DERLEME / *REVIEW*

Treatment of Acute Pulmonary Hypertension

AKUT PULMONER HİPERTANSİYON TEDAVİSİ

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Abstract

A dysfunctional pulmonary vascular endothelium with diminished release of nitric oxide (NO) and increased expression of endothelin-1 is thought to be the main pathophysiological inductive mechanism for acute pulmonary hypertension. New therapeutic approaches are aimed at ameliorating endothelial dysfunction in acute pulmonary hypertension. Whether or not acute pulmonary hypertension has to be treated depends on the degree of functional impairment of the right ventricle resulting from an acute increase in right ventricular afterload. The treatment of acute pulmonary hypertension comprises optimizing right ventricular preload, increasing contractility, lowering right ventricular afterload, improving coronary perfusion and, lastly, mechanical circulatory support. Most importantly, it is essential that pulmonary arterial pressures and right ventricular afterload be lowered in acute pulmonary hypertension. Systemic vasodilators to treat pulmonary hypertension are nonselective and may induce arterial hypotension. Inhaled NO in therapeutic doses selectively dilates the pulmonary vasculature without inducing systemic hypotension. To date, NO inhalation is only approved for the treatment of persistent pulmonary hypertension in newborns. For all other indications, NO therapy is only possible as "off-label use". Inhaled NO has been successfully used for all indications in the treatment of acute pulmonary hypertension following cardio-surgical interventions. It has proved to be especially effective after implantation of left ventricular assist devices and following heart and lung transplantations. As an alternative therapy, inhalation of aerosolized prostanoids similar to inhaled NO selectively decreases pulmonary arterial pressures, but is still awaiting medical approval. In the future, endothelin-receptor antagonists will be available to treat pulmonary hypertension; they are presently being evaluated in extensive clinical trials. Since the advent of the routine use by many centers of inhaled NO following heart transplantations and implantation of left ventricular assist devices, the incidence of right ventricular failure due to pulmonary hypertension is decreasing.

Key Words: Pulmonary hypertension, therapy, endothelin, nitric oxide

Özet

Nitrik oksit (NO) salınımının ortadan kalktığı ve endotelin-1'in artış gösterdiği fonksiyonları bozulmuş akciğer damar endotelinin, akut pulmoner hipertansiyona neden olan ana patofizyolojik mekanizma olduğu düşünülmektedir. Yeni tedavi yaklaşımları, akut pulmoner hipertansiyonda endotel fonksiyonlarındaki bu bozulmayı gidermeye yöneliktir. Akut pulmoner hipertansiyonun tedavi edilip edilmeyeceği, sağ ventrikül art yükündeki artışa bağlı olarak sağ ventrikül fonksiyonlarındaki bozulmanın derecesine bağlıdır. Akut pulmoner hipertansiyonun tedavisini sağ ventrikül ön yükünü optimize edilmesi, kontraktilitenin arttırılması, sağ ventrikül art yükünün azaltılması, koroner perfüzyonun iyileştirilmesi ve nihayetinde mekanik dolaşım desteğinin sağlanması oluşturur. Akut pulmoner hipertansiyonda, pulmoner arter basınçları ve sağ ventrikül artyükü azaltılması önemlidir. Pulmoner hipertansiyonun tedavisinde sistemik vazodilatörler seçici değildirler ve arteryel hipotansiyona neden olabilirler. Tedavi edici dozlarda NO inhalasyonu sistemik hipotansiyona neden olmadan seçici olarak pulmoner damar yatağını genişletir. Bugüne kadar NO inhalasyonu yenidoğanlarda persistan pulmoner hipertansiyon tedavisinde onaylanmış tek yöntemdir. Diğer tüm endikasyonlar için NO tedavisi "prospektüs dışı kullanım" ile mümkündür. Kardiyak cerrahi girişimler sonrası akut pulmoner hipertansiyonun tedavisinde NO inhalasyonu başarı ile kullanılmaktadır. Özellikle sol ventrikül destek cihazlarının (Assist Device) yerleştirilmesi ve kalp ve akciğer nakilleri sonrası etkili olduğu kanıtlanmıştır. Pulmoner hipertansiyona bağlı sağ ventrikül yetmezliği insidansı, birçok merkezde sol ventrikül destek cihazlarının yerleştirilmesi ve kalp ve akciğer nakilleri sonrası rutin NO kullanımına bağlı olarak azalmaktadır. Alternatif bir tedavi yöntemi olarak aerosol halinde prostanoidlerin inhalasyonu, benzer şekilde seçici olarak pulmoner arter basınçlarını azaltmaktadırlar. Ancak bunlar halen tıbbi onayı beklemektedirler. Gelecekte endotelin reseptör antagonistleri pulmoner hipertansiyon tedavisinde yerini alacaktır. Bu yenikuşak ilaçlar halen yaygın klinik çalışmalarla değerlendirilmektedir.

