

1. Standards are needed for the evaluation of continuous noninvasive blood pressure monitoring systems.
2. These standards should probably define separate benchmarks for systolic, diastolic, and mean arterial pressure. Because systolic, diastolic, and mean arterial pressure are inherently different by nature, different acceptability threshold should be applied.
3. These standards should probably develop a methodology for assessing the trending ability of these systems. Because these systems will be used as continuous monitors in the clinical setting, their trending ability is as important as their instantaneous accuracy.
4. When such standards exist, clinician scientists should follow them carefully when conducting clinical studies testing these systems.

In conclusion, we would like to thank Fortin *et al.* for echoing our main message and reinforcing it. We truly believe that the development and validation of this next generation of blood pressure monitoring systems is promising, but will require close collaboration between industry, clinician scientist, and regulatory agencies to make them beneficial to our patients.

### Competing Interests

Maxime Cannesson is a consultant for Edwards Lifesciences (Irvine, California), Covidien (Boulder, Colorado), Masimo Corp. (Irvine, California), ConMed (Irvine, California), and Philips Medical System (Suresnes, France). A Nexfin monitor (BMEYE B.V., Amsterdam, The Netherlands) and a CNAP monitor (CNSystems, Graz, Austria) were loaned to Maxime Cannesson and his research team in 2010. Maxime Cannesson publicly endorsed the Nexfin technology in a BMEYE newsletter. The other authors declare no competing interests.

**Maxime Cannesson, M.D., Ph.D., Joseph Rinehart, M.D., Sang-Hyun Kim, M.D., Ph.D.** University of California Irvine Health, Irvine, California (M.C.). mcannesson@uci.edu

### References

1. Kim SH, Lilot M, Sidhu KS, Rinehart J, Yu Z, Canales C, Cannesson M: Accuracy and precision of continuous non-invasive arterial pressure monitoring compared with invasive arterial pressure: A systematic review and meta-analysis. *ANESTHESIOLOGY* 2014; 120:1080-97
2. Non-invasive sphygmomanometers—Part 2: Clinical validation of automated measurement type, ANSI/AAMI/ISO 81060-2:2013. Arlington, Association for the Advancement of Medical Instrumentation, 2013, pp 1-22

(Accepted for publication September 3, 2014.)

## Inotrope Use in Cardiac Surgery: A Cause of Worse Outcomes, or Just a Marker of Patients Who Are at Risk?

To the Editor:

Although Dr. Nielsen *et al.*<sup>1</sup> are to be commended for their efforts to investigate the potential detrimental effects of

inotropic therapy in cardiac surgery, we believe that methodological problems significantly limit the validity of their conclusions.

1. Insufficient information about the result of the matching process is provided, but enough to indicate what appears to be a significant flaw in methodology. First, their matching algorithm discarded a large number of both treatment and control patients (n = 6,005 patients were identified to be “included” in analysis; after propensity matching, only n = 2,340 [39%] remained). This implies a considerable lack of common support (overlap between the propensity score distributions of the two cohorts), which, even in the presence of a good match, increases risk of bias through unmeasured confounders and makes the estimate of the treatment effect unreliable.<sup>2</sup> Second, the authors cite Donald Rubin (coinventor of propensity score matching), but use only one of the three metrics he recommends to judge the quality of a match: absolute standardized difference. Neither the variance ratios of the propensity scores between groups, nor the ratio of variance of the residuals of each covariate is reported.<sup>3,4</sup> These are important, because the match is vulnerable to systematic differences in how the propensity scores were assigned. Finally, greedy matching depends on the order of patients, so it should be preceded by randomizing the order of patients in the dataset, which the authors do not report.
2. These design decisions in the propensity matching algorithm leave the study open to the possibility that these unmeasured confounders—and not the effect of inotropic therapy—are responsible for the observed outcome difference. Some variables were treated as overly simplistic dichotomous variables, which fail to capture important differences between patients, such that inotropic support may continue to act as nothing more than a marker for sicker patients with less well-functioning ventricles. Left ventricular ejection fraction was treated as a binary variable: less than or equal to 30% or greater than 30%. Therefore, their propensity matching would not differentiate between a patient with a baseline left ventricular ejection fraction of 35% and one with a baseline left ventricular ejection fraction of 65%. Duration of myocardial insult was captured only by cardiopulmonary bypass (CPB) time, again treated as a dichotomous variable (>120 min or ≤120 min). There are two problems with this decision: first, the need for inotropic support is more closely related to the duration of myocardial ischemia, *i.e.*, the aortic cross-clamp time, than the time on bypass. Although CPB time is correlated with cross-clamp time, different surgeons may adopt different temporal approaches to weaning from bypass such that two surgeons with the same cross-clamp time will have very different CPB times. Indeed, the use of CPB time without cross-clamp time would prevent differentiation of a patient who had no aortic cross-clamp and no myocardial ischemia (*e.g.*, a

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)<sup>5</sup> 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.

**Bryan G. Maxwell, M.D., M.P.H., Jack O. Wasey, B.M., B.Ch., Eugenie S. Heitmiller, M.D.** Johns Hopkins University School of Medicine, Baltimore, Maryland (B.G.M.). bmaxwell@jhu.edu

## References

1. Nielsen DV, Hansen MK, Johnsen SP, Hansen M, Hindsholm K, Jakobsen CJ: Health outcomes with and without use of inotropic therapy in cardiac surgery: Results of a propensity score-matched analysis. *ANESTHESIOLOGY* 2014; 120:1098–108
2. Stuart EA: Matching methods for causal inference: A review and a look forward. *Stat Sci* 2010; 25:1–21
3. Rubin DB: Using propensity scores to help design observational studies: Application to the tobacco litigation. *Heal Serv Outcomes Res Methodol* 2001; 2:169–88
4. Rubin DB: The design *versus* the analysis of observational studies for causal effects: Parallels with the design of randomized trials. *Stat Med* 2007; 26:20–36
5. Gaies MG, Gurney JG, Yen AH, Napoli ML, Gajarski RJ, Ohye RG, Charpie JR, Hirsch JC: Vasoactive-inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. *Pediatr Crit Care Med* 2010; 11:234–8

(Accepted for publication September 16, 2014.)

## In Reply:

We thank Dr. Maxwell *et al.* for their interest and comments on our study,<sup>1</sup> 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 ratio 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).