

Neurogenic and Humoral Vasoconstriction in Acute Pulmonary Thromboembolism

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Pulmonary thromboembolism (PE) contributes to 50,000 to 200,000 deaths annually (1). A massive PE that results in circulatory shock can rapidly cause death (2). Patients who survive long enough to be diagnosed with a PE have a 6-mo mortality rate of 17% (3). Development of right ventricular failure after sudden pulmonary hypertension is a major determinant of death after PE (4). This sudden pulmonary hypertension is the result of a reduced cross-sectional pulmonary vascular area caused by mechanical obstruction of the pulmonary artery (PA) (4) and PA vasoconstriction (Fig. 1).

Anesthesiologists and intensivists often care for patients who have suffered massive PE. When encountered in the operating room, PE may present as sudden, refractory systemic hypotension or pulseless electrical activity. Classic symptoms and signs of PE (tachypnea, hypocarbia, and a normal or high arterial pH value) may be absent in the anesthetized, mechanically ventilated patient. Instead, severe hypoxia, hypercarbia, and a mixed acidosis may be present (5). Supporting the unstable circulation and rapidly initiating anticoagulation and judicious thrombolysis are logical and established treatment principles but fail to prevent fatal right ventricular failure (RVF) in up to 40% of patients (2). However, reversal of RVF occurred in some patients in extremis when therapy targeting pulmonary vasoconstriction was instituted (6–9). A better understanding of events leading to increased pulmonary artery pressure (PAP) and RVF is required to develop additional treatments and to further reduce mortality in this challenging patient population. This review focuses on neurogenic and humorally mediated pulmonary vasoconstriction and its contributions to the pathophysiology of PE. The section on therapeutic options focuses on drugs that might be useful adjuncts in the treatment of PE but are

difficult to evaluate systematically for this indication, owing to logistic and ethical constraints of conducting prospective investigations in very sick patients.

Unless otherwise specified, cited data were derived from animal experiments, and therefore, their application to the human condition must be done with caution.

Mechanical Obstruction

When a thrombus embolizes to the pulmonary vessels, part of the vasculature is obliterated. If cardiac output is preserved, pressure proximal to the obstruction increases. PAP does not increase unless 60%–70% of the pulmonary vasculature is obliterated by a nonhematogenous obstruction (10–14). However, only 25%–30% of the pulmonary vasculature must be obstructed to increase PAP when a thromboembolus causes the obstruction (1,15). Increased PAP increases right ventricular afterload and may lead to RVF (Fig. 1).

Whereas embolus size is important in determining outcome of PE, mechanical obstruction alone cannot explain the events occurring with an acute PE (1). Neural and humoral stimuli are important co-determinants of severity of hemodynamic disturbance in acute PE. Large and medium sized PAs, as well as pulmonary arterioles and pulmonary veins, are constricted to varying degrees by these stimuli (14). Constriction of PAs of $>1000 \mu\text{m}$ (e.g., by serotonin) and pulmonary arterioles of $<100 \mu\text{m}$ mainly decreases PA compliance (16). Constriction of small, muscular PAs (e.g., by hypoxia) increases pulmonary vascular resistance (PVR). Pulmonary venous constriction (e.g., by histamine) causes translocation of blood from the pulmonary venous compartment to either the alveoli or to the systemic circulation (14).

Neural Factors

PE elicits the von Bezold-Jarisch reflex (apnea, bradycardia, and hypotension), which may contribute to some of the instantaneous deaths after PE. There are conflicting reports regarding the type of receptor and the exact neuronal pathway responsible for

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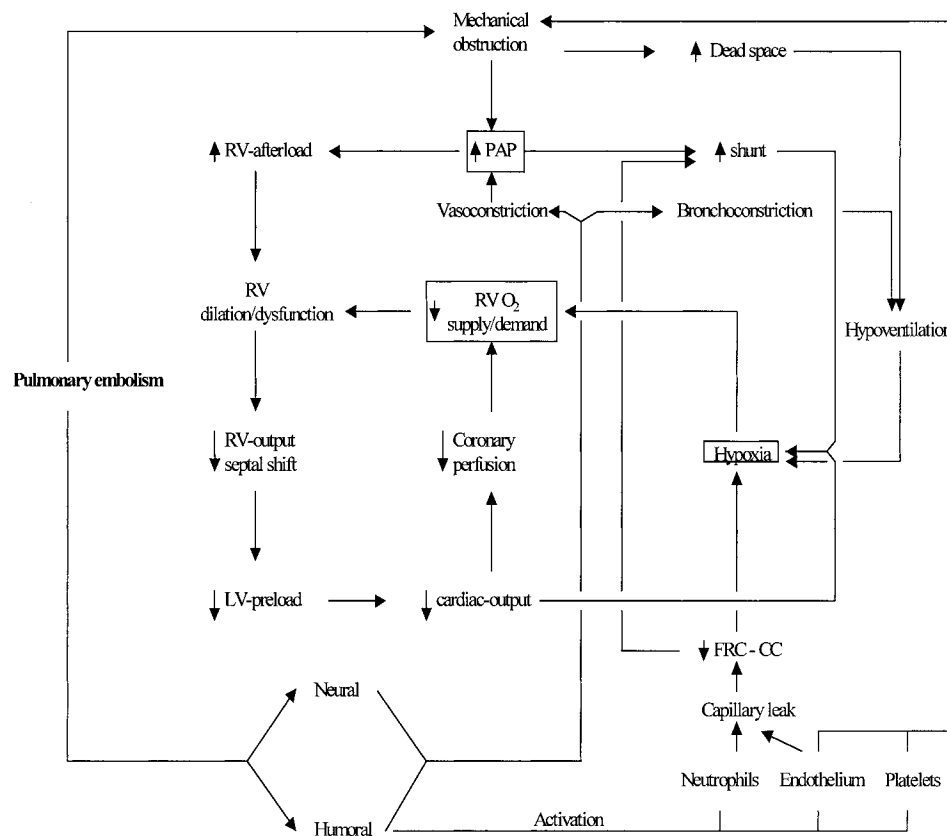


