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In Reply:

We appreciate the comments by (1) Palomero-Rodríguez, Suárez-Gonzalo, and Laporta-Baez, (2) Zaugg and Lucchinetti, and (3) Xue, Cui, Cheng, and Wang regarding our recent publication in Anesthesiology "The Anesthesia in Abdominal Aortic Surgery (ABSENT) Study: A Prospective, Randomized, Controlled Trial Comparing Troponin T Release with Fentanyl-Sevoflurane and Propofol-Remifentanil Anesthesia in Major Vascular Surgery."[1] We are pleased that our study has led to these comments, which raise several important elements.

In their comment, Dr. Palomero-Rodríguez *et al.* emphasize that thoracic epidural analgesia (TEA) throughout the surgical process concurrently with general anesthesia is beneficial in terms of improved balance of myocardial oxygen supply or demand and greater hemodynamic stability. In the ABSENT study, TEA (thoracic level, 6 to 10) started after opening of the aortic cross-clamp and continued postoperatively. We found no differences in use of TEA between the two groups. However, we cannot exclude that TEA may have had a beneficial effect so that a potential protective effect of an anesthetic agent may be overshadowed by a TEA component, as Palomero-Rodríguez *et al.* suggested.

There are conflicting data on the impact of TEA on perioperative mortality and morbidity in noncardiac surgery. Some meta-analyses[2,3] have demonstrated reduced mortality and morbidity with neuraxial blockade. However, several studies on abdominal aortic surgery have not shown lower incidence of early myocardial ischemia,[4,5] myocardial infarction, mortality, or postoperative complications using TEA, compared with intravenous morphine.[6,7] In a recent *post hoc* analysis of the Perioperative Ischemic Evaluation Study,[8] patients with high risk of cardiovascular morbidity in fact had a three-fold increased risk of the primary outcome (cardiovascular death, nonfatal myocardial infarction, and nonfatal cardiac arrest) receiving general anesthesia combined with TEA, compared with general anesthesia without TEA. In addition, a recent meta-analysis[9] did not prove any positive influence of TEA on perioperative in-hospital mortality in patients undergoing noncardiac surgery.

Palomero-Rodríguez *et al.* suggested that the results of the ABSENT study would have been different if TEA had not been included. Two Cochrane analyses concluded that TEA reduces postoperative pain compared with systemic opioids after abdominal aortic surgery[10] and intra-abdominal surgery.[11] On the basis of this knowledge, we found it unethical to design a study, in which patients would have more postoperative pain than if they were not included. This was the main reason for including TEA in the ABSENT study. In addition, we designed the study to reflect current clinical practice, and today, TEA is an important component of the perioperative analgesic regimen.

In the comment by Zaugg and Lucchinetti, several aspects and interpretations of our study are questioned. They disagree with our conclusion that "*potential cardioprotective effects of volatile anesthetics found in cardiac surgery are less obvious in major vascular surgery.*" Their interpretation

Table 1. Use of Noradrenaline and Dopamine in Patients Receiving Sevoflurane (Group S, n = 97) or TIVA (Group TIVA, n = 96)

Variable	Group S	Group TIVA	*P* Value
Use of noradrenaline during surgery	14 (14)	9 (9)	0.375
μg noradrenalin (total)	470	496	0.999
Use of dopamine during surgery	10 (10)	26 (27)	0.003
mg dopamine (total)	40	22	0.614
Use of noradrenalin day 0 after surgery	20 (21)	19 (20)	0.999
μg noradrenaline (total)	3,054	2,816	0.939
Use of dopamine day 0 after surgery	7 (7)	6 (6)	0.999
mg dopamine (total)	90	126	0.414
Use of noradrenalin first day after surgery	14 (15)	15 (16)	0.999
μg noradrenaline per hour	147	148	0.365
Use of dopamine first day after surgery	5 (5)	5 (5)	0.999
mg dopamine per hour	7.1	9.2	0.421
Use of noradrenalin second day after surgery	8 (8)	8 (8)	0.999
μg noradrenaline per hour	97.5	99.1	0.574
Use of dopamine second day after surgery	2 (2)	1 (1)	0.999

