Oximetric detection of intracardiac left-to-right shunts¹

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SUMMARY To assess prevailing guidelines for the oximetric detection of intracardiac left-to-right shunts, we examined the variability of right heart oxygen saturation step-ups in 1121 catheterisations in children with aortic and pulmonary stenosis, who were studied as part of the joint study of the natural history of congenital heart defects.

It is estimated that in the absence of intracardiac shunting, a step-up of more than 5.9 per cent between the superior vena cava and the pulmonary artery, 3.5 per cent between the right atrium and the pulmonary artery, and 3.6 per cent between the right ventricle and pulmonary artery, occurs 5 per cent of the time. By extrapolation from a 'normal' distribution, a step-up of 8.7 per cent between the superior vena cava and pulmonary artery, 5.6 per cent between the right atrium and pulmonary artery, and 5.2 per cent between the right ventricle and the pulmonary artery would occur 1 per cent of the time in the absence of intracardiac shunting. Assuming a normal haemoglobin concentration of 15 g/dl, the 1 per cent false positive rate corresponds to a step-up of 1.7 volumes per cent from the superior vena cava to the pulmonary artery, 1.1 volumes per cent from the right atrium to the pulmonary artery, and 1.0 volumes per cent from the right ventricle to the pulmonary artery.

These data provide guidelines for the detection of abnormal shunts, but other independent methods such as indicator dilution or angiography should be employed in borderline situations.

Cardiac catheterisation has been used to show the haemodynamic consequences of congenital heart disease since 1945 (Brannon *et al.*, 1945). It was soon recognised that left-to-right intracardiac shunting could be shown by an increase in the oxygen content in the right heart chambers, but it was also recognised that variations in oxygen content occurred even in the absence of shunting, because of incomplete mixing of the various venous streams as well as measurement errors (Brannon *et al.*, 1945; Courmand *et al.*, 1945; Baldwin *et al.*, 1946). Quantification of the normal variation became important to determine criteria for the recognition of intracardiac shunting. Dexter *et al.* (1947) in 28 patients, Barratt-Boyes and Wood (1957) in 26 patients, and Grayzel and Jameson (1963) in 63

patients studied this normal variation, but the numbers of subjects were small, the earlier methods of measuring oxygen saturation have been replaced by newer techniques, and most of their data were obtained in adults rather than in children in whom congenital heart disease is more common. Nevertheless, on the basis of these data, standards were established for the normal variability of right heart saturations and content, and have been employed extensively in the detection of intracardiac left-to-right shunting (Dalen, 1974; Jarmakani, 1977; Yang *et al.*, 1978).

In the joint study of congenital heart defects recently published (Nadas *et al.*, 1977), cardiac catheterisations were performed on over a thousand children and young adults without cardiac shunts. We have analysed these data to determine the normal range of differences in saturations in the right heart in the absence of shunts, and to define the false-positive rates for various oximetric criteria for intercardiac left-to-right shunts.

¹Supported in part by a joint study grant and a programme project grant from the National Institutes of Health, Bethesda, Maryland, USA.

Subjects and methods

The joint study of congenital heart defects was concerned with three lesions, aortic stenosis, pulmonary stenosis, and ventricular septal defect, from six institutions. Details of aims, results, and conclusions of the study have been published previously (Nadas *et al.*, 1977). For this report we have used the catheterisation data from children or young adults over 2 years and up to 21 years of age with aortic stenosis or pulmonary stenosis. Only investigations performed between 1 July 1966 and the conclusion of the study in mid-1973 were considered. These included the final catheterisation in the retrospective group and the initial and final catheterisations in the prospective group. A total of 1121 such catheterisations in 824 patients was available for analysis, 623 catheterisations in children with aortic stenosis and 498 in children with pulmonary stenosis.

Intracardiac left-to-right shunting was excluded by repeated clinical examination over four to eight years in all patients and at catheterisation by indicator dilution curves (green dye or fiberoptic) or angiocardiology in most. Patients with pulmonary stenosis with a gradient of more than 50 mmHg between the right ventricle and pulmonary artery were excluded because of the possibility of intra-cardiac right-to-left shunting in such patients.

