AGE- AND DISEASE-RELATED VARIATIONS IN B-TYPE NATRIURETIC PEPTIDE RESPONSE AFTER PEDIATRIC CARDIAC SURGERY

To the Editor:

We read with interest the article of Amirnovin and colleagues,[1] "B-type natriuretic peptide levels predict outcomes in infants undergoing cardiac surgery in a lesion-dependent fashion," recently published in the *Journal*. We appreciate and agree with the message of this work regarding the importance of B-type natriuretic peptide (BNP) as a prognostic marker in pediatric cardiac surgery.

The opposing patterns of BNP postsurgical response in the neonatal group (postsurgical drop) and older children (postoperative rise) are similar to those we described in a recent work involving 162 children undergoing cardiac surgery, including 57 neonates and 58 infants.[2] We consider important the division of patients by age and disease severity groups, with a particular attention to the neonatal age, because neonatal cardiac surgery carries on average a higher surgical risk and a more troublesome outcome.[2-4]

Certainly, disease severity plays an essential role in outcome and BNP response, and this may justify division by surgical intervention, such as that suggested by Amirnovin and colleagues.[1] At the same time, however, age per se continues to represent an important additional, independent factor affecting prognosis.[2] In our own work, both age and severity of disease independently affected BNP levels in children with congenital heart disease; when age and disease severity were considered together, however, only age remained significant.[2] Thus for the same disease severity class age plays an important role in hormonal response (and in the final outcome). For example, BNP levels in neonates with Aristotle Basic Complexity (ABC) scores II and II clearly differed from those in older children with the same ABC scores but did not differ from those in neonates with ABC score IV (Figure 1).[2]

In particular, it is important to consider how important maturational and adaptive changes in cardiac function (including cardiac endocrine function) occur early in life,[2,5] which may strongly affect BNP response in neonates and infants with congenital heart disease. A perfect system of dividing children with congenital heart disease undergoing cardiac surgery (by age, by intervention, by disease) is probably not easily achieved. Wider studies, which may allow a robust single-defect statistical analysis, are required to draw stronger conclusions. In the meantime, age and disease should be equally considered for correct evaluation of BNP values in children undergoing cardiac surgery.

