

Review

# Pathophysiology and treatment of haemodynamic instability in acute pulmonary embolism: the pivotal role of pulmonary vasoconstriction

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## Abstract

Acute massive pulmonary embolism has a high mortality rate. Fatal haemodynamic deterioration is caused by an acute increase in pulmonary vascular resistance. Traditionally, the degree of mechanical obstruction of the pulmonary vasculature by the embolic thrombus is considered to be the major determinant of this increase in right ventricular afterload. However, there is evidence to suggest that another factor plays an important role, since there is a marked discrepancy between the haemodynamic manifestations of acute pulmonary embolism and the degree of mechanical obstruction. Historic studies indicate that this discrepancy is largely explained by pulmonary vasoconstriction caused by vasoactive mediators, released mainly by activated platelets. Thromboxane- $A_2$  and serotonin are probably the two most important pulmonary vasoconstrictors in this context. Antagonising their effects dramatically increases tolerance to experimental pulmonary embolism in animals. In humans, this concept should eventually find its way into clinical practice. In the future, acute massive pulmonary embolism could be treated with antagonists to pulmonary vasoconstrictors, or with direct pulmonary vasodilators. © 2000 Elsevier Science B.V. All rights reserved.

**Keywords:** Pulmonary circulation; Thrombosis/embolism; Vasoconstriction/dilatation

## 1. Introduction

Pulmonary embolism (PE) is a frequently encountered disorder, especially in hospital settings. Estimations for the US are that PE occurs in about 600 000 patients annually, and causes 50 000–200 000 deaths [1–3]. PE is held responsible for — or at least contributes to — up to 15% of total in-hospital mortality [1,4,5]. PE often goes unrecognised, as reports indicate that only in about one third of all patients that died from PE was the correct diagnosis suspected antemortem [6,7]. Hospital mortality rates caused by clinically apparent PE are 30% for untreated patients, and around 2.5% for those receiving up-to-date treatment [8]. For acute massive PE with haemodynamic instability, the 1-h mortality rate approached 70% in the prethrombolysis era [9]. More recent studies, performed

after gain in surgical experience for thrombectomy, and after the introduction of thrombolytic therapy and catheter embolectomy, estimate mortality from PE in haemodynamically unstable patients at between 23 and 38% [10,11]. Death due to PE is often instantaneous (within minutes), and of all fatal cases, up to 90% succumb within 2 h after the onset of symptoms [7,9,12]. The rapid clinical deterioration, combined with the fact that the diagnosis of PE is frequently missed, both contribute to the fact that only a minority (an estimated 6.5%) of PE deaths occur in patients who are actually treated for PE [1].

Acute right-sided heart failure due to increased pulmonary vascular resistance (PVR) is the prime cause of death in PE [13]. The rapid rise in afterload causes dilatation of the right ventricle, which, together with systemic hypotension, compromises coronary perfusion, causing ischaemia and sometimes even myocardial infarction. The septal shift resulting from right ventricle dilatation further reduces left ventricular preload, and the patient enters a ‘vicious cycle’ of acute right sided heart failure [14,15]. Traditionally, the

*Abbreviations:* COX, cyclooxygenase; NO, nitric oxide; PAP, pulmonary artery pressure; PE, pulmonary embolism; PG, prostaglandin; PVR, pulmonary vascular resistance;  $TxA_2$ , thromboxane- $A_2$

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degree of mechanical obstruction of the pulmonary vascular bed was considered to be the only determinant of the PVR increase in PE. Over the years, however, a number of observations have challenged this concept. Firstly, several studies have shown that the correlation between the degree of mechanical obstruction and the haemodynamic manifestations of PE is either absent, or poor at best [16–18]. Furthermore, bringing about a strictly mechanical obstruction by cross-clamping the left or right pulmonary artery during a surgical procedure, or by unilateral balloon occlusion, causes only a modest rise in pulmonary artery pressure (PAP), and almost never results in right-sided heart failure [17,19,20], whereas PE with obstruction of only  $\pm 25\%$  of the pulmonary vascular tree can cause marked pulmonary hypertension [21]. Also, major PE can be found during autopsy in patients who never had any clinical manifestations of PE [1,6]. As early as in the 1940s and 1950s, it was acknowledged that vasoconstriction of the pulmonary vascular bed is present in PE. Case reports from this period showed that stellate ganglion blockade, performed on the symptomatic side in non-heparinised patients with PE, reduced cyanosis, dyspnea, and circulatory shock [22,23]. Stellate ganglion blockade can markedly attenuate pulmonary vasoconstriction [24]. Cross-transfusion experiments in sheep demonstrated increases in PAP in the non-embolised sheep, approximately 20–30 s after embolisation of its pairmate, providing support for a role of circulating vasoconstrictive mediators [25]. After the identification of several candidate vasoactive mediators, further evidence for their role in PE came from animal experiments in which these mediators were pharmacologically antagonised. In these studies, which will be discussed below, animals who were treated with such mediator antagonists could survive massive PE without marked haemodynamic disturbances, whereas the majority of control animals died or developed severe circulatory shock.