Anahtar Kelimeler: Pulmoner hipertansiyon, tedavi, endotelin, nitrik oksit

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Pulmonary hypertension is caused by a variety of factors and is associated with either an increase in blood flow, or an increase in resistance in the pulmonary vessel system. Physiologically, the lung is a low pressure system that compensates for fluctuations in blood flow by the

recruitment of less perfused pulmonary vessels and dilation of more highly perfused vessels. It is able to compensate for considerable fluctuations in blood flow with only little change in pulmonary arterial resistance.[1,2]

Independent of its etiology, 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. nitric oxide (NO) and prostacyclin.[3] In pulmonary hypertension, the finely tuned interplay of these opposing systems, in which the endothelium plays a crucial role in regulating pulmonary vessel tonus, is out of balance.[4] Thus, novel treatment modalities for acute pulmonary hypertension aim at alleviating endothelial dysfunction.

Pulmonary circulation is the major determinant of right ventricular afterload and determines the right ventricular ejection fraction. Independent of its etiology, 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 counter acute increases in pulmonary resistance.[6] Thus, the extent to which acute pulmonary hypertension is treatable depends in large part on right ventricular function under conditions of an acute increase in afterload.

Acute pulmonary hypertension with right ventricular dysfunction can be caused by mechanical obstruction of pulmonary vessels by massive embolism, by inflammation such as in sepsis or reperfusion, or by right ventricular failure after cardiopulmonary bypass. In these instances, right ventricular failure is almost always a consequence of increased afterload caused by an obstructed pulmonary circulation.

Right ventricular failure can develop acutely, such as in pulmonary embolism. Most often, however, it is caused by aggravation of existing pulmonary hypertension in critical illnesses, for example due to hypoxic pulmonary vasoconstriction in chronic obstructive pulmonary disease (COPD) or in cardiac surgery after cardiopulmonary bypass. The acute increase in right ventricular afterload or the progression of a chronic hypertensive condition results in an increase in right ventricular end-diastolic volume and a decrease in 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 fraction and cardiac output can decrease further and result in a low cardiac output syndrome with hypotension and shock.

Consideration of the underlying etiology of acute pulmonary hypertension is pertinent in a causative treatment regimen, such as in the event of massive pulmonary embolism, but is beyond the scope of this review. Therefore, the following comments on the therapy of acute pulmonary hypertension 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 right ventricular assist devices.

The aims of therapy are to avoid the development of a low cardiac output syndrome. Reduction of increased pulmonary resistance, improvement in myocardial oxygen consumption, and maintenance of adequate preload and coronary perfusion through sufficient aortic pressure, are important in this respect. Arrythmias and atrioventricular conduction disturbances have to be appropriately treated to maintain an adequate ejection volume and heart rate.

