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Review

Pulmonary regurgitation: not a benign lesion

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Pulmonary regurgitation (PR) is a common complication after surgical or percutaneous relief of pulmonary stenosis and following repair of tetralogy of Fallot. Significant PR is usually well tolerated in childhood. However, in the long term, chronic PR has a detrimental effect on right ventricular (RV) function and exercise capacity and leads to an increased risk of arrhythmia and sudden cardiac death (SCD). Recent advances in non-invasive imaging and, in particular, wider availability of cardiovascular magnetic resonance (CMR), have improved the assessment of PR and RV function in these patients. This in turn has facilitated decision making on the optimal timing for elective pulmonary valve replacement (PVR), which should be performed before irreversible RV dysfunction ensues.

Introduction

Pulmonary regurgitation (PR) is common after surgical or percutaneous relief of pulmonary stenosis and following repair of tetralogy of Fallot. PR is usually well tolerated in childhood. However, recent long-term studies have demonstrated that PR leads to progressive right ventricular (RV) dilatation and, with time, to RV dysfunction, exercise intolerance, ventricular tachycardia, and sudden cardiac death (SCD).[1–5] Furthermore, recent advances in non-invasive imaging, and in particular wider availability of cardiovascular magnetic resonance (CMR), have improved the assessment of PR and RV function in these patients.

In this article we discuss the impact of PR on RV function and clinical outcome, the role of different diagnostic modalities, and current management strategies for patients with PR.

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Morphological spectrum

PR is not usually found as an isolated congenital lesion, although physiological (mild) regurgitation is commonly detected by colour Doppler echocardiography in otherwise normal hearts (*Table 1*).

Tetralogy of Fallot

PR is extremely common in patients after repair of tetralogy of Fallot. While most of these patients carry an excellent prognosis,[6,7] there is a late morbidity and mortality related largely to RV dysfunction. PR in these patients is shown to relate to the use of a transannular patch—more liberally performed in an earlier surgical era—to reconstruct the RV outflow tract (RVOT). Furthermore, transannular patching and/or aggressive infundibulectomy predispose to RVOT aneurysms or akinetic regions. The latter, combined with chronic PR, have an adverse effect on RV function and overall prognosis.[8] As a result, routine and generous transannular patch type of repair has now been abandoned and limited RVOT patching with preservation of pulmonary

Table 1 Pathophysiology of chronic PR

Substrate	Post-repair of tetralogy of Fallot
	Post-valvotomy for pulmonary stenosis (balloon or surgical)
	Absent pulmonary valve syndrome (rare)
	Isolated congenital PR (rare)
Co-variable/s	Peripheral pulmonary artery stenosis (−)
	Pulmonary hypertension (−)
	RVOT aneurysm/akinesia (−)
	RV restrictive diastolic physiology (+ in the older patient)
Clinical progression	RV dilatation (there is usually a long compensatory phase while RV systolic function is maintained)
	QRS prolongation (associated with increased risk of sustained ventricular tachycardia and SCD)
	Onset of tricuspid regurgitation
	RV systolic dysfunction
	Overt symptoms ensue

(−/+) indicates negative or positive effect on PR and/or RV function.

valve function have become key therapeutic goals during primary repair of tetralogy in infancy.

Pulmonary stenosis

Balloon valvuloplasty has become the treatment of choice for patients with valvular pulmonary stenosis. Surgical valvotomy—widely employed in the 1960s and the 1970s—is now reserved for patients with supra- or sub-valvular stenosis. Variable degrees of PR are seen in more than 70% of patients after either a surgical or transcatheter intervention,[9–13] although PR appears to be less frequent following balloon valvuloplasty.[14] In the *Second Natural History Study of Congenital Heart Defects*, 87% of the surgically operated patients had PR on echocardiography, being more than moderate in 28%.[11] A number of these patients now return requiring pulmonary valve replacement (PVR).