In recent reviews and treatment recommendations for PE, the focus is exclusively on interventions aimed at removing the mechanical obstruction. Hence, it is necessary to reassess the potentially important role of pulmonary vasoconstriction in the increase in PVR after acute PE. This review primarily discusses the etiology of this vasoconstrictive response. The most important vasoactive mediators and their respective antagonists are discussed, as are the potential benefits of vasodilators in the treatment of haemodynamically unstable patients with PE.

## 2. Vasoactive mediators in pulmonary embolism

### 2.1. Thromboxane- $A_2$

There is strong evidence that thromboxane- $A_2$  (Tx $A_2$ ), a strong vasoconstrictor, plays a role in the pulmonary response to acute PE. Tx $A_2$  is one of the end products of

arachidonic acid metabolism [26]. There are two classical metabolic routes for arachidonic acid metabolism. One is the cyclooxygenase (COX) pathway, in which, through the enzymatic action of COX, arachidonic acid is converted to endoperoxides prostaglandin-G $_2$  (PGG $_2$ ) and PGH $_2$ . These two substances are intermediates in the formation of the biologically active prostaglandins: PGD $_2$ , PGE $_2$ , PGF $_{2\alpha}$ , PGI $_2$  (prostacyclin), and, through the action of thromboxane synthase, Tx $A_2$ . The alternative metabolic pathway for arachidonic acid is the 5-lipoxygenase pathway, which results in the synthesis of leukotrienes and 5-hydroxy-eicosatetraenoic acid. The lipoxygenase pathway is probably also activated after PE, but does not directly contribute to the rise in PVR [27]. For a more detailed discussion of arachidonic acid metabolism and thromboxane signal transduction, the reader is referred to recent literature [28–30]. Tx $A_2$  is produced primarily in platelets in response to platelet activation. Other potential sources of Tx $A_2$  production include the vascular endothelium and circulating monocytes, but these sources are quantitatively less important than platelets. The main physiologic role of Tx $A_2$  is to enhance platelet aggregation and to cause vasoconstriction, both in the interest of effective haemostasis. The vasoconstrictive effect of Tx $A_2$  applies to both the systemic and the pulmonary vascular system [26]. Tx $A_2$  production after acute PE has been studied using measurements of its stable degradation product TxB $_2$ . It should be stressed that TxB $_2$  measurements are not as precise in assessing Tx $A_2$  production as some of the more recently developed techniques, like analysis of plasma 11-dehydro-TxB $_2$  and urinary 11-dehydro-TxB $_2$  or 2,3-dinor-TxB $_2$  [26]. Except for one study in experimental fat embolism [31], these more recently developed analytical techniques have, to my knowledge, not been employed in the context of acute PE.

Several studies have shown that increased production of Tx $A_2$  takes place in PE, especially in the early stages (first 10–30 min) [32,33]. The degree of Tx $A_2$  production has been shown to correlate with the risk of mortality in experimentally induced PE in animals [32]. Also, the surge in Tx $A_2$  production is related to the respiratory response to acute PE [34]. Additional evidence for a role of Tx $A_2$  comes from experiments with antagonists of Tx $A_2$  in the setting of experimentally induced PE. One way to block Tx $A_2$  synthesis is to use a COX inhibitor. Several animal studies have been performed, especially in the 1970s and early 1980s. Experimental PE was induced either by autologous clot infusion [34–36], or microsphere/glass bead embolisation [37–39]. COX inhibition was accomplished by pretreatment of the animals with indomethacin [34,37], ibuprofen [38], meclofenamate [38,39], or acetylsalicylic acid [35]. These studies showed a markedly attenuated haemodynamic response in the animals pretreated with a COX inhibitor compared to controls. The rise in PAP after acute PE was about 40–60% of that observed in control animals [35,37–39]. Also, the increase

in PVR following an arachidonic acid or thrombin infusion is virtually abolished by pretreatment with a COX inhibitor [35,40]. The observation that this beneficial effect of COX inhibition is not accompanied by less platelet sequestration in the lungs suggests that it is the antagonism of the vasoconstrictive effect of  $\text{TxA}_2$ , rather than of its platelet aggregating effect, that explains the attenuation of the increase in PVR [41]. The effect of COX inhibitors in humans with PE has never been studied. The possible reasons for this are outlined in the discussion. It is, however, worth mentioning that ibuprofen has been used successfully to lower PAP in patients with adult respiratory distress syndrome, presumably also through an inhibitory effect on  $\text{TxA}_2$  production [42].

