ORIGINAL ARTICLE

A Multicenter Trial of Remote Ischemic Preconditioning for Heart Surgery

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ABSTRACT

BACKGROUND

Remote ischemic preconditioning (RIPC) is reported to reduce biomarkers of ischemic and reperfusion injury in patients undergoing cardiac surgery, but uncertainty about clinical outcomes remains.

METHODS

We conducted a prospective, double-blind, multicenter, randomized, controlled trial involving adults who were scheduled for elective cardiac surgery requiring cardiopulmonary bypass under total anesthesia with intravenous propofol. The trial compared upper-limb RIPC with a sham intervention. The primary end point was a composite of death, myocardial infarction, stroke, or acute renal failure up to the time of hospital discharge. Secondary end points included the occurrence of any individual component of the primary end point by day 90.

RESULTS

A total of 1403 patients underwent randomization. The full analysis set comprised 1385 patients (692 in the RIPC group and 693 in the sham-RIPC group). There was no significant between-group difference in the rate of the composite primary end point (99 patients [14.3%] in the RIPC group and 101 [14.6%] in the sham-RIPC group, P=0.89) or of any of the individual components: death (9 patients [1.3%] and 4 [0.6%], respectively; P=0.21), myocardial infarction (47 [6.8%] and 63 [9.1%], P=0.12), stroke (14 [2.0%] and 15 [2.2%], P=0.79), and acute renal failure (42 [6.1%] and 35 [5.1%], P=0.45). The results were similar in the per-protocol analysis. No treatment effect was found in any subgroup analysis. No significant differences between the RIPC group and the sham-RIPC group were seen in the level of troponin release, the duration of mechanical ventilation, the length of stay in the intensive care unit or the hospital, new onset of atrial fibrillation, and the incidence of postoperative delirium. No RIPC-related adverse events were observed.

CONCLUSIONS

Upper-limb RIPC performed while patients were under propofol-induced anesthesia did not show a relevant benefit among patients undergoing elective cardiac surgery. (Funded by the German Research Foundation; RIPHeart ClinicalTrials.gov number, NCT01067703.)

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*A complete list of investigators in the Remote Ischemic Preconditioning for Heart Surgery (RIPHeart) Study is provided in the Supplementary Appendix, available at NEJM.org.

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Cardiac surgery is associated with a predictable risk of end-organ ischemic and reperfusion injury. Transient ischemia of nonvital tissue, known as remote ischemic preconditioning (RIPC), is reported to help remote vital organs withstand a subsequent prolonged ischemic event.[1] Although proof-of-concept trials suggested that RIPC provides protection against myocardial and kidney injury, as determined by serum cardiac and renal biomarkers, in patients undergoing cardiovascular surgery,[2-4] more recent studies failed to show significant differences between the RIPC and control groups with respect to troponin release, inotropic or vasoconstrictor support, renal dysfunction, and lung injury.[5-10] Only a few studies have included clinical outcomes as primary end points, and most are limited by small samples.[4,6,11-13] Thus, a large, randomized study would be helpful to elucidate the role of this simple intervention in daily practice. We hypothesized that RIPC would improve clinical outcomes in patients undergoing elective cardiac surgery.

A Quick Take is available at NEJM.org

Methods

Trial Design and Oversight

The ethics committee at the University of Kiel and at each participating center approved the study protocol, patient information sheet, and informed-consent form. The patient data were deidentified. Patients were screened and underwent randomization during the period from January 2011 through May 2014 at 14 German university hospitals. The protocol, including details regarding trial conduct and the statistical analysis plan, has been published previously[14] and is available with the full text of this article at NEJM.org. The study was funded by the German Research Foundation, which was not involved in the design of the protocol, the conduct of the trial, or the analyses or reporting of the data. The writing committee (see the Supplementary Appendix, available at NEJM.org) prepared the first draft of the manuscript. Independent statisticians at the Clinical Trial Center Leipzig performed all the analyses. The site investigators were unaware of the study-group assignments until the data, excluding 1-year follow-up data, were locked in December 2014. All the authors had full and independent access to all the data and vouch for the integrity, accuracy, and completeness of the data and the fidelity of the study to the protocol. Staff at the Clinical Trial Center Leipzig monitored the trial data (see the Supplementary Appendix for details on the roles of the participating investigators and on randomization and quality monitoring).