Absent pulmonary valve syndrome

Absent pulmonary valve syndrome is a rare manifestation comprising faulty development and dysplasia or complete absence of pulmonary valve cusps leading to PR. It is commonly associated with tetralogy of Fallot although occasionally it is seen in isolation. Its management and prognosis are often determined by the degree of pulmonary arterial dilatation, which can be excessive in some patients causing external bronchial compression.

Pathophysiology of PR

The functional situation of a severely or freely regurgitant pulmonary valve is different from that of a severely regurgitant aortic valve for two reasons. First, as illustrated by the Fontan circulation, forward pulmonary blood flow can be maintained indirectly by the work of the left heart via the systemic venous return and by right atrial contraction. This occurs for part of each cycle in patients with severe PR and a 'restrictive right ventricle', in whom late diastolic forward flow in the pulmonary trunk coincident with atrial systole is seen and the right ventricle temporarily acts as a conduit (during late diastole). The second difference between PR and aortic regurgitation is that the pulmonary microvascular bed, compared with the systemic, is of low resistance and located close to the heart. The importance of this is that with each RV systole blood moves readily forwards through the pulmonary microvessels whose slight resistance acts as a 'watershed' into the pulmonary veins, which in turn are maintained at low pressure by action of the left heart. Flow that passes forward through alveolar capillaries in systole is unlikely to pass back again in diastole, there being no significant reversal of gradient. The pulmonary microvascular bed, therefore, has a valve-like effect in the setting of severe PR. This is borne out by the fact that severe or free PR is usually associated with a regurgitant fraction of only about 40%,[8,15] which is generally well tolerated for a long period of time. PR is, however, exacerbated by conditions that lead to elevated pulmonary artery pressure, e.g. branch pulmonary arterial stenosis, acquired bronchopulmonary disease, left ventricular dysfunction, or pulmonary vascular disease (uncommon in the setting of tetralogy).[16]

The adaptive RV response to volume overload resulting from PR depends on the degree and duration of the regurgitant flow[17] and the properties of the right ventricle and of the pulmonary arteries. More than moderate chronic PR produces RV volume overload, with increased end-diastolic volumes followed in time by an increase on end-systolic volumes, and progressive deterioration of myocardial function. It is of interest that immediate post-operative PR is well tolerated after repair of tetralogy of Fallot in infancy. In contrast, post-operative PR is poorly tolerated in the adult following late primary repair (personal communication, Darryl F. Shore, Royal Brompton Hospital, London, UK). Adult patients, therefore, should be considered for pulmonary valve implantation at the time of repair if native pulmonary valve function cannot be preserved. We speculate that this relates to poor adaptation of a hypertrophied and relatively non-compliant right ventricle in the adult patient, further compromised by the acute volume overload of significant PR that can be induced following late repair of tetralogy of Fallot in adulthood.

Significant tricuspid regurgitation, present in about 32% of adult patients with repaired tetralogy of Fallot in a recent report, appears to be the result of either progressive RV and tricuspid annulus dilatation or, occasionally, secondary to iatrogenic tricuspid valve injury during ventricular septal defect closure. Tricuspid regurgitation in turn contributes to additional dilatation of the right ventricle and right atrium.[18] Furthermore, RV dilatation and stretch slows interventricular conduction and

creates a mechano-electrical substrate for re-entry circuits, predisposing to sustained ventricular tachycardia. There has been a loose but consistent correlation between QRS prolongation and RV dilatation.[8,19] A QRS duration of 180 ms or more is shown to be a highly sensitive predictor of sustained ventricular tachycardia and SCD in patients with previous tetralogy repair.[19] While QRS lengthening, seen immediately after repair, reflects surgical injury to the myocardium and on the right bundle branch, late QRS prolongation almost universally reflects RV dilatation, mostly due to PR. Interval change in QRS duration, thus, may have a greater prognostic value for sustained ventricular tachycardia and SCD than absolute QRS measurements at any point in time.[5] This is particularly relevant to contemporary cohorts undergoing tetralogy repair via a transatrial/transpulmonary approach, where direct myocardial damage is limited, thus initial post-operative QRS prolongation is less compared with older cohorts who underwent tetralogy repair via a right ventriculotomy.[20]

Clinical presentation of PR

PR is usually well tolerated for many years. Patients often remain free of overt symptoms until marked RV dilatation and systolic dysfunction ensue.[21] Patients with early RV dysfunction are often New York Heart Association (NYHA) class 1, although variable degrees of exercise intolerance on exercise testing are to be expected.[1,2,22] When patients become symptomatic, RV dysfunction is usually well established and may have become irreversible.

