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REVIEW

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Acute right ventricular failure—from pathophysiology to new treatments

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Abstract The right ventricle (RV) provides sustained low-pressure perfusion of the pulmonary vasculature, but is sensitive to changes in loading conditions and intrinsic contractility. Factors that affect right ventricular preload, afterload or left ventricular function can adversely influence the functioning of the RV, causing ischaemia and right ventricular failure (RVF). As RVF progresses, a pronounced tricuspid regurgitation further decreases cardiac output and worsens organ congestion. This can degenerate into an irreversible vicious cycle.

The effective diagnosis of RVF is optimally performed by a combination of techniques including echocardiography and catheterisation, which can also be used to monitor treatment efficacy. Treatment of RVF focuses on alleviating congestion, improving right ventricular contractility and right coronary artery perfusion and reducing right ventricular afterload. As part of the treatment, inhaled nitric oxide or prostacyclin effectively reduces afterload by vasodilating the pulmonary vasculature. Traditional positive inotropic drugs enhance contractility by increasing the intracellular calcium concentration and oxygen consumption of cardiac myocytes, while vasopressors such as norepinephrine increase arterial blood pressure, which improves cardiac perfusion but increases afterload. A new treatment, the calcium sensitiser, levosimendan, increases cardiac contractility without increasing myocardial oxygen demand, while preserving myocardial relaxation. Furthermore, it increases coronary perfusion and decreases afterload. Conversely, traditional treatments of circulatory failure, such as mechanical ventilation and volume loading, could be harmful in the case of RVF. This review outlines the pathophysiology, diagnosis and treatment of RVF, illustrated with clinical case studies.

Keywords Heart failure · Levosimendan · Vasodilator agents · Inotropic agents · Pathophysiology · Pharmacology

Introduction

Until fairly recently, right ventricular failure (RVF) was a relatively neglected medical condition. The right ventricle (RV) was considered as a moderately passive conduit between the systemic and pulmonary circulations. This belief was supported by studies showing that complete destruction of the right ventricular free wall in dogs had no detectable impairment on overall cardiac performance [1]. However, investigations in the 1970s demonstrated that RVF has significant haemodynamic and cardiac performance effects, as illustrated by Cohen et al.in six patients following a myocardial infarction involving the RV [2]. The patients had severe hypotension, diminished peripheral perfusion and severely impaired pressure generation in the RV, with almost no

pressure gradient from the right atrium to the pulmonary artery [2].

Precipitating factors for RVF are common in surgical and medical intensive care units (ICUs). These include increased pulmonary vascular resistance, such as after cardiac transplantation; acute respiratory distress syndrome; the presence of a left ventricular assist device; positive pressure mechanical ventilation and sepsis. There is also a higher incidence of RVF occurring in ICUs than is generally recognised.

Right ventricular failure has a similar incidence to left-sided heart failure, with each affecting about 1 in 20 of the population [3]. Left-sided heart failure is often a chronic, progressive disease with mortality four to eight times greater than that of the age-matched general population [4]. In contrast, the outcome of RVF is largely dependent on the underlying cause, resulting in either an acute or chronic condition. Patients in cardiogenic shock due to an infarction predominantly affecting either the left or right ventricle experience a similar rate of mortality, despite patients with RVF being younger and having a higher prevalence of single vessel disease [5]. Furthermore, ischaemia following a myocardial infarction involving both the right ventricle (RV) and the left, results in a greater risk of mortality than isolated left ventricular ischaemia [6, 7].

The pathophysiology, diagnosis and treatment of RVF in the ICU is associated with some controversy. This review provides an informed opinion on a number of these issues, the effects of some newer treatment options for RVF involving pulmonary vasodilation and enhancing cardiac contraction are described, and their therapeutic benefits are demonstrated in three case studies that are summarised here and described in full in the electronic supplementary material (ESM).

Physiology of the right ventricle and pathophysiology of right ventricular failure

The primary function of the RV is to maintain a low right atrial pressure, optimising venous return and to provide sustained low-pressure perfusion through the lungs. To achieve this, the RV ejects blood quasi-continuously from the right atria to the lungs, continuously emptying the right atria. This 'continuous' ejection is possible because of the favourable characteristics of the pulmonary vascular bed, which is a low pressure, low resistance and high compliance circuit with a pressure gradient of 5 mmHg. Conversely, the left ventricle generates high-pressure pulsatile flow through arterial vessels with low compliance. The right cardiac and pulmonary pressures observed in a healthy spontaneously breathing adult are summarised in Table 1.