In this prospective, randomized, double-blind, multicenter, parallel-group, controlled trial involving 1403 patients undergoing cardiac surgery, randomization was performed centrally at the Clinical Trial Center Leipzig and was stratified according to center and individual risk of perioperative death, as assessed with the use of the logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE). The EuroSCORE is a risk model that incorporates 17 preoperative items of information about the patient and the planned type of surgery and uses logistic regression to calculate the risk of death within 30 days after surgery. A higher score indicates a higher risk of death.[15] The conduct of the trial and the safety of the participants were overseen by the steering committee.

Patients

Patients 18 years of age or older who were scheduled for elective cardiovascular surgery requiring cardiopulmonary bypass and who provided written informed consent were eligible for enrollment. Key exclusion criteria were related to specific surgical procedures (e.g., off-pump heart surgery or urgent surgery) and severe organ dysfunction (e.g., ejection fraction <30% or severe renal failure). Further details of the exclusion criteria are provided in the Supplementary Appendix.

Intervention and Blinding

RIPC was induced by four cycles of upper-limb ischemia (5-minute blood-pressure cuff inflation to ≥200 mm Hg, but at least 15 mm Hg higher than the patient's actual systolic arterial pressure, followed by 5-minute cuff deflation) by appointed staff who were aware of the study-group assignments. For patients assigned to sham RIPC, a dummy arm was used for similar cycles of inflation and deflation. To ensure double blinding, the intervention was performed on patients who were already anesthetized, on the arm with no arterial line, and surgical drapes were used to cover the blood-pressure cuffs on both the patient's arm and the dummy arm. The individual patient, the staff involved in intraoperative care

(anesthesia and cardiac-surgery team) and postoperative care, the investigators who obtained and documented data and performed follow-up assessments, and the clinical end-point committee, whose members assessed all available electrocardiograms for reference analysis, were unaware of the study-group assignments.

PRIMARY AND SECONDARY END POINTS

The primary end point was a binary composite end point of death from any cause, nonfatal myocardial infarction, new stroke, or acute renal failure up to the time of hospital discharge (to a maximum of 14 days if the hospital stay was longer than that). Nonfatal myocardial infarction was defined by biomarker (e.g., troponin) values more than five times the 99th percentile of the normal reference range plus one or more of the following: new pathologic Q waves or new left bundle-branch block within the first 72 hours after surgery, standard clinical criteria for myocardial infarction from 72 hours onward, a new finding of ischemia by echocardiography or angiography, or myocardial infarction diagnosed at autopsy.[16] Stroke was defined by any new, temporary or permanent, focal or global neurologic deficit, evaluated according to the National Institutes of Health Stroke Scale (with stroke defined as a score of ≥4 points on a scale of 0 to 42, with higher scores indicating greater severity)[17] or by evidence of stroke on autopsy. Acute renal failure was defined by an increase in the serum creatinine level by a factor of 2 or more from baseline, a urine output of no more than 0.5 ml per kilogram per hour for 12 hours,[18] the use of renal-replacement therapy, or evidence of renal failure on autopsy.

Secondary end points were the occurrence of any individual component of the composite end point at 30 days, 90 days, and 12 months after surgery (12-month follow-up data are not presented here), duration of mechanical ventilation, length of stay in the intensive care unit and total hospital stay, levels of troponin T and I, creatinine level, new onset of atrial fibrillation, and incidence of postoperative delirium (for full definitions and a complete list of end points, see the Supplementary Appendix).

STATISTICAL ANALYSIS

Anticipating a pooled overall complication rate of 10% and assuming a 10% dropout rate, we originally determined that enrollment of 2070 patients would give the study 80% power to detect a 33% lower risk of the primary end point with RIPC than with sham RIPC (8% vs. 12%) with the use of a two-sided chi-square test with continuity correction, at a significance level of 0.05. No formal interim analysis was planned. Because patient enrollment was lower than expected after the first 3 years, a blinded sample-size recalculation that was based on pooled data of the first 724 patients who could be evaluated and that did not affect the type I error rate was performed.[19] We observed a higher-than-expected pooled complication rate (17.4% instead of 10%) and a much lower dropout rate (1.4% instead of 10%). Conservatively assuming a complication rate of 17% in the sham-RIPC group and a dropout rate of 2% in the total study cohort, we calculated that a total sample of 1400 would give the study 90% power to detect a 33% lower risk of the primary end point with RIPC. After consent of the independent data and safety monitoring committee and the steering committee, we stopped enrollment in May 2014, with 1400 patients enrolled.