Optimizing right ventricular preload

Beneficial hemodynamic effects of volume therapy to improve right ventricular preload have been described in acute pulmonary hypertension.[7] However, there are strict limitations. Volume therapy is restricted to those instances in which a larger expansion of the right ventricle in diastole is expected to make use of a higher preload reserve by increasing right ventricular end-diastolic volume and cardiac output through the Frank-Starling mechanism. In contrast, however, many experi-

mental animal studies in acute pulmonary hypertension have shown a deterioration in hemodynamics. Hemodynamic consequences of volume therapy depend on volume status and the degree of right ventricular function impairment under the conditions of an acute increase in pulmonary resistance. In effect, individual volume requirements in a given patient can only be clarified by volume therapy itself, administered under close hemodynamic monitoring. If, under volume therapy, only right atrial filling pressure rises without a concomitant increase in cardiac output, further volume therapy is not indicated. Central venous pressure (CVP) can serve as a rough orientation in this respect, with volume therapy indicated at a CVP below 10 mmHg, and possibly useful up to a CVP of 15 mmHg. Volume therapy is not indicated in the presence of high right ventricular filling pressure with a consecutive low cardiac output syndrome and systemic arterial hypotension.

Increasing contractility

Patients with acute pulmonary hypertension and consecutive right ventricular dysfunction require positive inotropic therapy to improve myocardial contractility. The catecholamines dopamine, dobutamine and epinephrine are commonly administered. In patients with a low cardiac index but normal systemic blood pressure, dopamine and dobutamine are preferred.[8] Because of dobutamine's predominantly ß-agonistic effect and minimal α-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 used with caution in patients with systemic hypotension. In patients with systemic hypotension and a low cardiac output syndrome, in whom right ventricular preload has to be considered and optimized if necessary, epinephrine is used in order to achieve an adequate cardiac index and perfusion pressure.[10] Catecholamines increase myocardial oxygen consumption, are arrhythmogenic, and lead to tachyphylaxia if used for longer periods of time. At higher dosages, the positive inotropic effects of dopamine and epinephrine are neutralized by dose-dependent vasoconstriction, which also affects the pulmonary vessel system.

A useful supplement to catecholamine therapy is found in phosphodiesterase III inhibitors, such as enoximone and milrinone. This class of substances acts as positive inotropes as well as relaxing agents on smooth muscle. 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 ß-receptors, which can be down-regulated or desensitized in prolonged catecholamine therapy or heart failure.[11] Thus, the combination of ß-agonists and phosphodiesterase III inhibitors leads to an increase in cAMP levels and synergistic hemodynamic effects via two independent mechanisms. The fact that phosphodiesterase III inhibitors do not increase myocardial oxygen consumption is attributed to a concomitant lowering effect on afterload. These considerations also explain the potential side-effect in which an ensuing drop in arterial blood pressure can quickly fall below a critical systemic pressure, 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 compounds.

Another advantage of phosphodiesterase III inhibitors is pulmonary vasodilation with beneficial effects in patients with pulmonary hypertension and increased right ventricular load.[12]

Reduction of right ventricular afterload

Pulmonary arterial pressure depends largely on right ventricular function. In acute pulmonary hypertension, the non-adapted right ventricle is able to produce pressures of 45-50 mmHg. Further pressure increase leads to progressive right ventricular failure with a decrease in cardiac index and a low cardiac output syndrome. If pulmonary hypertension develops slowly and the right ventricle is given the opportunity to adapt, much higher pulmonary arterial pressures can be generated.

Conversely, when right ventricular failure occurs, the pulmonary arterial pressures can be relatively low, although the pulmonary vascular resistance is high.

The treatment of acute pulmonary hypertension focuses on lowering the pulmonary arterial pressure and thus reducing 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 coronary perfusion pressure. The deleterious effects of a drop in blood pressure caused by vasodilatory therapy in pulmonary hypertension have been known for a long time.[13] With the exception of inhaled NO therapy, all other substances administered systemically for the treatment of increased pulmonary vascular resistance and pulmonary hypertension are nonselective vasodilators and can induce arterial hypotension.