Note that COX inhibition is a relatively non-specific way of inhibiting  $\text{TxA}_2$  synthesis, since the production of the prostaglandins is also impaired. This effect may contribute to some of the effects of COX inhibitors other than reduction of pulmonary vasoconstriction. For example, COX inhibitors may also reduce PE-related hypoxaemia, probably because  $\text{TxA}_2$  and prostaglandins, by their combined effects on vasal and bronchial tonus, play a role in PE-related ventilation–perfusion mismatch [34,43]. Other effects of COX inhibitors in animal PE models include reduction of pulmonary edema [37,40], and better preservation of myocardial contractility, possibly by reducing circulating negative inotropic prostaglandins [33]. More specific  $\text{TxA}_2$  antagonists include  $\text{TxA}_2$  synthase inhibitors (like dazoxiben and related imidazol derivatives),  $\text{TxA}_2$  receptors blockers (daltroban, vapiprost) and picotamide, which is both a  $\text{TxA}_2$  synthase inhibitor and a  $\text{TxA}_2$  receptor antagonist. These agents could theoretically perform better than COX inhibitors, since these do not inhibit prostacyclin synthesis, but rather cause a shift in endoperoxide metabolism towards increased formation of prostacyclin [44–46]. On the other hand, this shift also stimulates  $\text{PGF}_{2\alpha}$  synthesis, which may overrule the beneficial effects of  $\text{TxA}_2$  inhibition and prostacyclin stimulation [47]. Some studies of experimental PE have been performed using these drugs, and the results are largely, but not unequivocally [48], in accordance with those of the COX inhibition studies [34,44,49].

## 2.2. Serotonin

Serotonin (5-hydroxytryptamine) plays a role in various types of primary and secondary pulmonary hypertension [50]. It can be produced by gastrointestinal enterochromaffin cells, serotonergic neurons, pulmonary neuroendocrine cells, and by activated platelets. On a molar basis, serotonin is the single most powerful pulmonary vasoconstrictor known, whereas in the systemic circulation, it causes vasodilation [51]. A detailed discussion of the wide variety of serotonin receptors is outside the scope of this review [50]. In addition to effects on vascular tone, serotonin has positive inotropic properties [52].

The role of serotonin in pulmonary vasoconstriction after PE has been recognised since the 1960s. Infusion of serotonin in dogs can accurately simulate signs and symptoms of PE [53,54]. Also, depletion of platelet serotonin by reserpine decreases vascular responsiveness to PE [55,56], whereas pretreatment with a monoamine oxidase inhibitor which increases platelet serotonin content, aggravates the haemodynamic response to PE [57]. Serum serotonin concentrations increase in animals after experimental induction of haemodynamically significant PE [58].

Several animal studies with serotonin antagonists have been performed. One of the most studied antagonists is methysergide. In various models of autologous-clot-induced PE, methysergide markedly attenuated the haemodynamic response to PE [35,36,57]. Another serotonin antagonist, cyproheptadine, could completely block the rise in PVR after autologous clot infusion in dogs [58]. Serotonin antagonists have also shown a beneficial effect on gas exchange after PE [59]. When both a COX inhibitor and a serotonin antagonist (methysergide) were used, the partial attenuation of the rise in PVR seen with methysergide alone was replaced by an almost complete abolishment of the haemodynamic response to autologous clot infusion [35]. Also, the combination of a  $\text{TxA}_2$  and a serotonin antagonist can dramatically reduce the mortality rate from experimentally induced massive PE in rabbits from 55 to 0% [36]. In humans, there is no experience with serotonin blockers in the setting of acute PE, except for ketanserin. Ketanserin inhibits serotonin at serotonin-type-2 receptor sites [60,61], which are located on platelets and on vascular and bronchial smooth muscle [62,63]. On the other hand, ketanserin also has  $\alpha_1$ -adrenergic blocking properties, which are responsible for its systemic vasodilatory effect [61]. As such, it is used as a systemic vasodilator in the treatment of hypertension, and its role in PE will be discussed below (see under Vasodilator therapy).