As prespecified in the protocol, logistic-regression models that adjusted for factors known to affect outcome (EuroSCORE [0 to 2 points, 3 to 5 points, or ≥6 points],[15] status with respect to diabetes mellitus [yes or no],[20] and concomitant treatment with cholesterol-lowering drugs [yes or no][21]) and that incorporated study center as a random effect were used in the primary analysis to estimate the treatment effect on the odds-ratio scale, with two-sided 95% confidence intervals provided. Analogous adjustment was used in regression analyses of secondary end points. We performed the primary analyses in the full analysis set, from which patients who did not undergo surgery or who withdrew consent before assessment of the primary end point were excluded. In addition, we repeated the analyses in the per-protocol set, further excluding patients with major protocol deviations. The subgroup analyses performed were not prespecified and are exploratory only.

RESULTS

STUDY POPULATION

A total of 1403 patients underwent randomization, 1385 fulfilled the criteria for the full analysis

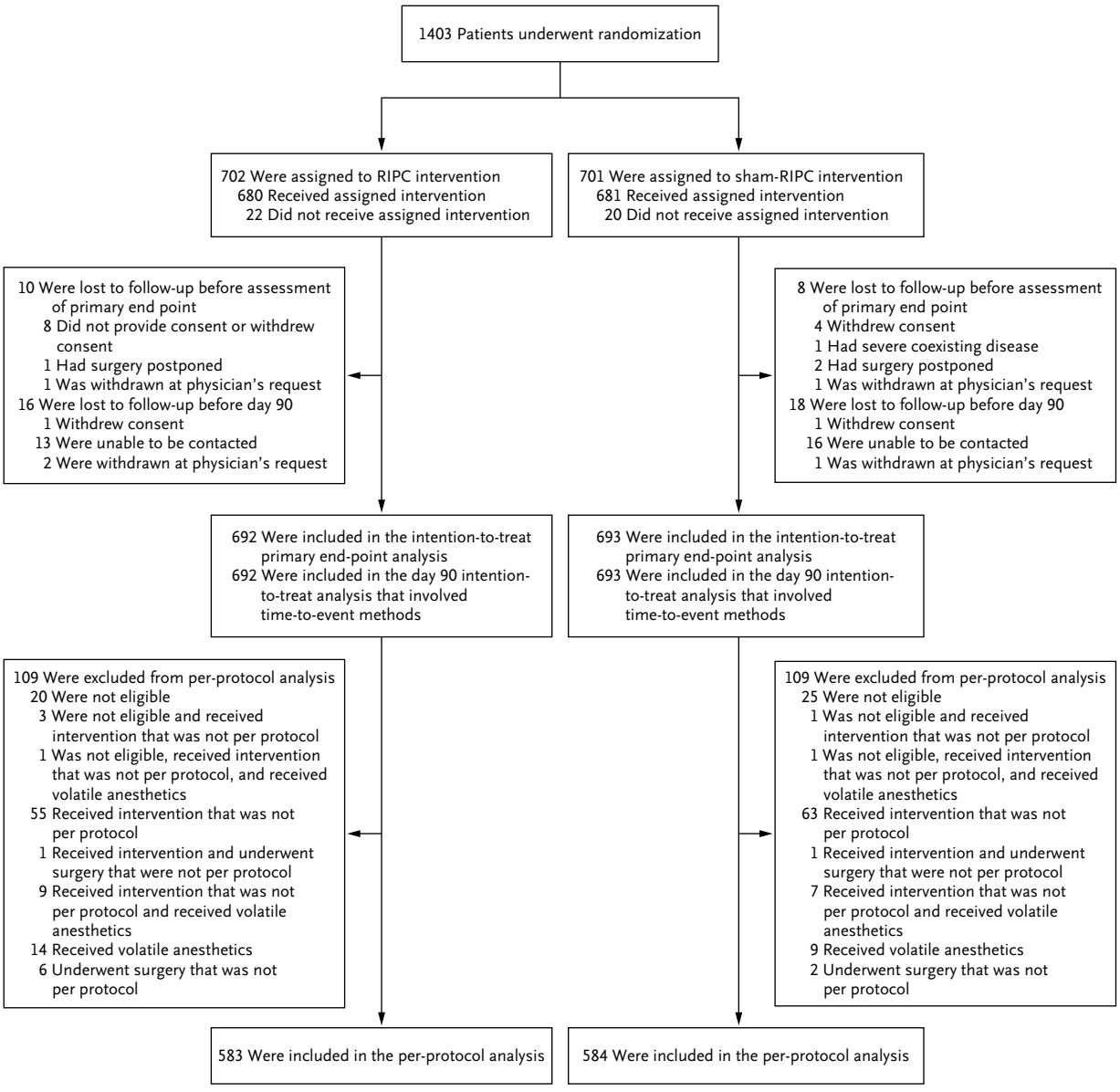

Figure 1. Randomization and Follow-up.