By the same token, organic nitrates lead to pulmonary vasodilation, but at dosages required they also lead to a drop in systemic blood pressure and may aggravate hypoxia through a mismatch between pulmonary ventilation and perfusion.[14,15]

The same holds true for the physiologically present prostanoids prostaglandine E_1 and I_2 that 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 considerably limits their therapeutic use.[16] For example, prostanoids have been investigated in pulmonary hypertension during and after heart transplantation, and a decrease in pulmonary arterial resistance with a reduction of right ventricular load could be demonstrated.[17,18] Comparing nitroglycerine, nitroprusside and prostacycline, the pulmonary vasodilating effect of prostacycline was more pronounced than that of nitroglycerine, but comparable to that of nitroprusside. Systemic vasodilation caused by prostacycline was, however, considerably higher than that caused by nitroglycerine or nitroprusside. On balance, prostacycline was not more pulmonary selective than nitroprusside, but compared with organic nitro compounds, prostacycline was the most potent systemic vasodilator. In contrast to nitroprusside and prostacycline, only under NO inhalation could a pulmonary selective effect be proven, and NO was the only substance that did not require the administration of a vasopressor to raise arterial blood pressure.[19,20]

Likewise, adenosine is effective as a pulmonary vasodilator with a very short half-life. It is being used in the evaluation of transplant candidates with pulmonary hypertension and, like prostanoids and NO, in some centers in preoperative protocols to test the pharmacological reversibility of pulmonary hypertension. The vasodilating effect of adenosine is mediated by the membrane-bound A_2 receptors of vascular smooth muscle cells and leads to an increase in cAMP by activating adenylate cyclase. Adenosine is deactivated during passage through the lung by adenosine deaminase. When infused in a dose of 50 μg/kg/min, adenosine led to a decrease of pulmonary arterial pressures, without induction of vasodilation.[21] At higher doses of 70 μg/kg/min however, systemic vasodilation was observed.[22] Under adenosine infusion an increase of pulmonary capillary occlusion pressure with the danger of acute pulmonary edema has been reported. For these reasons, adenosine has so far not been used in therapeutic regimens for acute pulmonary hypertension.

NO is formed by oxidation of the amino acid L-arginine. It is released as a free radical from vascular endothelial cells, among others, and is a potent endogenous vasodilator. After being generated in the vascular endothelium, NO diffuses to neighboring vascular smooth muscle cells and leads to vascular relaxation by an increase in intracellular cGMP levels.[23]

Inhalation of NO in therapeutic doses causes selective pulmonary vascular dilation without systemic hypotension. The physiological preconditions for pulmonary selectivity are its administration by inhalation, its short half-life of a matter of

seconds, and its high affinity for hemoglobin, by which it is deactivated.[24] NO inhaled into the alveoles 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.[25] 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 end nearly simultaneously with its administration.[23]

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.[26] 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 corroborated. 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.[27] 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.[28] These rebound phenomena are well known in clinical practice and suggest the gradual reduction of NO therapy with immediate availability of a replacement NO inhalation device in case of an equipment failure. In clinical use, controlled admixture of the gas close to the patient, intensive monitoring, use of the smallest doses possible, and avoidance of the generation of toxic nitric oxides are recommended internationally.[29]

Inhaled NO therapy is being employed increasingly often to treat pulmonary failure or pulmonary hypertension with consecutive right heart failure. So far, NO inhalation is only approved for use in persisting pulmonary hypertension of the newborn (PPHN). In this indication, under NO therapy a decrease in pulmonary arterial pressures, an improvement in oxygenation, and less frequent need of ECMO have been documented.[30,31] For all other indications, NO therapy can only be used "off-label".

NO doses required in the treatment of pulmonary hypertension are generally higher than in adult respiratory distress syndrome (ARDS). Since the response to inhaled NO differs markedly from patient to patient, individual dose titration is necessary 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. Dose-dependent effects have been described.