The RV is anatomically adapted for the generation of a sustained low-pressure perfusion. It comprises two anatomically and functionally different cavities, termed the sinus and the cone. The sinus generates pressure during systole and the cone regulates this pressure [8]. Right ventricular contraction occurs in three phases; contraction of the papillary muscles, then movement of the right ventricular free wall towards the inter-ventricular septum and, finally, contraction of the left ventricle causes a 'wringing' which further empties the RV. The net effect is pressure generation in the sinus with a peristaltic motion starting at the apex moving towards the cone and, due to the compliance of the upper cone region of the thin-walled RV, the peak pressure is reduced and prolonged. Therefore, ejection into the pulmonary circulation is sustained until the RV has completed its emptying, end-diastolic pressure is minimal and venous return is optimal. Notably, right ventricular preload is determined by both the compliance of the RV and the venous return. The latter depends on the pressure gradient from the periphery to the right atria and the venous resistance. Despite the thin muscular walls of the RV, it adapts to small changes in venous return, such as those occurring during respiration, without altering cavity pressures or volumes. However, larger changes in venous return affect the right ventricular end-diastolic volume.

Table 1 'Normal' right atrial, right ventricular and pulmonary artery pressures for a spontaneously breathing patient

Variable	Value
Right atrial pressure	
Mean	0–7 mmHg
Right ventricular pressure	
Systolic	15–25 mmHg
Diastolic	0–8 mmHg
Pulmonary artery pressure	
Systolic	15–25 mmHg
Diastolic	8–15 mmHg
Mean	10–20 mmHg
Wedge	6–12 mmHg[a]
Pulmonary vascular resistance	100–250 dynes/s per cm^5

[a] Should be less than the pulmonary artery diastolic pressure

Effect of an increase in right ventricular afterload: chronic pulmonary hypertension or acute cor pulmonale

The pressure-volume characteristics for the RV differ markedly from those of the left ventricle (Fig. 1) [9]. The right ventricular pressure-volume loop has a more triangular shape compared with that of the left ventricle, with only brief periods of isovolaemic contraction and relaxation. There is sustained ejection during pressure development that, more importantly, continues during pressure decline. This prolonged low-pressure emptying