Of 1403 patients who underwent randomization, 1361 received the intervention (remote ischemic preconditioning [RIPC] or sham RIPC) according to the randomization assignment and 42 did not receive the assigned intervention, owing mainly to logistic reasons. The full analysis set for primary and secondary end-point analyses comprised 1385 patients (692 in the RIPC group and 693 in the sham-RIPC group). A total of 18 patients (10 in the RIPC group and 8 in the sham-RIPC group) were not included in the full analysis set, because no information on the primary end point was available. A total of 218 patients had protocol violations, resulting in 1167 patients in the per-protocol set. Screening assessment was incomplete, so no data on screening are provided.

set, and 1167 were included in the per-protocol set (Fig. 1). Baseline demographic and clinical characteristics are shown in Table 1. There were no relevant imbalances between the groups at baseline except with respect to the use of a cholesterol-lowering drug ($P=0.03$). A total of 383 of 1385 patients (27.7%) had New York Heart Association class III or class IV congestive heart failure, and 433 of 1385 patients (31.3%) had a EuroSCORE of 6 or higher before surgery, representing a high proportion of high-risk patients.

Table 1. Baseline Patient Characteristics.*

Characteristic	RIPC (N=692)	Sham RIPC (N=693)
Age — yr	65.8±10.7	66.0±10.0
Male sex — no. (%)	508 (73.4)	520 (75.0)
Preexisting conditions — no./total no. (%)		
Ischemic heart disease	510/691 (73.8)	531/691 (76.8)
Valve disorder		
Mitral-valve regurgitation		
None	231/536 (43.1)	234/519 (45.1)
Mild	254/536 (47.4)	232/519 (44.7)
Moderate	31/536 (5.8)	25/519 (4.8)
Severe	20/536 (3.7)	28/519 (5.4)
Aortic-valve regurgitation		
None	298/534 (55.8)	304/521 (58.3)
Mild	162/534 (30.3)	158/521 (30.3)
Moderate	48/534 (9.0)	38/521 (7.3)
Severe	26/534 (4.9)	21/521 (4.0)
Aortic-valve stenosis		
None	287/532 (53.9)	301/524 (57.4)
Mild	13/532 (2.4)	20/524 (3.8)
Moderate	43/532 (8.1)	30/524 (5.7)
Severe	189/532 (35.5)	173/524 (33.0)
Aneurysm of the ascending aorta	89/691 (12.9)	87/692 (12.6)
Previous myocardial infarction	197/689 (28.6)	203/692 (29.3)
Chronic heart failure	154/690 (22.3)	142/688 (20.6)
Chronic obstructive pulmonary disease	52/692 (7.5)	63/693 (9.1)
Current tobacco use	135/691 (19.5)	146/693 (21.1)
Peripheral vascular disease	43/691 (6.2)	53/688 (7.7)
Chronic kidney disease	79/692 (11.4)	76/689 (11.0)
Diabetes mellitus	166/691 (24.0)	178/693 (25.7)
Previous stroke	49/692 (7.1)	37/690 (5.4)
Anemia†	95/685 (13.9)	106/687 (15.4)
Chronic arterial hypertension	573/690 (83.0)	573/691 (82.9)
Medications at time of randomization — no. (%)		
Cholesterol-lowering drug‡	434 (62.7)	473 (68.3)
Beta-blocker	435 (62.9)	440 (63.5)
ACE inhibitor	346 (50.0)	370 (53.4)
Left ventricular ejection fraction — no./total no. (%)		
>55%	456/604 (75.5)	450/595 (75.6)
30–55%	147/604 (24.3)	145/595 (24.4)
<30%	1/604 (0.2)	0/595
NYHA class — no./total no. (%)		
I	156/686 (22.7)	132/691 (19.1)
II	345/686 (50.3)	361/691 (52.2)
III	178/686 (25.9)	191/691 (27.6)
IV	7/686 (1.0)	7/691 (1.0)
Logistic EuroSCORE§	4.2±2.6	4.2±2.5

* Plus–minus values are means ±SD. There were no significant differences between the two groups except with respect to the use of a cholesterol-lowering drug (P=0.03). ACE denotes angiotensin-converting enzyme, NYHA New York Heart Association, and RIPC remote ischemic preconditioning.