All patients were sedated with Demerol compound (pethidine hydrochloride 25 mg/ml, promethazine hydrochloride 6.25 mg/ml, or chlorpromazine 6.25 mg/ml) in a dose of 1 ml/20 lb (1 ml/9 kg) with a maximum of 2 ml. If additional sedation was needed, pethidine hydrochloride (1 mg/kg) or chloral hydrate (30 mg/kg oral) was used. Blood samples were obtained from the pulmonary artery (PA) (branch or main), right ventricle (RV) (outflow or body), right atrium (RA) (mid-lateral), and superior vena cava (SVC) in rapid succession before indicator-dilution study or angiography. The oxygen saturation was measured by reflection oximeter or transmission spectrophotometer, periodically checked against saturations derived from PO_2 measured with a Clark electrode, calibrated using known oxygen concentrations.

Although some variations in technique were inevitable since studies were done by scores of individuals in six centres over a seven-year period, an attempt was made to standardise the order and timing of samples; work sheets were supplied to each laboratory to provide for primary recording of the data (Nadas *et al.*, 1977).

Although in most previous studies oxygen saturation or content has been compared between adjacent chambers (SVC-RA, RA-RV, and RV-PA)

we compared the saturations in the individual right heart chambers with that in the pulmonary artery sample, since the latter is widely accepted to be the most completely mixed and therefore most representative sample in the absence of left-to-right shunting (Barratt-Boyes and Wood, 1957). The superior vena cava, right atrial, and right ventricular saturations were subtracted from the pulmonary artery saturation to obtain the respective percentage step-ups (which had a negative value if SVC, RA, or RV exceeded PA). Some of the reports were incomplete, with no saturation values for some of the sites. To determine whether the level of mixed venous saturation affected the variability, the data were stratified according to mixed venous saturation computed by averaging the PA saturation with the SVC, RA, or RV saturation, whichever was involved in the difference under study.

Data were extracted from the master tape and means and various centiles were calculated. Since in the range of interest the distribution followed a Gaussian pattern (data available on request), the extreme values were extrapolated from the measured 70th and 95th centile values using arithmetic normal graph paper.

Results

The cumulative distribution of the oxygen saturation difference between PA and SVC, PA and RA, and PA and RV, in the absence of intracardiac shunt, is shown in the Fig. On average the SVC and RV saturations closely approximated that in the PA, but the RA saturation was, on the average,

Fig. Cumulative distribution of the differences in the oxygen saturation between the pulmonary artery (PA) and superior vena cava (SVC), right atrium (RA) and right ventricle (RV).

Table False positive rate for various saturation step-up criteria

	% Step-up							
	3	4	5	6	7	8	9	10
Superior vena cava to pulmonary artery	17	12	8	5	3	1.6	0.6	0.4
Right atrium to pulmonary artery	7	4	2	0.4	0.3	0.1		
Right ventricle to pulmonary artery	9	4	1.3	0.4	0.1			

0.7 per cent higher than the PA. The PA-SVC differences had the most scatter and the PA-RV differences the least variation, though when positive differences alone were considered, the distributions of the PA-RA and PA-RV differences were quite similar. The 95th centile values for PA-SVC, PA-RA, and PA-RV were 5.9, 3.5, and 3.6 per cent, respectively. The 99th centile values, obtained by extrapolation from the Gaussian distribution, were 8.7 per cent for the PA-SVC, 5.6 per cent for the PA-RA, and 5.2 per cent for PA-RV difference. Thus, in the absence of intracardiac shunting, differences larger than these are estimated to occur in less than 1 per cent of all catheterisations.

Oxygen content was not analysed but if one assumes a normal oxygen capacity of 20.0 volumes per cent corresponding to a haemoglobin of 15 g/100 ml, the 99th centile values correspond to differences of about 1.7 volume per cent between PA and SVC, 1.1 volume per cent between PA and RA, and 1.0 volume per cent between PA and RV.