Platelets are the major source of  $\text{TxA}_2$  and serotonin production in PE, but exactly which platelets are responsible is unclear. The embolus itself is a fibrin-rich clot, and the degree to which the relatively limited number of platelets embedded in this clot can still contribute to the release of  $\text{TxA}_2$  and serotonin is questionable. Microscopic studies have however shown that the surface of a clot that has caused PE is covered with freshly aggregated platelets. Thrombin-platelet interaction at the clot surface is presumably of key importance in this platelet activation. The possible role of other platelet activators, such as ADP and platelet-activating factor, is unknown. Also, we do not know to what extent local endothelial cell activation stimulates platelet aggregation. In any case, it is likely that the platelets aggregated at the surface of the embolic clot are largely responsible for mediator release [57,64]. The number of circulating platelets prior to the experimental induction of PE is related to the mortality rate [65]. The rise in  $\text{TxA}_2$  and serotonin in serum corresponds closely to

the post-PE fall in platelet counts, suggesting that these mediators originate from aggregated platelets [34,58]. Thus, platelets that were circulating prior to PE are probably the major source of production of vasoconstrictive mediators after PE. This argumentation applies both to  $\text{TxA}_2$  and to serotonin. A decrease in serotonin content in circulating platelets has also been observed following PE, suggesting that not only aggregated, but also circulating platelets are activated after PE [66]. The contribution of other possible production sites of vasoconstrictors (i.e. the vascular wall for  $\text{TxA}_2$ , and pulmonary neuroendocrine cells for serotonin) in acute PE is not known.

### 2.3. Other vasoconstrictive mediators

Endothelin is produced by the vascular endothelium, and causes marked and sustained vasoconstriction. There are several subtypes, of which endothelin-1 is known in particular for its ability to cause pulmonary hypertension [50]. Few data are available to define the role of endothelin-1 in the vasoconstrictive response to PE. A recent study of air emboli in isolated rabbit lungs showed that the endothelin type-A receptor antagonist LU-135252 significantly reduced the short term increase in PAP. Interestingly, this endothelin antagonist also reduced the increase in  $\text{TxB}_2$  levels that were observed in the control animals. The pressure–time curve for the endothelin receptor antagonist was similar to the curve obtained after pretreatment with diclofenac, with no evidence of an additive effect of both drugs [67]. These and previous [68] data thus suggest that endothelin-1 may exert its pulmonary vasoconstrictive effect through activation of  $\text{TxA}_2$  generation. Release of endothelin, or rather of its precursor big-endothelin, from the lungs after PE has another unfavourable effect in the form of coronary vasoconstriction, which may contribute to cardiodepression [69].

Prostaglandin  $\text{F}_{2\alpha}$  ( $\text{PGF}_{2\alpha}$ ) is also released following PE, and contributes to pulmonary vasoconstriction [47]. Its precise role is unknown, but is probably less important than that of the previously discussed vasoconstrictors. The same is true for prostaglandins- $\text{H}_2$ ,  $-\text{D}_2$ ,  $-\text{E}_2$  and leukotriene- $\text{D}_4$ , which are all pulmonary vasoconstrictors, and whose role in acute PE remains to be determined. In addition, histamine may also add to pulmonary vasoconstriction, as antihistamines have been shown to moderately attenuate the rise in PVR after microembolisation in dogs [39].

One final possible contributor to pulmonary vasoconstriction needs to be addressed, namely hypoxic pulmonary vasoconstriction. Hypoxaemia in PE is variably present, and certainly does not appear to be a prerequisite for haemodynamic instability. Its pathogenesis is complex [70], and is outside the scope of this review. Probably, hypoxic pulmonary vasoconstriction is not an important contributor to the increase in PVR. Studies have shown that the hypoxic pulmonary vasoconstrictive response is blunted in patients with PE, conceivably because its

mechanism is overruled by the abundant presence of vasoactive mediators [71]. If marked hypoxaemia is present in PE, supplemental oxygen administration has, however, been reported to cause a reduction in PVR [72].

### 2.4. Vasodilatory mediators

Prostacyclin ( $\text{PGI}_2$ ) is probably the most important vasodilatory mediator released after PE. Prostacyclin is produced mainly by endothelial cells in response to vascular injury and platelet activation, and in these cells, it is the principal metabolite of arachidonic acid. It is the natural antagonist of  $\text{TxA}_2$ , inhibiting platelet aggregation and activation, and counteracting the vasoconstrictive action of  $\text{TxA}_2$  [26]. Prostacyclin also reduces serotonin release from platelets, and inhibits pulmonary endothelial uptake of serotonin [58]. In addition, it may have bronchodilating [73] and positive inotropic actions [74]. Prostacyclin (measured by its stable metabolite 6-keto- $\text{PGF}_{1\alpha}$ ) is released into the pulmonary circulation in response to PE, and appears to reach its peak levels some time after the peak in  $\text{TxA}_2$  and serotonin release [32]. Blocking prostacyclin synthesis or action in this phase can result in haemodynamic deterioration (see Discussion). The therapeutic potential of using prostacyclin as a pulmonary vasodilator will be discussed below.