† Anemia was defined as a hemoglobin level of less than 13 g per deciliter in men and less than 12 g per deciliter in women.

‡ Examples include statins and fibrates.

§ The European System for Cardiac Operative Risk Evaluation (EuroSCORE) is a risk model that incorporates 17 preoperative items of information about the patient and the planned type of surgery and that uses logistic regression to calculate the risk of death within 30 days after surgery. A higher score indicates a higher risk of death.[15]

Table 2. Results of Unadjusted and Adjusted End-Point Analyses.*

End Point	RIPC (N=692)	Sham RIPC (N=693)	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)†	P Value†
Primary end point — no. of patients (%)‡	99 (14.3)	101 (14.6)	1.02 (0.76–1.38)	1.02 (0.75–1.39)	0.89
Death	9 (1.3)	4 (0.6)	0.44 (0.12–1.36)	0.46 (0.14–1.54)	0.21
Myocardial infarction	47 (6.8)	63 (9.1)	1.37 (0.93–2.04)	1.37 (0.92–2.03)	0.12
Stroke	14 (2.0)	15 (2.2)	1.07 (0.51–2.26)	1.10 (0.53–2.31)	0.79
Acute renal failure	42 (6.1)	35 (5.1)	0.82 (0.52–1.30)	0.83 (0.52–1.34)	0.45
New onset of atrial fibrillation — no. of patients/total no. (%)	147/690 (21.3)	160/690 (23.2)	1.12 (0.87–1.44)	1.17 (0.90–1.52)	0.25
Delirium — no. of patients/total no. (%)§	99/672 (14.7)	89/676 (13.2)	0.88 (0.64–1.19)	0.85 (0.79–1.79)	0.31

* CI denotes confidence interval.
† The logistic-regression analyses were adjusted for EuroSCORE (0 to 2 points, 3 to 5 points, or ≥6 points), status with respect to diabetes mellitus (yes or no), concomitant treatment with cholesterol-lowering drugs (yes or no), and study center (as a random effect).
‡ The primary end point was a composite of death, myocardial infarction, stroke, or acute renal failure until hospital discharge (to a maximum of 14 days if the hospital stay was longer than that). An individual patient could have had multiple primary end-point events (e.g., both stroke and acute renal failure).
§ Delirium was assessed with the use of the Confusion Assessment Method for the Intensive Care Unit.

STUDY INTERVENTION

The intervention was performed according to the study protocol in 1243 patients (623 of 692 patients [90.0%] in the RIPC group and 620 of 693 patients [89.5%] in the sham-RIPC group) (Table S1 in the Supplementary Appendix). Detailed data on intraoperative procedures, medications, and cumulative fluid intake are provided in Table S2 in the Supplementary Appendix.

END-POINT RESULTS

There was no significant between-group difference in the rate of the primary end point (99 patients [14.3%] in the RIPC group and 101 patients [14.6%] in the sham-RIPC group; difference in rate, −0.3 percentage points [95% confidence interval, −4.1 to 3.6]; P=0.89 by logistic regression) or in the rate of any of its components: death (9 patients [1.3%] in the RIPC group and 4 patients [0.6%] in the sham-RIPC group, P=0.21), myocardial infarction (47 patients [6.8%] and 63 patients [9.1%], respectively; P=0.12), stroke (14 patients [2.0%] and 15 patients [2.2%], P=0.79), and acute renal failure (42 patients [6.1%] and 35 patients [5.1%], P=0.45) (Table 2). Kaplan–Meier estimates of event-free survival in the RIPC group and the sham-RIPC group were 85.2% and 85.0%, respectively, at 30 days after surgery and 84.5% and 84.4%, respectively, at 90 days after surgery (Fig. 2, and Table S3 in the Supplementary Appendix).

The cumulative incidence of the individual components of the composite end point (with death treated as a competing risk) is shown in Figure S1 in the Supplementary Appendix; we observed no benefit of RIPC treatment. Subgroup analyses of the primary end point did not reveal any significant variation in treatment effects according to the type of surgery, the use or nonuse of cholesterol-lowering drugs, the presence or absence of diabetes, or the EuroSCORE (Fig. 3, and Table S4 in the Supplementary Appendix). Of the prespecified covariates, only the EuroSCORE was prognostic for the risk of a primary end-point event: 10.1% of the patients (41 of 405) with a EuroSCORE of 0 to 2, 12.8% of the patients (70 of 547) with a EuroSCORE of 3 to 5, and 20.6% of the patients (89 of 433) with a EuroSCORE of 6 or higher had a primary end-point event (P<0.001 for all comparisons, by logistic regression). The multiplicity patterns for the individual components of the primary end point are presented in Figure S2 in the Supplementary Appendix.