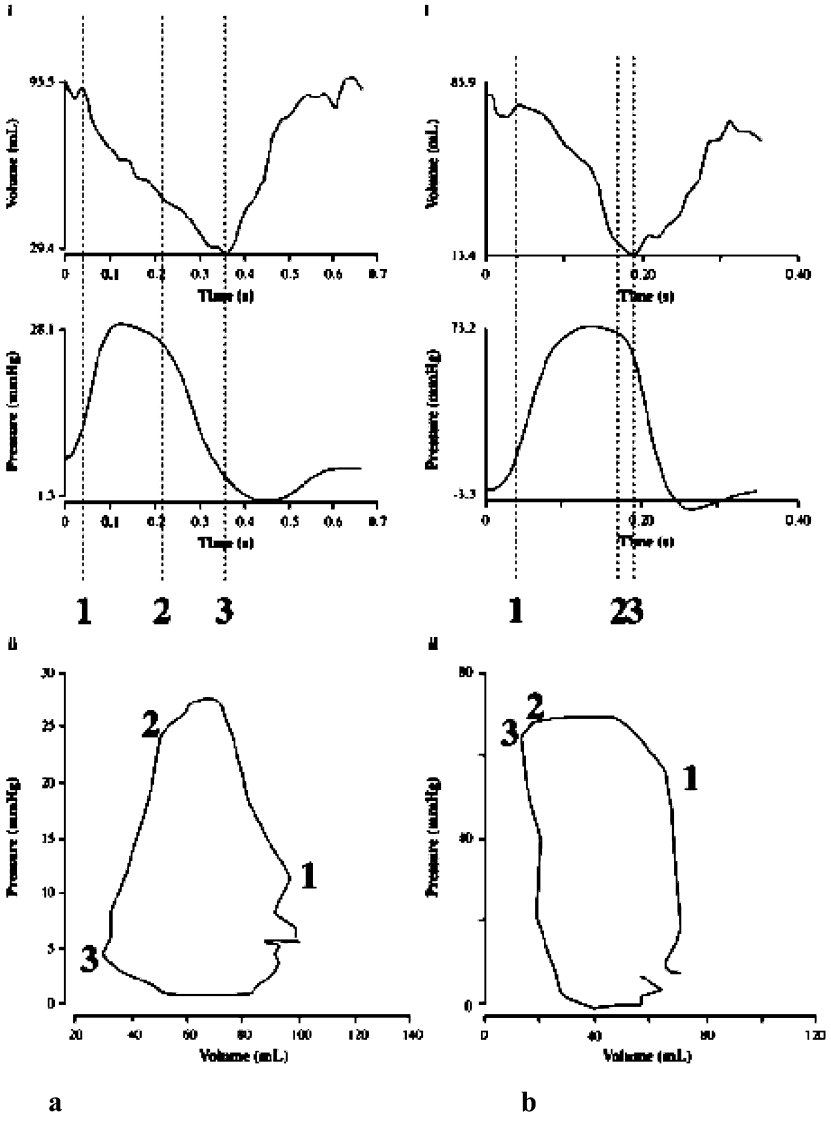

Fig. 1 Pressure and volume changes against time during a contraction cycle (i) and the pressure-volume loop derived from these measurements (ii) are shown for a normal patient (**a**) and for a patient with pulmonary stenosis (**b**). The numbers indicate: 1, the opening of the pulmonary valve marking the start of the ejection phase; 2, the onset of relaxation; 3, the closing of the pulmonary valve marking the end of the ejection phase. In (**a**), the pressure-volume loop is more triangular than that of the left ventricle. Ejection from the right ventricle starts early during the pressure increase and the isovolaemic contraction phase is consequently not well defined. It is interesting to note that ejection continued after the peak pressure during pressure decline (between points 2 and 3). In (**b**), the pressure-volume loop resembles that of the left ventricle. There is a well defined end systolic shoulder and there is no ejection during the pressure decline ([**a**] reproduced from *British Heart Journal* 1988; volume 59, pages 23–30 with permission from BMJ Publishing Group [9]; [**b**] reproduced from *British Heart Journal* 1990; volume 63, pages 45–49, with permission from BMJ Publishing Group [10])

implies that right ventricular emptying is very sensitive to changes in afterload. Thus, in a patient with pulmonary hypertension, the right ventricular pressure-volume loop is not triangular and resembles that of the left ventricle (Fig. 1b) [10]. To compensate, the RV dilates to maintain the stroke volume, though the ejection fraction is reduced [11], and the peristaltic contraction is lost, causing an accelerated increase in pulmonary artery pressure and flow.

The increased afterload also prolongs the isovolaemic contraction phase and ejection time and, therefore, increases myocardial oxygen consumption. Under physiological conditions, there may be increased perfusion of the right coronary artery. However, partial occlusion of the right coronary artery may prevent this compensatory mechanism, resulting in ischaemia [12]. Therefore, in a patient with decreased right coronary artery perfusion, it is important to reduce right ventricular afterload to improve the oxygen supply/demand ratio in the RV to maintain right ventricular function. (This is demonstrated in the first illustrative case study.)

The RV is predominantly perfused by the right coronary artery with supply of some regions by the left anterior descending branch of the left coronary artery. Physiologically, right coronary artery perfusion occurs during both diastole and systole, in contrast to the left coronary artery, that supplies the left ventricular muscle mostly during diastole. However, when pulmonary artery hypertension is present, right coronary artery perfusion occurs quasi-exclusively during diastole, potentially reducing the oxygen supply to the RV during increased oxygen demand.

Acute cor pulmonale relates to a sudden increase in afterload, most often due to a massive pulmonary embo-

lism or acute respiratory distress syndrome in adults [13, 14, 15, 16]. In either setting, right ventricular outflow impedance is suddenly increased, right ventricular ejection is impaired and the RV is enlarged. Thus, both systolic and diastolic function are impaired, which may cause or precipitate circulatory failure in critically ill patients. Acute cor pulmonale is reversible when the cause of increased afterload is removed.

Ventricular interdependence

There is a high degree of ventricular interdependence due to the interaction of the inter-ventricular septum in the contraction of both ventricles, which is pronounced due to the existence of the pericardium [17]. The load on a ventricle is dependent on the passive filling of the contralateral ventricle [18]. The close association between the cardiac cavities can be seen in echocardiography images of the four chambers, such as those shown for the first and the third case studies (Fig. 3 and the ESM) and in recently published papers [14, 16]. Indeed, increases in the end-diastolic volume of the left ventricle are transmitted to the RV by movement of the inter-ventricular septum towards the right cavity, increasing the end-diastolic pressure of the RV [20]. Similarly, when the right ventricular end-diastolic volume is increased, the inter-ventricular septum shifts towards the left cavity during diastole due to the restrictions imposed by the pericardium on the RV as the cavity volume increases. This leftward shift impairs the function of the left ventricle due to the reduction in left ventricular volume, decreasing both left ventricular filling and compliance, manifested as increased muscle stiffness. Thus, in a canine model, ischaemia and acute dilatation of the RV decreased the compliance of the left ventricle, resulting in decreased cardiac output due to a leftward shift in the inter-ventricular septum, which was attenuated by the opening of the pericardium [21].

Ventricular interdependence can also cause RVF during left ventricular assist device support. As the left ventricular assist device unloads the left ventricle, the inter-ventricular septum is shifted left. This alters the right ventricular compliance decreasing force and rate of contraction together with a decreased afterload and increased preload. In a healthy heart, cardiac output may be maintained but, with pre-existing pathology, the decrease in contractility may result in RVF [22]. It is therefore crucial to support right ventricular function during the first days following insertion of a left ventricular assist device.

Vicious cycle of auto-aggravation

Compared to the left ventricle, RVF progresses quickly from compensated to end-stage because of a vicious cycle of auto-aggravation. This is unique to the RV and is not a consequence of isolated left ventricular failure. The elevated right atrial and ventricular end-diastolic pressures eventually lead to an increased right ventricular end-diastolic volume, insufficiency of the tricuspid valve and regurgitation. The tricuspid insufficiency aggravates hepatic and kidney congestion and decreases cardiac output; the heart is, therefore, unable to maintain an adequate function. Thus, the auto-aggravation becomes an irreversible vicious cycle. In addition, decreased venous return to the left ventricle reduces left ventricular preload. This further exacerbates the situation as it causes decreased left ventricular output and systemic blood pressure and hence further impairment of organ perfusion, including the coronary arteries. This ischaemia further diminishes cardiac function and the cycle of worsening output, congestion and ischaemia continues. Therefore, any sign of RVF should result in immediate treatment to avoid the start of the vicious cycle of auto-aggravation.

