right-sided procedure done with the heart perfused and beating continuously) from one with the same duration of bypass but with a cross-clamp and cardioplegia. Second, the dose–response pattern of a need for greater inotropic support with longer periods of cross-clamping is unlikely to be a simple threshold effect at 120 min. The dichotomous treatment of CPB time is unable to distinguish, for instance, between patients on bypass for 125 min *versus* 325 min. Linear or at least multilevel treatment of left ventricular ejection fraction and cross-clamp time would have improved the ability to adjust for the potential confounding effect of differences in baseline function and of longer periods of myocardial ischemia.

3. The two cohorts are separated only by the presence or absence of inotrope use; there is no ability to study the dose–response of low- *versus* high-dose inotropes, multiple inotropes, and so on. A subsequent logistic regression in the inotrope group could have assessed the relationship between inotrope dose (for instance, using a scoring system such as Vasoactive-Inotropic Score)[5] and mortality. Also, why was the use of norepinephrine excluded (resulting in 967 patients excluded from analysis)? It has positive inotropic qualities in addition to being a "vasopressor" (as the authors state), and in many institutions is the first-line agent in heart surgery.
4. The larger design flaw in this study is that the retrospective approach fails to compensate for the differences between patients that would lead anesthesiologists and surgeons to make the decision to use an inotrope in the first place. Propensity matching (even with better variable selection) probably cannot ever capture important variables that affect this decision: the quality of cardioplegia and myocardial protection, the presence of air emboli to the coronary arteries during or immediately after weaning from CPB, and most importantly, the appearance (by gross visualization and echocardiography) of ventricular function before weaning from CPB. Although it is probably true that at least some surgeons and anesthesiologists use inotropes routinely even in patients who have no objective evidence that they need them, the retrospective design does not isolate this subgroup. The concomitant use of a vasodilator (to control blood pressure in the setting of hyperdynamic and/or hypertensive physiology when an inotrope is added to an already well-functioning ventricle) might be a better marker for patients who do not need the inotrope. That comparison—inotrope plus vasodilator *versus* neither—would be a more interesting guide for clinicians, as it could answer a more important question: does raising cardiac output (independent of changing blood pressure) improve or worsen outcomes?

As is, the Nielsen study mostly can be said to demonstrate that inotrope use is a marker for poor cardiac function after bypass and hence worse outcomes (hardly surprising), and it risks broadly discouraging the use of an important therapy that is lifesaving in selected patients.

Competing Interests

The authors declare no competing interests.

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In Reply:

We thank Dr. Maxwell *et al.* for their interest and comments on our study,[1] and we will try to address some of their concerns regarding the methodology that was used in the study and our interpretation of the findings.

Dr. Maxwell *et al.* express concern about the propensity score–based matching process. We were able to match 56% of the patients treated with inotropic therapy with a nontreated patient. The fact that it was not possible to match 100% of the patients indicates that the distribution of the propensity score among the treated and nontreated patients did not fully overlap. However, we do not agree that discarding patients in the matching process from the original cohort *per se* implies that the internal validity of the study is affected. It may, however, imply that concern should be taken before extrapolating the findings to patients that differ from the characteristics of our matched population. When matching our patients, we assessed the balance using both absolute standardized differences and variance ratios.

The variance ratios of the individual covariates in the matched population ranged from a low of 0.86 (critical preoperative state) to high of 1.18 (off pump surgery; table 1). Along with the standardized differences of less than 10%, we find strong indications of a well-balanced matching. Notably, the covariate postinfarct septal rupture had a very low variance ration of 0.6, which is probably due to the very few patients characterized by this covariate (five patient in treated group and three with no inotropic therapy).