There were no significant between-group differences with respect to the secondary end points (Tables S5, S6, and S7 and Fig. S3 through S6 in the Supplementary Appendix). No RIPC-related adverse events were observed. The level

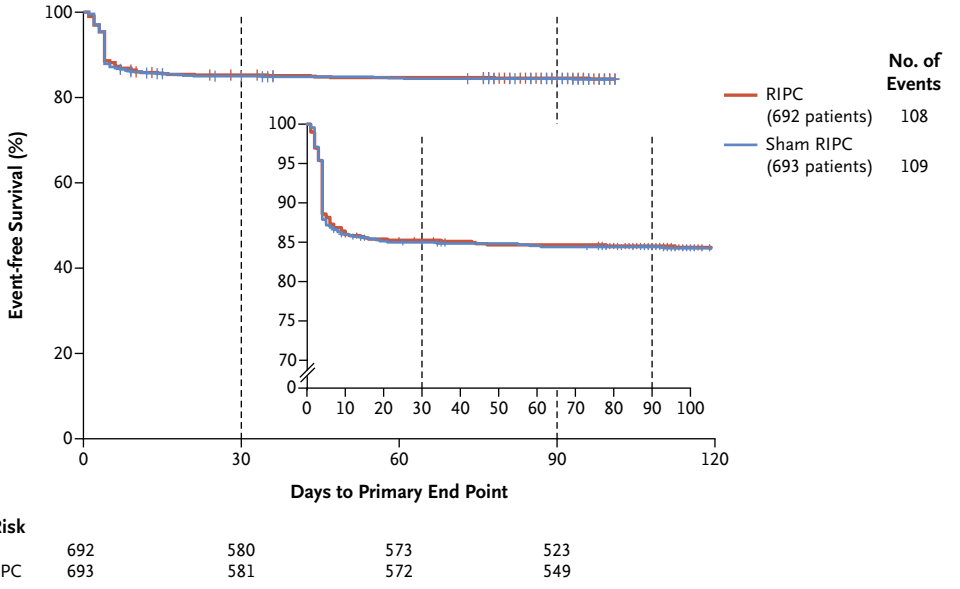

Figure 2. Kaplan–Meier Estimates of Event-free Survival.

Kaplan–Meier estimates are shown for the two intervention groups in the full analysis set. Data on 10 patients in the RIPC group and 9 patients in the sham-RIPC group were censored before day 30; data on 62 patients in the RIPC group and 36 patients in the sham-RIPC group were censored before day 90. Event-free survival did not differ significantly between the two groups (P=0.75 by Cox regression analysis, with adjustment for the stratification variables). The inset shows the same data on an enlarged y axis.

of troponin release was associated with the number of surgical procedures but did not differ significantly between the two study groups (Fig. S5 and S6 in the Supplementary Appendix).

With respect to the per-protocol set, 218 patients were excluded from the per-protocol analysis for the following reasons (some patients had more than one reason): 142 received an inadequate intervention (e.g., the cuff pressure was too low or was applied for too short a time), 41 received volatile anesthetics, 10 underwent a different type of surgery (e.g., off-pump coronary-artery bypass surgery), and 51 met other prespecified exclusion criteria (e.g., previous myocardial infarction ≤7 days before randomization or severe chronic obstructive pulmonary disease). Among the remaining 1167 patients (583 in the RIPC group and 584 in the sham-RIPC group), there was no significant between-group difference in the rate of the primary end point (81 patients [13.9%] in the RIPC group and 80 patients [13.7%] in the sham-RIPC group, P=0.88) or in the rate of any of its components: death (6 patients [1.0%] in the RIPC group and 3 patients [0.5%] in the sham-RIPC group, P=0.38), myocardial infarction (41 patients [7.0%] and 49 patients [8.4%], respectively; P=0.41), stroke (11 patients [1.9%] and 12 patients [2.1%], P=0.80), and acute renal failure (33 patients [5.7%] and 27 patients [4.6%], P=0.50) (Table S8 in the Supplementary Appendix). In addition, there was no significant between-group difference with respect to any secondary end point (Tables S8 and S9 and Fig. S7 in the Supplementary Appendix).

