

- natriuretic peptide and blood volume during red cell transfusion in preterm infants. *Arch Dis Child* 1991;66:395-7.
- 2 Mollison PL, Veall N, Cutbush M. Red cell and plasma volume in newborn infants. *Arch Dis Child* 1950;25:242-53.
  - 3 Lawson HC. The volume of blood—a critical examination of methods for its measurement. In: Hamilton WF, Dow P, eds. *Handbook of physiology*. Vol 1. Washington DC: American Physiological Society, 1962:23-49.
  - 4 Phillips HM, Abdel-Moiz A, Jones JG, et al. Determination of red-cell mass in assessment and management of anaemia in babies needing blood transfusion. *Lancet* 1986;i:882-4.

#### Drs Rascher and Linderkamp comment:

Dr Anthony and Professor Levene have raised important questions concerning the blood volume method used in our study. They point to the following possible pitfalls: (1) the method of red cell mass measurement may not be reliable. We used a method described by Phillips *et al* (that is, dilution of fetal haemoglobin by transfused adult red blood cells).<sup>1</sup> Phillips *et al* report a maximum coefficient of variation of less than 3.6%.<sup>1</sup> In 20 double measurements of fetal haemoglobin we found a mean variability ( $V = [A-B]/[A+B]/2$ ) of 3.4%. This variability may have caused a mean error of a single red cell mass determination of 7%. This is in the range of other red cell mass methods.<sup>2,3</sup> The variability of fetal haemoglobin measurement and thus the error of red cell mass increases with decreasing fetal haemoglobin. (2) the microfuge packed cell volume has to be corrected for trapped plasma. Trapped plasma is about 2% for neonatal and adult red cells<sup>4</sup> and can thus be neglected. (3) the whole body packed cell volume differs from the venous (central) packed cell volume. In adults, the body:venous packed cell volume ratio is about 0.91. In full term neonates ratios of 0.87<sup>5</sup> and 0.90<sup>2</sup> have been reported, and in severely ill preterm infants ratios of 0.82 to 0.89 have been determined.<sup>3</sup> The use of a mean body:venous packed cell volume ratio derived from another study merely changes the blood volumes by a constant factor. The maximum error for blood volume calculation from red cell mass and packed cell volume using a constant ratio of 0.855 for preterm infant is 4%.

As plasma volume measurements may be associated with an error of 6%,<sup>6</sup> a double label technique using a red cell and a plasma indicator probably does not appreciably increase the reliability of whole blood volume estimation. On the other hand, we agree with Dr Anthony and Professor Levene that the use of a plasma protein label would have been more reliable for plasma volume measurement. However, determination of plasma volume was not the primary purpose of our study. Moreover, Evans blue is no longer commercially available and radioactively labelled proteins are not used any more in newborn infants for ethical reasons.

We conclude that the fetal haemoglobin dilution technique is a reliable method for red cell mass measurement and whole blood volume estimation. As blood volume did not change during transfusion, the increase in red cell mass was certainly associated with a decrease in plasma volume. A simple measurement of a change in packed cell volume would not have been as informative as the estimation of blood volume from red cell mass and packed cell volume.

- 1 Phillips HM, Abdel-Moiz A, Jones JG, et al. Determination of red-cell mass in assessment and management of anaemia in babies needing blood transfusion. *Lancet* 1986;i:882-4.
- 2 Bratteby LE. Studies on erythro-kinetics in infancy VIII. Mixing, disappearance rate and

- distribution volume of labelled erythrocytes and plasma proteins in early infancy. *Acta Soc Med Upsal* 1967;72:249-56.
- 3 Linderkamp O, Betke K, Fendel H, et al. Tc-99m-labelled red blood cells for red cell mass measurement in newborn infants. *J Nucl Med* 1980;21:637-40.
  - 4 Linderkamp O, Meiselman HJ, Wu PYK, Miller FC. Blood and plasma viscosity and optimal hematocrit in the normal newborn infant. *Clinical Hemorheology* 1981;1:575-85.
  - 5 Mollison PL, Veall N, Cutbush M. Red cell and plasma volume in newborn infants. *Arch Dis Child* 1950;25:242-53.
  - 6 Linderkamp O, Mader T, Butenandt O, et al. Plasma volume estimation in severely ill infants and children using a simplified Evans blue method. *Eur J Pediatr* 1977;125:135-41.