Values are median or numbers of patients (%).
TIVA = total intravenous anesthesia.

of our data is that there in fact are cardioprotective effects of sevoflurane that we have misinterpreted. Their conclusion of our data is therefore that cardioprotective effects of sevoflurane are "*very similar*" to what has been reported for volatile anesthetics in previous studies both in on-pump and off-pump cardiac surgery. What we can agree about is that data from cardiac surgery have shown a cardioprotective effect of volatile anesthetics,[12–15] which is supported by two meta-analyses.[16,17] The discrepancy is whether or not data in our study[1] can be interpreted as absence or presence of cardioprotection in the sevoflurane group.

We reported that more patients were given dopamine in the total intravenous anesthesia (TIVA) group compared with that in the sevoflurane group ($P = 0.003$). Zaugg and Lucchinetti interpret this as improved cardiac function reflecting a clear advantage in the sevoflurane group. However, it should be emphasized that increased use of dopamine in the TIVA group was observed only during surgery and not after surgery. Propofol is known to have a substantially negative inotropic effect,[18] more pronounced than sevoflurane.[19] This direct hemodynamic effect may explain why dopamine was used to a greater extent in the TIVA group compared with that in the sevoflurane group during surgery. As demonstrated in table 1, there were no significant differences in the use of noradrenaline or dopamine between the two anesthetic groups during the first postoperative days. In addition, there were no significant differences in postoperative use of phenylephrine or ephedrine between the two groups. Thus, use of vasoactive drugs in the two anesthetic groups does not indicate cardioprotection in the sevoflurane group, as suggested by Zaugg and Lucchinetti. Because the study was not specifically designed to detect differences in use of vasoactive drugs, and because these drugs were administered at the discretion of the attending anesthesiologist, postoperative data were not given in the publication.

Zaugg and Lucchinetti point out that in addition to the "definitive standard" of cardioprotection, release of cardiac enzymes, other relevant outcome variables, might also be clinically important. We fully agree because patient care in most countries has reached high standards. Any additional protection may be unable to further reduce the release of cardiac enzymes, especially if most patients are treated with statins, aspirin, and β-blockers and have a TEA. In the ABSENT study, the primary endpoint was increased troponin T levels (>13 ng/l) on the first postoperative day, measured with a fifth-generation immunoassay. However, in prespecified substudies of the ABSENT study, echocardiographic indices of cardiac function and *N*-terminal prohormone of brain natriuretic peptide[20] and different biomarkers of inflammation and endothelial activation (unpublished data: December 31, 2013; Espen E. Lindholm, M.D.; Erlend Aune, M.D., Ph.D.; Ingebjørg Seljeflot, M.D., Ph.D.; Jan E. Otterstad, M.D., Ph.D.; Knut A. Kirkebøen, M.D., Ph.D.; Tønsberg, Norway) have also been evaluated. Thus, we have indeed measured other outcome variables. These data are reported separately because it was impossible to incorporate all the data in one publication.

Zaugg and Lucchinetti requesting serial postoperative determinations of troponin T levels in the ABSENT study. We agree that postoperative serial troponin measurements may reveal increased levels. In our study, according to protocol, blood samples were taken preoperatively, 30 min, 8 h after arrival at intensive care unit, first, second, and 30 days after surgery. Only plasma samples obtained preoperatively, 30 min, and first day after surgery were kept frozen at −80°C and analyzed after completion of the study, with a fifth-generation immunoassay. Preoperative and first-day data are reported in our publication.[1] However, plasma samples obtained at all time points (preoperatively, 30 min and 8 h after arrival at intensive care unit, first, second, and 30 days after surgery) were analyzed with a fourth-generation

Table 2. TnT Values (μg/l) Measured with a Fourth-generation Immunoassay in Patients Undergoing Abdominal Aortic Surgery in the Sevoflurane Group (Group S) or TIVA (Group TIVA)