The extent to which other vasodilatory mediators (like  $\text{PGE}_1$ ) play a role in attenuating the response to pulmonary vasoconstrictors is undetermined. It is possible that increased nitric oxide (NO) synthesis occurs after PE, but this has not been studied. Other endothelium-derived vasodilators also deserve further study. Possibly, increased production of atrial natriuretic peptide also attenuates pulmonary vasoconstriction after PE [75].

## 3. Vasodilator therapy in pulmonary embolism

In addition to specific antagonists of vasoconstrictive mediators, vasodilators may offer therapeutic benefit in haemodynamically unstable patients with PE. The main concern, however, is the lack of specificity of these drugs for the pulmonary vasculature. Arterial hypotension can be expected to worsen, certainly if the reduction in systemic vascular resistance exceeds that of PVR. Vasodilators that specifically cause pulmonary vasodilation are not available. One solution would be the intravenous administration of vasodilators with a high pulmonary extraction rate, like the vasodilatory prostaglandins [76]. Alternatively, vasodilators may be given locally by inhalation. The effects of different vasodilators in animals and in humans with PE will be discussed, starting with two ‘natural’ vasodilators: prostacyclin and NO.

### 3.1. Prostacyclin

Prostacyclin is, as discussed above, a physiological

vasodilatory mediator in PE, but it is also available as a therapeutic agent. Its vasodilatory action is, however, not at all specific for the pulmonary vessels. Intravenous prostacyclin has been used for the treatment of haemodynamically unstable dogs with autologous clot PE [34,77]. The fall in systemic blood pressure in these experiments approached or slightly outweighed the fall in PAP, whereas gas exchange parameters improved. Prostacyclin can also be administered by inhalation, but the literature regarding the effects of inhaled prostacyclin is limited. In a canine model of glass bead microembolisation and oleic acid pulmonary edema, prostacyclin inhalation was ineffective [78]. A case report described a beneficial effect of inhaled prostacyclin in a patient with massive PE, in whom PAP decreased by 15 mmHg without a fall in systemic blood pressure, and oxygenation improved markedly, but this effect was transient [79].

### 3.2. Nitric oxide

NO is a potent endothelium-derived vasodilator. Inhaled NO has been shown to cause selective pulmonary vasodilation, and can be effective in primary and secondary pulmonary hypertension [80], as well as in adult respiratory distress syndrome, in which it improves oxygenation by reducing ventilation–perfusion mismatching [81]. Not only is inhaled NO a vasodilator, it also has platelet-inhibitory properties that could be beneficial in terms of reducing platelet-derived vasoconstrictive mediators [82–84]. Several animal studies of acute and chronic pulmonary hypertension resulting from experimentally induced PE have shown that NO inhalation can markedly reduce PVR without adversely affecting systemic haemodynamics or oxygenation [85–88]. In humans, several case reports have been published, which invariably report a marked haemodynamic improvement after NO inhalation [89–91]. Systemic blood pressure, as expected, was not adversely affected by NO inhalation in any of these cases. One case was reported in which NO inhalation resulted in closure of a patent foramen ovale in a patient with PE [92]. Inhaled NO was also reported to be effective when an increased PAP persisted after surgically successful thrombectomy [93]. Finally, in one recently described case, NO inhalation was used during cardiopulmonary resuscitation for massive PE, and was followed by restoration of spontaneous circulation [90]. NO has been reported to cause moderate oxygen desaturation in a single case report [94], possibly by causing an increase in ventilation–perfusion mismatch, or by opening previously unperfused shunt units. In all other reported cases, such a side effect was not observed.

