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# Latest insights in therapeutic options for systemic right ventricular failure: a comparison with left ventricular failure

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## ABSTRACT

The number of adult patients with a systemic right ventricle (RV) is steadily increasing. Survival is relatively good in these patients, but deterioration of the systemic RV seems inevitable. Although therapeutic options for patients with LV failure are well established, their role in patients with systemic RV failure is often undefined. To appreciate the potency of LV failure therapy in patients with a systemic RV, insight into pathophysiology of systemic RV failure and into recent developments in therapeutic research are indispensable. This review provides these insights, and will facilitate and ameliorate therapeutic decision making in patients with a systemic RV.

The number of adult patients with a congenital heart defect is steadily increasing, because of constant improvements in cardiac surgery. A substantial portion of these patients have a morphological right ventricle (RV) supporting the systemic circulation (for example, patients with congenitally corrected transposition of the great arteries (ccTGA) and patients with complete transposition of the great arteries (TGA) after an atrial switch operation). Patients with ccTGA have a double discordance; the atria are connected to the opposite ventricles, and the ventricles to the opposite arteries. Although circulation is not impaired, the RV supports the systemic circulation. In patients with complete TGA the atria are concordantly connected to the ventricles, whereas the ventricles are connected discordantly to the arteries, creating two parallel circulations. Until the mid 1980s, most patients with TGA were palliated with an atrial switch operation, leaving the RV responsible for the systemic circulation.<sup>1</sup> Complications early in life are common in both groups, with dysfunction of the systemic RV being the most important contributor to morbidity and mortality.<sup>2</sup>

In 2000 there were approximately 11 000 adult patients with a TGA in the United States alone, and many more worldwide.<sup>3</sup> As patients are now reaching adulthood, they are becoming a more commonly seen patient group in the adult cardiology department. Unfortunately, exact knowledge on the pathophysiology of commonly seen complications and evidence-based treatment regimens are lacking. This is caused by difficulties in performing prospective and sufficiently powered research in this small and heterogeneous patient group.

## MECHANISMS OF RIGHT VENTRICULAR DYSFUNCTION

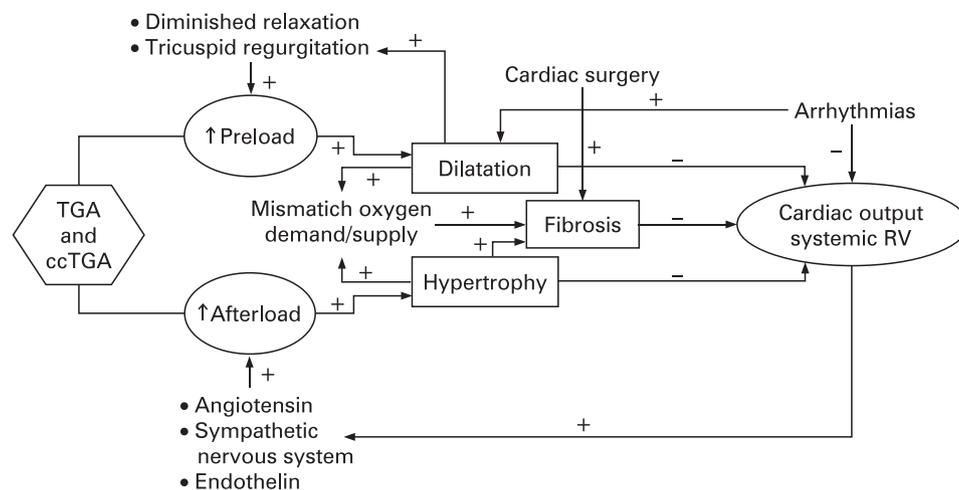
Although progressive deterioration of systemic right ventricular function is common in patients with a systemic RV, its exact cause is largely unknown.<sup>2</sup> Many pathophysiological pathways have been described to have an important role. Damage to the myocardium in the perioperative period could importantly influence right ventricular function later in life, both in atrially switched TGA patients and in ccTGA patients with associated anomalies.<sup>4</sup> Moreover, the geometry of the RV makes the RV more suitable to handle a volume overload, and less suitable to handle the constant pressure overload of the systemic circulation.<sup>5</sup> This pressure overload causes systemic right ventricular hypertrophy, which reduces myocardial capillary density and flow reserve. This creates demand ischaemia, further deteriorating the systemic right ventricular function.<sup>6</sup> Data on whether the deterioration caused by demand ischaemia is caused by secondary myocardial scarring remain contradictory.<sup>7</sup> The often seen anomalous anatomy of the coronary arteries in TGA and ccTGA patients, may aggravate the mismatch in oxygen supply/demand.<sup>8</sup> The tricuspid valve becomes insufficient, as a result of dilatation of the valve annulus and of morphological abnormalities of the tricuspid valve. The tricuspid valve regurgitation causes additional strain to the stressed ventricle as a result of an increase in volume overload.<sup>2 4 9</sup> Moreover, arrhythmias are frequently seen and contribute to the deterioration of systemic right ventricular function.<sup>10</sup> More general heart failure mechanisms are also triggered by the failing systemic RV. Neuroendocrinal activation causes vasoconstriction, fluid retention, ventricular remodelling and myocardial necrosis, apoptosis and fibrosis. Although these processes compensate for the diminished contractility at first, they will eventually overstrain the failing ventricle.<sup>11</sup>

