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Monitoring and management of right ventricular function following cardiac transplantation

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Abstract

In cardiac transplantation postoperative right ventricular dysfunction is a major cause of morbidity and mortality. Recipients with pulmonary hypertension due to end-stage heart failure and a donor heart, fragile because of ischemia-reperfusion injury, and not previously adapted to an elevated pulmonary resistance are the causes of right ventricular dysfunction, that unless aggressively treated may progress to overt right ventricular failure. Dysfunctional pulmonary vascular endothelium with diminished release of NO and increased expression of endothelin-1 is considered to be the primary pathophysiology that induces pulmonary hypertension. New therapeutic approaches are aimed at ameliorating endothelial dysfunction. How extensively pulmonary hypertension has to be treated depends on the degree of functional impairment of the right ventricle resulting from the acute increase of right ventricular afterload at heart transplantation. Mainstays in the treatment of pulmonary hypertension are optimizing right ventricular preload, increasing contractility, lowering right ventricular afterload, improving coronary perfusion and failing these therapeutic interventions mechanical circulatory support. Judicious use of volume therapy is mandatory to avoid volume overload in the postoperative setting. As a general rule to explore right ventricular preload reserve volume should only be carefully administered by observing filling pressures up to a maximum of a central venous pressure of 10 mm Hg. Volume administration is not indicated if it only increases right atrial filling pressure without subsequently increasing cardiac output. In most cases relative volume overload is the clinical problem and not hypovolemia. In this situation aggressive diuretic therapy and in cases of acute renal failure renal replacement therapy is mandatory.
Positive inotropic therapy is indicated to treat consecutive right ventricular dysfunction. Dobutamine may be a choice in the presence of a low cardiac index but preserved systemic pressures and epinephrine in cases of low cardiac output syndrome and systemic hypotension. A useful adjunct to catecholamine therapy is phosphodiesterase-III-inhibitors in the absence of arterial hypotension. Most importantly, pulmonary arterial pressures and right ventricular afterload have to be lowered in pulmonary hypertension compromising right ventricular function. Systemic vasodilators to treat pulmonary hypertension are non-selective and may induce arterial hypotension. This also applies to intravenously administered prostanoids. Inhaled NO in therapeutic doses selectively dilates the pulmonary vasculature without inducing systemic hypotension. To prevent a rebound phenomenon, inhaled NO therapy has to be slowly weaned. To account for the individually different response to inhaled NO, dose titration is recommended with doses of 10–50 ppm NO to lower pulmonary arterial pressures. Inhaled NO has been successfully used for all indications in the treatment of pulmonary hypertension in cardiac surgery. It has proved to be especially effective after implantation of left ventricular assist devices and following heart transplantations. As an alternative therapy, inhalation of aerosolized prostanoids similar to inhaled NO selectively decreases pulmonary arterial pressures.

In recent years there has been growing evidence that the orally available phosphodiesterase 5 inhibitor sildenafil may be a useful adjunct to therapy in right ventricular failure. Inhibition of posphodiesterase 5 by sildenafil selectively induces pulmonary vasodilatation without deleterious effects on the systemic circulation. It can also be employed to facilitate weaning heart transplant recipients of inhaled NO, catecholamines and mechanical ventilator support. It has also been reported to have synergistic effects with inhaled NO and may be a treatment option in refractory cases. Potential drug interactions with immunosuppressive drugs have to be accounted for.
Although clinical data are still limited administration of the calcium sensitizer levosimendan with reported inotropic effects and at the same time decreasing pulmonary pressures may be an attractive treatment option in patients after heart transplantation presenting with right ventricular dysfunction.
Endothelin antagonists are effective in the treatment of moderate to severe pulmonary hypertension, but their future role still has to be determined in further studies.
Supportive therapeutic measures in acute pulmonary hypertension are the use of 100% oxygen, moderate hyperventilation and correction of acidosis.
If right ventricular failure progresses to a low cardiac output syndrome, implantation of an intraaortic balloon pump has to be considered to improve coronary perfusion. In refractive pulmonary hypertension and frank right ventricular failure implantation of a right ventricular assist device remains the last resort for treatment.