### 3.3. Ketanserin

Ketanserin is one of the most intensively studied vasodilators in the context of PE. Although it was believed to antagonise the pulmonary vasoconstrictive action of serotonin, this is doubtful, since recent evidence suggests

that, in humans, serotonin-type-1 rather than type-2 receptors mediate this response [50]. The serotonin-type-2 blocking effects of ketanserin may still explain its pulmonary vasodilatory effect by reduction of serotonin-mediated platelet activation with subsequent release of vasoconstrictive mediators [53,63]. However, ketanserin also has other, potentially unfavourable, effects. It has  $\alpha_1$  adrenergic blocking properties, which are responsible for the systemic vasodilation seen with this drug [52,95]. In addition, ketanserin appears to block the positive inotropic effect of serotonin [54]. Several animal studies have assessed the effects of ketanserin in PE models. In a model of autologous blood clot infusion in dogs, pretreatment with ketanserin markedly attenuated the rise in PVR from 5 to 120 min after PE, and also inhibited both the post-PE fall in circulating platelets, arterial hypoxaemia, and pulmonary edema [53]. Unfortunately, the effects of ketanserin on systemic haemodynamics were not reported in this study. In an earlier, similar dog study, post-PE administration of ketanserin decreases PAP by 50%, as opposed to only a 10% drop in systemic blood pressure, and also improved gas exchange parameters [66]. In humans, a marginally beneficial effect of ketanserin has been suggested by Huet et al., who described the haemodynamic response in ten patients with severe PE to 14 mg of ketanserin, administered during the course of 1 h [96]. Mean PAP (–12%) and PVR (–16%) decreased only slightly more than systemic blood pressure (–9%) and systemic vascular resistance (–10%), whereas cardiac output remained unchanged. Also, oxygenation improved slightly with ketanserin in this study.

### 3.4. Hydralazine

The direct vasodilator hydralazine has been the subject of several animal studies. In a canine model of autologous blood clot PE, hydralazine caused a 41% reduction in PVR and a doubling of cardiac output, at the expense of only a 5% reduction in systemic blood pressure, and a 31% rise in intrapulmonary shunt fraction, without affecting arterial partial oxygen pressure [97]. The effect of hydralazine on systemic blood pressure appears to be more dose-dependent than the effect on PVR [97,98]. In humans, the experience is limited to case reports. A marked improvement of PVR and cardiac index in response to oral hydralazine was reported in an elderly woman with extensive bilateral PE at the cost of only a minor reduction in systemic blood pressure [99]. Hydralazine theoretically has additional benefits in that it is a weak inhibitor of  $\text{TxA}_2$  synthase [100], and has positive inotropic properties [101].

### 3.5. Phosphodiesterase inhibitors

The phosphodiesterase type-III inhibitor amrinone has been studied in both animals and humans with PE. This type of drug has both vasodilatory and positive inotropic

actions. Amrinone has shown excellent results in a canine model of autologous blood clot PE, with a 20% fall in PAP and an almost complete recovery of severe systemic hypotension [102]. There is one case report of a patient with haemodynamic instability due to PE, whose haemodynamic and gas exchange parameters all improved after amrinone therapy [103]. Apart from amrinone, other phosphodiesterase-III inhibitors also improved haemodynamic instability in dogs with experimental PE, with evidence of a more marked vasodilatory effect on the pulmonary than on systemic vasculature [104,105]. Finally, some phosphodiesterase inhibitors have been shown to inhibit platelet aggregation, which may represent an additional benefit [106].

### 3.6. Other vasodilators

The experience with isoproterenol in experimental PE in animals or clinically in humans is generally disappointing [107,108]. Nitroglycerine causes both venous and arterial vasodilation, but the effect on the venous system is more pronounced. In the setting of PE, it has been shown to reduce PVR at the cost of a relatively mild decrease in systemic blood pressure, but this effect required substantial intravenous volume loading to compensate for increased intravascular volume [109]. Nitroprusside is an ultra short acting vasodilator with less venous vasodilation compared to nitroglycerine. Its effect in experimental PE has been studied only in comparative studies with other vasodilators, discussed below. Finally, captopril was shown to be ineffective in a canine microembolisation model [110]. The role of other vasodilators in PE has not been studied.

### 3.7. Comparative studies

Comparative studies of vasodilators in PE are only available for animals. In one study, nitroprusside, hydralazine and PGE<sub>1</sub>, given in fixed doses, were compared in a canine model of autologous blood clot PE [98]. PGE<sub>1</sub> was not effective in reducing PAP, whereas nitroprusside and hydralazine both decreased PAP by 19%, at the expense of a 44% reduction in systemic blood pressure. Neither nitroprusside nor hydralazine changed ventilation–perfusion distributions. Hydralazine and nitroprusside were also compared in another canine autologous blood clot model [111]. In this study, hydralazine was superior to nitroprusside, which, in contrast to hydralazine, did not reduce PVR or increase cardiac output. Finally, hydralazine, nitroglycerin, and PGE<sub>1</sub> were compared in a canine model of acute PE by autologous muscle injection. Again, hydralazine was superior to both other drugs in its effect on PVR, but even more so in its effect on cardiac performance [112].