#### Non-invasive assessment of pulmonary arterial pressure in healthy neonates

SIR,—We read with interest the study by Skinner *et al*.<sup>1</sup> We would however, take issue with the statement that the method we used in our study to assess pulmonary artery pressure,<sup>2</sup> the inverse relationship with the ratio of the time to peak velocity (TPV) of pulmonary artery flow and the right ventricular ejection time (RVET), is less suitable for study of the newborn. The advantage of TPV:RVET ratio as a means of studying physiological changes is that we obtained quantitative data in 100% of our studies. Using tricuspid regurgitation, Dr Skinner *et al* obtained quantitative data in only 22% of term studies and 45% of preterm studies.

Our data suggested that pulmonary artery pressure falls slightly but significantly more slowly in healthy preterm than in term infants.<sup>2</sup> Dr Skinner *et al* did not find this difference and suggested that factors other than pulmonary artery pressure which can affect TPV:RVET might have influenced our results. We do not believe that to be the case for the following reasons, taking each of these factors in turn. Firstly, that the positioning of the pulsed Doppler sample is critical. We used a constant site in the centre of the artery distal to the pulmonary valve, not technically difficult in early life. Secondly, myocardial function, which if poor will prolong TPV. All infants in the study referred to were healthy and had good myocardial function. Any reduction in contractility resulting from lower gestational age would cause the difference which we found between preterm and term infants to be an underestimate. Thirdly, tricuspid regurgitation, here Dr Skinner *et al* have misread the reference cited. Kitabatake *et al* could find no statistically significant effect of tricuspid regurgitation on the relationship between TPV and pulmonary artery pressure.<sup>3</sup> Finally, heart rate, which will slightly reduce TPV:RVET as it increases.<sup>4</sup> The term babies in our study had a mean heart rate of 129 compared with 143 in those preterm. From the regression analysis provided by the data of Akiba *et al*,<sup>4</sup> this difference would cause a change in TPV:RVET of 0.005, not likely to affect the significance of our data. For example, between 25 and 36 hours after birth mean TPV:RVET was 0.36 in the term infants compared with 0.29 in the preterms. In addition the difference in heart rate between the two groups remained constant through the study period while the differences in TPV:RVET did not.

Tricuspid regurgitation is a good method for estimating pulmonary artery pressure, so why did Skinner *et al* not find the same differences? While lack of longitudinal data may be part of the problem, the important information missing from this paper is the distribution of gestation within the wide range quoted (28 to 35 weeks) and even more

importantly the gestation of the seven infants in whom longitudinal quantitative analysis was possible. Healthy infants of less than 31 weeks are not common, this tends to bias the selection of infants in this type of study towards higher gestations. Thirty seven percent of the preterm infants in our study were of less than 31 weeks, this may be why we were able to demonstrate a difference.

Tricuspid regurgitation, when present, and TPV:RVET are both good methods for non-invasively assessing pulmonary artery pressure. Like all Doppler methods they both have limitations. Within the practice of paediatric cardiology, where both methods were developed and validated, tricuspid regurgitation has advantages particularly in children with large intracardiac left to right shunts. However, we would argue that a method which allows data collection in only a minority of normal subjects may not be the best for describing physiological changes.

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- 1 Skinner JR, Boys RJ, Hunter S, Hey EN. Non-invasive assessment of pulmonary arterial pressure in healthy neonates. *Arch Dis Child* 1990;66:386-90.
- 2 Evans NJ, Archer LNJ. Postnatal circulatory adaptation in healthy term and preterm neonates. *Arch Dis Child* 1990;65:24-6.
- 3 Kitabatake A, Inoue M, Asao M, et al. Non invasive evaluation of pulmonary hypertension by a pulsed Doppler technique. *Circulation* 1983;68:302-9.
- 4 Akiba T, Yoshikawa M, Otaki S, et al. Prediction of peak pulmonary artery pressure by continuous wave Doppler echo cardiography in infants and children. *Pediatr Cardiol* 1988;9:225-9.

#### Dr Skinner *et al* comment:

We thank Drs Evans and Archer for their comments. There are now three Doppler techniques for assessing neonatal pulmonary arterial pressure: the TPV:RVET ratio, regurgitant tricuspid flow, and the analysis of ductal flow.<sup>1</sup> The TPV:RVET ratio can be measured serially in all infants, but is it as accurate a measure as that provided by tricuspid regurgitation when present and measurable?