Inhaled NO therapy is able to reduce pulmonary hypertension in a variety of diseases of different etiology, e.g. in hypoxic vasoconstriction, COPD, ARDS, primary pulmonary hypertension, congenital heart diseases and mitral valve diseases.[25,32-36] In patients with chronic heart failure, inhaled NO therapy led to a decrease in pulmonary vascular resistance, with the pre-treatment value of pulmonary vascular resistance serving as a predictor for expected maximum effects.[37]

Inhaled NO therapy has successfully been used in all indications after cardiac surgery in which acute pulmonary hypertension develops postoperatively.[38,39] Acute pulmonary hypertension with an increase in pulmonary vascular resistance after cardiopulmonary bypass is in many cases associated with severe acute right ventricular failure, its incidence being highest after the implantation of left ventricular assist devices (> 20%), followed by orthotopic heart transplantation (> 10%).[40,41] Clinical effects of inhaled NO therapy have been investigated in patients who developed right ventricular dysfunction with postoperative low cardiac output syndrome after implantation of a left ventricular assist device. With a dose titration

of 5-40 ppm NO, pulmonary arterial pressures decreased in a dose-dependent manner, while at the same time cardiac index increased without systemic hypotension developing. During long-term administration of NO with further hemodynamic improvement catecholamine therapy could be progressively reduced, and finally inhaled NO therapy gradually weaned and then terminated. After therapy, no hemodynamic deterioration occurred, and pulmonary vascular resistance remained significantly below the pre-treatment values.[42]

Similarly, inhaled NO therapy was also effective after heart and lung transplantation.[43-45] Inhaled NO therapy led to a selective reduction in 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.[46] It has therefore been proposed that NO therapy in pulmonary hypertension should be initiated immediately after heart transplantation in order to prevent right ventricular failure.[47] In known cases of pulmonary hypertension in heart transplant patients, NO therapy is often begun 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.[41] In some cases of lung transplantation, inhaled NO therapy has been a life-saving measure to treat the most severe forms of reperfusion edema.[48] In addition, the incidence of reperfusion damage has been reduced by prophylactic inhaled NO therapy after lung transplantation.[49] Some centers have therefore begun to administer inhaled NO therapy prophylactically after left ventricular assist device implantation and after the transplantation of thoracic organs.[50]

An alternative to NO therapy is the use of inhaled prostanoids, which can be administered as aerosols with jet or ultrasound nebulizers. In animal experiments simulating hypoxic pulmonary hypertension, prostacycline has been shown to selectively reduce pulmonary arterial pressures, similar to inhaled NO.[51,52] The pulmonary selective effect of prostacycline has been demonstrated in clinical studies in ARDS and after cardiac surgery, and it has been confirmed in tests of the pharmacological reversibility of pulmonary hypertension before transplantation of thoracic organs. The inhalation of 10 μg/mL prostacycline showed a comparable acute effect to that of 40 ppm NO with respect to pulmonary vasodilation.[53] Prostacycline inhalation has also been described as a therapeutic alternative to ventilation with NO in reperfusion damage after lung transplantation.[54] Iloprost has been used successfully in the long-term therapy of primary pulmonary hypertension.[55] Inhaled administration of prostanoids is not clinically approved at present. 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 until now.

In patients with primary and secondary pulmonary hypertension, significantly increased plasma levels of endothelin-1 were found, and increased expression of endothelin-1 was seen in the lungs.[56,57] Since then, a number of studies have shown that endothelin-1 plays a role in the pathophysiology of pulmonary arterial hypertension, due to its mitogenic and vasoconstrictive properties.[58] Endothelin-1 can increase resistance and lead to pulmonary vascular hypertrophy, suggesting that local production of endothelin-1 in the lung is associated with the pathological vascular changes in pulmonary hypertension.[57] Due to these pulmonary vascular effects, and since production and clearance of ET-1 primarily take place in the lungs, endothelin receptor antagonists are a new therapeutic option in the treatment of pulmonary hypertension.[59] These substances are still in the development phase, but have been evaluated in animal models and clinical trials.

