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Factors associated with the presence of tricuspid valve regurgitation in patients with systemic right ventricles following atrial switch

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Abstract

Background: *The development of significant tricuspid regurgitation (TR) is associated with an unfavorable clinical outcome in patients with systemic right ventricles. Increased knowledge about the factors contributing to its presence would help prevent its progression.*

Methods: *This was a retrospective analysis of the factors predictive of significant TR in 60 patients with systemic right ventricles following an atrial switch procedure for complete transposition of the great arteries. Data from echocardiographic examinations, exercise radionuclide angiography, and myocardial perfusion imaging were analyzed.*

Results: *Significant TR was present in 20% of patients. Compared to patients without significant TR, patients with significant TR were older at the time of surgery ($p \leq 0.001$), with a higher body mass index ($p \leq 0.005$), lower right ventricular ejection fraction (RVEF; $p \leq 0.01$), higher exercise perfusion abnormalities score on radionuclide angiography ($p \leq 0.03$), and higher systolic blood pressure ($p \leq 0.02$). At univariate logistic regression analysis systolic blood pressure ($p = 0.03$), increasing age at surgery ($p = 0.01$), and RVEF ($p = 0.02$), were predictors of significant tricuspid regurgitation. The latter two remained significant at multivariate analysis.*

Conclusions: *Patients operated upon later in life, with decreased RVEF and higher blood pressure, are at risk of significant tricuspid regurgitation and therefore warrant special attention. Prospective studies are needed to ascertain whether appropriate pharmacological intervention would prevent the development and/or progression of TR in these patients.* (Cardiol J 2010; 17, 1: 29–34)

Key words: congenital heart disease, tricuspid regurgitation, transposition of the great arteries

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Introduction

Between the 1960s and the 1980s, simple transposition (D-transposition) of the great arteries was repaired mainly with an atrial switch procedure, either Mustard or Senning. Most patients who survived this surgery are thus now young or middle aged. The problems associated with atrial correction via complete transposition are mainly arrhythmias, systemic ventricular dysfunction and tricuspid regurgitation (TR). The data on the prevalence of severe TR during a long-term follow-up are somewhat inconclusive. Its prevalence ranges from 1.1% to 20% [1–3]. Moderate TR is found in 6% to 27.5% of patients [3, 4]. An analysis of the factors associated with the presence of systemic TR has never been performed. The results of such analysis would be of practical value, because the results of surgical therapy are not favorable [5] and preventing the development and progression of systemic tricuspid valve regurgitation is of the utmost importance. Therefore, we evaluated factors associated with the presence of significant TR in patients with systemic right ventricles following Mustard or Senning operations for complete transposition.

Methods

This was a retrospective analysis of data from patients who had simple transposition of the great arteries following an atrial switch procedure performed between 1982 and 1990. Patients younger than eight years, and those with moderate-to-large ventricular septal defects (VSD), were excluded. Data from echocardiographic examinations, exercise radionuclide angiography, and myocardial perfusion imaging using technetium 99-m methoxyisobutyl isonitrile were analyzed. The right ventricular ejection fraction (RVEF) was calculated from the background-corrected end-diastolic and end-systolic counts of the first-pass angiogram. The right ventricular cross-sectional horizontal long-axis and vertical long-axis views were analyzed. Lesions, defined as areas of reduced radioactivity, were graded in a 5-point scale. Scores from 3 to 5 were defined as moderate-to-severe perfusion abnormalities. Transthoracic two-dimensional and Doppler scans were performed with commercially available equipment. Tricuspid regurgitation was classified using a standard semi-quantitative colour Doppler method as nil, mild, moderate or severe, based on the spatial distribution of the regurgitant jet area in the right atrium, how much it impinged upon the right atrial wall, the presence of prominent proximal flow convergence and vena contracta.

The study protocol was approved by the Human Ethics Committee at our Institution.

Statistical analysis

For comparison, patients were divided into groups with significant (moderate or severe) TR and non-significant/absent (nil, trace or mild) TR. The subgroup of patients with severe TR was also compared to the other patients. The data was presented as a mean ± standard deviation (SD), median and range, where appropriate. Student's t test (Mann-Whitney U test when data was not normally distributed), analysis of variance and univariate logistic regression were used for the statistical analysis of the data. Variables that were statistically significant on univariate analysis were evaluated by multivariate analysis using multivariate logistic regression. Correlations between variables were assessed by Pearson or Spearman correlation coefficients. A p value equal to, or less than, 0.05 was considered significant.