In patients with isolated congenital PR, and otherwise normal hearts, symptoms are rare before the age of 30. After the age of 40, however, patients manifest symptoms of right heart failure[23] (*Figure 1*) and may also present with SCD. In contrast, symptoms in patients with repaired tetralogy of Fallot may appear at an earlier stage. We speculate that this relates largely to associated lesions and also to the adverse effects of early cyanosis, ventricular hypertrophy, and of previous operations, on myocardial function.

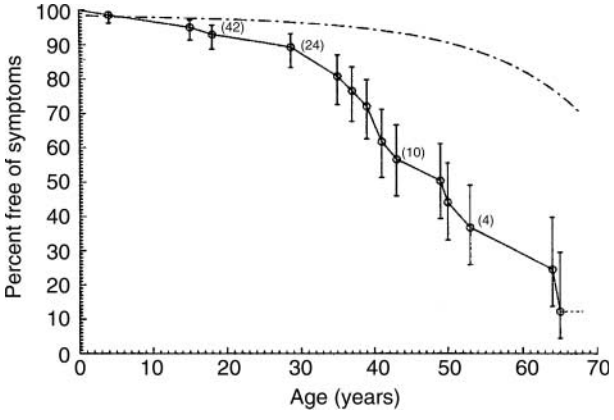

Figure 1 Actuarial freedom from symptoms in patients with isolated congenital pulmonary valve regurgitation ($n = 72$, 17 events). The vertical bars enclose the 70% confidence limits (one standard deviation). The numbers in parentheses indicate the number of patients traced beyond the indicated age. The dash-dot-dash line at the top is the actuarial survival of the US general population starting at birth. Used with permission from Y. Shimazaki, *Thorac Cardiovasc Surgeon* 1984;**32**:257.

Clinical manifestations comprise exercise intolerance, congestive heart failure, atrial and ventricular arrhythmia, and SCD.[4] Elevated jugular venous pressure, liver enlargement, and peripheral oedema can all be present when there is RV dysfunction with clinical heart failure. However, this is uncommon.

Severity of PR is notoriously difficult to assess by clinical examination. Nevertheless, patients with moderate to severe PR often have a RV heave with a single second heart sound and a to and fro murmur. The extent of the regurgitant murmur into diastole is important as early termination (i.e. a short diastolic murmur) suggests severe PR.[24]

Investigations for PR

ECG

Most patients are in sinus rhythm although atrial arrhythmia can be present. In patients with isolated PR the presence of QRS prolongation, with rSr morphology in the right pre-cordial leads, reflects volume overload of the RV. Right bundle branch block is extremely common in patients who underwent tetralogy repair via a right ventriculotomy and may mask RV hypertrophy. QRS duration in these patients increases with time, reflecting progressive RV enlargement and potentially RV dysfunction. As discussed above, QRS duration and QRS change have prognostic implications for malignant arrhythmia and SCD in these patients.[5,19]

Chest X-ray

Patients with severe PR characteristically have dilatation of the pulmonary trunk and central pulmonary arteries. There is also RV enlargement, evident as filling of the retrosternal space on lateral projections.