DISCUSSION

In this multicenter, double-blind, randomized trial involving 1403 patients who were scheduled to undergo elective cardiac surgery while under anesthesia with intravenous propofol, upper-limb RIPC did not show a relevant clinical benefit. RIPC was described more than 20 years ago. It has been suggested that the technique induces adaptive responses that markedly enhance the ability of vital organs (e.g., the heart) to withstand prolonged ischemic and reperfusion injury.[22] Initial laboratory studies of RIPC led to encouraging proof-of-principle human studies. Initial studies that used surrogate end points in patients

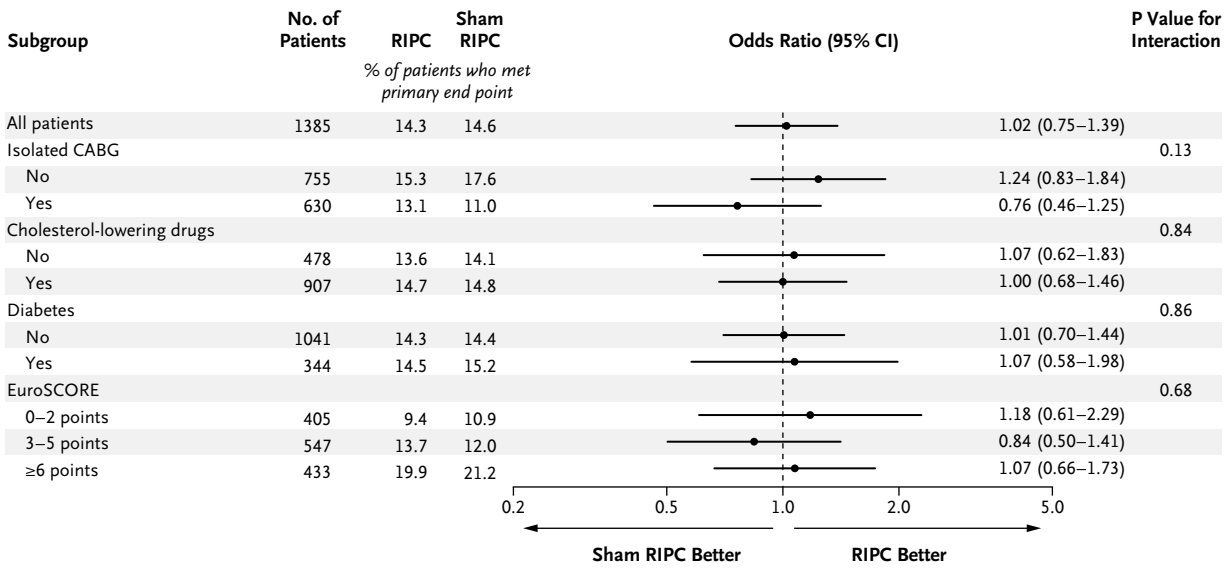

Figure 3. Prespecified Subgroup Analysis of the Primary End Point.

Explorative subgroup analyses did not reveal any significant between-group differences with respect to the type of surgery, the use or nonuse of cholesterol-lowering drugs, the presence or absence of diabetes, and the European System for Cardiac Operative Risk Evaluation (EuroSCORE) value (a higher value indicates a higher risk of death). The results of all model-based tests for treatment-by-subgroup interactions were nonsignificant. CABG denotes coronary-artery bypass grafting, and CI confidence interval.

undergoing cardiovascular surgery[2,3,23,24] or coronary intervention[25,26] or in patients with stroke[27] showed organ-protective effects, and some studies even showed improved clinical outcomes.[3,25,26] For example, 329 patients who were undergoing coronary-artery bypass grafting (CABG) were randomly assigned to RIPC or to a control intervention in a single-center trial.[3] The level of troponin I release, which was the primary end point, was significantly lower in the RIPC group than in the control group.

Other trials of RIPC in cardiac surgery failed to show beneficial effects.[5,6,28] Possible explanations for the divergent results of the trials are that most of the positive trials[2-4,24,29-31] used surrogate end points, were conducted at a single center, used a single-blind design, had a small sample size, included mostly patients undergoing isolated CABG, or were not standardized with respect to the anesthesia regimen. For example, propofol anesthesia was shown to attenuate RIPC-mediated effects in a small study,[32] but volatile anesthetics were also shown to attenuate cardioprotection by RIPC in a recent meta-analysis of 15 randomized trials.[33]