The false positive rate, that is the proportion of cases in which a shunt is thought to be present when none in fact exists, at different step-ups between PA and SVC, PA and RA, and PA and RV are illustrated in the Table. If a false positive rate of 5 per cent is accepted, shunt criteria would be differences of 6 per cent between PA and SVC, 4 per cent between PA and RA, and 4 per cent between PA and RV. Stricter criteria, with a false positive rate of 1 per cent, would be differences of 9, 6, and 6 per cent, respectively.

When the data were stratified by the mean level of the two venous saturations (less than 70%, 70 to 74%, 75 to 79%, 80 to 84%, and greater than 84%) no significant trend was found in the PA-SVC, PA-RA, or PA-RV distribution.

The distributions were similar in the patients with aortic and in those with pulmonary stenosis.

Discussion

The present data suggest that a step-up of 9 per cent from SVC to PA, 6 per cent from RA to PA, and 6 per cent from RV to PA occurs in less than 1 per cent of all catheterisations in the absence of a left-to-right shunt. This agrees well with data published earlier.

Most of the early publications were concerned

with oxygen content measured by the method of Van Slyke and Neill, 1924. In 22 'normal' patients in whom atrial and ventricular samples were obtained in rapid succession, Cournand *et al.* (1945) found that the RV-RA difference ranged from -1.2 to 0.6 volumes per cent. Dexter *et al.* (1947) measured oxygen content in 13 patients without heart disease and 15 patients with a wide variety of diseases (including a few with congenital heart disease) and found a maximum step-up in oxygen content of 1.9 volumes per cent from SVC to RA, 0.9 volumes per cent from RA to RV, and 0.5 volumes per cent from RV to PA. Interestingly, these data have remained the basis of criteria for the presence of left-to-right shunt (Dalen, 1974; Yang *et al.*, 1978) for over 30 years.

Rudolph and Cayler (1958) advocated criteria based on the use of oxygen saturation rather than oxygen content for the recognition of left-to-right shunts, since saturation data are independent of haemoglobin concentration and thus unaffected by anaemia or polycythaemia. In the normal range of oxygen capacity (17.7 to 21.6 volume %) (Wood, 1949) the differences are not great, however. Barratt-Boyes and Wood (1957) studied oxygen saturations in 26 normal subjects and found that saturation differences between paired samples obtained in rapid succession had a standard deviation of 3.0 per cent for SVC and RA (82 sample pairs in 26 subjects), 2.9 per cent for RA and RV (44 sample pairs in 24 subjects), and 1.7 per cent for RV and PA (23 sample pairs in 18 subjects). The variability could be reduced to SD of 2.3 per cent, 1.6 per cent, and 1.2 per cent if two or more samples were taken from each site. From these data they concluded that the presence of a left-to-right shunt could be deduced when the RA saturation exceeds the SVC saturation on two paired samples by more than 8 per cent, when the RV saturation exceeds the RA saturation by 3 per cent, or when the PA saturation exceeds the RV saturation by more than 2 per cent, or from an extrapolation of their data, 9, 6, or 4 per cent respectively on single paired samples.

Rudolph and Cayler (1958) took the view that an increase in saturation of 10 per cent from SVC to RA, 7 per cent from RA to RV, and 5 per cent from RV to PA were the minimum changes indicative of a left-to-right shunt on a single set of paired

samples. This was based on experience with cardiac catheterisation in over 1250 children with all types of congenital and acquired heart disease, but no further information about the basis of these conclusions was made available and no systemic study seems to have been done. Our data indicate that use of Rudolph and Cayler's criteria would be associated with a false positive rate of 0.4 per cent for PA-SVC, 0.3 per cent for PA-RA, and 1.3 per cent for PA-RV.

It should be recognised that an observed step-up less than the diagnostic cut-off value does not indicate absence of an intracardiac shunt. Even an appreciable shunt may fail to produce a step-up higher than which can be found, though rarely, in the absence of shunt. Our data provide no criteria for the exclusion of a shunt.

