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EDITORIAL COMMENT

B-Type Natriuretic Peptide in Children

Step by Step. . .*

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Neonate and pediatric cardiovascular patients present an extra challenge to most physicians because of a lack of a well-communicated history. Symptoms for this cohort include dyspnea, failure to thrive, swelling, hypotension, and so on (1). Rapid evaluation of patients presenting with these symptoms is needed so that they receive appropriate treatment and can be referred quickly to a cardiologist if necessary. Natriuretic peptides (NPs), such a B-type natriuretic peptide (BNP), could possibly help this scenario to guide management quickly and effectively; however, at the same time, the utility of NPs in this age group is not established.

The Better Not Pout Children! Study conducted by Law et al. (1), and in this issue of the *Journal*, is therefore an important and needed addition to our current knowledge on the use of BNP as a diagnostic tool in neonate and pediatric patients presenting with findings that could be attributed to significant cardiovascular disease.

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NPs are currently cutting-edge tools used in modern medical centers as a way to quickly identify heart failure in adult populations. These endogenous peptides are rapidly synthesized and secreted by the right and left cardiac ventricles as the 32-amino acid polypeptide BNP and its inactive amino terminal NT-proBNP (2). In adults, the main catalyst for the release of these peptides is left ventricular end diastolic wall stress and wall stiffness (3).

Studies have demonstrated higher NP levels in healthy neonates as compared with older age groups. They play an important role in homeostasis during the transition of the circulation from fetal to maturity. Due to the normal total body water increases in newborns, there exists an increase in systemic pre-load and afterload in pulmonary arterial circulation compounding with the normal stiff myocardium in this age group, which leads to a dramatic release of NPs (4). In addition, the lack of sensitivity to NPs that is seen in newborns causes more production and secretion of NPs to maintain adequate diuresis (1,5).

Law et al. (1) addresses the possibility of using NPs to diagnose cardiovascular diseases in the age range of neonates to 19-year-olds. This prospective study from a single pediatric center further divided this group of 102 patients into neonatal (0 to 7 days, n = 42) and older age groups (>7 days to 19 years, n = 58). These cases of unknown cardiovascular pathology were eligible for enrollment upon request of an urgent cardiologist consult from a noncardiologist when presentation included a symptom of suspect cardiovascular abnormality. Subjects were enrolled from the emergency department, inpatient wards, nursery, and intensive care unit. BNP samples were obtained within 24 h of the consult. Upon examination by a cardiologist, blinded to BNP results, the disease groups were defined as "significant" when either function or structure was altered; patients were further divided into those with and without an anatomic defect. Abnormal function included systolic dysfunction with shortening fraction <28% or a qualitative decrease, diastolic dysfunction such as enlarged atria, or heart failure in the absence of systolic failure. Altered structure included abnormality in chamber size, myocardial thickness, and cardiovascular abnormality without an anatomic defect (e.g., pulmonary hypertension). Anatomic defects included both congenital and acquired, for example, coarctation of the aorta or rheumatic valve disease, respectively. Further investigations of chest X-ray and echocardiogram were performed and were included in the gold standard diagnosis (1).

Importantly, plasma BNP was higher in the neonatal group with or without significant cardiac disease in comparison with that of the older age group. Median BNP for neonates with disease (n = 31) was 526 pg/ml (mean 1,017 ± 1,128 pg/ml) versus 96 pg/ml (mean 134 ± 130 pg/ml, $p < 0.001$) for those without the disease (n = 11). Median BNP for the older age group with disease (n = 31) was 122 pg/ml (mean 824 ± 1,330 pg/ml) versus 22 pg/ml (mean 66 ± 96 pg/ml, $p < 0.001$) for those without the disease (n = 27). In cases of cardiovascular disease with an anatomic defect, the values for BNP increase in both groups. The area under the receiver-operating characteristics curve for the diagnosis of cardiovascular disease was 0.90 in neonates and 0.81 in the older age group. With the cutoff levels suggested in their article (170 pg/ml for neonates and 41 pg/ml for the older age group), the sensitivity was 94% and 87%, respectively (1).

When considering application of these data in clinical practice, it may be important to note 2 methodological

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limitations and 2 relevant differences between children and adults.

