline in Prop-anesthetized animals with RIPC ($P < .05$). During experiments, mean aortic pressure decreased during reperfusion period compared to baseline in all experimental groups ($P < .05$). No interactions have been reported for the hemodynamic variables.

DISCUSSION

Our study shows that cardio protection by RIPC depends on the anesthetic regimen: Prop anesthesia completely abolishes cardio protection by RIPC, whereas Sevo has no influence on RIPC-induced infarct size reduction in rat hearts in vivo.

RIPC is considered to be a promising noninvasive, easy-to-use cardioprotective strategy, but its clinical implementation remains difficult as clinical data are contradictive. Recently 2 large phase III trials (ERICCA[5] and RIPHeart[4]) did not confirm any beneficial effects of RIPC in cardiac surgical patients. However, results from a single-center proof-of-concept study by Thielmann et al[3] showed that RIPC in elective coronary artery bypass graft surgery led to reduced troponin levels over 72 hours after cardiopulmonary bypass and a lower rate of major adverse cardiac and cerebrovascular events and myocardial infarction. A recent Cochrane meta-analysis found no evidence that RIPC has a treatment effect on clinical outcomes, but there is moderate-quality evidence that RIPC reduces the cardiac troponin T release at 72 hours after surgery.[10] The authors encourage further adequately designed studies, especially focusing on influencing factors, for example, with regard to anesthetic management.

Zarbock et al[11] demonstrated that RIPC in the absence of Prop during cardiac surgery reduced the rate of acute kidney injury and use of renal replacement therapy. Additionally, a current meta-analysis by Zhou et al[12] suggests that—besides the reduction of the incidence of acute kidney injury after cardiac surgery—RIPC may also shorten mechanical ventilation duration and intensive care unit stay.

Cardio protection by conditioning strategies is influenced by numerous confounding factors.[7] Especially, comorbidities and comedication are known to interact with the beneficial effects of ischemic preconditioning. We have recently demonstrated that infarct size reduction by RIPC is completely blocked in the aged rat heart in vivo, unraveling aging as a limiting factor for the cardioprotective effect of RIPC.[9] Additionally, the anesthetic regimen during surgery might have an impact on the protective actions of RIPC. In ERICCA and RIPHeart trials >90%[5] to 100%[4] of patients were anesthetized with Prop during surgery, whereas Thielmann et al,[3] who did show beneficial effects of RIPC, maintained anesthesia with isoflurane, although the use of Prop was initially planned for their study. The authors state "After use in some patients, however, we became aware of apparent interference of Prop with RIPC and discontinued its use for the remainder of the study."[3] For those 72 patients, Kottenberg et al[6] showed by post hoc analysis that RIPC decreased troponin levels over 72 hours after cardiopulmonary bypass during isoflurane, but not during Prop anesthesia. Therefore, Prop is thought to be 1 confounding factor that interferes with cardioprotective interventions. However, the number of patients investigated by the post hoc analysis was very small, and patients undergoing cardiac surgery possess various confounding factors that do interfere with cardioprotective strategies.

Subsequently, we excluded all confounding factors to test the exclusive influence of the anesthetic regime on cardio protection by RIPC in an experimental setting with young healthy animals. The underlying molecular reasons for the blockade of Prop of the beneficial effects by RIPC remain unknown. Heusch et al[13] identified protection by RIPC to be associated with the activation of signal transducer and activator of transcription 5 (Stat5) in left ventricular biopsies of 24 patients undergoing coronary artery bypass graft surgery during isoflurane anesthesia. In a follow-up study with 24 nondiabetic patients with 3-vessel coronary artery disease undergoing cardiac surgery with Prop anesthesia, RIPC did not evoke activation of Stat5 or cardio protection.[14] The authors therefore concluded that Prop interferes with cardioprotective signaling upstream of Stat5. However,

Table. Hemodynamic Variables

			Ischemia	Reperfusion	
	Baseline	Washout 4	15 Min	30 Min	120 Min
Heart rate (BPM)					
Con	438 ± 41	431 ± 39	427 ± 30	393 ± 35	389 ± 33
RIPC	438 ± 25	405 ± 38	405 ± 40	395 ± 38	386 ± 30
Sevo-Con	427 ± 31	419 ± 45	403 ± 37	380 ± 33	387 ± 36
Sevo-RIPC	412 ± 27	400 ± 17	396 ± 14	382 ± 22	388 ± 33
Prop-Con	430 ± 33	428 ± 37	384 ± 56	394 ± 31	387 ± 21
Prop-RIPC	424 ± 32	424 ± 23	406 ± 25	385 ± 28	361 ± 36[a]
Mean aortic pressure (mm Hg)					
Con	118 ± 22	111 ± 31	104 ± 19	90 ± 15[a]	83 ± 24[a]
RIPC	120 ± 21	102 ± 18	94 ± 16	84 ± 15[a]	71 ± 17[a]
Sevo-Con	120 ± 19	114 ± 18	92 ± 25[a]	87 ± 17[a]	86 ± 18[a]
Sevo-RIPC	121 ± 12	113 ± 13	109 ± 25	98 ± 19	87 ± 30[a]
Prop-Con	132 ± 25	123 ± 19	102 ± 21[a]	74 ± 24[a]	70 ± 13[a]
Prop-RIPC	120 ± 18	118 ± 18	118 ± 26	104 ± 30	92 ± 32[a]

Data are mean ± SD.

Abbreviations: BPM, beats per minute; Con, control; Prop, propofol; RIPC, remote ischemic preconditioning; Sevo, sevoflurane.

[a]$P < .05$ versus baseline, each group n = 6.

RIPC did not increase Stat5 phosphorylation in myocardium of pigs and rats.[15] Skyschally et al[15] recently provided evidence that in both isolated rat hearts and pigs in situ, the myocardial signal transduction of RIPC is identical to that of local ischemic postconditioning, that is, reperfusion injury salvage kinase (RISK) and survivor activating factor enhancement (SAFE) pathways. Especially, activation of Stat3 is causally involved in cardio protection by RIPC in pigs and rats.[15] Furthermore, Shravah et al[16] demonstrated a connection between Prop and Stat3. Prop mediated Stat3 phosphorylation in H9c2 cells, but not in the presence of phosphoinositide 3-kinase/protein kinase B inhibitors.[16] If this is possibly associated with loss of cardio protection by RIPC during Prop, anesthesia needs to be evaluated in further studies. On the other hand, RIPC may depend on cardiac vagal nerve activation, and Prop is known to influence g-aminobutyric acid–mediated central nervous control of cardiac nerves.[17]

Our data are purely descriptive, and it is a limitation of the study that we did not establish the underlying blockade mechanism that was beyond the scope of our study. The aim of our study was to elucidate a possible confounding factor for the contradictory results from clinical studies on RIPC.

We set out to determine the effect of anesthetic regimes used in daily clinical routine on cardio protection induced by RIPC and found a complete blockade of the cardioprotective effect in Prop-based anesthesia in the rat heart in vivo. Our data support the statement that Prop might be responsible for the neutral effects of RIPC in large clinical trials in cardiac surgery.

DISCLOSURES

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Contribution: This author helped design the study, analyze and interpret the data, and write the manuscript.
This manuscript was handled by: Alexander Zarbock, MD.

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