Br Heart J 1992;67:470-3

Exercise capacity after complete repair of tetralogy of Fallot: deleterious effects of residual pulmonary regurgitation

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Abstract

***Objective*—To determine the effects of residual pulmonary regurgitation on exercise tolerance after complete repair of tetralogy of Fallot.**

***Design*—Prospective study of symptom free patients more than five years after complete repair. Graded exercise performance was measured with standard Bruce protocol. Maximal oxygen uptake and ventilatory anaerobic threshold were measured by respiratory mass spectrometry. Measurement of pulmonary regurgitant fraction was from pressure-volume loops constructed from measurements of right ventricular volume obtained from biplane angiograms and simultaneous pressures measured with a micromanometer.**

***Setting*—Tertiary referral centre.**

***Patients*—16 patients were studied. Two patients had been excluded because of residual cardiac lesions or inadequate data from cardiac catheterisation. Four were later excluded because they failed to reach a respiratory quotient of $>1\cdot0$ during graded exercise.**

***Results*—There was a significant negative correlation between the degree of residual regurgitation and both total duration of exercise and maximal heart rate achieved. Maximal heart rate and total duration of exercise were significantly lower in the patients than in normal controls. Patients with an abnormal maximal oxygen uptake (less than 85% of the predicted normal value) had significantly greater residual pulmonary regurgitation than those in whom oxygen uptake was normal.**

***Conclusions*—Impaired exercise capacity after complete repair of tetralogy of Fallot is directly related to the degree of residual pulmonary regurgitation. These data should be taken into account when deciding the optimal timing and nature of corrective surgery.**

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Accepted for publication 19 September 1991

To achieve complete relief of obstruction of the right ventricular outflow tract after repair of tetralogy of Fallot a pulmonary valvotomy, insertion of an outflow tract patch, or a transannular patch may be required.[1] Consequently, pulmonary regurgitation is present in most patients after corrective surgery, although it is difficult to quantify.

The importance of chronic pulmonary regurgitation in the long term is not established. Previous studies, in which chronic pulmonary regurgitation was assessed qualitatively, suggested that impaired right ventricular function may be related to the degree of pulmonary regurgitation.[2,3] In another study right ventricular volumes were increased and the ejection fraction decreased in patients with a residual ventricular septal defect or pulmonary regurgitation, or both.[4] Several studies have shown impaired exercise ability after complete repair.[5-7] Wessel *et al* found a relation between the degree of impairment of exercise and the heart size on chest radiography, which led them to speculate that residual pulmonary incompetence may be related to exercise ability after operation.[5]

We recently described a new method of measuring the amount of pulmonary regurgitation by analysing right ventricular pressure-volume loops.[8] In our study there was a linear relation between the pulmonary regurgitant volume and right ventricular end diastolic and end systolic volumes. No such relation could be shown, however, between regurgitant volume and the right ventricular ejection fraction.

In the present study we used this technique to examine the possible influence of pulmonary regurgitation on patients' exercise ability after complete repair.

Patients and methods

PATIENTS

The initial study group comprised 18 patients. In two patients data from cardiac catheterisation were unsatisfactory (residual ventricular septal defect (VSD) in one, unsuitable data for analysis in one), and a further four patients failed to achieve a respiratory quotient $>1\cdot0$ during graded exercise testing (see below). These six patients were not included in the analysis.

Satisfactory data from cardiac catheterisation and exercise were therefore obtained for 12 patients. The table shows the anthropometric data and details of previous surgery for each of the patients. Their median age at the time of corrective surgery was 2·7 (range 0·5–7·7) years with a median follow up of 8·7 (range 5·4–12·7) years. All the patients were well and leading

Demographic, follow up, and exercise data

Patient	Age (years)	Age at operation (years)	RVOT gradient (mm Hg)	RVEF (%)	PR (%)	Minutes run	Max Vo_2 (ml/kg/min)	Surgery
1	14·0	7·7	15	48	27	10	34·2	TAP
2	12·4	2·7	0	60	20	19	55·7	OTP
3	8·7	1·3	10	57	5	15	61·1	TAP
4	14·2	2·7	3	61	0	16·5	55·0	TAP
5	8·4	1·7	47	56	23	14	56·7	TAP
6	13·6	1·7	20	57	58	11	35·5	TAP
7	7·5	0·9	15	47	30	13·5	44·8	PV
8	13·4	3·2	20	48	48	12	45·2	TAP
9	14·4	1·7	18	50	45	11	55·4	TAP
10	8·0	2·8	22	63	50	10	40·8	TAP
11	14·4	5·5	10	64	0	13	44·0	PV
12	10·8	0·5	5	44	39	14	48·0	TAP