First, this study has an inherent limitation, as it included patients presenting with a broad range of symptoms and findings that could be attributed to significant cardiovascular disease. This makes the translation of their results to our and your clinical practice more difficult than those of studies that used a specific symptom like acute dyspnea, which was done, for example, in the BNP (Breathing Not Properly) study, the PRIDE (ProBNP Investigation of Dyspnea in the Emergency Department) study, and the BASEL (B-Type Natriuretic Peptide for Acute Shortness of Breath Evaluation) study (6–8). Second, as appropriately acknowledged by the authors, this study nicely shows that BNP levels are closely associated with cardiovascular disease, but did not evaluate whether the additional use of BNP increases diagnostic accuracy on top of all available information in the acute care setting. This step must follow in future studies. It is worthwhile to remember that in adults, we have both evidence from large observational studies that the additional use of BNP increases diagnostic accuracy in the emergency department, as well as data from 3 large randomized controlled studies that the additional use of NP improves patient management, as quantified by time to discharge or total cost of treatment (2,9).

Among the important differences between the diagnosis of heart failure in children and adults, the following 2 factors may be particularly relevant. First, it is worthwhile to point out that physical examination in children is often much more telling than in adults. For example, the presence of a cardiac murmur and/or hepatomegaly strongly suggests cardiovascular disease in children, whereas most clinical signs in adults are present in <50% of patients with acute heart failure (10,11). Second, in children, anatomical defects are common causes of heart failure. Therefore, echocardiography has a profound role in patient management in the majority of patients and has a greater impact on final diagnosis. These echocardiographic findings can quickly lead the physician to consult not only a cardiologist, but even possibly a surgeon when necessary for treatment. In adults, imaging is recommended in all patients with heart failure, but the immediate consequences on patient management are much smaller.

BNP assessment is not the final answer in cardiological diagnosis; this remains true in all age groups. It is not a standalone test; further evaluation is in general needed, although it has clear value in bringing a front-line physician to a diagnosis. It is critical to diagnose neonatal and pediatric patients as quickly as possible; because of lack of a clear history, the gravity of the situation is not always measured properly. In this regard, BNP may have a great future in children as a possible tool in adding details to the whole story.

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REFERENCES

1. Law YM, Hoyer AW, Reller MD, Silberbach M. Accuracy of plasma B-type natriuretic peptide to diagnose significant cardiovascular disease in children: the Better Not Pout Children! Study. J Am Coll Cardiol 2009;54:1467–75.
2. Mueller C, Breidthardt T, Laule-Kilian K, Christ M, Perruchoud AP. The integration of BNP and NT-proBNP into clinical medicine. Swiss Med Wkly 2007;137:4–12.
3. Maisel A, Mueller C, Adams K Jr, et al. State of the art: using natriuretic peptide levels in clinical practice. Eur J Heart Failure 2008;10:824–39.
4. Cameron VA, Ellmers LJ. Minireview: natriuretic peptides during development of the fetal heart and circulation. Endocrinology 2003; 144:2191–4.
5. Nir A, Lindinger A, Rauh M, et al. NT-pro-B-type natriuretic peptide in infants and children: reference values based on combined data from four studies. Pediatr Cardiol 2009;30:3–8.
6. Rutten JHW, Steyerberg EW, Boomsma F. N-terminal pro-brain natriuretic peptide testing in the emergency department: beneficial effects on hospitalization, cost and outcome. Am Heart J 2008;156: 71–7.
7. Mueller C, Scholer A, Laule-Kilian K, et al. Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. N Engl J Med 2004;350:647–54.
8. Moe GW, Howlett J, Januzzi JL, Zowall H, for Canadian Multicenter Improved Management of Patients With Congestive Heart Failure (IMPROVE-CHF) Study Investigators. N-terminal pro-B-type natriuretic peptide testing improves the management of patients with suspected acute heart failure: primary results of the Canadian prospective randomized multicenter IMPROVE-CHF study. Circulation 2007;115:3103–10.
9. Mueller C. Cost-effectiveness of B-type natriuretic peptide testing. Congest Heart Fail 2008;14 Suppl 1:35–7.
10. Wang CS, FitzGerald JM, Schulzer M, Mak E, Ayas NT. Does this dyspneic patient in the emergency department have congestive heart failure? JAMA 2005;294:1944–56.
11. Mueller C, Frana B, Rodriguez D, Laule-Kilian K, Perruchoud AP. Emergency diagnosis of congestive heart failure: impact of signs and symptoms. Can J Cardiol 2005;21:921–4.

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