Table 1. Variance Ratios in Propensity Matched Sample

Covariates	Variance Ratio
Demographics	
Age (yr)	1.01
Females	1.01
EuroSCORE	1.00
Patient-related EuroSCORE variables	
Chronic pulmonary disease	0.98
Extra cardiac arteriopathy	0.99
Neurologic dysfunction disease	0.93
Previous cardiac surgery	0.91
Serum creatinine >200 μmol/l	1.05
Active endocarditis	0.87
Critical preoperative state	0.86
Other patient-related variables	
Preoperative arrhythmia	1.00
Preoperative RRT	0.87
Cardiac-related EuroSCORE variables	
Unstable angina	0.86
Recent myocardial infarction	1.05
Pulmonary hypertension	1.00
LVEF ≤30%	0.91
Procedure-related EuroSCORE variables	
Emergency surgery	0.89
CABG only	0.98
Thoracic aortic surgery	0.99
Postinfarct septal rupture	0.60
Other procedure-related variables	
Intravenous anesthesia	0.99
Epidural supplement	1.09
CPB time >120 min	1.01
Off-pump surgery	1.18
Cardiac center	
Center A	1.00
Center B	1.00
Center C	1.03

CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; LVEF = left ventricular ejection fraction; RRT = renal replacement therapy.

Table 2. One-year Mortality by Left Ventricular Function and Treatment Group

EuroSCORE EF Definition	Control	Inotropes
LVEF ≥50	27 (3.76%)	80 (11.10%)
LVEF 31–49	19 (4.85%)	45 (11.90%)
LVEF ≤30	3 (5.00%)	8 (11.27%)
P value	0.6538	0.9223

EF = ejection fraction; LVEF = left ventricular ejection fraction.

Furthermore, the order of the patients was randomized before matching although this was not specified in the article.

As we already discussed in our article, we were not able to control for residual confounding relating to intraoperative events not accounted for by procedure scoring.

We agree that extracorporeal circulation (ECC) time and perhaps especially cross-clamp (CC) time have some impact on whether patients are treated with inotropes and with which dose. We also agree that there might be a correlation between ECC/CC times and mortality. Thus, it is possible that the dichotomization with on/off bypass and then ECC time greater than/less than 120 min was too "tight." However, we could not demonstrate any statistically significant difference in the mortality when the treated and nontreated was handled individually according to ECC time in either 30- or 60-min intervals. Including CC time in a conditional linear regression analysis on the matched cohort reduced the risk estimate of 30-day mortality from adjusted hazard ratio 3.71 (2.11–6.53, 95% CI) to a hazard ratio 2.39 (1.57–3.63, 95% CI).

The authors likewise express concern about our dichotomization of ventricular function into less than or equal to 30% and greater than 30%. It could be argued that a more detailed categorization of patients with normal left ventricular function would be relevant.

However as table 2 indicates, there was no significant difference in mortality between different states of left ventricular function but a constant difference between treated and nontreated patients.

As we wanted to primarily investigate the effect of inotropic therapy, we excluded the patients who had exclusively received vasopressors and we think it is well established that norepinephrine has only minimal inotropic effect, as it is primarily an α-receptor agonist and only have very little, if any, direct β-effect.

Dr. Maxwell and colleagues suggest studying the dose-response of inotropic therapy by a vasoactive-active scoring system. To our knowledge the scoring system in concern has been validated only on a neonatal and infant population, and we do not find it appropriate to apply on an adult population. Our data were not granular enough to distinguish whether inotropes were given in parallel or sequential therapy, but we have future studies on a larger population size that will focus on the association between specific inotropes, dosages, and outcome.

The problem of capturing the anesthesiologists "gut feeling" will exist in both propensity score matching studies and in a randomized clinical trial, unless a very fixed protocol. We know that initiation of inotropes is highly dependent on the name of the anesthetist,[2] thus we tried to adjust for the provider effect in the conditional regression analysis.