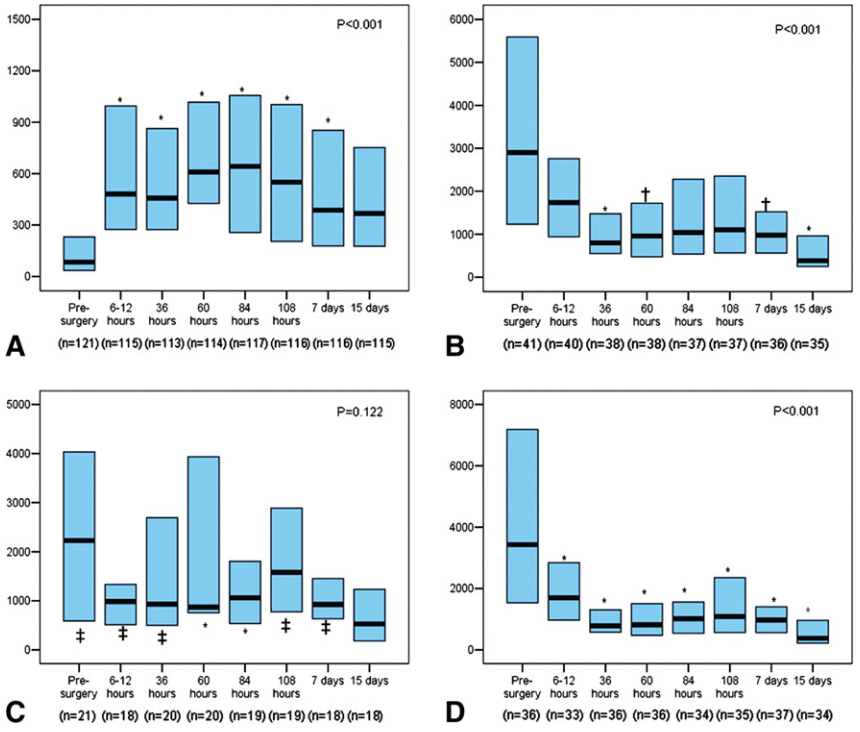

FIGURE 1. B-type natriuretic peptide *(BNP)* level time course in the whole population and in neonates according to disease severity. A, Values overall in Aristotle categories I, II, and III. B, Values overall in Aristotle category IV. C, Values in neonates in Aristotle categories II and III. D, Values in neonates in Aristotle category IV. *Bold horizontal line* represents median; *box* represents interquartile range. At each time point, *asterisk* indicates $P < .001$ for difference from presurgery level; *dagger* indicates $P < .05$ for difference from presurgery level; *double dagger* indicates $P < .001$ for difference between neonates and older age group (infants, toddlers, and children); *section mark* indicates $P < .05$ for difference between neonates and older age group (infants, toddlers, and children).

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Reply to the Editor:

We appreciate the thoughtful comments that Cantinotti and colleagues expressed in their letter. Cantinotti and colleagues are to be commended for their important body of work, which has advanced the understanding of B-type natriuretic peptide (BNP) levels in pediatric patients with congenital heart disease.[1]

We agree that levels of BNP are age dependent both in healthy neonates and in those with congenital heart disease. Also, as we indicated in the recent article under discussion,[2] the rapid changes in BNP levels after surgical intervention (within hours of the operation) imply that there are physiologic changes associated with the specific surgical interventions because of the particular underlying cardiac defects that determine the release of BNP. Indeed, neonates with univentricular physiology have very high preoperative BNP levels relative to those of age-matched healthy neonates and also relative to those with left-to-right shunts. In our study, there was also a trend toward higher BNP levels in neonates with univentricular physiology relative to those undergoing an arterial switch operation. We believe this is one reason that studies grouping neonates into single cohorts,[3,4] without consideration for the specific cardiac defects, have not found the postoperative decreases in BNP that both we[2] and Cantinotti and colleagues[1] found.

We therefore caution against relying on disease severity scoring systems that group diverse cardiac defects within particular categories or combine various diagnostic criteria, such as the Risk Adjustment for Congenital Heart Surgery 1 and Aristotle Basic Complexity scores, for the interpretation of perioperative BNP levels. Indeed, these scoring systems do not fully account for the variability in outcomes seen, demonstrating that other factors remain important.[5] In attempting to understand better the physiologic release of a biomarker and its implications for prognostication and goal-directed therapy, the use of such scoring systems is therefore likely to fall short in accounting for the variability in levels of the biomarker. In fact, in Figure 1 of the letter of Cantinotti and colleagues, neonates in Aristotle Basic Complexity categories II and III can be seen to have more variability in BNP levels than those in category IV, probably because of the differences in cardiac lesions and the physiologic changes associated with surgery that inherently differ by category in these systems. A further example of the specificity we described in our study was shown in preliminary data from our previous work, where we found that *preoperative* BNP level in patients undergoing a total cavopulmonary connection (Fontan procedure) was the only significant predictor of adverse postoperative outcomes.[6]

There is clearly much to learn about the mechanisms involved in BNP release in patients with congenital heart disease and the utility of this biomarker in this population. We agree with Cantinotti and colleagues that further investigations into BNP changes during the perioperative period are warranted. On the basis of our combined data to date, we believe that fully understanding and interpreting perioperative BNP changes will require accounting for age, the cardiac lesion, and the intervention that is undertaken. We thank both the Editor and Cantinotti and colleagues for this opportunity to highlight this important topic.

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TRACHEAL REGENERATION: MYTH OR FACT?

To the Editor:

We read with great interest the article entitled, ''Tracheal regeneration: Evidence of bone marrow mesenchymal stem cell involvement,'' by Seguin and coworkers.[1] We congratulate Seguin and coworkers[1] for their convincing demonstration of bone marrow–derived stem cell migration to the grafted area after tracheal replacement