RVOT, right ventricular outflow tract; RVEF, right ventricular ejection fraction; PR, pulmonary regurgitant fraction; Vo_2, oxygen uptake; TAP, transannular patch; OTP, outflow tract patch; PV, pulmonary valvotomy.

normal lives with no overt symptoms of reduced exercise tolerance. Cardiac catheterisation and exercise testing were performed according to a protocol agreed by Brompton Hospital's ethical committee, and informed written consent was obtained from the parents of all the patients. Exercise data from the patients were compared with data obtained from 12 controls matched for age, sex, and height.

METHODS

Each patient performed graded maximal exercise, using the progressive treadmill test described by Bruce *et al.*[9] All studies were performed at least one hour after a normal breakfast. A 12 lead electrocardiogram and results of ear oximetry were recorded continuously, and fractional concentrations of all expired gases were measured by respiratory mass spectrometry. Carbon dioxide production, oxygen consumption (Vo_2), and minute ventilation were calculated every 30 seconds with a method described previously.[10] The ventilatory anaerobic threshold was calculated from a plot of minute ventilation against Vo_2.[11] This threshold was defined as the point at which the rate of increase in minute ventilation *v* Vo_2 diverged from a regression line derived from data points during the first half of the exercise test. All measurements were made until the end of the study. Patients were encouraged to exercise to their limit. Each control underwent a similar protocol. Patients and controls in whom the respiratory quotient at maximal exercise failed to exceed 1·0 were excluded because inadequate effort may have limited their performance.

Cardiac catheterisation was undertaken within 24 hours of the exercise test. All studies were performed under general anaesthesia. Routine haemodynamic measurements were made before angiography. Calibrated biplane right ventriculograms were obtained in 30° right anterior oblique and 60° left anterior oblique projections. Each angiogram was digitised frame by frame throughout a selected cardiac cycle. Extrasystoles, immediate post-extrasystoles, and complexes occurring during the injection of contrast were not analysed. Right ventricular volume was calculated with our multiple slice method.[12] Right ventricular ejection fraction was calculated in the usual way, and peak rates of right ventricular filling and emptying were normalised by dividing by the end diastolic volume.

Simultaneous measurements of intraventricular pressure were taken during ventriculography and recorded at a paper speed of 100 cm/s. The waveform corresponding to the cycle selected from the angiogram was digitised by the same equipment and a pressure-volume loop constructed. The pulmonary regurgitant fraction was calculated from these loops by a method described in detail elsewhere.[8] Briefly, the method allows the pulmonary regurgitation occurring during right ventricular isovolumic relaxation to be measured as the increase in right ventricular volume from the point of end systole until opening of the tricuspid valve (fig 1). This may be expressed as an absolute volume or as a fraction of the total right

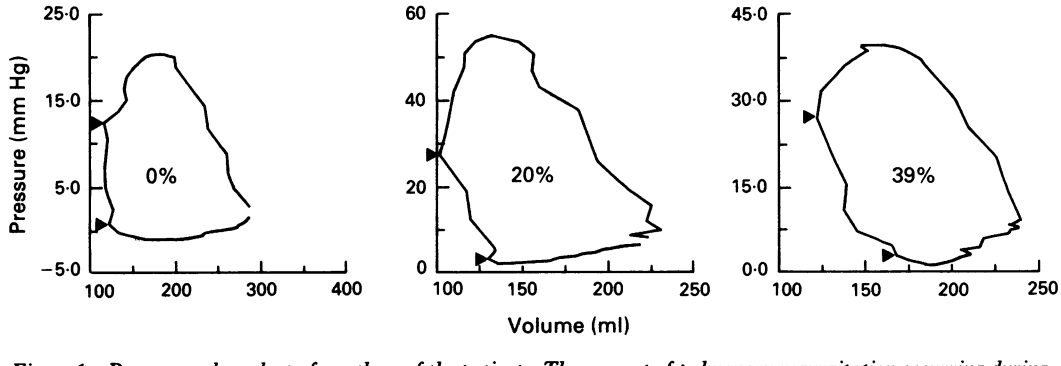

Figure 1 Pressure-volume loops from three of the patients. The amount of pulmonary regurgitation occurring during isovolumic relaxation is measured from the point of minimum cavity volume to the point when the tricuspid valve opens (marked with arrows). The ratio of regurgitant volume to total stroke volume is displayed within the loops and is of increasing severity in these patients.

ventricular stroke volume. Because of concerns about the precision of the calibration process in two of the patients we have chosen to analyse the data only in terms of relative volumes; this does not influence the validity of the data.