Although an observational study as the present always will be challenged with the risk of confounding by indication, we believe that the design and statistical analyses of our study are enough robust to interpret data as to raise concern about a possible harmful effect of inotropic therapy in cardiac surgery. The concern of a possible risk that could exceed the beneficial effect of inotropic therapy to some patients is not novel. There is a growing body of literature, especially from large-scale randomized trials of nonsurgical heart failure patients that indicate that inotropic therapy may cause more harm than good. In the light

of the lack of randomized clinical trials demonstrating any improvement of clinical outcomes including mortality from perioperative inotropic therapy,[3–5] we are restraint to ignore or explain away the underlying signal our data raise.

Competing Interests

The authors declare no competing interests.

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Lung Ultrasonography for the Detection of Anesthesia-induced Lung Atelectasis

To the Editor:

We have read with great interest the article by Acosta *et al.*[1] exploring the use of lung ultrasound as a mean to detect intraoperative atelectasis. However, despite their statement to the contrary, the occurrence of B lines in the setting of atelectasis has already been described by others. Although B lines were initially thought to originate from the interaction of the ultrasound beam with thickened subpleural interlobular septa found in alveolar-interstitial pathologies,[2] recent work has challenged this hypothesis. In an elegant series of experiments, Soldati *et al.*[3–5] have shown that B lines are observed when the ultrasound beam interacts at the pleural surface with lung tissue of a specific density. Although this can occur with the replacement of subpleural air by an ultrasound-conductive substance (*e.g.*, water, pus, blood, and fibrous tissue), the withdrawal of air (*e.g.*, resorption atelectasis) will also lead to the genesis of B lines. Demonstrating this last point, in an *ex vivo* animal model of graded atelectasis, B lines were observed in increasing numbers with increasing atelectasis. Pathologic examination of the excised lungs showed diffusely compressed alveoli mixed with sporadic areas of normally expanded distal air spaces.[5]

The study by Acosta *et al.* comes at an interesting moment. The recent publication of two randomized controlled trials[6,7] exploring the impact of intraoperative mechanical ventilation parameters on postoperative pulmonary complications has generated much interest.[8] Although some have linked the negative results of the PROVHILO (PROtective Ventilation using HIgh versus LOw positive end-expiratory pressure) trial to a lack of regular recruitment maneuvers and a positive end-expiratory pressure set too high,[9] others blame the use of inappropriately high tidal volumes in the control group for the positive results in the IMPROVE (Intraoperative PROtective VEntilation) trial.[10] In the absence of imagery supporting claims of atelectasis or overdistention, the culprits usually blamed for the development of postoperative pulmonary complications, it is unlikely this question will be resolved before more data becomes available. Interestingly, recent anesthesiology literature has demonstrated the advantage of hemodynamic optimization[11] championing the concept that individualization is preferable to a "one size fits all" approach. Likewise, individualization of mechanical ventilation parameters might be an interesting avenue to explore if we wish to decrease the occurrence of postoperative respiratory complications. This hypothesis is supported by spiral computed tomography studies reporting significant interpatient variability in the amount of atelectasis induced by general anesthesia.[12,13] Therefore, we believe that bedside monitoring to detect lung atelectasis or overdistention is needed. Although magnetic resonance imaging and computed tomography fulfill this requirement, they cannot be used in an intraoperative setting except in specially designed operating rooms and could not realistically be repeated throughout a procedure. Because lung ultrasonography can be performed at the bedside and is devoid of any ionizing radiation, the present study by Acosta *et al.*, although interesting in and of itself, is an important milestone toward establishing lung ultrasonography as a tool to optimize intraoperative mechanical ventilation parameters. Other investigators have described loss of aeration scales that have allowed the study of the therapeutic effects of antibiotics in ventilator-associated pneumonia,[14] the effect of different levels of positive end-expiratory pressure in patients with acute respiratory distress syndrome on lung reexpansion[15] and the detection of patients likely to fail extubation after a successful spontaneous breathing trial.[16] Although not developed specifically for the diagnosis and monitoring of anesthesia-induced atelectasis, the use of these scales would have been an interesting addition to the study by Acosta *et al.* Whether to optimize intraoperative mechanical ventilation parameters or to assist anesthesiologists in the care of hypoxemic patients,