Diagnosis of right ventricular failure—identifying organ dysfunction

Traditional non-specific approach

The diagnosis of acute RVF in patients in the ICU is complicated by the lack of clinical and biological specific signs. Some biological signs which may be indicative of cardiac dysfunction appear very early during acute RVF. The organs most affected by RVF-induced congestion are the liver and kidneys. Decreased perfusion of the kidneys is manifested as a reduction in both urine output and creatinine clearance. Decreased hepatic perfusion results in increased plasma lactate due to an impaired lactate clearance, a reduction in the synthesis of coagulation factors (observed as a decrease in prothrombin time) and hepatic cytolysis. Interestingly, Fig. 2 and Fig. S1 in the ESM show two examples of the effects of very severe liver and kidney congestion related to RVF.

The sensitivity of conventional chest X-ray techniques to identify changes in right ventricular form is limited by the unusual shape of the RV and the unpredictable manner in which it dilates. Inferential diagnosis may be possible by identification of other radiographic changes, such as the state of the pulmonary circulation and the position of the heart in the chest. Changes in the left ventricle may be apparent on chest X-ray, resulting from the decreased left ventricular preload that is a consequence of RVF.

Echocardiography

Echocardiography is an alternative, more accessible technique for the diagnosis of RVF and for the intermit-

tent repetitive follow-up of the dynamics of therapeutic responses. Its advantage is that a qualitative conclusion can be reached instantaneously. When RVF is secondary to an increase in afterload, the isovolaemic contraction phase and ejection time are prolonged, and increases in pulmonary artery pressure and flow are accelerated. Echocardiography also provides information about the mechanisms of RVF, such as pericardial effusion with or without tamponade, tricuspid insufficiency, pulmonary emboli or right ventricular ischaemia and the resulting acute cor pulmonale [14].

Additionally, echocardiography enables the simultaneous evaluation of left ventricular function, a possible component of the RVF. Due to the geometry and location of the RV, the accuracy and necessity of determining exact right ventricular dimensions remains questionable and an experienced intensivist familiar with performing and evaluating echocardiography is essential. Although echocardiography can be repeated infinitely, the continuous flow of information provided by right heart catheterisation is difficult to reproduce and when technical or human limitations render echocardiography impossible, right heart catheterisation becomes the diagnostic tool of choice.

Pulmonary artery catheterisation

Catheterisation of the pulmonary artery is more invasive but useful to evaluate right ventricular function and confirm the presence of RVF in patients in the ICU. The Swan–Ganz catheter measures both mixed venous oxygen saturation and intravascular pressures or pressure changes in the RV as well as pulmonary artery pressure and pulmonary capillary wedge pressure. Despite difficulties in the interpretation of mean intravascular pressure values, the tracings showing changes in pressure and flow enable the assessment of the impact of treatment on right ventricular function. This cautious interpretation accounts for the almost constant reflux due to the tricuspid insufficiency, which can be observed by central venous and right atrial pressure changes (see Fig. 3 and the illustrative example described in the ESM). Such regurgitation could be used as a hallmark for RVF and as a marker for treatment efficacy.

A more advanced pulmonary catheter, equipped with a fast-response thermistor, is another valuable diagnostic tool enabling clinical assessment of right ventricular volume and haemodynamic parameters by thermodilution. It may also measure cardiac output more precisely even in the presence of tricuspid insufficiency, a particular problem during mechanical ventilation. Indeed, the more widespread introduction of thermodilution techniques to assess pump function has contributed to the recognition of the inherent pathology of RVF. Values for cardiac performance obtained from this technique compare favourably with those using radionucleotides or two-dimensional echocardiography [24, 25].

If a central venous pressure or pulmonary artery catheter is in place, haemodynamic parameters that can aid in the diagnosis of RVF include an increase in right atrial pressure and a decrease in arterial blood pressure, cardiac output and mixed venous oxygen saturation, despite a usually preserved pulmonary artery pressure and pulmonary capillary wedge pressure. For difficult cases, a technique often cited in the literature for the diagnosis of RVF involves the administration of 250 ml of crystalloids or colloids over 10 min [26]. If the patient is suffering from RVF, all the above haemodynamic parameters worsen, including a dramatic increase in right atrial pressure with no change in cardiac output. This test should not be performed in patients who are in acute RVF, as there is a risk of severe aggravation of tricuspid insufficiency and organ congestion after volume loading (see below).

Management of right ventricular failure

The principal therapeutic goals of RVF depend on its underlying aetiology, but generally involve breaking the vicious cycle of reduced cardiac output by restoring adequate oxygen delivery to the myocardium and reducing right ventricular overload. Treatment usually focuses on alleviating congestion, improving right ventricular contractility and/or reducing right ventricular afterload.