STATISTICAL ANALYSIS

Group data were expressed as mean (1 SD). Group data were compared with Student's *t* test or the Mann-Whitney U test. The relations between pulmonary regurgitation and indices of exercise function were examined with a Kendall rank correlation test. The null hypothesis was rejected when $p \leqslant 0{\cdot}05$.

Results

EXERCISE FUNCTION: COMPARISON WITH NORMAL

All patients and controls included in the analysis, developed a respiratory quotient >1 at maximal exercise. No differences in respiratory quotient, age, height, or body surface area were found between the two groups.

The total duration of exercise was significantly lower in the patients (13·4 (2·7) *v* 18·4 (3·2) min, $p = 0{\cdot}0004$). Maximal heart rate was also lower (180 (17) *v* 197 (6) beats/min, $p < 0{\cdot}01$), as was maximal oxygen uptake (48 (8·8) *v* 52 (7·1) ml/kg/min), although this failed to reach significance. Five patients but only one control failed to reach 85% of the predicted value for maximal Vo_2, suggesting an abnormal response in these subjects.[11] Ventilatory anaerobic threshold tended to be lower in the patients (36·9 (4·6) *v* 39·5 (4·7) ml oxygen kg/min), but this difference also failed to reach significance.

PRESSURE-VOLUME RELATION

None of the patients included in the analysis had appreciable tricuspid regurgitation or residual ventricular septal defect.

The right ventricular end diastolic pressure ranged from 2 to 13 mm Hg (median 6 mm Hg), and only one patient had a pressure gradient across the right ventricular outflow tract of more than 22 mm Hg (table). Analysis of the pressure-volume loops showed that the right ventricular ejection fraction ranged from 44% to 63% (median 57%). Considerable pulmonary regurgitation was present in all but two of the patients, ranging from 0% to 58% of the total stroke volume. There was a significant relation between the degree of pulmonary regurgitation and the gradient across the outflow tract ($r = 0{\cdot}49$, $p = 0{\cdot}025$), reflecting this increased stroke volume. There was no significant relation between the pulmonary regurgitant fraction and right ventricular end diastolic pressure, ejection fraction, or normalised peak rate of ventricular filling or emptying.

EXERCISE FUNCTION AND PULMONARY REGURGITATION

There was a significant relation between the degree of pulmonary regurgitation and both duration of exercise ($r = -0{\cdot}43$, $p < 0{\cdot}05$) and maximum heart rate ($r = -0{\cdot}46$, $p < 0{\cdot}05$). A similar relation was found between the pressure gradient across the right ventricular outflow tract and total duration of exercise ($r = -0{\cdot}55$, $p = 0{\cdot}012$), which almost certainly reflected the relation between pulmonary regurgitation and gradient (see above) rather than being directly linked to the modest residual obstruction in most of the patients.

There was no significant relation between the regurgitant fraction and either maximal oxygen uptake or ventilatory anaerobic threshold. Figure 2 shows that in the five patients in whom the Vo_2 was less than 85% of the predicted normal value the pulmonary regurgitant fraction was significantly higher than that in the remainder of the group (43 (13) *v* 19 (18), $p < 0{\cdot}03$).

Discussion

This study shows a clear relation between the degree of residual pulmonary regurgitation and reduced exercise tolerance in patients after complete repair of tetralogy of Fallot.

Our data confirm the findings of previous studies and show that, when compared with normal subjects, these patients have a reduced maximal exercise tolerance.[5–7] The reason for this has, to date, remained unclear. Right ventricular enlargement and a reduced ejection fraction have been shown in several studies[3,4] but these variables in themselves do not seem to be related to exercise ability. The link between exercise ability and pulmonary regurgitation has not previously been examined in detail. This is because of the difficulty in measuring accurately the amount of regurgitation present in individual patients.