Key words: right ventricular function, heart transplantation, donor heart

Introduction

Right ventricular dysfunction of the donor heart, which may progress to overt right ventricular failure, is a leading cause of postoperative morbidity and mortality following heart transplantation. Right ventricular dysfunction of the donor heart is of multifactorial origin and importantly can not be possibly avoided. In principle the donor heart, which is not adapted to an increased pulmonary artery pressure and resistance is exposed to post transplant pulmonary hypertension in the recipient (1). Pulmonary hypertension, which is usually present in the recipient due to end-stage chronic heart failure may additionally be aggravated in the postoperative situation due to adverse effects of the cardiopulmonary bypass and other reasons such as hypoxemia, blood products, bleeding disorders and protamine administration (2). The non adapted right ventricle of the donor heart conversely may be compromised in its function by ischemia-reperfusion injury and the sequelae of organ preservation. Thus the clinical picture is that of a postoperatively dysfunctional right ventricle of the donor heart being acutely exposed to pulmonary hypertension for its first time.

Independent of its aetiology, pulmonary hypertension is at least partially caused by an excess of endogenous vasoconstrictors, e.g. endothelin and angiotensin II, relative to endogenous vasodilators, e.g. nitrous oxide (NO) and prostacyclin (3). In pulmonary hypertension, the physiologic interplay of these opposing systems, in which the endothelium plays a crucial role in regulating pulmonary vessel tonus, is tipped out of balance (4). Novel therapies for acute pulmonary hypertension therefore aim at alleviating endothelial dysfunction.

Pulmonary circulation is the major determinant of right ventricular afterload and determines right ventricular ejection fraction. Pulmonary hypertension results in increased

right ventricular afterload. The thin-walled, trapezoid right ventricle is highly compliant and is able to tolerate a considerable volume load (5). However, it possesses only limited contractile reserves and adaptive mechanisms to work against an acutely increased pulmonary resistance (6). Thus, the extent to which acute pulmonary hypertension is treatable largely depends on right ventricular function under conditions of an acute increase in afterload.

The acute increase in right ventricular afterload results in an increase in right ventricular end-diastolic volume and a decrease in the right ventricular ejection fraction. Right ventricular failure can in turn cause a decrease in left ventricular end-diastolic volume with septal shift to the left and ballooning of the right ventricle. In these instances, left ventricular ejection volume and cardiac output can decrease further and result in a low cardiac output syndrome with hypotension and shock.

The following recommendations on the therapy of pulmonary hypertension following cardiac transplantation are restricted to symptomatic approaches, i.e. optimizing right ventricular preload, increasing contractility, decreasing right ventricular afterload, improving coronary perfusion, and applying mechanical circulatory assistance, including implantation of an intraaortic balloon pump or right ventricular assist devices as last resort of treatment.

Therapy is ultimately directed at preventing a low cardiac output syndrome. Alleviating elevated pulmonary resistance, improving myocardial oxygen consumption, and maintaining adequate preload and coronary perfusion by ensuring sufficient aortic pressure are important aspects.

At all times preservation of sinus rhythm is of utmost importance, and also arrhythmias and atrio-ventricular conduction disturbances have to be appropriately treated in order to maintain a heart rate of about 100/min supporting an adequate ejection volume.

Optimizing right ventricular preload

Favorable hemodynamic effects of volume therapy to improve right ventricular preload have been described through the Frank-Starling mechanism in pulmonary hypertension (7). However, there are strict limitations to the administration of volume in this postoperative setting. Hemodynamic consequences of volume therapy depend on volume status and the degree of right ventricular dysfunction under the conditions of a very vulnerable right donor ventricle not adapted to high pulmonary resistances. Individual volume requirements can only be determined by volume therapy itself, administered under tight hemodynamic monitoring. If volume therapy only increases right filling pressures without a concomitant rise in cardiac output, further volume therapy should immediately be stopped. Central venous pressure gives a rough guidance and volume therapy may be indicated in CVP below 10 mm Hg. As a general practical rule a CVP of 10 mm Hg should not be exceeded. In most cases the presenting problem in this patient population is not hypovolemia but fluid overload. Volume therapy is contraindicated in the presence of high right ventricular filling pressure associated with low cardiac output syndrome and systemic arterial hypotension. In cases of volume overload aggressive diuretic therapy should be performed or if spontaneous urine output stopped renal replacement therapy should be initiated to reduce excessive volume.

Increasing contractility

In heart transplant recipients with pulmonary hypotension and consecutive right ventricular dysfunction positive inotropic therapy is mandatory to improve myocardial contractility. The catecholamines of choice are dobutamine and epinephrine. In patients with a low cardiac index but normal systemic blood pressure, dobutamine may be preferred (8).