When RVF is related to occlusion of the right coronary artery, reperfusion by coronary angioplasty may help restore contractile function to the ischaemic myocardium and improve the clinical outcome [27]. Revascularisation of the right coronary artery may also be prudent when inserting a left ventricular assist device in patients with right coronary artery-associated ischaemia, to avoid subsequent RVF [28]. Patients who have RVF related to atrial fibrillation may benefit from aggressive anti-arrhythmic treatment to improve cardiac output, and temporary pericardiotomy may benefit patients following sternotomy for cardiac surgery.

Volume management

Volume management is a difficult but important task in the treatment of RVF. In very few cases of RVF with normal pulmonary vascular resistance, volume loading may be useful in increasing preload, which increases right ventricular end-diastolic volume and cardiac output [29]. However in the large majority of RVF patients, this compensatory mechanism is potentially limited beyond a mean pulmonary artery pressure of 30 mmHg [30] and therefore caution is warranted when considering volume loading. Volume overload is common during RVF and

volume loading may further dilate the RV, increase tricuspid regurgitation and, consequently, worsen hepatic and renal congestion and RVF. A sharp rise in left- or right-sided filling pressures without a concomitant increase in cardiac output may indicate when further volume loading is detrimental.

In this scenario, fluid withdrawal should be started with diuretics and haemofiltration. If the RV is dilated and the inter-ventricular septum shifted, one should first try diuretics. If this is unsuccessful, haemofiltration is urgently recommended, often under inotropic support.

Pulmonary vasodilators

Systemic therapy

In the presence of elevated pulmonary vascular resistances, vasodilator therapy may reduce right ventricular afterload. This will improve right ventricular function by decreasing right ventricular myocardial oxygen consumption and improving left ventricular filling, which will eventually increase systemic blood pressure and right coronary artery perfusion pressure. This will, in turn, decrease right atrial pressure and organ congestion. Thus, intravenous vasodilators such as nitroglycerin, nitroprusside or prostaglandin E1 may be beneficial in patients with isolated RVF [31, 32]. However, systemic pulmonary vasodilators reverse hypoxic pulmonary vasoconstriction, worsening ventilation-perfusion matching within the lung and decreasing arterial oxygen saturation. Also, they decrease diastolic pressure, resulting in decreased right coronary artery perfusion, which worsens ischaemia [33, 34].

Inhaled therapies

Inhalational vasodilatory agents, such as prostacyclin or its analogues and nitric oxide (NO), have a direct, selective effect on the pulmonary vasculature [23, 35, 36, 37]. NO diffuses into the pulmonary vascular smooth muscle cells, causing vasodilation, and its effects are localised as it rapidly binds to plasma proteins and haemoglobin. Following prolonged administration, rebound pulmonary hypertension has been frequently reported when NO inhalation is suddenly withdrawn [38]. Despite its haemodynamic benefits, a survival advantage for patients with RVF who respond to NO therapy has not been proven [39]. Inhaled sodium nitroprusside, a NO donor drug, is a possible alternative for the future [40].

Beneficial effects of inhaled NO have also been described in the management of RVF associated with a patent foramen ovale. As a patent foramen ovale, together with right-left shunt, is frequently found in patients who have RVF with elevated right atrial pressures, its role in maintaining (or restoring) left ventricular preload, albeit by simultaneously compromising arterial oxygenation, cannot be ignored [41, 42].

An alternative to inhaled NO is inhaled prostacyclin (= prostaglandin I_2). Besides its vasodilator properties, inhaled prostacyclin is the most potent platelet aggregation inhibitor known. Prostacyclin also stimulates endothelial release of NO, and vice versa. A potentially substantial advantage of inhaled, versus intravenous, prostacyclin is that rebound pulmonary hypertension after abrupt discontinuation has so far not been reported. This suggests that, in comparison with inhaled NO, inhaled prostacyclin may treat pulmonary hypertension more effectively. Prostacyclinhas no known toxic effects or active metabolites and it is cheaper than NO, both in terms of the equipment necessary for its administration and the substance itself [43, 44].

Iloprost is the stable carbacyclin derivative of prostacyclin. It has several advantageous properties compared to prostacyclin, including saline solubility, lower viscosity and a significantly longer duration of action with a half-life of 20–30 min and haemodynamic effects that last for 1 h [45].

Contractility enhancing agents

The right ventricular ejection can be directly increased by the insertion of a right ventricular assist device, which may be beneficial for the short-term prophylaxis in patients following cardiac surgery or transplantation, enabling the stunned heart to recover [46].