Echocardiography

Evaluation of the pulmonary valve, RVOT morphology, and the presence and severity of PR can be performed with echocardiography. The complex RV geometry further distorted by previous surgery may limit complete assessment, however. The presence of retrograde colour flow from the distal main pulmonary artery, or its branches, and a high regurgitant fraction calculated with pulsed Doppler[25] have been used until recently as echo markers of severe PR. Our group and others recently reported good agreements between duration of pulmonary regurgitant flow (expressed as a percentage of the total diastolic time on continuous wave Doppler) and CMR-derived pulmonary regurgitant fraction[26,27] (*Figure 2*). The size and function of the right ventricle

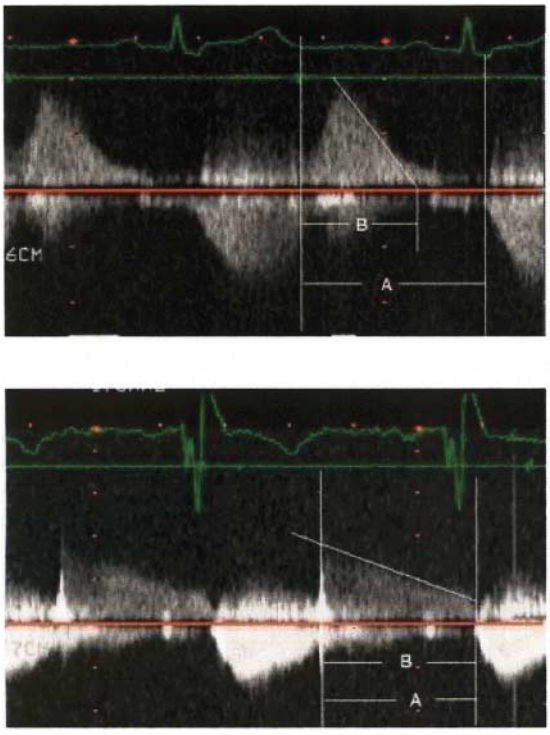

Figure 2 Severity of PR assessed by continuous wave Doppler. Continuous wave Doppler echocardiographic recordings of pulmonary flow from a patient with severe (top) and mild (bottom) PR. The duration of regurgitant flow (B) with respect to total diastole (A) is shorter in the patient with severe PR (top). Used with permission from W. Li, *Am Heart J*, 2004;**147**:165–172.

should also be evaluated. RV systolic function in the presence of severe PR can be maintained, but ultimately deterioration occurs following prolonged exposure to volume overload. Interventricular septal motion is usually paradoxical in these patients, again reflecting volume overload.

Adult patients with repaired tetralogy may exhibit restrictive RV physiology. In these patients, a stiff right ventricle is acting as a conduit between the right atrium and the pulmonary artery at the end of diastole, counteracting the effects of PR and contributing to forward pulmonary flow and thus cardiac output (see Pathophysiology above). RV restriction can be detected with pulsed wave Doppler as a laminar diastolic pulmonary flow coincident with atrial systole, and seems to limit the degree of RV dilatation. Consequently, patients with RV restrictive physiology may have smaller RV volumes and better exercise tolerance.[28]

CMR

This non-invasive imaging modality has become the gold standard for the periodic evaluation and follow-up of patients with PR.[8,21] Systolic and diastolic flow through the pulmonary valve can be accurately quantified by velocity mapping, allowing for calculation of pulmonary regurgitant fraction[8,15,29,30] (*Figure 3*). There are clear advantages of CMR vs. echocardiography in that CMR is

