thereby the global hemodynamic burden imposed on the LV. In this context, the calculation of Z_{va} allows the detection of patients having an abnormally high hemodynamic load occulted by paradoxical low flow and associated pseudonormalization of gradient and blood pressure. The Z_{va} also provides more insight into the pathophysiology of symptomatic patients with the combination of hypertension and less-than-severe AS. In the discussion, we have nonetheless emphasized that in this situation future studies are necessary to determine how these findings can be translated into clinical practice to improve the diagnosis, treatment, and prognosis.

In time, the development of LV dysfunction and the occurrence of adverse events (including symptoms, atrial fibrillation, heart failure, cardiovascular deaths, and so on) should logically be related to the global hemodynamic burden imposed by AS and/or hypertension on the LV and upstream cardiac chambers. We thus believe that the first essential step in the evaluation of these patients is to estimate the global hemodynamic load to determine whether the patient is at risk for poor outcome. The Z_{va} is particularly useful in this regard as it provides a simple and noninvasive parameter for estimating the global load and predicting outcomes. The second step is then to dissect the respective contributions of AS and hypertension to the increased global burden by examining the indexes of the valvular and arterial loads, respectively. To this effect, the clinician should be cautious about the use of transvalvular gradient and blood pressure for clinical decision making because these indexes may be pseudonormalized. They should preferably use indexes that are less flow dependent, such as the aortic valve area or energy loss index for assessment of valvular load and arterial compliance and vascular resistance for the assessment of arterial load.

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Decision Levels for Plasma B-Type Natriuretic Peptide Assay to Diagnose Significant Cardiovascular Disease in Children

We read with interest the paper of Law et al. (1) regarding the accuracy of B-type natriuretic peptide (BNP) to diagnose significant cardiovascular disease in children. In their prospective study the authors enrolled 100 children (including 42 neonates) presenting with signs and symptoms that might be attributable to cardiovascular abnormalities. Their results clearly showed how the use of BNP was helpful in discriminating children with structural or functional cardiovascular diseases. They indicated how, up to 7 days of life, the cutoff of 170 ng/l had a positive predictive value of 91% in ruling out cardiac disease, whereas in older children a BNP value of 41 ng/l had a positive predictive value of 77%. Plasma BNP was measured with a point-of-care testing method (Triage BNP, Biosite, Inc., San Diego, California).

On the basis of our experience, we appreciate and encourage the idea to use BNP in the integrated approach of newborns and children with suspected cardiovascular diseases. However, we believe that the use of 2 different cutoffs—1 for newborns up to 7 days and the other for all the other children—might represent an oversimplification. We assessed the reference interval limits of BNP assay in newborns and infants in a wide population of healthy subjects, with the same triage BNP method, performed on the fully automated Access platform (Triage BNP reagents, Access Immunoassay Systems, REF 98200, Beckman Coulter, Inc., Fullerton, California) (2). Plasma BNP was measured in 190 apparently healthy newborns and infants throughout the first month of extra-uterine life, as well as in 184 healthy infants, with ages ranging from 1 month to 12 years. The BNP showed the highest levels in the first 2 days of life (median 229.0 ng/l, range 41 to 866 ng/l, 97.5th percentile, 745 ng/l, n = 91) with a progressive decline in the next days (BNP values from 49 to 190 h of life: median 110.0 ng/l, range 10 to 739 ng/l, 97.5th percentile, 480 ng/l, n = 69). Moreover, due to the great variability of circulating levels, the diagnostic accuracy of BNP assay might be significantly lower in the first days of life, especially if incorrect cutoff values are taken into account. Considering the 97.5th percentile as a possible upper limit for the reference interval, we propose 3 different decision levels for the diagnosis of cardiovascular disease in children: 1 for the first 2 days of life (i.e., 750 ng/l), 1 from the third to seventh day (i.e., 480 ng/l), and the other from 2 weeks to 10 years (i.e., 45 ng/l).

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Reply

Cantinotti et al. (1) propose adopting the 97.5th percentile value as a cutoff for B-type natriuretic peptide (BNP) levels based on the results of their excellent study in presumed healthy newborns. Using cutoff values based on the distribution from a healthy population is fundamentally different from the derivation of cutoffs from a study of disease and nondisease subjects. The Better Not Pout Children! Study (2) was a field test of sick infants and children whose presentation could be caused by cardiovascular disease. The results are intended to be applied to similar patients in clinical practice. In the presence of trial data, use of 97.5th-percentile cutoffs fails to take advantage of valuable information from individuals who suffer from the disease but have test values that fall within 2 SDs above the mean of healthy subjects. For example, with the cutoffs proposed by Cantinotti et al. (1), the sensitivity was only 43% and 49% for the 0- to 2-day-old and 3- to 7-day-old groups, respectively, and 100% specific for both groups of subjects from our study. Thus, the result of using this methodology, choosing the 97.5th percentile cutoff and applying it to a different group of subjects, would have increased test specificity and sacrificed sensitivity. We found in our study that, between birth and 7 days of age, a cutoff of 170 pg/ml was sufficient to diagnose significant cardiovascular disease with excellent sensitivity (93%) and reasonable specificity (73%). We believe that optimization of the sensitivity is clinically important in the identification of significant cardiovascular disease in the sick infant by the frontline physician.

A second point relates to the dramatic fall in BNP values during the first week of life. Multiple works (1,3) have shown that BNP values decrease dramatically in the first week of life and vary widely within each age group even when separated by a single day. Thus, it would be preferable to determine daily cutoffs during this critical and rapidly changing early phase of life. Unfortunately, our study was neither intended nor powered to address this important question.

Properly conducted prospective trials in pediatric cardiology are lacking. Instead of extrapolating data from normative values, retrospective studies, or adult trials, prospective trials in children should be conducted. Ours was one of the early trials and hopefully not the last to assess BNP in children. Future studies should address: 1) neonatal cutoffs by expanding the pool and sample size of sick neonates; and 2) whether using BNP actually enhances the diagnostic process and the outcome of the patient. There is much promise in the use of BNP to diagnose significant cardiovascular disease in children. But because of the tremendous physiological and disease heterogeneity in children, that test cutoff is truly a moving target, and much work still has to be done.

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