Positive inotropic agents are also commonly used to improve right ventricular function. Left ventricular contraction assists the ejection from the RV; therefore, inotropic drugs that increase the contraction of the whole heart will improve right ventricular function both by directly enhancing right-sided contractility and by their effects on the entire myocardium. Positive inotropic agents—β-adrenoceptor agonists and phosphodiesterase inhibitors—enhance myocardial contractility by increasing the intracellular calcium concentration in both ventricles due to their actions on cAMP [47]. In the treatment of chronic heart failure patients, vasoactive β-agonists produce a net increase in cardiac output providing a short-term benefit, but the increased contractility, working against a greater afterload, increases the workload of the heart, resulting in an increase in energy utilisation. Therefore, the oxygen consumption of the myocardium is increased without increasing oxygen supply, which may cause or worsen ischaemia and arrhythmias. Thus, the use of some of these agents has been associated with an increase in long-term mortality [48, 49, 50] and, in the case of dobutamine, tolerance develops after a short time [51]. The treatment of RVF is comparatively short and repeated dosing less common than for chronic heart

failure, therefore tolerance may not be relevant in this setting. However, the effects of sympathomimetics on long-term outcome should perhaps be considered when selecting appropriate treatment for RVF.

A newer class of drugs, the calcium sensitisers, also improve cardiac function by increasing the contraction of the myocardium, but without significantly increasing intracellular calcium levels. Levosimendan, the first calcium sensitiser in clinical use, increases the sensitivity of the cardiac myofilaments to calcium during systole without affecting diastole. The increased calcium sensitivity increases the force and rate of contraction of the myocardium. Moreover, as it only increases systolic calcium sensitivity, it does not affect the relaxation kinetics, in contrast to the traditional inotropic drugs. Hence, levosimendan has no adverse effects on diastolic function [52] and is not associated with a significant increase in myocardial oxygen consumption in patients with chronic heart failure [53], though this result remains to be confirmed.

Levosimendan also induces dilatation of the pulmonary, systemic and coronary vasculature by activation of ATP-sensitive potassium channels resulting in a decreased systemic and pulmonary vascular resistance [54, 55]. This may cause under-perfusion of the myocardium, but the dilation of the coronary arteries results in improved myocardial blood flow [53]. Levosimendan improved haemodynamic performance and decreased the risk of worsening heart failure and mortality in different heart failure populations, compared with dobutamine or placebo [56, 57]. Indeed, all the evidence described comes from studies in patients with chronic heart failure, and the direct effects of levosimendan on RVF are currently unproven. However, from its known effects, including a demonstrated improvement in right ventricular contractile efficiency [53], beneficial effects in RVF may also be expected. The haemodynamic effects of levosimendan may be sustained for days, or even weeks, due to an active metabolite with a half-life of over 3 days [58].

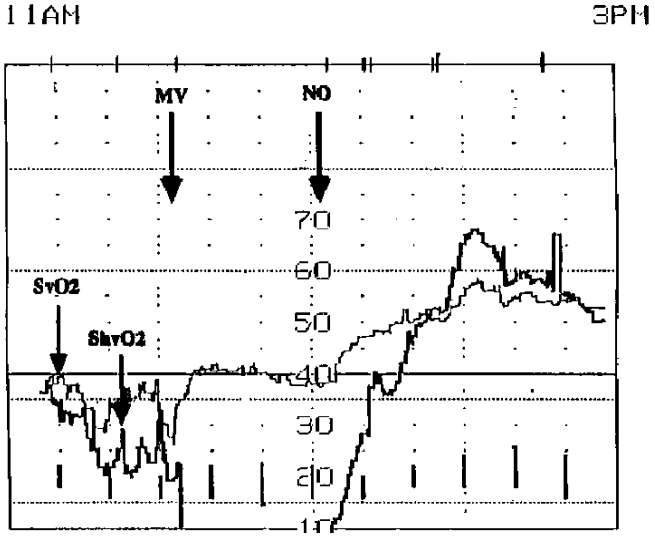

Fig. 2 Mixed venous oxygen saturation (SvO_2) increases and hepatic venous oxygen saturation ($ShvO_2$) decreases in response to the start of mechanical ventilation in a patient with predominantly right-sided congestive heart failure due to increased preload that worsens right ventricular function and hence organ congestion. Following nitric oxide inhalation, $ShvO_2$ increases indicating improved right ventricular function due to decreased preload and relieved liver congestion. *MV* start of mechanical ventilation, *NO* start of nitric oxide inhalation (18 ppm) (reproduced from Gatecel et al., 1995, with permission [23])

Vasopressors

Vasopressors directly increase arterial blood pressure and improve coronary artery perfusion, though also increasing afterload. Their benefits in RVF were pioneered by Prewitt and co-workers and they may be critical in the treatment of RVF, preventing the vicious cycle by improving right coronary artery perfusion and right ventricular contraction [59, 60]. Norepinephrine, a potent α-adrenergic-agonist is recommended to improve right coronary artery perfusion pressure and right ventricular function, and it is more effective than phenylephrine, another selective α-adrenergic agonist [61]. In patients with septic shock, norepinephrine increased mean arterial pressure, with a moderate increase in mean pulmonary artery pressure, improving right coronary artery perfusion pressure and right ventricular contraction [60]. However, in the case report of sepsis-induced RVF (see below), norepinephrine increased organ perfusion pressure but not cardiac output, and combination with inhaled NO was therefore needed.