The treatment of PE with positive inotropic and vasopressor agents is outside the scope of this paper. The reader is referred to another review [107].

## 4. Other treatments that may influence pulmonary vascular tone

The cornerstone of current PE treatment is anticoagulation with heparin in haemodynamically stable patients, and fibrinolytic therapy in patients presenting with haemodynamic instability or respiratory failure. Traditionally, the effect of these therapies is considered to be based on inhibition of clot growth (heparin), enabling endogenous fibrinolysis to occur, or on drug-induced fibrinolysis (streptokinase, urokinase, recombinant tissue plasminogen activator). It is possible, however, that these therapies also reduce pulmonary vasoconstriction. Anticoagulation with heparin inhibits thrombin and reduces thrombin formation, thereby interrupting thrombin-induced platelet activation, which may reduce the release of platelet-derived vasoconstrictive mediators. The importance of thrombin–platelet interaction in the setting of PE was demonstrated already in 1968, when Gurewich et al. showed that pretreatment with heparin blunted, in a dose-dependent fashion, the haemodynamic response to clot-induced PE in rabbits [57]. Later, this effect was also shown in a canine microembolisation model [113]. Note that, in haemodynamically unstable PE patients, this effect of heparin represents a theoretical benefit of an intravenous bolus of heparin immediately after the diagnosis of PE, as opposed to treatment with subcutaneous low-molecular-weight heparin. In fact, in the early days of heparin treatment, when 15 000 U were administered intravenously, the recommendation was to do so immediately after the diagnosis of PE, because of an immediate favourable clinical response to this bolus injection [114]. It is also of note that heparin may cause modest endothelium-dependent vasodilation [115,116], and may preserve endothelial vasodilatory function after ischaemic injury [117].

How fibrinolytic therapy reduces the release of vasoactive mediators is more difficult to understand, but two observations suggest that these drugs may do more than just cause clot lysis. Firstly, a haemodynamic response to these agents is often seen earlier than one would expect substantial clot lysis to occur. Secondly, and most importantly, the haemodynamic improvement after thrombolytic therapy correlates poorly, at least in some studies, to the angiographically determined resolution of mechanical vascular obstruction [118].

Finally, the effect of anti-platelet drugs other than COX-inhibitors or specific TxA<sub>2</sub> inhibitors on haemodynamic manifestations of PE is unknown, but certainly not without potential clinical relevance.

## 5. Discussion

Based on the evidence presented, it is plausible that pulmonary vasoconstriction, caused by the release of predominantly vasoconstrictive mediators, is an important

contributor to the increase in PVR in patients with acute PE. As discussed, most patients who succumb to PE do so within minutes to few hours after the onset of symptoms. This is not surprising considering the time–pressure curves of experimentally induced PE, which invariably show a strong initial rise in PAP, followed by a slow-decrease or a plateau phase, during which PAP is still higher than baseline, but clearly lower than during the initial 30 to 60 min [35,39,53,77]. This suggests that pulmonary vasoconstriction may be most important in the early stages of PE, which may have therapeutic implications in the sense that drugs that antagonise vasoconstrictive mediators could be most effective if given in the initial phase of haemodynamic instability. The clinical implication of this hypothesis is that early treatment of pulmonary vasoconstriction should be considered in haemodynamically unstable patients with PE. However, there are several uncertainties that need to be addressed before clinical use of mediator antagonists or vasodilators can be advocated.

Firstly, the administration of antagonists to  $\text{TxA}_2$  and serotonin has been studied exclusively in animals. Also, most studies addressed the effects of pretreatment with these antagonists, so the results of these experiments cannot be extrapolated automatically to patients who already have PE. Although one could consider pretreatment in humans, for example in those with very extensive venous thrombosis, these patients will usually be treated with heparin. As discussed previously, heparin (in sufficiently high doses) impairs coagulation–platelet interaction. All studies addressing the effect of antagonists of vasoactive mediators have been in non-heparinised animals, and it is unknown whether  $\text{TxA}_2$  or serotonin antagonists are at all effective on top of heparin treatment. Also, the animal experiments often studied very high doses of vasoconstrictor antagonists (up to 250 mg/kg of acetylsalicylic acid, or 3 mg/kg of methysergide). The evidence for a similar effect of doses that are closer to those normally used in patients is more discordant [34,37,119].