Because of dobutamine's predominantly β-agonistic effect and minimal β-agonistic activity, it is advantageous in instances in which vasoconstrictive effects are not desired (9). As its peripheral vasodilatory effect can cause a decrease in blood pressure, dobutamine has to be cautiously used in patients with systemic hypotension. In patients with systemic hypotension and low cardiac output syndrome epinephrine is the drug of choice to achieve an adequate cardiac output and perfusion pressure (10). Catecholamines increase myocardial oxygen consumption, are arrhythmogenic, and lead to tachyphylaxia if used for longer periods of time. At higher doses, the positive inotropic effects of dopamine and adrenaline are neutralized by dose-dependent vasoconstriction, which also affects the pulmonary vessels.

Catecholamine therapy may be supplemented by phosphodiesterase III inhibitors, such as enoximone and milrinone. This class of compounds acts as a positive inotrope as well as a smooth muscle relaxant. The cAMP-mediated increase in intracellular cGMP concentration is independent of adrenoceptor activity and circulating catecholamine levels. The effect of phosphodiesterase III inhibitors therefore does not rely on the stimulation of β-receptors, which can be down-regulated or desensitized in prolonged catecholamine therapy or cardiac insufficiency (11). Thus, the combination of β-agonists and phosphodiesterase III inhibitors leads to an increase in cAMP levels and synergistic hemodynamic effects via two independent mechanisms. Phosphodiesterase III inhibitors do not increase myocardial oxygen consumption as they concomitantly decrease afterload. These considerations also explain the potential side-effect in that the arterial blood pressure can quickly fall below the critical systemic pressure threshold, particularly in patients with acute pulmonary hypertension and right ventricular failure with systemic hypotension. In such situations, the use of phosphodiesterase III inhibitors should be considered only with great caution, particularly in view of the long half-life of these substances. Another advantage of phosphodiesterase III inhibitors is pulmonary vasodilation with beneficial effects in patients with pulmonary hypertension and increased right ventricular load (12).

Levosimendan is an inodilator with both calcium sensitizing and phophodiesterase III inhibitory effects. The calcium sensitizing effects enhances cardiac contractility without increasing intracellular calcium concentration, and via PDE III inhibition levosimendan has vasodilating properties. It thus may be used as a unique adjunct in the inotropic therapy in these postoperative patients (13).

Reduction of right ventricular afterload

Pulmonary arterial pressure largely depends on right ventricular function. Acutely exposed to pulmonary hypertension, the non-adapted right ventricle is able to maximally produce pressures of 45-50 mmHg. Further pressure increase leads to progressive right ventricular failure with a decrease in cardiac index and low cardiac output syndrome. Conversely, when right ventricular failure occurs, the pulmonary arterial pressures can be relatively low, although the pulmonary vascular resistance is high.

The treatment of pulmonary hypertension focuses on lowering pulmonary arterial pressure and resistance to reduce right ventricular afterload (4).The aim is to induce dilation of the pulmonary vessels and lowering of the pulmonary vascular resistance without a decrease in the arterial systemic blood pressure or in coronary arterial perfusion. The deleterious effects of a drop in blood pressure caused by vasodilatory therapy of pulmonary hypertension have long been known (14). With the exception of inhaled nitric oxide (NO) therapy, all other substances administered systemically for the treatment of increased pulmonary vascular resistance and pulmonary hypertension are non-selective vasodilators and can induce arterial hypotension.

The prostanoids prostaglandine E1 and I2 have a half-life of only a few minutes. Therapeutically they are used as prostacycline and epoprostenole and as the derivative iloprost, which has a considerably longer half-life of 30 minutes. Prostanoids are potent pulmonary vasodilators that, when administered intravenously, lead to a simultaneous decrease in systemic blood pressure, which limit their therapeutic use (15).

Likewise, adenosine is effective as a pulmonary vasodilator with a very short half-life. It is being used in the evaluation of cardiac transplant candidates presenting with pulmonary hypertension and, like prostanoids and NO, in some centers in pre-operative protocols to test the pharmacological reversibility of pulmonary hypertension. When infused at a dose of 50 µg/kg/min, adenosine decreases pulmonary arterial pressures without induction of vasodilation (16). At higher doses of 70 µg/kg/min however, systemic vasodilation was observed (17). Under adenosine infusion an increase of pulmonary capillary occlusion pressure with the danger of acute pulmonary edema has been reported. For these reasons, administering adenosine has so far only been anecdotally reported in the treatment of pulmonary hypertension.