Time of Measurement	Group S	Group TIVA	*P* Value
Preoperative	0.000 [0.000, 0.003] (0.000–0.067)	0.000 [0.000, 0.000] (0.000–0.035)	0.375
Number of patients (n)	94	96	
(n) with TnT >0.013 ng/l	16 (17)	10 (10)	0.210
Half-hour after ICU arrival	0.000 [0.000, 0.012] (0.000–0.070)	0.000 [0.000, 0.011] (0.000–0.210)	0.593
Number of patients (n)	97	96	
(n) with TnT >0.013 ng/l	19 (20)	18 (19)	0.999
8 h after ICU arrival	0.000 [0.000, 0.014] (0.000–0.150)	0.000 [0.000, 0.013] (0.000–0.230)	0.836
Number of patients (n)	96	96	
(n) with TnT >0.013 ng/l	25 (26)	22 (23)	0.737
First postoperative day	0.000 [0.000, 0.021] (0.000–0.640)	0.000 [0.000, 0.017] (0.000–0.370)	0.765
Number of patients (n)	96	96	
(n) with TnT >0.013 ng/l	34 (35)	30 (31)	0.646
Second postoperative day	0.011 [0.000, 0.028] (0.000–1.950)	0.010 [0.000, 0.028] (0.000–1.000)	0.499
Number of patients (n)	95	93	
(n) with TnT >0.013 ng/l	45 (47)	41 (44)	0.663
30 days	0.000 [0.000, 0.016] (0.000–0.210)	0.000 [0.000, 0.014] (0.000–0.284)	0.635
Number of patients (n)	86	84	
(n) with TnT >0.013 ng/l	26 (30)	21 (25)	0.495

Values are median [25%, 75% percentile] (range) or numbers of patients (%).
ICU = intensive care unit; TIVA = total intravenous anesthesia; TnT = troponin T.

immunoassay. Not to confuse the reader by mixing data from the fourth- and the fifth-generation immunoassay, data obtained by the fourth-generation immunoassay were not included in our publication. Serial postoperative determinations by fourth-generation immunoassay did not show significant differences between the two groups at any time points (table 2).

Because fentanyl was used to potentiate sevoflurane anesthesia in the sevoflurane group and remifentanil in the TIVA group, Zaugg and Lucchinetti claim that the ABSENT study cannot answer the hypothesis whether a sevoflurane-based anesthesia is more cardioprotective than propofol-based anesthesia. We are aware of both experimental[21,22] data (although mostly in rats) and clinical[23] data indicating a cardioprotective effect of remifentanil. Also, fentanyl has been shown to have a cardioprotective effect.[24] For induction of anesthesia, thiopental was used in the sevoflurane group and propofol, which also has been shown to be cardioprotective,[25–27] in the TIVA group. Cardioprotective effect of thiopental is controversial.[28,29] In the current study, fentanyl was used for induction of anesthesia in both groups. Thus, there are data indicating protective effects not only for remifentanil but also for fentanyl, propofol, and thiopental. Avoiding these agents is not possible. In the publication, we therefore state: "The use of opioids and choice of induction agents might have influenced the results and made the results harder to interpret."

When designing the ABSENT study, we aimed to compare the two most clinically used methods to anesthetize patients undergoing major noncardiac surgery in the Nordic countries (sevoflurane combined with fentanyl or propofol combined with remifentanil). Of course, we could have designed a perfect "scientific" study, which would not have been so clinically applicable (no TEA, sevoflurane combined with opioid X *vs.* propofol combined with opioid X, identical induction agents in the two groups, only inclusion of patients not on β-blockade or aspirin or cholesterol-lowering medication). Our study design does not allow a direct comparison between cardioprotection with sevoflurane and propofol. However, the study design can answer the hypothesis whether a *sevoflurane-based* anesthesia (in our study fentanyl) is more cardioprotective than a *propofol-based* anesthesia (in our study remifentanil). In the publication, we therefore state: "We hypothesized that sevoflurane-*based* anesthesia is cardioprotective compared with TIVA also in elective abdominal aortic surgery."

Zaugg and Lucchinetti do have a point that aspirin was used significantly more in the TIVA group compared with in the sevoflurane group (73 *vs.* 60 patients). This aspect is discussed in our publication and might theoretically influence the results. However, it is questionable whether 13 more patients on aspirin in the TIVA group had a major impact on the primary endpoint (increased troponin T levels on the first postoperative day), which had a *P* value of 0.999 between the two anesthetic groups. Zaugg and Lucchinetti claim that more patients were on β-blockade in the TIVA group. However, there was no significant difference between the two groups (46 *vs.* 38 patients; $P = 0.221$).