Secondly, some antagonists are not without potential side-effects. COX inhibitors in particular have potential disadvantages. Firstly, they may increase rather than decrease PVR. This effect has been demonstrated in a canine model of autologous clot PE, in which COX inhibitors were used as treatment (1 h after the onset of PE), rather than as *pre*-treatment [120]. Another study showed that COX inhibitors may potentiate, rather than attenuate, the vasopressor response to serotonin [121]. It is likely that  $\text{TxA}_2$ , and possibly also  $\text{PGF}_{2\alpha}$ , dominate the vasomotor response early in the course of PE, and that serotonin and prostacyclin are more active in the later stages [32,47]. Thus, the apparently inconsistent effect of COX-inhibitors in the subacute phase after PE may be explained by impairment of prostacyclin production. The risk of an adverse response may apply in particular to higher doses of COX-inhibitors, since in the low doses,

$\text{TxA}_2$  synthesis inhibition is much stronger compared to prostacyclin synthesis inhibition [26]. Unfortunately, no animal studies have been performed comparing the effects of low- and high-dose COX inhibitors. The second important limitation of the use of COX inhibitors is of course the risk of gastrointestinal bleeding, especially in combination with anticoagulation or fibrinolytic therapy.

In summary, pretreatment with  $\text{TxA}_2$  inhibitors will attenuate the rise in PVR in the early phase of PE, but could increase PVR in later stages. Since it is the early phase of PE which is often fatal, these agents may still be able to reduce acute mortality. In this respect, the results of the recent Pulmonary Embolism Prevention trial are intriguing. This large randomised placebo controlled study showed that aspirin reduced the incidence of PE after hip surgery or arthroplasty. However, a sub-analysis indicated that the incidence of fatal PE was reduced much more than that of non-fatal PE (risk reduction 58% versus 26%, respectively) [122]. It is certainly possible that this difference reflects a protective effect of pretreatment with aspirin in patients who develop post-surgery PE.

As for serotonin antagonists, the animal experiments suggest that these agents could be beneficial for human use, but no human studies have been performed with methysergide, which appears to work so well in animals, or with any other specific serotonin antagonist, like pizotifen. Side effects of serotonin antagonists have not been reported. A paradoxical rise in PVR, as in the case of COX inhibitors, is unlikely to occur with serotonin blockers. The role of ketanserin as a serotonin antagonist has been discussed above.

As discussed, vasodilators may be effective both in the initial and in the later stages of PE. Clinicians will, however, intuitively be reluctant to administer vasodilators to hypotensive patients. The potentially effective approach of combined intravenous vasodilation and aggressive fluid filling to compensate for increased intravascular volume has never been specifically studied. However, it has been shown that volume expansion alone is safe in patients with PE [123], and may in fact be more beneficial than vasodilation alone [109]. Of the systemically administered vasodilators studied, ketanserin, one of the phosphodiesterase-III inhibitors, or hydralazine may be first choice. The most direct way of causing specific pulmonary vasodilation is local administration of a vasodilator. Both prostacyclin and NO inhalation have been used for this purpose. The experience with NO is more extensive, and almost uniformly positive. Because of its vasodilatory action and its antiplatelet activity, NO may aggravate haemostasis problems, especially in combination with anticoagulants or thrombolytic agents. Therefore, it should be used with caution if haemorrhage accompanies PE, which is rarely the case.

The limitations of this review are predominantly related to the extrapolation of various animals experiments to the human situation. It is known that inter-species variability

in pulmonary vascular reactivity to a variety of stimuli exists [124]. Also, the models of experimentally induced PE may not reliably represent 'natural' PE. Autologous blot clot injection is probably a reasonably good model of real PE, but does not provoke an equally profound haemodynamic response as in vivo formed thrombus [125]. Microsphere injection/glass bead embolism, and air embolism may also cause different responses than real PE.

Also, there are a number of other candidate substances that may influence pulmonary vascular tone after PE, which have not been discussed because we know so little about them. These include proinflammatory cytokines, free radicals, and various endothelium-derived vasoconstrictors other than endothelin-1. Until we know more about the role of these substances, it may be preliminary to conclude that TxA<sub>2</sub> and serotonin are the key substances in the pathogenesis of PE-related pulmonary vasoconstriction.

In conclusion, there is evidence that, at least in the initial stages of PE, the pulmonary vasoconstrictive response is a major determinant of haemodynamic deterioration. It is remarkable that, more than 50 years after the first observations of pulmonary vasoconstriction in acute PE, no anti-vasoconstrictive therapy has been seriously studied for clinical use. Such therapy should, however, be considered in haemodynamically unstable patients, pending the effects of heparin, thrombolysis or surgery, which remain the cornerstones of PE management. In particular, inhaled NO appears to be often effective in reducing PAP. Controlled trials in humans are needed to define the potential of anti-mediator and vasodilatory drugs in severe PE.

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