A strong relation between atrial (A-type) natriuretic peptide (ANP) in plasma and patent ductus arteriosus (PDA) in preterm infants was first described in 1987 [1]. Subsequent studies have confirmed these findings [2], and recently the diagnostic value of the N-terminal fragment of the ANP prohormone (N-terminal proANP) was described [3]. Sparse information exists regarding the clinical utility of measurement of another natriuretic peptide, the predominantly ventricular-derived brain (B-type) natriuretic peptide (BNP), in this patient population [3]. In this issue of Clinical Science, Puddy and colleagues provide an important contribution to this intriguing field of medicine, confirming and extending previous results by demonstrating a strong relationship between circulating BNP and the presence of PDA in preterm infants [4]. Although no direct comparisons were made, BNP appears to be as accurate as ANP in detecting PDA.

A number of factors may affect circulating natriuretic peptide levels in preterm infants. Theoretically, the effect of a PDA on BNP release may be obscured by a number of other factors commonly seen in this patient population, including increased pulmonary vascular resistance and subsequent right ventricular pressure overload, concomitant renal impairment, hydration status, and the effect of medical therapy with corticosteroids or positive inotropic agents. Although these potentially confounding factors were not taken into account in the study by Puddy et al., the presence of PDA was associated with markedly increased levels of BNP [4]. After the exclusion of patients with major congenital cardiac anomalies, elevated BNP concentrations on day 3 after birth were predictive of the presence of PDA at the end of the first week. Of note, in the study by Puddy et al. the preterm infants with PDA had a significantly younger gestational age and a lower weight at birth than those without PDA at the end of the first week of life [4]. Probably because of the limited statistical power, no attempt was made to adjust for gestational age, weight at birth, or other confounding factors. Clearly, to be of clinical value BNP measurements should provide diagnostic information above and beyond that obtained from these basic variables.

In the study by Puddy et al., at 3 days of age four out of twelve children without PDA had BNP levels in the same range as children with PDA [4]. This indicates that the diagnostic accuracy of blood samples obtained on day 3 of life may be reduced by a high false-positive rate. However, it is possible that elevated BNP levels on day 3 may have been due to a ductus arteriosus that closed spontaneously before the echocardiographic examination on day 7 was performed. A sample taken between days 4 and 6 of life might thus yield a lower false-positive rate. In a recent study with a similar design, we investigated the diagnostic value of repeated measurements of natriuretic peptides, including BNP, and found a decline in the false-positive results from 22 to 15% during the first week [3]. In that study the diagnostic value of BNP and N-terminal proANP, for detecting the presence of PDA, were found to be similar.

Puddy et al. argue that BNP measurements may represent an alternative to echocardiography in the diagnosis of PDA in preterm infants, in particular in neonatal units with limited access to, or experience with, this methodology [4]. It should be noted, however, that although widely used, echocardiography as the reference standard for haemodynamically important PDA is not unproblematic. Echocardiographic criteria for the assessment of the degree of shunting through a PDA are poorly defined [5], and echocardiography basically provides a subjective interpretation of haemodynamic status, an interpretation that may be influenced by equipment and operator skill. In contrast, BNP concentrations are a direct measure of the physiologic response to haemodynamic stress. BNP determination may thus represent an complimentary diagnostic approach with different advantages and limitations. In particular, it is crucial to recognize that BNP is a non-specific indicator of cardiac disease. Accordingly, circulating BNP levels are increased in a number of cardiac conditions in the newborn, including cardiomyopathies, serious arrhythmias and many congenital heart defects. An elevated BNP value in a preterm infant will not discriminate between these conditions. However, in a patient with a PDA and no other obvious cardiac abnormality, BNP may provide information not obtained from echocardiography concerning the haemodynamic importance of the shunt. BNP should therefore not be regarded as a substitute, but as a complementary tool to echocardiography.

With regard to the practical interpretation of results, in the absence of other cardiac structural anomalies, the combined findings of a markedly elevated natriuretic peptide value and a large PDA on echocardiographic examination confirm the need for medical or surgical
intervention. Natriuretic peptide measurements may guide decisions as to whether intervention is indicated in children with a PDA of uncertain significance. In children with a high natriuretic peptide level without a demonstrable PDA, other causes of haemodynamic imbalance should be looked for. In children with a low BNP concentration, a PDA, as well as the presence of other haemodynamically important defects, is unlikely. Repeated natriuretic peptide measurements may be of value in determining whether changes in clinical course relate to haemodynamic factors.

Recently, rapid tests for BNP and the N-terminal fragment of its prohormone (N-terminal proBNP) have become commercially available. Is the scientific rationale strong enough for introduction of these tests for routine use in neonatal units? As is often the case in neonatal medicine, results from large-scale clinical trials are lacking. Ideally, one would like to see the results of a well-powered clinical trial in which the group randomized to combined echocardiography and BNP measurements was shown to have a better outcome than patients randomized to echocardiography alone. Without such data available, we still feel that guarded clinical use of natriuretic peptide measurements may be justified to gain experience locally. The scientific documentation for natriuretic peptide determination in this setting is now probably better than that for several other conventional biochemical analyses currently in use.

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REFERENCES