Results

Sixty patients, 43 male and 17 female, were available for this analysis. Their mean age was 14.9 ± ± 4.5 years (range 8–23 years). Average age at the time of surgery was 3.3 ± 3.3 years (range 0.9––14 years). Before the definitive surgery, 52 patients (86.7%) underwent Rashkind procedures and one had undergone a Blalock-Taussig shunt. Mustard procedure was performed on 19 patients (31.7%) and Senning procedure on the other 41 patients (68.3%). At the time of the last follow-up, patients were aged on average 11.5 ± 2.7 (range 6–14 years) years after the surgery. Fifty-five patients were in New York Heart Association functional class I, and five were in class II.

Transthoracic echocardiography did not detect any significant obstruction of pulmonary and systemic inflow. Small VSD with hemodynamically insignificant left-to-right shunt was present in six (10.0%) patients. Insignificant baffle leak was present in two patients (3.3%). Left ventricular outflow tract obstruction, with gradients from 20 mm Hg to 65 mm Hg, due to systolic anterior movement of the mitral leaflet, was detected in nine (15.0%) patients.

Colour Doppler echocardiography detected trace or mild TR in 28 (46.7%) patients and 12 patients (20%) had significant TR, including nine (15.0%) with moderate and three (5.0%) with

Table 1. Comparison of patients with and without significant tricuspid regurgitation.

	Tricuspid regurgitation		P
	Significant	Non-significant/nil	
Age at surgery (years)	6.0 ± 5.2	2.6 ± 2.3	0.001
Time from surgery to last follow-up visit (years)	12.9 ± 2.4	11.2 ± 2.7	0.045
Weight [kg]	54.4 ± 15.0	40.1 ± 16.3	0.01
Height [cm]	163.8 ± 14.9	146.6 ± 16.3	0.002
Right ventricular ejection fraction (ECHO)	31.3 ± 12.0	44.9 ± 10.2	0.0001
Right ventricular ejection fraction (radionuclide)	30.7 ± 5.0	36.8 ± 7.3	0.013
Left ventricular ejection fraction (radionuclide)	49.2 ± 11.8	53.1 ± 8.9	0.2
Perfusion score at rest	2.5 ± 1.8	2.2 ± 1.4	0.5
Perfusion score at exercise	3.6 ± 1.4	2.6 ± 1.4	0.03
Body mass index [kg/m^2]	1.6 ± 0.3	1.3 ± 0.3	0.005
Systolic blood pressure [mm Hg]	141.4 ± 11.4	130.2 ± 14.7	0.02
Diastolic blood pressure [mm Hg]	78.2 ± 10.3	73.1 ± 11.8	0.2

severe regurgitation. Twenty patients (33.3%) had no TR. Echocardiography did not reveal any obvious congenital malformations of the tricuspid valve, such as Ebstein anomaly or leaflet dysplasia.

Compared to the group without significant TR, patients with significant TR did not differ with respect to sex, Rashkind procedure in infancy, Mustard or Senning procedure, the presence of left ventricular tract obstruction or VSD.

The time from surgery to the last follow-up visit was longer in patients with significant TR. These patients were also significantly older at the time of surgery, compared to the group without significant TR. Their body surface area was higher, radionuclide and echocardiographic RVEF were lower and exercise perfusion abnormalities score and systolic blood pressure were higher. There were no differences with respect to diastolic blood pressure values (Table 1). Systolic blood pressure increased across all categories of severity of TR, and differed significantly in patients with severe TR, compared to patients with no TR ($p = 0.003$) and, although non-significantly, compared to patients with mild ($p = 0.06$) TR and moderate TR ($p = 0.08$; Fig. 1). The same tendency was noted for perfusion abnormalities at exercise (Fig. 2), and body mass index (BMI). The differences, however, were not statistically significant ($p = 0.08$ and $p = 0.11$, respectively).

At univariate logistic regression analysis, age at surgery, RVEF, and systolic blood pressure were significantly predictive of the presence of significant TR. The length of time from surgery to the last follow-up visit, and perfusion abnormalities at exercise, were of borderline significance (Table 2).

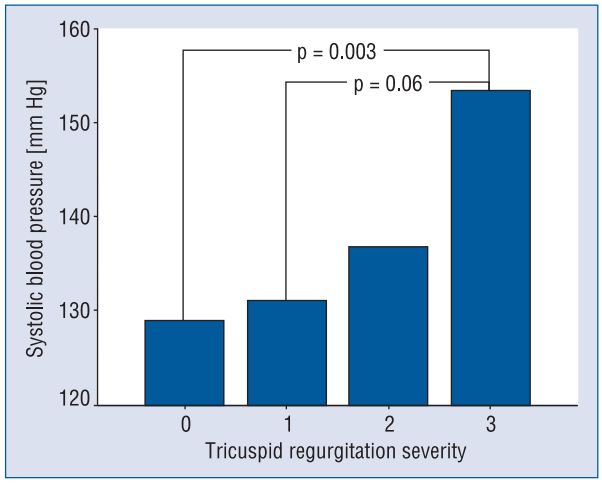

Figure 1. Relationship between the degree of tricuspid regurgitation and systolic blood pressure values.