Mechanical ventilation

Mechanical ventilation is the usual treatment for shock, however it may worsen RVF as elevated transpulmonary pressures increase right ventricular output impedance and, hence, decrease stroke output. An example of severe hepatic and renal congestion due to subacute RVF markedly aggravated by mechanical ventilation is shown in Fig. 2 [23]. The patient had a low hepatic venous oxygen saturation caused by a high hepatic venous back-pressure that was reducing liver blood flow despite a maintained cardiac output. Due to respiratory fatigue, the patient was mechanically ventilated, which resulted in an improved mixed venous oxygen saturation, from 28 to 40%, related to the decreased respiratory work and, thus, systemic oxygen consumption. However, mechanical ventilation caused an abrupt decrease in hepatic venous oxygen saturation to an undetectable

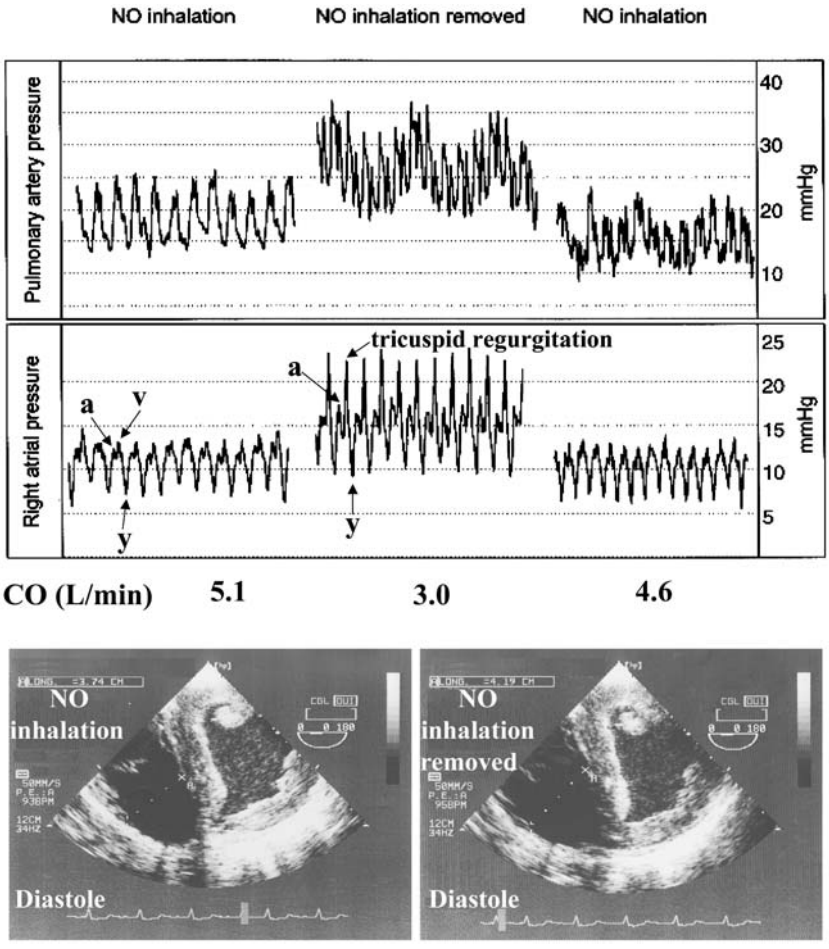

Fig. 3 Patient haemodynamics with and without inhaled nitric oxide (NO). Inhaled NO withdrawal in this patient with ischaemia-induced right ventricular failure increased mean pulmonary artery pressure from 18 to 25 mmHg. During NO inhalation and preserved right ventricular function, right atrial pressure showed 'a' waves (auricular contraction) followed by 'v' waves (passive atrial filling due to venous return) and 'y' waves (beginning of diastole: rapid ventricular filling and passive atrial emptying). When inhaled NO was removed, although pulmonary artery pressure remained in the normal range, the slight increase resulted in a deterioration of right ventricular function and dilation of the right ventricle. Right atrial pressure showed that a tricuspid insufficiency emerged (positive waves) that worsened cardiac output (CO) despite the increase in auricular contraction (increase in 'a' waves). Echocardiography shows the close association between the left and right ventricles separated by the inter-ventricular septum. An enlargement of the right ventricle can be seen, with the end-diastolic diameter increasing from 37 mm to 42 mm when NO inhalation was removed (Reproduced from 2002 Yearbook of Intensive Care and Emergency Medicine, Acute right ventricular failure: physiology and therapy by Renaud E, Karpati P, Mebazaa A, page 211, Fig. 1, and page 212, Fig. 2, 2002, Springer-Verlag, with permission [19])

level, which resulted from worsening RVF related to an increased right ventricular afterload due to positive pressure breathing. Consequently, right atrial pressure was raised, worsening the hepatic congestion. The subsequent use of NO inhalation decreased right ventricular afterload, improved right ventricular function and relieved liver congestion, demonstrated by the rapid increase in hepatic venous oxygen saturation as RVF was successfully controlled.

In summary, although several tools could be used to improve RVF, volume loading and mechanical ventilation should be used with caution because they may precipitate or aggravate RVF.