Nitric oxide is released as a free radical from vascular endothelial cells and is a potent endogenous vasodilator. After being generated in the vascular endothelium, NO diffuses to neighbouring vascular smooth muscle cells and induces vascular relaxation by increasing intracellular cGMP levels (18).

Inhalation of NO at therapeutic doses causes selective pulmonary vasodilation without systemic hypotension. The physiological preconditions for pulmonary selectivity are its administration by inhalation, its short half-life of only a few seconds, and its high affinity for hemoglobin, by which it is deactivated (19). Nitric oxide inhaled into the alveoli passes the alveolo-capillary membrane by diffusion and relaxes the vascular smooth muscle cells of pulmonary vessels. Systemic vasodilation does not occur, as NO is inactivated quickly by binding to hemoglobin in the lumen of perfused vessels. Since the vasodilating effect of NO is restricted to ventilated areas of the lung, NO has the additional benefit of reducing intrapulmonary shunt volume and thus improves oxygenation (20). When NO inhalation is abruptly discontinued, its vasodilating effect ceases as quickly as it commences, due to the short half-life of cGMP of less than 1 minute, i.e. for practical purposes the pharmacological effects of NO stop almost simultaneously with its administration (18).

As potential side effects the formation of toxic nitric oxides such as NO_2, the generation of methemoglobin, and the prolongation of bleeding time caused by inhibition of thrombocytes have been reported. The generation of toxic nitric oxides is dependent on the NO dose administered and the duration of oxygen contact and increases exponentially with inspiratory oxygen concentration (21). Toxic methemoglobinemia is highly unlikely to occur with the doses of NO used therapeutically, and in clinical use a higher bleeding tendency could not be found. In the literature, the rate of side effects described is generally low, and in numerous controlled studies it was hardly ever necessary to discontinue its use due to unwanted side effects (22). However, a potentially lethal complication can result from abrupt discontinuation of NO administration, which can lead to a dramatic deterioration in gas exchange and hemodynamic collapse (23). These rebound phenomena are well known in clinical practice and mandate gradual weaning of NO therapy with immediate availability of a replacement inhalation device in case of an equipment failure. In clinical use, controlled admixture of the gas close to the patient, intensive monitoring and use of the smallest doses possible are recommended internationally (24).

Inhaled NO therapy is routinely used to treat postoperative pulmonary hypertension following cardiac surgery worldwide. Its limitations are the administration via a special delivery system in the breathing circuit requiring oro-tracheal intubation and mechanical venti-

lation. So far, NO inhalation is only approved for use in persisting pulmonary hypertension of the newborn (25). For all other indications, NO therapy can only be used "off-label".

Individual dose titration is useful for optimal treatment with the smallest possible dose. Hemodynamic effects are expected above 10 ppm NO, and to effectively reduce pulmonary pressures, up to 50 ppm may be required.

In patients with chronic heart failure, inhaled NO therapy led to a decrease in pulmonary vascular resistance, with the pretreatment value of pulmonary vascular resistance serving as a predictor for expected maximum effects (26).

Inhaled NO therapy selectively reduced pulmonary vascular resistance in pulmonary hypertension after heart transplantation, an improvement in right ventricular ejection volume, and a decrease in the incidence of postoperative right ventricular dysfunction (27, 28). It has therefore been proposed that NO therapy in pulmonary hypertension be begun immediately after heart transplantation in order to prevent right ventricular failure (29). In known cases of pulmonary hypertension in heart transplant patients, NO therapy is frequently started immediately after the induction of anesthesia and intubation to "condition" the pulmonary vessel bed, interrupted during cardiopulmonary bypass, and restarted after the termination of extracorporeal circulation. Some centers have therefore begun to administer inhaled NO therapy routinely after cardiac transplantation (28).

Over the last decade the effects of the orally available phosphodiesterase 5 inhibitor sildenafil has been investigated in cardiac transplant patients and found to be a therapeutic option in the treatment of right ventricular dysfunction (30). Inhibition of posphodiesterase 5 by sildenafil selectively induces pulmonary vasodilatation without untoward effects on the systemic circulation. In a comparative evaluation of the effects of inhaled NO and results obtained with sildenafil in patients that were evaluated for heart and lung transplantations, both drugs had comparable effects (31). Sildenafil can also be orally administered to facilitate weaning heart transplant recipients of inhaled NO, catecholamines and mechanical ventilator support. Synergistic and additive effects with inhaled NO have been reported and combination therapy may be an option in refractory cases. Sildenafil may lead to adverse drug-drug interactions e.g. with immunosuppressive drugs which have to be accounted for and may limit the use of this otherwise attractive drug candidate in heart transplant patients.