Consequently, the pathophysiology of systemic right ventricular dysfunction is multifactorial. Surgical intervention, morphological aspects and physiological processes all contribute to the deterioration of the systemic right ventricular function as well as to the decline of the patient's clinical status (fig 1).

## THERAPEUTIC OPTIONS

Although treatment regimens of patients with left ventricular failure are well established, clinical management of patients with systemic right

**Figure 1** Pathophysiological pathways of systemic right ventricular (RV) dysfunction.



ventricular dysfunction remains challenging. Left ventricular failure is most often caused by coronary artery disease, hypertension and dilated cardiomyopathy, whereas the development of systemic right ventricular dysfunction is more complicated, as mentioned above. This possibly necessitates a different therapeutic approach. Until now, no convincing data have been published on the effect of standard left ventricular failure regimens in patients with systemic right ventricular dysfunction.

### Pharmacological therapy

$\beta$ -Adrenergic receptor blockers ( $\beta$ -blockers) lower both left ventricular failure-related morbidity and mortality.<sup>12</sup> The beneficial effects of  $\beta$ -blockers are achieved by their ability to restore the efficiency of the adrenergic signalling pathway and by their cardioprotective properties (for example, decelerating noradrenaline (norepinephrine)-mediated myocardial fibrosis, altering genetic expression and thereby influencing left ventricular remodelling).<sup>15</sup> Theoretically, treatment with  $\beta$ -blockers would be equally beneficial in patients with systemic right ventricular failure, as there is no difference in  $\beta$ -adrenergic receptor density between the RV and the left ventricle (LV), and the downregulation of the  $\beta_1$ -receptors in the failing LV is similar to that of the failing RV.<sup>14</sup> However, depressing sinus node function, and atrioventricular conduction time and prolonging atrial refractory period could exacerbate pre-existing bradycardia and atrioventricular (AV) block in patients with a systemic RV. Several studies have been performed on  $\beta$ -blocker therapy in patients with a systemic RV, showing promising but divergent results. Three studies found positive results of  $\beta$ -blocker therapy, with an increase in systemic right ventricular ejection fraction or exercise duration, or a trend towards such an increase.<sup>15-17</sup> However, Giardini *et al* found no improvement in systemic right ventricular ejection-fraction or in degree of tricuspid regurgitation in 31 patients after 10 (SD 7) months of treatment with a  $\beta$ -blocker (table 1).<sup>18</sup> Sufficiently powered, prospective trials are needed to definitely establish the role of  $\beta$ -blocker treatment in patients with a systemic RV.

No convincing evidence is available for the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB) in patients with a systemic RV either. Although their role in the treatment of patients with left ventricular failure is well established, it is far from clear that they should be prescribed in patients with systemic right ventricular