If the TPV:RVET ratio is influenced by pulmonary arterial pressure only and it is valid to compare subjects of different size, absolute values can be obtained by imposing Evans' ratios on Kitabatake's regression from adults, which correlates TPV:RVET with pulmonary arterial pressure. However, Evans' ratio of 0.2:1 in preterm infants at six hours implies a mean arterial pressure of 100 mmHg; almost three times average systemic pressure! Similarly, the lower ratios seen in the preterm babies imply higher pressures than in term babies.

As aortic TPV is shortened by mitral regurgitation,<sup>2</sup> Kitabatake postulated that pulmonary TPV might be shortened by tricuspid regurgitation, and found nine of 11 adult patients with tricuspid regurgitation had TPV values below the regression line for the whole group. Although the regression for patients with tricuspid regurgitation did not differ significantly from this regression, a third of the whole group had tricuspid regurgitation. No comparison was reported between those with and without tricuspid regurgitation.

Serial measurement is clearly the best way to assess the speed with which pulmonary arterial pressure falls, and we presented our serial data on seven preterm babies graphically. They were the same mean gestational age

(31.6 weeks) as those studied by Evans and Archer (one at 28, one at 30, two at 32, and three at 33 weeks). Furthermore our results were substantiated by analysis of ductal flow. Unfortunately Drs Evans and Archer did not utilise the potential of their technique for serial measurement to the full; results were presented in a cross sectional manner, with different numbers studied at each age. Group means were compared when it would have been better to analyse the rate of fall in each individual separately.

In truth, neither of these papers can probably come to a definite conclusion about the relative rate of fall of pulmonary arterial pressure in term and preterm babies. However, three potentially useful Doppler techniques have been introduced to neonatology and this discussion helps to clarify some of the potential merits and shortcomings of each.

- Musewe NN, Poppe D, Smallhorn JF, *et al.* Doppler echocardiographic measurement of pulmonary artery pressure from ductal Doppler velocities in the newborn. *J Am Coll Cardiol* 1990;15:446-56.
- Elkins RC, Morrow AG, Vasko JS, Braunwald E. The effects of mitral regurgitation on the pattern of instantaneous aortic blood flow: clinical and experimental observations. *Circulation* 1967;36:45-53.

#### Accuracy of height measurements

SIR,—In their study of the accuracy of measurements made by health visitors, Ahmed *et al* assume that a reading by a trained auxologist on a Harpenden stadiometer was obtained without error.<sup>1</sup> Not only is this assumption dangerous and unjustified, it is also unnecessary, as the authors' analysis happens to contain an estimate of the error's variability. The column headed 'children' in table 2 of their paper does not, as may be thought, provide the variance of the heights of the children who took part in the experiment. For children selected at random from the population, or even from a day nursery, as in the study, this should be of the order 15–20 cm<sup>2</sup>. Moreover, the effect due to a child is removed, in the analysis, by the differencing that occurs when the auxologist's measurement is subtracted from that of a health visitor. The column headed 'children' gives, in fact, the variance of the auxologist's measurement error. Averaging over the rows of the table leads to an estimated standard deviation of 0.31 cm, which is comparable with the values obtained by experienced auxologists in our own experiments.<sup>2</sup>

Not only is this variability not negligible, it is of a similar order of magnitude to that which obtains on instruments such as the Microtoise. The reason, as we have pointed out, is that almost all the variance in a height measurement is due to the elasticity of the child, and very little to the inadequacies of the instrument or the observer. It therefore becomes necessary to talk of estimating not the true height of a child, as the authors do, but the mean height.

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1 Ahmed ML, Yudin PL, Macfarlane JA,

McPherson K, Dunger DB. Are measurements of height made by health visitors sufficiently accurate for routine screening of growth? *Arch Dis Child* 1990;65:1345-8.

- Voss LD, Bailey BJR, Cumming K, Wilkin TJ, Betts PR. The reliability of height measurement (the Wessex Growth Study). *Arch Dis Child* 1990;65:1340-4.

#### Mrs Yudkin and Dr Dunger comment:

Mr Bailey and Ms Voss do not appear to be challenging the results of our study but rather questioning whether the label 'children' in table 2 is appropriate. Their suggestion that the variance in the column headed 'children' in this table should be of the order of 15–20 cm<sup>2</sup> is, we believe, misleading. A variance of this size would relate to the actual heights of children, whereas we were concerned only with the variance in child 'biases'; that is, differences between measurements recorded by health visitor and auxologist.