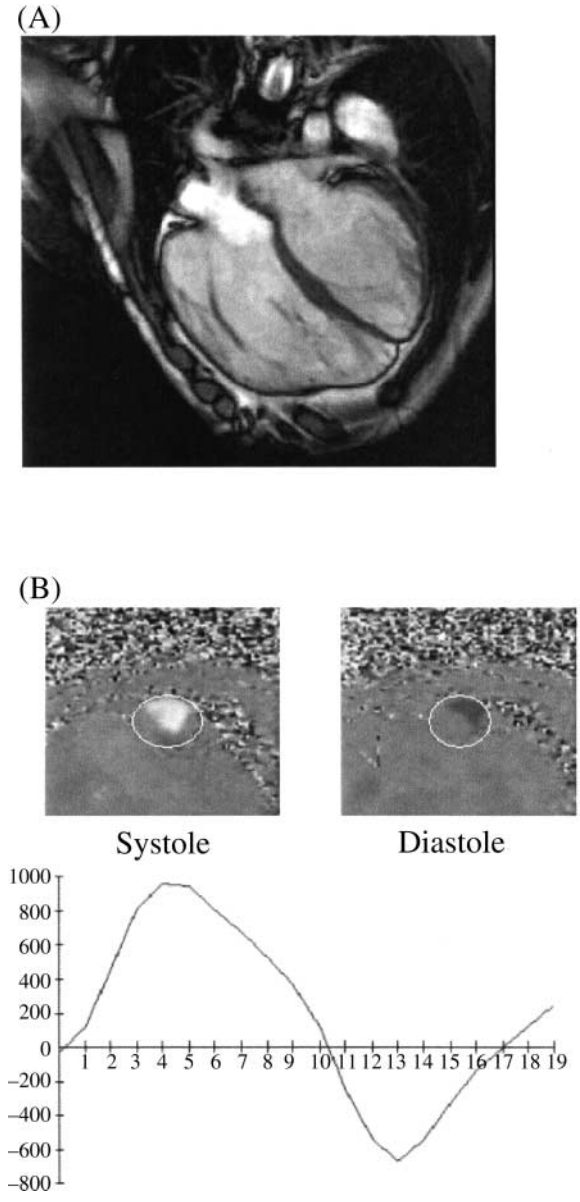

Figure 3 CMR for assessment of biventricular function, mass, and PR in a patient following repair of tetralogy of Fallot. (*A*) Four chamber view shows RV dilatation and hypertrophy in a patient with severe PR. (*B*) Phase velocity mapping measuring the flow across the pulmonary artery in systole and diastole (below the curve) in the same patient.

independent of geometrical assumptions for evaluation of RV mass, volumes, and function, and its wide field of view permits an unrestricted evaluation of RVOT aneurysmal or akinetic regions. Quantification of ventricular dimensions and function gives invaluable information for the management of patients with repaired Fallot and significant PR. Increased right and left ventricular indexed systolic volumes ($\geq$95 and $\geq$50 mL/m^2) respectively) are indicative of ventricular dysfunction, and a depressed ejection fraction ($\leq$35% for the right ventricle and $\leq$50% for the left ventricle) is associated with worse functional class.[21] As discussed later in the paper, PVR should be performed in these patients before irreversible

ventricular dysfunction develops. However, the optimal timing for PVR remains a challenge and decisions need to be made on an individual patient basis. Furthermore, CMR can assess better extracardiac lesions such as conduit or distal pulmonary artery stenosis,[15,29,30] and dilatation of the ascending aorta compared with transthoracic echocardiography.[31] CMR thus provides essential complementary data facilitating both management and prognosis for these patients.

Exercise test

Exercise testing is a useful adjunct for the evaluation of severity of PR, and of the degree of RV dysfunction, and objectively documents functional class of the patient. Changes in exercise capacity with serial testing may precede the onset of overt symptoms and assist in deciding on timing of PVR in these patients.

Cardiac catheterization

Cardiac catheterization is nowadays reserved for the few patients whose haemodynamic status cannot be accurately assessed non-invasively (as in patients with poor echocardiographic windows and/or pacemakers, the latter not suitable for CMR), for patients undergoing catheter interventional procedures, or when specific invasive haemodynamic data are required prior to surgery.

Management of PR

Medical

Diuretics have a role for patients presenting with symptoms of right heart failure, although identification of residual lesions and elective intervention prior to clinical decompensation is clearly desirable. Recent evidence suggests that patients with tetralogy of Fallot have both neurohormonal activation and impaired cardiac autonomic nervous activity.[32,33] Neurohormonal antagonism, therefore, with ACE-inhibitors and/or beta-blockers, and other interventions such as physical conditioning (known to modulate the autonomic nervous system) may convey symptomatic benefits, improve prognostication, and delay the need for re-operation. Clearly, prospective controlled studies in this area are needed.