dysfunction.<sup>19</sup> Several studies have been performed on the effect of ACE inhibitors and ARBs in patients with a systemic RV with equivocal conclusions. In four recent studies, no significant effects on exercise capacity and cardiac function were found (table 1).<sup>20-23</sup> Lester *et al*<sup>24</sup> a significant improvement in both exercise time and right ventricular ejection fraction. Although adverse drug reactions to afterload reducing therapy have been described (for example, hypotension, dizziness, fatigue and nausea) in other heart failure studies, no such effects were documented in patients with a systemic RV. However, most studies were underpowered, had short follow-up periods or had a retrospective study set-up. In theory, one would expect a predominantly positive effect of ACE inhibitors or ARBs in patients with a systemic RV, as the renin-angiotensin-aldosterone system is activated in all patients with cardiac failure, irrespective of the affected ventricle.<sup>11</sup> In patients with left ventricular failure ACE inhibitors and ARBs diminish the effects of increased angiotensin II levels, slowing down the progressive deterioration of the LV and improving morbidity and mortality.<sup>19</sup> As the angiotensin II receptor density of the RV is equal to the receptor density in the LV, both ventricles should be equally susceptible to these medications.<sup>25</sup> However, arguments against the treatment of patients with a systemic RV with ACE inhibitors and ARBs are also postulated. Activation of the renin-angiotensin-aldosterone system could be a necessary compensatory mechanism in patients with pressure overloaded systemic RV, as is seen in patients with a pressure overloaded subpulmonary RV (for example, patients with chronic cor pulmonale).<sup>26</sup> The conclusion, the need to implement ACE inhibitors and ARBs in the standard therapy of patients with a systemic RV, remains speculative.

Diuretics are still essential for symptomatic treatment of patients with left ventricular failure.<sup>27</sup> No scientific evidence exists for the role of these medications in the treatment of patients with systemic right ventricular failure. However, the need for such evidence is questionable, as empirical prescription of diuretics to alleviate right ventricular failure-related symptoms is common and harmless. Aldosterone antagonists could add to the positive effects of diuretics, by reducing aldosterone-induced fibrosis. Reducing serum aldosterone levels leads to lower morbidity and mortality in patients with left ventricular failure.<sup>28</sup> Currently, no data are available for patients with a systemic RV.

In summary, the evidence base for the implementation of left ventricular failure treatment regimens in patients with a

**Table 1** Summary of trials with  $\beta$ -blockers, ACE inhibitors and ATII antagonists in patients with a systemic right ventricle

	Agent	TGA/ccTGA	No	Follow-up (months)	MRI*	VO <sub>2</sub> max	NYHA	Pro/retro
<b><math>\beta</math>-blocker</b>								
Lindenfeld <i>et al</i> <sup>17</sup>	Carvedilol	ccTGA	1	7	↑	ND	ND	pro
Giardini <i>et al</i> <sup>18</sup>	Carvedilol	both	8	12	↑	=	↑	pro
Josephson <i>et al</i> <sup>16</sup>	Various	TGA	8	36	ND	ND†	↑	retro
Doughan <i>et al</i> <sup>15</sup>	Various	TGA	31	4	ND	ND	↑	retro
<b>ACE inhibitor</b>								
Hechter <i>et al</i> <sup>21</sup>	Various	TGA	14	24	=	=	ND	retro
Robinson <i>et al</i> <sup>22</sup>	Enalapril	TGA	9	12	ND	=	ND	pro
Therrien <i>et al</i> <sup>23</sup>	Ramipril	TGA	17	12	=	=	ND	pro
<b>ATII antagonist</b>								
Dore <i>et al</i> <sup>26</sup>	Losartan	both	29	3.5	ND	=	ND	pro
Lester <i>et al</i> <sup>24</sup>	Losartan	TGA	7	2	↑ ‡	ND	ND	pro

\*Right ventricular ejection fraction as determined by MRI; †determined in minority of patients; ‡right ventricular ejection fraction as determined by echocardiography.

ACE, angiotensin-converting enzyme; ATII, angiotensin II; ccTGA, congenitally corrected transposition of the great arteries; MRI, magnetic resonance imaging; ND, not determined; NYHA, New York Heart Association class; pro, prospective study design; retro, retrospective study designs; ↑, significant improvement; =, no significant change.

systemic RV is poor. However, harmful effects of these drugs in patients with a systemic RV have not been described. Therefore, the pragmatic use of drugs seems appropriate until the results of sufficiently powered, prospective trials in these patients become available.

### CARDIAC DEVICES

As medicinal options are not always sufficient to relieve symptoms, more aggressive measures are often needed. This involves the implantation of cardiac devices, as well as surgical intervention. Pacemaker implantation is often performed to restore physiological cardiac rhythm, with more than 20% of pacemaker dependency reported in the adult population of both ccTGA and TGA patients.<sup>4 10</sup> Furthermore, new device technology for patients with left ventricular failure is upcoming and could be a promising addition to standard device therapy in patients with a systemic RV.