An alternative to NO therapy is the use of inhaled prostanoids, which can be administered as aerosols with jet or ultrasound nebulizers. The pulmonary selective effect of prostacycline has been demonstrated in clinical studies after cardiac surgery, and it has been confirmed in tests of the pharmacological reversibility of pulmonary hypertension before heart transplantation. The inhalation of 10 µg/ml prostacycline showed a comparable acute effect to that of 40 ppm NO with respect to pulmonary vasodilation (32). Iloprost has been used successfully in the long-term therapy of primary pulmonary hypertension (33). Inhaled administration of prostanoids is so far not clinically approved. Arterial hypotension is possible with large doses, if a sufficient concentration is reached in the systemic circulation by resorption. Toxic side effects have not been published to date.

In patients with primary and secondary pulmonary hypertension, significantly increased plasma levels of endothelin-1 were found (34), and increased expression of endothelin-1 was seen in the lung (35). Due to these pulmonary vascular effects, and since the lung is the place where production and clearance of ET-1 primarily take place (36), endothelin receptor antagonists are a potential option in the treatment of pulmonary hypertension.

In several studies, the perioperative increase in pulmonary resistance after cardiopulmonary bypass has been explained by an increase in endothelin-1 plasma levels,

suggesting the use of endothelin antagonists in the management of pulmonary hypertension after cardiac surgery (37). However, further studies are required to define the role of endothelin antagonists in more detail.

It has long been known that the administration of 100% oxygen leads to a decrease in pulmonary vascular resistance and, conversely, that hypoxemia is associated with pulmonary vasoconstriction. Delivery of 100% oxygen, independent of pre-treatment oxygenation and hemodynamics, decreases mean pulmonary arterial pressure and pulmonary vascular resistance, and increases cardiac index (38). So far it is unclear how long the favourable acute hemodynamic effects persist. Nevertheless, in the treatment of acute pulmonary hypertension the temporary administration of 100% oxygen is viewed as one of the first measures.

Conversely, hypercapnia and acidosis lead to an increase in pulmonary vascular resistance and may aggravate pulmonary hypertension. Therefore, care should also be taken to achieve acid-base balance and a somewhat lowered pCO_2 through moderate hyperventilation.

Improvement of coronary perfusion

If an acute increase of pulmonary vascular resistance leads to right ventricular failure with low cardiac output syndrome, the implantation of an intra-aortic balloon pump should be considered. Although intra-aortic counterpulsation does not support right ventricular function directly and is therefore primarily used in left ventricular failure, favourable hemodynamic effects with an increase in cardiac output could also be shown in acute right ventricular dysfunction. This may be explained by an improvement in coronary perfusion pressure (39). In addition, the reduction in afterload by an intra-aortic balloon pump can potentially lead to an improvement in the ejection fraction of the left ventricle in patients in shock and with already compromised left ventricular function (40).

The administration of vasoconstrictors to raise perfusion pressure is in most instances not indicated since, with the increase in systemic resistance, pulmonary vascular resistance also rises. Therefore, with an increase in pulmonary arterial pressure, deleterious effects on right ventricular function are likely, even with a rise in systemic and coronary perfusion pressure (41). The temporary administration of norepinephrine is possible under exceptional circumstances in pulmonary hypertension, when right heart failure with shock and systemic hypotension are present (42).

Mechanical circulatory support with assist devices

In pulmonary hypertension with consecutive right ventricular failure of the donor heart that proves to be refractory to conventional therapy, the implantation of a right ventricular assist device is the last resort. Since many centers began to routinely employ NO inhalation after cardiac operations such as heart transplantation and implantation of left ventricular assist devices, the incidence of right ventricular failure has significantly dropped. Initial results with right ventricular assist devices in pulmonary hypertension refractory to therapy were poor (43). Of great importance, beside sufficient experience, is the timely implantation before multi-organ failure sets in, which has led to improved results (44). Ideally, a right ventricular assist device should be implanted when, despite all measures for the treatment of pulmonary hypertension the right ventricle progressively fails. Mechanical support should be continued until right ventricular function recovers and a reduction in central venous and pulmonary arterial pressures has taken place (1).

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