Mr Bailey and Ms Voss have raised an interesting theoretical question, but our study design does not allow its resolution. The main point at issue is whether measurements made by a trained auxologist using the Harpenden stadiometer and applying traction are affected by the child's 'elasticity' as much as measurements made by a health visitor, using a Microtoise or wallchart. Mr Bailey and Ms Voss suggest that they are, by their statement that 'the effect due to a child is removed, in the analysis, by the differencing that occurs when the auxologist's measurement is subtracted from that of a health visitor'. Our standpoint, on the other hand, is that the auxologist's measurement is the best available, and the purpose of our study was to examine how health visitor measurements compared with this best.

#### Prolonged low dose indomethacin for persistent ductus arteriosus

SIR,—We reviewed with great interest the article by Rennie and Cooke.<sup>1</sup> The treatment of patent ductus arteriosus remains an important issue in the care of the premature infant. However, we would like to address several areas in order to clarify the results achieved by the investigators. Certain specific descriptions were missing in the methods section that would be helpful in justifying prolonged low dose indomethacin as an alternative treatment.

Our first concern is the basis for the diagnosis of the patent ductus arteriosus and its relapse. While clinical symptoms are important diagnostic parameters, they are subject to observer bias especially in a study spanning different institutions. Echocardiography, the preferred diagnostic method, would strengthen the initial diagnosis and the presence or absence of relapse.<sup>2</sup> This improvement could have provided an important prospective diagnostic definition to describe the patient population more accurately.

Secondly, the many clinical factors that influence the patency of the ductus were excluded.<sup>3</sup> There was no mention of important confounding variables such as fluid management, methods of ventilation, use of exogenous surfactant, or severity of the respiratory disease. In addition, the lack of serum indomethacin concentrations leaves an important void in the clinical results.<sup>4</sup>

The premise for this study, to find a safer treatment for the persistent ductus, is applauded. However, the lack of more detailed description of the patients and methods prevents this investigation from the universal

acceptance desired by its authors. We would like to obtain the missing information or, if unavailable, suggest that repetition of the investigation controlling for the confounding variables. The results of such a study would provide an alternative way for the management of an all too common neonatal concern.

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- Rennie JM, Cooke RWI. Prolonged low dose indomethacin for persistent ductus arteriosus. *Arch Dis Child* 1991;66:55-8.
- Bayle BG, Meyer RA, Kaplan S, *et al.* The critically ill premature infant with patent ductus arteriosus and pulmonary disease—an echocardiographic assessment. *J Pediatr* 1975; 86:423-32.
- Bell EF, Warburton D, Sonstreet BS, Oh W. Effect of fluid administration on the development of symptomatic patent ductus arteriosus and congestive heart failure in premature infants. *N Engl J Med* 1980;302:598-604.
- Brash AR, Hickey DE, Graham TP, Stahlman MT, Oates JA, Cotton RB. Pharmacokinetics of indomethacin in the neonate: the relationship of indomethacin plasma levels to response of the ductus arteriosus. *N Engl J Med* 1981;305: 67-72.

#### Drs Rennie and Cooke comment:

We thank Dr Marino and his colleagues for their interest in our paper. We accept that echocardiographic diagnosis of patent ductus arteriosus would have provided more objective evidence on which to enrol and subsequently assess subjects, but at the time this study was started the technique was not available to us in either centre. We would obviously use this method in any future studies.

The problem of differences in management should have been taken care of by the fact that this study was randomised. Fluid management was fairly uniform, with fluid restriction to 120 ml/kg/24 hours in both centres being used for significant patent ductus arteriosus. During much of the time that this study was in progress we were also recruiting infants to a randomised surfactant trial. The problem of the severity of disease was partly addressed by the demonstration that by chance the long course group tended to be nursed in higher ambient oxygen at enrollment.

We would not agree that serum indomethacin concentrations are essential for the management of patent ductus arteriosus. Our experience with measuring concentrations of this drug<sup>1</sup> confirmed the large and unpredictable variation noted by Brash *et al.*<sup>2</sup> We were unable to establish a threshold at which clinical response was certain and felt that this was due to the fact that even low levels of indomethacin were associated with cessation of prostaglandin synthesis. These observations led to the present study as we felt, like Seyberth *et al* that resurgence of prostaglandin synthesis could be important in relapse.<sup>3</sup>

- Rennie JM, Doyle J, Cooke RWI. Early administration of indomethacin to preterm infants. *Arch Dis Child* 1986;61:233-8.