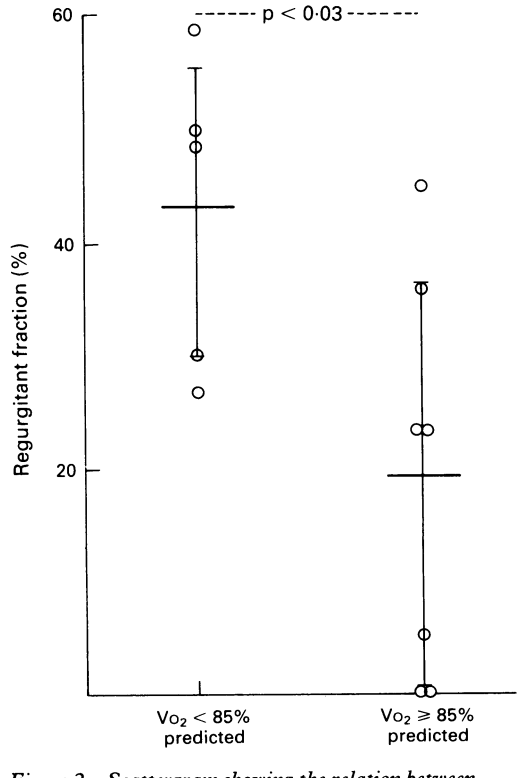

Figure 2 Scattergram showing the relation between pulmonary regurgitant fraction and maximum oxygen uptake (Vo_2).

We recently described a new method of assessing pulmonary regurgitation from analysing right ventricular pressure-volume loops.[8] Our data showed that increased right ventricular volumes, but not ejection fraction, were linearly related to the degree of residual regurgitation. Wessel *et al*'s data are interesting in this regard.[5] They showed that reduced exercise capacity in patients after operation could be related to the heart size measured from the chest radiograph. They speculated that this may in turn reflect the degree of pulmonary regurgitation present and suggested a possible link between residual pulmonary regurgitation and intolerance to exercise in these patients. Our results confirm that this is indeed the case. Pulmonary regurgitation had a deleterious effect on exercise capacity in our patients, whom we studied at least five years after complete correction. The reduction in total duration of exercise and maximum heart rate were both directly related to the degree of regurgitation. In the subgroup of patients with an abnormal maximal oxygen uptake, pulmonary regurgitation was significantly greater than that in the patients in whom maximal oxygen uptake was normal.[11]

These results have obvious clinical implications. Residual pulmonary regurgitation is clearly undesirable, and efforts to reduce it may benefit patients, exercise ability in the long-term after complete repair. Whereas our data suggest a similar relation between residual obstruction of the right ventricular outflow tract and exercise capacity, the residual gradient was less than 25 mm Hg in 11 of the 12 patients. These modest gradients are almost certainly directly related to the degree of pulmonary regurgitation with its consequent increase in stroke volume rather than representing haemodynamically important obstruction. Indeed, there was no relation between more severe obstruction and exercise ability in the patients studied by Wessel *et al*.[5]

These data may influence surgical decision making. Some residual obstruction of the right ventricular outflow tract may be more desirable than complete relief of obstruction at the expense of increased pulmonary regurgitation. The potentially harmful effects of a high right ventricular to left ventricular pressure ratio soon after operation cannot, however, be ignored.[13] An alternative approach is to place a homograft monocusp in the right ventricular outflow tract. Although this technique probably reduces early regurgitation, the function of these valves in the longer term is unknown. Our department is currently investigating this.

Frequently a transannular patch will be required to ensure adequate relief of obstruction of the right ventricular outflow tract in patients with tetralogy of Fallot. If a monocusp valve is not inserted there may well be free pulmonary regurgitation. This must be taken into account when considering the trend towards earlier, usually primary, complete repair during infancy. The frequency of applying transannular patches is undoubtedly higher in young infants[14] and though there may be theoretical advantages to earlier surgery, the documented adverse effects of chronic pulmonary regurgitation on both exercise performance and the incidence of late arrythmias cannot be disregarded.[3] Although we followed up our patients for five to 12 years after operation, the potential effects of chronic pulmonary regurgitation in the longer term need to be examined. These patients will require careful extended follow up.

In summary, we have shown a direct relation between the degree of pulmonary regurgitation and impaired exercise ability in patients after repair of tetralogy of Fallot. This must be taken into account when deciding the optimal timing and nature of corrective surgery.

We thank Dr J Bowyer for providing the control data and the members of the Brompton Hospital lung function unit for their help with the exercise studies.

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