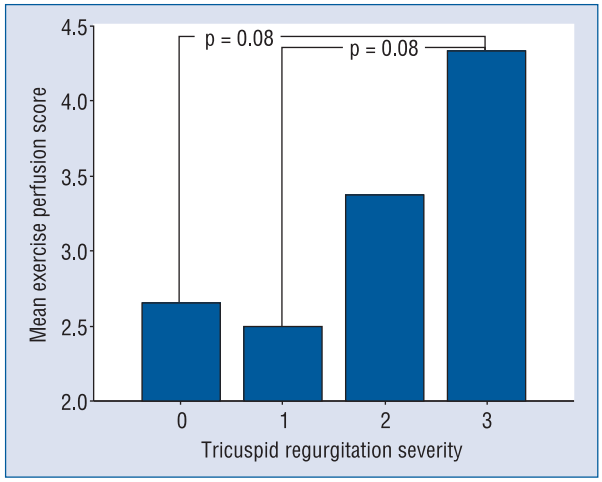

Figure 2. Relationship between the degree of tricuspid regurgitation and exercise perfusion score.

Table 2. Univariate logistic regression analysis.

Variable	Exp(B)	95% confidence interval for Exp(B)	P
Age at surgery (years)	1.30	1.06–1.59	0.01
Time from surgery to last follow-up visit (years)	1.27	1.04–1.62	0.04
Right ventricular ejection fraction	0.8627	0.76–0.98	0.02
Significant perfusion abnormalities at exercise	4.50	0.88–23.14	0.07
Significant perfusion abnormalities at rest	0.62	0.16–2.34	0.48
Systolic blood pressure [mm Hg]	1.05	1.01–1.10	0.03
Body mass index [kg/m^2]	1.16	0.97–1.4036	0.1
Mustard *vs* Senning	1.73	0.47–6.39	0.4
Ventricular septal defect	0.45	0.07–2.83	0.4

Table 3. Multivariate logistic regression analysis.

Variable	Exp(B)	95% confidence interval for Exp(B)	P
Systolic blood pressure [mm Hg]	0.98	0.91–1.03	0.30
Right ventricular ejection fraction	0.87	0.76–0.99	0.04
Time from surgery to last follow-up visit (years)	1.32	0.99–2.01	0.05
Age at surgery (years)	1.35	1.07–1.69	0.01
Perfusion abnormalities at exercise	5.56	0.39–78.78	0.20

At multivariate logistic regression analysis, age at surgery and RVEF were significant predictors of significant TR (Table 3).

Discussion

In hearts of normal anatomy, both organic and functional chronic mitral regurgitation cause chronic volume overload and remodelling and have a significant impact on prognosis [6, 7]. There is no reason to believe that this is not the case with the tricuspid valve and systemic right ventricle. In addition, surgical management does not change the very unfavorable outcome of those patients with systemic right ventricle in whom TR has already developed [5]. Therefore, preventing its development and progression is of the utmost importance. We have demonstrated that advanced age at surgery, depressed systemic right ventricular function, elevated blood pressure values and possibly perfusion abnormalities are associated with the presence of significant TR. Some of these factors are modifiable and demand our attention as they may contribute to the future development or current progression of TR in patients following atrial switch.

The presence of TR may be explained by several potential mechanisms: congenital abnormalities of the tricuspid valve apparatus [8], dysfunction of the systemic ventricle caused by the chronic pressure overload, ischemia and/or fibrosis of the ventricle [9–11], right-to-left septal shift [12], increased retrograde transtricuspid pressure gradient associated with the systemic position of the tricuspid valve [13], and iatrogenic causes.

Congenital abnormalities of the tricuspid valve apparatus

Congenital abnormalities of the tricuspid valve are very common (70%) in congenitally corrected transposition [14], less so in patients with complete transposition and VSD (31%) [8], and less so again in patients with complete transposition without VSD (21%) [15]. In our study, no congenital valve abnormalities were detected. We found no association between TR and the presence of VSD, but patients with significant VSD had been excluded. Similarly, Deal et al. [16] did not detect any abnormalities of tricuspid valve in pediatric patients with simple transposition (without VSD), although they were detectable in children with VSD. The reason might be that in patients without VSD the majority of tricuspid valve apparatus abnormalities consist of some displacement or hypoplasia of papillary muscles [15], which is a challenging diagnosis for a sonographer, even in normal right ventricles.