Surgical

PVR for PR is usually required in about 15% of patients with repaired tetralogy.[34] This is a low-risk intervention with a peri-operative mortality of 1–4%[35] and excellent mid-term survival (10-year survival of 86–95%).[35–37] Young adults undergoing PVR are likely to require further surgery as prostheses have a limited lifespan. Optimal timing of pulmonary valve implantation is, therefore, crucial for preserving RV function (not too late) and avoiding the need for early subsequent pulmonary valve implantation (not too early). Peri-operative risk is higher in patients with established RV dysfunction at the time of pulmonary valve implantation.[37] While such patients should still be considered for PVR (with the exception of the occasional patient with advanced left ventricular dysfunction) as they will benefit from a competent pulmonary valve, they usually require longer post-operative intensive care. The rate of freedom from further valve replacement is 81% at 5 years, 58% at 10 years, and 41% at 15 years.[38] However, these data refer to a mixture of children and adults. The lifespan of pulmonary valve prostheses in adult patients is known to be longer, ranging between 15 and 30 years. With regard to the type of valve prosthesis employed, bioprosthetic valves (homograft or porcine), have a lower complication rate compared with mechanical prostheses, and thus have established themselves as the valves of choice for PVR.[39,40] Patients with severe RV dilatation and large akinetic or aneurysmal region in the RVOT should be considered for additional pulmonary infundibuloplasty, shown to improve RV performance by reducing RV volumes and restoring RV geometry.[41] In such patients, employing a stented tissue valve as opposed to a free-standing human homograft is advisable, as it may secure a longer lifespan for the bioprosthesis.

Indications for surgery

Therapeutic goals of PVR should be improved functional class and quality of life, maintenance of right (and left) ventricular function, risk modification of arrhythmia and SCD and overall improved prognostication. In general, patients should be considered for PVR when both moderate-to-severe or severe PR, and progressive RV dilatation are present, irrespective of the presence of overt symptoms (such as shortness of breath, clinical arrhythmia etc).[37,42] Delaying surgery in such patients risks irreversible RV dysfunction. A combination of clinical signs (new onset tricuspid regurgitation murmur) with an enlarging cardiothoracic ratio, further QRS prolongation, echocardiographic RV dilatation, and/or increasing RV end-systolic volumes (exceeding normal CMR values) constitute reasons for elective PVR.

Outcome after PVR

Most patients (even those who consider themselves asymptomatic) improve their functional class after PVR. There are conflicting reports, however, regarding recovery of RV function following PVR. When timely PVR is performed there is, almost universally, reduction of RV size and improvement of RV ejection fraction.[37,42–44] In contrast, when PVR is performed late, RV recovery is incomplete.[45] We submit that to preserve RV function, PVR in adults should be considered before RV dysfunction and overt symptoms of RV failure ensue.[42]

Although PVR *per se* reduces RV size and stabilizes QRS duration, thus reducing the risk of arrhythmia and SCD,[37] additional concomitant ablative procedures, and particularly implantation of an intra-cardiac defibrillator, should be considered for patients at risk of sustained ventricular tachycardia, and SCD.[37] Prospective data in this area are clearly required.

Percutaneous implantation of a pulmonary valve

Percutaneous implantation of a bovine valve of jugular veins mounted in a stent in the pulmonary position has been recently reported.[46] While still experimental, this technique has been shown to relieve obstruction in RVOT conduits, restore competence of the RVOT, and to be relatively safe. Although many adult patients with marked aneurysmal dilatation of the RVOT will not be eligible for this method at present, there will be others likely to benefit from this new intervention. It has to be mentioned, however, that RVOT aneurysms, and/or akinesia, which in themselves are often the focus of sustained ventricular tachycardia, cannot be addressed with a solely transcatheter approach.[8] Nevertheless, this is an important advance with evolving indications that will have an impact on patients with PR.

Conclusions

Chronic PR has a detrimental effect on RV function and exercise capacity and leads to an increased risk of arrhythmia and SCD. Severity of PR and its impact on RV function can now be assessed quantitatively with echocardiography and CMR. An increasing number of adult patients with previous valvotomy for pulmonary stenosis or repair of tetralogy of Fallot will require elective PVR, and this should be offered before irreversible RV dysfunction ensues.

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