Two subtypes of endothelin receptors are known: ET_A and ET_B. ET_A receptors are located on vascular smooth muscle cells and have a vasoconstrictive and mitogenic effect, while ET_B receptors are expressed in vascular endothelial cells and act vasodilatively. It is hoped that, with the availability of non-selective antagonists, such as bosentan, and subtype-specific ET_A and ET_B endothelin receptor

antagonists, the role of endothelin receptor subtypes will be elucidated and new therapeutic avenues opened.[60] In the treatment of patients with moderate to severe pulmonary hypertension, endothelin antagonists seem to be promising with respect to efficacy and oral bio-availability. In animal models, a significant reduction of pulmonary hypertension and right ventricular hypertrophy and prolongation of survival have been shown with endothelin antagonists.[61] In a clinical trial with 32 patients, the non-selective and orally available endothelin antagonist bosentan was investigated for its effects on exercise tolerance, cardiopulmonary hemodynamics, and for safety and efficacy. This double-blind and placebo-controlled study showed that bosentan given orally (62.5 mg twice daily for 4 weeks, then 125 mg twice daily for at least 12 weeks) improves physical exercise capacity and hemodynamics in patients with pulmonary hypertension. The effect of bosentan on pulmonary hemodynamics consisted of a decrease in pulmonary vascular resistance, mean pulmonary arterial pressure and central venous pressure, without a significant reduction in systemic arterial blood pressure. The dose administered was tolerated well in this clinical trial.[62] As a result of this and other studies endothelin antagonists are increasingly being used in the clinical management of pulmonary hypertension. However, further studies are required to define the role of endothelin antagonists in more detail.

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 acute pulmonary hypertension after cardiac surgery as well.[63]

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. Likewise, the administration of 100% oxygen is integrated into pre-operative protocols to test the reversibility of pulmonary hypertension. Continuous oxygen therapy is used successfully as a pulmonary vasodilator in pulmonary hypertension and hypoxic states. It could be shown recently that the acute administration of 100% oxygen, independent of pre-treatment oxygenation and hemodynamics, decreases mean pulmonary arterial pressure and pulmonary vascular resistance, and increases cardiac index.[64] So far it is unclear how long the favorable 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. After correction of congenital heart defects with a postoperative acute increase in pulmonary hypertension, hyperventilation has been used successfully for many years to reduce pCO_2 and pulmonary arterial pressures.[65] Therefore, in the treatment of adults care should also be taken to achieve a good 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, favorable hemodynamic effects with an increase in cardiac output could also be shown in acute hemodynamically relevant right ventricular dysfunction. This may be explained by an improvement in coronary perfusion pressure.[66] 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.[67] The pulmonary arterial implantation of a balloon pump has not found widespread use, and today it is only of historical interest.[68]

The administration of vasoconstrictors to raise perfusion pressure is in most instances not indi-

cated 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.[69] The temporary administration of norepinephrine, which possesses α and β_1-mimetic properties, is possible under exceptional circumstances in pulmonary hypertension, when right heart failure with shock and systemic hypotension are present.[70] The administration of norepinephrine via the left atrium has not been successful, as the selective effect on systemic circulation sometimes claimed could not be proven in clinical practice, not to mention the risks of a left atrial infusion after cardiac surgery.

Mechanical circulatory support with assist devices

In acute pulmonary hypertension with consequent right ventricular failure that proves to be refractory to 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.[71] Of great importance, beside sufficient experience, is the timely implantation before multi-organ failure sets in, which has led to improved results.[72] Ideally, a right ventricular assist device should be implanted when, despite all measures for the treatment of acute pulmonary hypertension, progressive right ventricular dysfunction looms. Mechanical support should be continued until right ventricular function recovers and a reduction in central venous and pulmonary arterial pressures has taken place.[41]