Dysfunction of the systemic ventricle

The association between the dysfunction of the systemic ventricle and TR is well established [1–4]. However, the 'chicken-and-egg question': whether regurgitation promotes ventricular dysfunction or ventricular dysfunction causes regurgitation, remains unanswered. Right ventricular dysfunction was predictive of significant TR also in our study. We found the presence of significant TR was associated with the duration of the exposition of the valve to systemic pressures (the duration of the time from the surgery to the last follow-up visit). This is in accordance with the results of Roos-Hesselink et al. [2], who found an increased prevalence of TR and ventricular dysfunction over time.

We found an association between perfusion abnormalities during exercise and TR severity at univariate analysis. Our previous analysis [11] and other papers [10, 17, 18] confirm the presence of reversible and fixed perfusion defects, as well as reduced coronary flow reserve in the pathogenesis of right ventricular dysfunction but, to the best of our knowledge, there is no data concerning their association with the degree of TR. A very indirect indicator of the association of ischemia with TR might be a reduction of the degree of TR following beta-blockade in Mustard or Senning patients [19]. The other argument that suggests myocardial dysfunction is cause rather than effect is the fact that tricuspid valve repair or replacement may not improve right ventricular function in patients with a failing right ventricle following atrial switch [20]. On the other hand, it has been demonstrated that even in hearts of normal anatomy, functional TR may produce irreversible deterioration of right ventricular function [21]. In a study by Kirjavainen et al. [22] of Senning patients, TR preceded the onset of right ventricular dysfunction by a mean interval of 3.6 years in 64% of them, suggesting a reverse causal relationship. It is not known whether pharmacotherapy of right ventricular dysfunction would improve tricuspid regurgitation.

Increased retrograde transtricuspid pressure gradient

In hearts of normal anatomy, the usual right ventricular systolic pressure is 20 to 25 mm Hg, and pulmonary hypertension is the most frequent cause of TR [23]. Increased retrograde pressure gradient caused by the systemic position of the tricuspid valve may therefore contribute to TR following atrial switch. We found a relationship between systolic blood pressure values and the degree of regurgitation at univariate, but not at multivariate, analysis. This may suggest an indirect relationship, mediated probably by ventricular dysfunction [13], but again the 'chicken-and-egg question' remains unanswered.

Whatever the relationship, restoration of a low-pressure system by the arterial switch operation reduces TR [24].

Except for beta-blockers [19] there is no data concerning the effect of antihypertensive drugs on TR. Our data suggests that a trial of antihypertensive therapy may be warranted in order to prevent the deterioration of tricuspid regurgitation.

Body mass index was significantly higher in patients with severe TR, but was not statistically significantly predictive of its presence. Patients with TR were older and hence with a larger BMI. However, in the light of the obesity epidemic in adolescents, it is worth remembering that in an otherwise healthy adult population, increased BMI is associated with elevated blood pressure values and diastolic dysfunction of the systemic left ventricle.

Iatrogenic tricuspid regurgitation

Our patients were operated upon late, compared to their counterparts in other centres [3]. We found a significant association between age at surgery and risk of developing TR. Therefore patients operated upon late should get more attention from their consulting cardiologists, as they are at risk of late complications. Very early corrective surgery might be important for other groups of patients with systemic right ventricles.

In our group TR was non-significantly commoner following the Mustard procedure. Contrary to that, Moons et al. [3] found TR non-significantly commoner following the Senning procedure.

Limitations of the study

Our study had limitations, including those inherently associated with the retrospective character of the analysis. The latter obviously limits the conclusions concerning the cause-and-effect relationship between advanced age at surgery, reduced RVEF, perfusion abnormalities, elevated blood pressure, and the development of systemic TR. In the absence of prospective data however, these markers may guide the use of preventive measures such as blood pressure lowering therapy. They may also suggest that the threshold for the initiation of unloading therapy should probably be lower in patients operated upon late, irrespective of right ventricular systolic function.

While we performed the multivariate logistic regression analysis to further define the factors

independently associated with TR, the small number of patients available for statistical analysis means we must proceed with caution in interpreting its results, especially with reference to the factors excluded from the multivariate statistical model.

Conclusions

Functional mitral regurgitation is a hotly debated topic, with a plethora of papers published on its pathophysiology and management. There is no reason to believe that the consequences of TR for the systemic right ventricle are less important than the consequences of mitral regurgitation for the systemic left ventricle. We found several factors predictive of significant TR. Although the retrospective character of the analysis hampers definitive conclusions, it suggests that patients operated upon late in life, with decreased RVEF and higher blood pressure values, are at risk of significant TR and so warrant special attention.

Acknowledgemetns

The authors do not any conflict of interest regarding this work.

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