Resynchronisation therapy is known to relieve symptoms in patients with left ventricular failure who are on maximal medical treatment and who meet the criteria set by several resynchronisation therapy trials (for example, New York Heart Association class III/IV, ventricular dilatation, ventricular dysfunction, and QRS-duration >120 ms).<sup>29</sup> Likewise, in patients with a systemic RV, ventricular function might improve with cardiac resynchronisation therapy. Diller *et al* found that up to 9% of all patients with a systemic RV meet the above-mentioned criteria for resynchronisation therapy, and could possibly benefit from resynchronisation therapy. Until now, specific resynchronisation therapy criteria for patients with a systemic RV are unavailable, and screening for ventricular dyssynchrony is seldom performed.<sup>30</sup>

Although implantable cardioverter-defibrillators do not prevent or treat systemic right ventricular dysfunction, they are placed with increasing frequency in patients with congenital heart disease. Surgical scars, cellular injury caused by hypoxia and ventricular dilatation could lead to malignant arrhythmias and sudden death, with atrially switched TGA patients being most susceptible.<sup>31</sup> It is assumed that most sudden cardiac deaths in these patients are related to atrial tachycardias in combination with systemic right ventricular failure. Therefore, the prevention of sudden death should primarily be focused on the prevention of these atrial arrhythmias.<sup>32</sup> Only limited data are available on the implications of cardioverter-defibrillators implantation in patients with congenital heart disease. Alexander *et al* demonstrated appropriate device therapy in

28% of patients within two years after cardioverter-defibrillators implantation for secondary prevention. However, complications were common with inappropriate device therapy in 25%, lead failure in 16% and infections in 3%. Moreover, only five patients with TGA were included in this retrospective study.<sup>33</sup>

### CARDIOTHORACIC SURGERY

The fact that patients with TGA are now reaching adulthood is predominantly the result of improvements in cardiothoracic surgery. Numerous associated anomalies frequently necessitate (re-)intervention at some point in these patients' lives. Tricuspid valve insufficiency is often seen, particularly in ccTGA patients, and replacement of the insufficient valve should be considered at the earliest sign of right ventricular dysfunction, as long-term survival seems closely correlated with the preoperative ejection fraction. Reports have been published stating a 10-year survival of 100% in ccTGA patients with good preoperative right ventricular function ( $\geq 44\%$  right ventricular ejection fraction measured by means of echocardiography), and only 19.5% 10-year survival in those with lower preoperative right ventricular ejection fraction (overall 10-year survival was 67.5%).<sup>34</sup> However, surgical intervention is not without risk, with early deaths in 10% of operated patients, and the necessity to reoperate in another 25% of patients.<sup>34</sup> Prospective and sufficiently powered studies are essential to determine whether positive long-term survival through early intervention outweighs these risks, before persuading young, asymptomatic patients to undergo such intervention.

If all of the above-mentioned strategies fail, two surgical options remain to release the systemic RV from its constant overload; anatomical correction of the systemic RV and orthotopic heart transplantation. Anatomically correcting patients with a systemic RV has been described in both ccTGA and atrially switched TGA patients.<sup>35 36</sup> The procedure should only be performed after retraining of the subpulmonary LV by pulmonary artery banding to handle systemic pressures. However, the capability of the subpulmonary LV to adapt to the increased pressure decreases with age, which diminishes the number of eligible adult patients.<sup>37</sup> Moreover, complications are numerous, and a mortality rate of up to 28% of patients eight years after surgery has been reported.<sup>37 38</sup> To set indications for such extensive surgical intervention, prospective follow-up studies are much needed. However, banding the pulmonary artery in itself can cause a positive change in left ventricular

geometry, improving tricuspid valve leaflet coaptation and reducing right ventricular volume overload.<sup>37</sup>

Although challenging for both patient and clinician, orthotopic heart transplantation can become an unavoidable therapeutic possibility. Nowadays, heart transplantation is a well established treatment strategy for patients with end-stage left ventricular failure, with survival rates up to 69.8% for five years after transplantation.<sup>39</sup> Results have been published in patients with complex congenital heart disease, like transposition of the great arteries, with overall survival estimates similar to those of patients without congenital heart disease. Male patients and children (after the neonatal period) tend to have the best prognosis.<sup>40</sup>

## CONCLUSIONS

Progressive dysfunction of the systemic right ventricle is an inevitable complication in patients with corrected TGA. The exact pathophysiology remains unclear, but seems multifactorial and heterogeneous. Although treatment regimens for left ventricular failure are well established, convincing data on the treatment of patients with a systemic right ventricle remain sparse. Combined efforts to perform prospective, randomised trials could overcome this shortcoming and provide these patients with an optimal long-term treatment and a better future.

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