Summary: Procedures in acute pulmonary hypertension

The vascular endothelium plays a decisive role in the regulation of vascular tone in pulmonary vessels. Today, pulmonary hypertension is explained in large part by a dysfunction of vascular endothelium in the pulmonary circulation, which is to some degree associated with lowered release of NO and increased expression of endothelin-1. From this starting point, new therapies to ameliorate endothelial dysfunction and pulmonary hypertension are emerging. Whether acute pulmonary hypertension needs to be treated depends mainly on the degree of right ventricular failure during an acute increase of right ventricular afterload. Since causal therapy is only appropriate in a few instances of acute pulmonary hypertension, a symptomatic treatment approach is normally adopted. This means optimizing right ventricular preload, increasing contractility, reducing right ventricular afterload, improving coronary perfusion, and if necessary mechanical circulatory assistance including right ventricular assist devices.

Volume therapy is indicated in those instances in which utilization of a preload reserve of the right ventricle can be achieved. A target central venous pressure of 10-15 mmHg can serve as orientation. If solely right atrial filling pressure increases without an increase in cardiac output, further volume therapy should be avoided, as it should if systemic hypotension already exists together with high right filling pressure and a low cardiac output syndrome.

In right ventricular dysfunction due to acute pulmonary hypertension, positive inotropic therapy is necessary. In normotensive patients with low cardiac index, dopamine and dobutamine are indicated. In patients with systemic hypotension in low cardiac output syndrome, epinephrine is used. Catecholamine therapy can be complemented with phosphodiesterase III inhibitors with synergistic hemodynamic effects. In hypotensive patients, phosphodiesterase III inhibitors should be used only with great caution to prevent a further decrease in blood pressure.

Of the greatest importance in the treatment of acute pulmonary hypertension is the reduction of pulmonary vascular resistance and right ventricular afterload. With the exception of inhaled NO therapy, all substances administered systemically to

treat pulmonary hypertension are non-selective vasodilators and may induce arterial hypotension. This holds true for example for intravenous therapy with the prostanoids prostacycline, epoprostenol and iloprost, the effects of which last longer. Inhaled NO in therapeutic doses results in selective pulmonary vascular dilation, without causing systemic hypotension. Since rebound phenomena can occur if NO supply is abruptly discontinued, inhaled NO therapy should be gradually weaned off. So far, NO inhalation is only approved in the PPHN. For all other indications, inhaled NO therapy is only possible as "compassionate" use. Since responsiveness to inhaled NO differs between individuals, dose titration is helpful. To reduce pulmonary arterial pressures, doses of 10-50 ppm NO may be required. Inhaled NO therapy has been employed successfully for all indications following cardiac surgery with pulmonary hypertension requiring treatment. Inhaled NO therapy has been especially effective after the implantation of left ventricular assist devices and after heart and lung transplantation, and some centers have begun to use NO therapy prophylactically for these indications.

An alternative to NO therapy is the administration of inhaled prostanoids which, like inhaled NO, selectively lower pulmonary arterial pressures. The administration of 10 µg/mL inhaled prostacycline is believed to have an acute effect comparable to that of 40 ppm NO regarding pulmonary vasodilation. Inhalation of prostanoids is so far not clinically approved.

Endothelin receptor antagonists are likely to present a future therapeutic option in pulmonary hypertension. They appear to be promising in the treatment of moderate to severe pulmonary hypertension, although further studies are required to determine their clinical value.

In addition, the temporary administration of 100% oxygen is one of the first measures, as well as moderate hyperventilation and correction of acidosis.

In right ventricular failure with low cardiac output syndrome, the implantation of an intra-aortic balloon pump should be considered to improve coronary perfusion. In exceptional circumstances, noradrenaline may be administered temporarily to raise perfusion pressure when right ventricular failure, systemic hypotension and shock are present. In acute pulmonary hypertension refractory to treatment with consequent right ventricular failure, the implantation of a right ventricular assist device remains the last possibility. The incidence of right ventricular failure due to pulmonary hypertension has decreased considerably since routine use of NO inhalation was introduced in many centers after heart transplantation and implantation of left ventricular assist devices.

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