We do not agree that open abdominal aortic repair and off-pump coronary bypass graft surgery are comparable types of surgery, as Zaugg and Lucchinetti suggested. Off-pump coronary bypass surgery involves manipulation of the heart and coronary arteries, which might lead to myocardial injury.[30] In both on-pump and off-pump coronary

Table 3. Hemoglobin (g/dl) in Patients Undergoing Abdominal Aortic Surgery in the Sevoflurane Group (Group S, n = 97) and in the TIVA (Group TIVA, n = 96)

Time of Measurement	Group S	Group TIVA	*P* Value
Half-hour after surgery	10.4 (±1.3)	10.4 (±1.1)	0.826
First day after surgery	10.2 (±1.1)	10.1 (±1.0)	0.727
Second day after surgery	10.0 (±1.2)	10.0 (±0.9)	0.747

Values are mean (±SD).
TIVA = total intravenous anesthesia.

bypass surgery, one cannot exclude some degree of regional ischemia, in contrast to open abdominal aortic repair where direct manipulation of the heart never occurs.

On the basis of own data,[31] Zaugg and Lucchinetti suggested that sevoflurane may have masked a cardioprotective effect by remote ischemic preconditioning through aortic cross-clamping or declamping. The opposite might theoretically also have occurred: remote ischemic preconditioning might have masked a cardioprotective effect of sevoflurane. Gerd Heusch group in Essen recently published an elegant study[32] demonstrating a remote ischemic preconditioning effect during coronary bypass surgery by three cycles of 5-min upper arm ischemia/5-min reperfusion before induction of anesthesia. This procedure led to reduced release of troponin I and reduced 1.5-yr mortality, even though anesthesia was maintained with isoflurane (0.6 to 1.0%). The same group has also demonstrated an effect of remote preconditioning during coronary bypass surgery when isoflurane, but not propofol,[33] was used to maintain anesthesia, opposite the suggestions of Zaugg and Lucchinetti. The above-mentioned studies are on coronary bypass surgery with repeated single-limb ischemia lasting a few minutes to induce protection. This is in major contrast to major vascular surgery where aorta clamping (lasting often >1 h) is a standard part of the surgical procedure. In our study, the aortic cross-clamp time did not differ between the two groups. However, we agree that the procedure might have affected the results. In the publication, we therefore state: "We cannot exclude that remote protection may have masked anesthetic cardioprotective differences."

Due to regulatory rules in Norway, only data on total long-term mortality can be obtained, with no possibility to separate cardiovascular and noncardiovascular death. From a clinical view, we believe that total mortality itself has some interest. We focused our publication on the primary endpoint. However, we also reported outcomes such as complications, length of stay, and mortality as secondary endpoints. We acknowledge that the study was not adequately powered to comment definitively on these secondary endpoints. Thus, it would not be appropriate to perform logistic regression analyses to identify independent variables associated with long-term mortality. The study did not aim to identify predictors of death or troponin release, so performing logistic regression analyses or multivariate Cox proportional hazards models was beyond the purpose of the publication.

Zaugg and Lucchinetti refer several times to on-pump and off-pump coronary surgery and not to noncardiac surgery when arguing for a cardioprotective effect of volatile anesthetics. We believe that it is important to differentiate between cardiac- and noncardiac surgery in this matter. Evidence so far supports that one should be careful to cite data obtained in cardiac surgery when arguing for a cardioprotective effect of volatile agents in noncardiac surgery.

Xue *et al.* highlight perioperative hemoglobin and anemia as important prognostic factors in patients undergoing major vascular surgery and we fully agree. As stated in the publication, patients were transfused according to the protocol if hemoglobin level was less than 8.0 g/dl. Within the 2 first postoperative days, the mean hemoglobin level was approximately 10 g/dl (table 3) with no intergroup differences. Thus, differences in hemoglobin level between the two groups did not affect our results.