We have not used oxygen saturation criteria for patient inclusion or exclusion in this study since such criteria would bias the study. It is possible that a few patients with a small shunt have been included, and some patients without a shunt may have been excluded on the basis of a large rise in oxygen saturation between SVC and PA. Evidence of associated cardiac disease was, however, diligently sought, and, if found, called for exclusion from the natural history study. All patients had yearly clinical examinations and at least one and, in more than two-thirds of the cases, two cardiac catheterisations including angiocardiology and dye dilution studies. While it is conceivable that some intracardiac shunts have been missed, the number must be quite small. Likewise, the number of patients who were excluded from the natural history study, because of the erroneous belief that a shunt was present, must also be small. Most of the patients with aortic stenosis or pulmonary stenosis in whom an associated shunt was suspected had additional tests such as dye-dilution studies or angiocardiology, and were included when these failed to confirm the presence of a shunt. If patients with large step-ups had been excluded, asymmetry of the step-up distribution would have been seen with partial truncation at the top as a result of removal of these patients; no such asymmetry is apparent in the Fig.

These are three probable reasons for the observed variation between SVC, RA, RV, and PA saturations in the absence of a left-to-right shunt: measurement error in the oxygen analysis, changes in the physiological state of the patient during the sampling run, and incomplete mixing of the venous streams in the right heart. The 'gold standard' for oxygen analysis has been the manometric method of Van Slyke and Neill (1924). This technique, however, is cumbersome and time con-

suming and has been replaced almost completely by direct measurements of oxygen saturation by spectrophotometer, reflection oximeter, or indirect measurements from pH and P_{O_2} using Severinghaus oxygen dissociation curves. These three methods have been shown to correlate very well (Lopez-Majano *et al.*, 1971) and, though some measurement variability is inevitable, it can probably be reduced to no more than 1 per cent if the oximeters are calibrated and standardised regularly (Barrett-Boyes and Wood, 1957). Sources of error related to the physiological state of the patient include changes in cardiac output, oxygen consumption, or ventilation while the samples are being obtained. These errors are minimised if the samples are obtained in rapid succession with the patient in a steady state. Incomplete mixing resulting from laminar flow probably represents the major source of error. Inferior vena caval blood is so poorly mixed that many observers no longer use this sample at all (Rudolph and Cayler, 1958). It is widely agreed that the pulmonary arterial sample is the best mixed because turbulence in the right ventricle destroys laminar flow. Better mixing can presumably be achieved in the right atrium by sampling in the mid-lateral position, away from the coronary sinus return, and in the right ventricle by sampling from the outflow tract, but evidence for this is lacking.

The magnitude of the variability caused by poor mixing cannot be separated from that caused by the other two factors in our study. Samples from the SVC and PA were more widely separated in the time than the RV and RA samples, thus allowing possible changes in the physiological state of the patients to confuse the results. The data from Barratt-Boyes and Wood (1957), however, where SVC and RA, RA and RV, and RV and PA samples were obtained at the same intervals, show, as did our data, least variability in the more distal samples. This suggests that the lesser variability in the distal samples in our study is indeed the result of better mixing rather than of changes in the physiological states of the patients. It is not possible, however, from our study to say whether the RV-PA differences resulted from incomplete mixing or measurement error.

Our data contribute to the understanding of the magnitude of the variability in oxygen saturation step-ups in the absence of an intracardiac left-to-right shunt, and provide guidelines for the detection of these shunts. The 99 centile levels (8% for shunt at atrial level, 6% for shunt at ventricular level, and 5% for aortopulmonary shunt) are only guidelines, however, and in borderline situations other independent methods such as indicator dilution curves or angiocardiology should be employed.

We are grateful to the 27 investigators and their staffs at the participating centres of the joint study on the natural history of congenital heart defects for allowing us to use their data. We also thank Mr John Rees for help in data extraction and analysis.

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