To overcome these limitations, we used a double-blind design with a dummy arm for the sham intervention and included patients undergoing CABG and complex cardiovascular surgery requiring cardiopulmonary bypass. With regard to the primary end point, no significant differences between treatment groups were found. In addition, no significant differences between treatment groups were found at the 30-day and 90-day follow-up. Secondary clinical end points, such as troponin and creatinine release, duration of mechanical ventilation, length of stay in the intensive care unit or the hospital, new onset of atrial fibrillation, and incidence of postoperative delirium, also did not differ significantly between the groups, although other confounders not recorded in this trial may have affected these variables. Neutral results were confirmed by logistic-regression analyses adjusted for the EuroSCORE, status with respect to diabetes mellitus, concomitant treatment with cholesterol-lowering drugs, and study center. Results in the full analysis set and the per-protocol set were completely concordant. The blinding of the endpoint assessors was a particular strength of this

trial. Subgroup analysis did not indicate that RIPC might yield a particular benefit in any relevant subgroup.

The neutral results in the current trial are consistent with those of the most recent meta-analysis by the Remote Preconditioning Trialists' Group, which included 23 trials of RIPC involving a total of 2200 patients undergoing cardiovascular surgery.[34] In that meta-analysis, RIPC did not have a significant effect on clinical end points, including death, myocardial infarction, acute renal failure, stroke, mesenteric ischemia, and hospital or critical care length of stay. Encouraging pilot data may not be able to be applied successfully to the clinical setting owing to a greater number of cardiovascular risk factors (e.g., older age, diabetes, and hyperlipidemia) and of concomitant medications (e.g., nitrates, statins, beta-blockers, and anesthetic agents) in the clinical setting than among patients in a pilot study.[35]

Under certain conditions, it is conceivable that RIPC may do more harm than good. Lucchinetti et al.[28] reported a higher incidence of the composite end point of arrhythmias or myocardial infarction among patients who received RIPC than among those who received a placebo intervention. Hong et al.[10] randomly assigned 1280 patients undergoing on-pump or off-pump CABG to receive RIPC plus remote postconditioning or to receive a control intervention; among patients who underwent off-pump CABG, those who received RIPC plus remote ischemic postconditioning had worse outcomes than those who received the control intervention.

Our study has certain limitations. First, we expected a composite complication rate of 12% in the control group in order to be able to detect a lower rate of 8% in the RIPC group (i.e., an absolute difference of 4 percentage points, corresponding to a 33% lower risk). With that relatively low complication rate, a 33% lower risk would indicate that, on average, 25 patients would need to be treated for 1 to benefit. The observation of higher-than-anticipated complication rates, as well as lower dropout rates, led to a sample-size reduction. Nevertheless, the present study had adequate power. Second, generalizability may be affected owing to the use of propofol anesthesia, which is uncommon in some areas, and owing to our exclusion criteria (e.g., urgent surgery, reoperations, recent myocardial infarction, and severe renal or liver disease). Furthermore, other RIPC protocols (e.g., involving lower-limb RIPC, a longer duration of ischemia, or more cycles) may still be protective. Third, the intended RIPC intervention may have been inadequate in approximately 8% of the patients because the cuff pressure was lower than specified in the protocol instructions. However, when analyzing the 1167 patients in the per-protocol set, we also did not observe any significant between-group differences, which suggests that any potential effect of RIPC might have been small in our trial. Finally, we cannot exclude the possibility that other outcome variables that were not measured (e.g., cardiac function) might have shown better results in the RIPC group.

In conclusion, in our large-scale, double-blind, multicenter trial, no significant difference was observed between upper-limb RIPC and a sham intervention with respect to the rate of postoperative myocardial infarction, stroke, renal failure, and death within 90 days after elective cardiac surgery.

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Dr. Bein reports receiving fees for serving on advisory boards from Pulsion Medical Systems, 3M, and Merck Sharp & Dohme; acting as medical advisor to the Medicines Company; receiving consulting and lecture fees from Edwards Lifesciences, CSL Behring, Orion Pharma, AbbVie, and GE Healthcare; receiving devices for research purposes from 3M; and receiving grant support from AbbVie and GE Healthcare. Dr. Böning reports receiving honoraria for presentations from Maquet, Bayer, AstraZeneca, and Orion Pharma. Dr. Stehr reports receiving honoraria and travel support from Teva/Ratiopharm. Dr. Heringlake reports receiving consulting and lecture fees from Orion Pharma. Dr. Sander reports receiving grant support from Ratiopharm, Pulsion Medical Systems, Edwards Lifesciences, the Medicines Company, and Fresenius Medical Care. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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