In the ABSENT study, patients received sevoflurane with a minimal alveolar concentration (MAC) of 0.7 to 1.5, as stated in the publication. The protocol was followed rigorously. In terms of the lowest MAC to obtain a cardioprotective effect, we do not agree with Xue *et al.* that 1.0 MAC or more is needed. In animal studies, concentrations as low as 0.25 MAC have induced a protective effect. However, it seems to be a dose-dependent effect.[34] Concerning the comments by Xue *et al.* on use of opioids, vasoactive drugs, and repeated troponin measurements, we kindly refer to the above replay.

We feel that our conclusion: "potential cardioprotective effects of volatile anesthetics found in cardiac surgery are less obvious in major vascular surgery" remains firm with adequate and sufficient documentation. We believe that further research on volatile anesthetics and cardioprotection in noncardiac surgery should proceed in the direction of further studies in noncardiac surgery and not by extrapolation from data obtained in cardiac surgery.

Competing Interests

Dr. Lindholm has received fees for presentations (low-flow anesthesia and use of desflurane) by Baxter AS, Oslo, Norway. The other authors declare no competing interests.

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Predicting Postoperative Morbidity: In What Procedures and What Patients?

To the Editor:

In an extensive effort, Moonesinghe *et al.*[1] summarize risk-stratification tools for predicting morbidity and mortality after major surgery and conclude that studies have limitations and further international studies are required regarding clinical decision making and patient outcome. Although this review is a laudable effort, unfortunately the review predominantly is based on studies published before 2010 and may otherwise not provide a critical reassessment to the question raised in 2013 for several reasons:

1. First of all, the review fails to discuss that surgical techniques have changed over the last decade regarding the use of different minimal invasive techniques which may decrease postoperative morbidity, and thereby hindering translation of previous prediction studies from open procedures to minimal invasive surgery.
2. There is a need for procedure-specific studies and not a combination of prediction studies from different surgeries, because different procedures have different outcome problems and different pathogenic mechanisms.
3. There is no mentioning in the review by Moonesinghe *et al.*[1] of the implications of the fast-track methodology (or Enhanced Recovery Programs) for the value of predictive scores. This may be important, because these optimized perioperative care programs have been demonstrated to decrease postoperative morbidity,[2–4] but neither included nor mentioned in the reported studies. Therefore, valid future predictive tools must be based on well-defined, procedure-specific, evidence-based care programs including details on choice of anesthetic and analgesic techniques, which may also modify outcomes. Such assessments may preferably be based on studies based on the question "Why is the surgical high-risk patient at risk?,"[3] or in other words whether new predictive tools will show whether the previous risk indices may or may not be exported to fast-track surgery.[3,4]

In conclusion, there is an urgent need for new and better tools to predict postoperative morbidity after major surgery compared with previous data. Such efforts should consider developments in surgical techniques, surgical care and anesthetic and opioid-sparing multimodal analgesic techniques, and then on a procedure-specific basis. Otherwise, we will continue to look at data which reflect the past surgical and perioperative care programs which may not be able to provide relevant information where modern care principles have been introduced.

Competing Interests

The authors declare no competing interests.

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In Reply:

We thank Dr. Kehlet for his comments on our article.[1] His letter raises important issues which we broadly agree with. The implementation of fast-track or "enhanced recovery" programs and the increasing use of minimally invasive surgical approaches are two examples of how surgical practice has changed in recent years, at least in some parts of the world. These may have impact on the risk of patient morbidity and mortality, particularly in the short term. Furthermore, improvements in the medical management of some chronic illnesses (*e.g.*, ischemic heart disease) mean that the implications of such illnesses for patient health and perioperative prognostication are quite different today, compared with 20 yr ago when some of the risk-stratification tools featured in our systematic review were first developed and validated.

Thus, we agree that an approach to risk stratification is warranted which is responsive to such changes in practice and will also enable specialty-specific risks to be taken into consideration. The use of technology (such as mobile apps) and large datasets ("big data") present opportunities to refine existing risk-stratification methodology for the modern era, leading to the development, validation, and regular reevaluation and recalibration of risk-prediction tools. However, the challenge of implementing the collection of such large datasets in a systematic manner remains significant in many