Illustrative case studies

The treatment of RVF often requires a multi-modal approach with continuous haemodynamic monitoring to observe the patient's progress. Three case studies are summarised below (and described in detail in the ESM) that highlight the diagnosis and treatment of acute RVF with therapy tailored specifically to the patient's diagnosis and haemodynamic status. These cases demonstrate that there are a number of treatment approaches that may result in a successful outcome. The new myocardial contractility-enhancing agents may obviate the use of some agents with a questionable long-term benefit.

Table 2 The treatment of sepsis-induced right ventricular failure with 'traditional' positive inotropic agents: the value of each parameter before and after the corresponding treatment (*DO* dobutamine, *NE* norepinephrine, *NO* inhaled nitric oxide, *VL* volume loading: 250 ml of colloids) had been given

Time	14:00 VL	15:30 VL	16:30 NE	20:30 DO/NO	23:30
HR (bpm)	90	90	90	94	92
BP (mmHg)	96/56	95/49	110/55	130/70	115/68
PAP (mmHg)	35/24	42/28	43/30	46/32	31/21
RAP (mmHg)	12	13	20	16	8
PCWP (mmHg)	12	12	14	15	10
SvO_2 (%)	70	71	65	63	74
CI (l/min per m^2)	2.3	2.3	2.0	1.9	2.8
Lactate (mmol/l)	3.3	3.6	3.8	4.0	4.1

HR heart rate, *BP* arterial blood pressure, *PAP* pulmonary artery pressure, *RAP* right atrial pressure, *PCWP* pulmonary capillary wedge pressure, *SvO_2* mixed venous oxygen saturation, *CI* cardiac index

Effects of inhaled nitric oxide on ischaemia-related right ventricular failure following cardiac surgery

A 30-year-old male with acute RVF was treated with inhaled NO, 8 ppm, to reduce the afterload, which rapidly restored haemodynamics. When NO was withdrawn, right atrial pressure increased, cardiac output and arterial blood pressure dropped, there was tricuspid regurgitation and echocardiography showed a severe dilation of the RV (Fig. 3). NO was restored and the patient was weaned from treatment on the 7th postoperative day.

Sepsis-induced right ventricular failure treated with the combination of traditional positive inotropic agents and inhaled nitric oxide

A 55-year-old male had sepsis-induced myocardial dysfunction with a predominant RVF confirmed by echocardiography. Norepinephrine increased blood pressure but could not improve right ventricular function. The patient was subsequently treated with dobutamine, 5 µg/kg per min, and inhaled NO, 5 ppm (Table 2). The combination induced a large, rapid and sustained decrease in right atrial pressure, pulmonary capillary wedge pressure was restored, mixed venous oxygen saturation and cardiac index were approaching normal values. A volume loading of 250 ml was given to improve organ perfusion pressure and subsequently the patient was haemodynamically stable and all parameters returned to values towards or within the normal range.

Ischaemia-induced right ventricular failure treated with calcium sensitiser monotherapy

Following coronary artery bypass graft surgery, a 71-year-old male was diagnosed with RVF and treated with levosimendan, 6 µg/kg loading dose given over 10 min followed by a 0.1 µg/kg per min infusion for 24 h. Four hours after the start of the levosimendan infusion, echocardiograhy showed an improvement in cardiac performance. At 24 h, echocardiography and haemodynamic values were almost restored to normal and the patient reported symptomatic improvement (echocardiography video available in the ESM). This improvement in right ventricular function was related to an improvement in right ventricular contractility and vasodilatory effects on the pulmonary circulation (decrease in pulmonary artery pressure).

Conclusion

It is now evident that the RV plays a pivotal role in haemodynamic homeostasis, and changes in right ventricular function can have profound effects on the pulmonary and systemic circulation. Therefore, it is important that RVF is diagnosed quickly and accurately before it degenerates into the vicious cycle of auto-aggravation with tricuspid deficiency, worsening cardiac ischaemia and multiple organ congestion. Diagnosis should include an assessment of the patient and the use of diagnostic tools that also enable the clinician to follow the progress of treatment.

The management of RVF should focus on restoring right ventricular function with the treatment dictated by the underlying aetiology. The primary cause of RVF should be corrected wherever possible. The right ventricular afterload should be reduced, if necessary, by decreasing the pulmonary artery pressure (e.g. by administering pulmonary vasodilators such as inhaled NO or prostacyclin) and limiting plateau pressure in mechanically ventilated patients, the preload should be increased cautiously with volume loading and an adequate right coronary artery perfusion maintained. Positive inotropic agents have an important role in the treatment of RVF by improving cardiac output and coronary perfusion. However, traditional inotropic drugs increase myocardial contractility by their sympathomimetic action at the expense of increasing myocardial intracellular calcium concentration and oxygen consumption. Calcium sensitisers, specifically levosimendan, enhance contractility without increasing

myocardial oxygen consumption. If the beneficial effects that have been observed in chronic heart failure patients are validated in RVF in clinical studies, this class of agents may represent a valuable addition to the clinician's armamentarium for the management of this condition.

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