Figure 1. Simplified overview of pathophysiologic events during acute pulmonary thromboembolism (PE). Cardiovascular events culminate in a downward spiral originating from, and culminating in, an unfavorable ratio of right ventricular (RV) oxygen supply and demand. This is augmented by respiratory consequences of the embolism. FRC-CC = functional residual capacity minus closing capacity; LV = left ventricular; RV = right ventricular; PAP = pulmonary artery pressure.

this reflex, but J-receptors, pulmonary irritant receptors, and pulmonary C-fibers may all be involved (17-20). Although mediated by the same cranial nerve, vagally induced changes in lung mechanics after PE, such as rapid, shallow breathing, are dependent on vagally mediated cardiovascular changes (21). Blocking the vagus nerve bilaterally completely abolishes the serotonin-induced Bezold-Jarish reflex but fails to modulate increases in PA and right ventricle (RV) pressures (22). Blocking this nerve also fails to prevent the systemic hemodynamic collapse after experimental thromboembolism or serotonin infusion in cats (10). The theoretical benefit of parasympathectomy on the Bezold-Jarish reflex is offset by the above observations and the fact that the hemodynamic effects of the Bezold-Jarish reflex last for only minutes (22).

General neurogenic pulmonary vasoconstriction also occurs, presumably by effects on sympathetic efferents to both the affected and the nonaffected lung (23,24). There are reports that sympathectomy (stellate ganglion block in humans (6,7,25) and thoracic epidural analgesia in pigs (26)) may have beneficial effects after PE.

Neurohumoral Factors

In the normal PA tree, vascular tone is either absent (23,27) or low (28). Consequently, at rest, the PA is nearly maximally dilated. Noradrenergic vasoconstrictive innervation extends throughout the pulmonary vascular system. However, vasodilating innervation varies with diameter of the pulmonary vessel and is only consistently present in arteries of $>700 \mu\text{m}$ (29). The response to sympathetic stimulation when the intravascular pressures are normal is different from that observed when the intravascular pressures are high. In animals, increased pressure is generally induced by ventilation with 10% O_2 or by IV administration of thromboxane analogs (23). The effect of various sympathomimetics at normal and increased PAP is summarized in Table 1 (30-34). The effect of an 8-Hz electrical stimulation of the stellate ganglia when PAPs are increased is brief vasoconstriction followed by vasodilation (23). Pulmonary venous tone also increases and may contribute to the increase in PVR (28). However, acetylcholine decreases PVR indirectly through release of nitrous oxide (NO) from endothelial cells (35) and by inhibiting norepinephrine release from sympathetic nerve terminals (23) (Table 1).

Table 1. Effects of Some Sympathomimetics and of Acetylcholine on Pulmonary Artery Pressure (PAP) as a Function of Resting PAP

	Normal baseline PAP	Increased baseline PAP
Epinephrine	Constricts	Dilates
Norepinephrine	Constricts	Constricts, dilates (31) ^a
Phenylephrine	Constricts	Constricts (32), dilates (30) ^a
Acetylcholine	Constricts, dilates ^a	Dilates

All listed sympathomimetics are pulmonary vasoconstrictors at normal baseline Pulmonary Artery (PA) pressures, whereas with increased PAPs, only norepinephrine, and possibly phenylephrine, causes further vasoconstriction. These changes occur only in PAs that are actively constricted, as opposed to those in which PAP is increased passively (pulmonary vein constriction) and are qualitatively dose-independent (17). Data are from cats (23), unless specified otherwise. PAPs were increased by infusion of the PG-endoperoxide analogue U46618.

^a“Constricts, Dilates” indicates controversial evidence in the literature. For example, Vlahakes et al (30) showed in an elegant experiment that phenylephrine decreases PAP and improves survival in dogs in extremis after Pulmonary Embolism (PE). A study by Rich et al (32) in humans disputes these findings, but subjects in this study had chronic, not PE-induced, increases in PAPs, which may differ from the vascular reactivity seen after acute PE.

The differential effect of catecholamines at different PAPs is thought to be due to (a) variations in number or sensitivity of adrenoceptors and (b) shape change in smooth muscle cell membrane at increased PAP (23). The effect of acetylcholine on the PA at normal PAP is controversial. There is evidence that it causes pulmonary vasodilation via release of nitric oxide from pulmonary vascular endothelium and inhibition of norepinephrine release from sympathetic nerve terminals (23, 33) and opposing evidence that it causes vasoconstriction via the release of Endothelin and Thromboxane A₂ (34), whereas vasodilation is induced in precontracted pulmonary vessels (23, 34).

Other neurotransmitters are released from nerves innervating pulmonary vessels, but little is known of their role in regulating the tone of these vessels. The neurogenic increase in vasomotor tone with acute PE may be a prerequisite for subsequent augmentation of PVR by humoral factors (27).

Cellular and Humoral Factors

In 1953, Comroe et al. (22) were the first to provide convincing evidence that vasoconstriction of the pulmonary vasculature is responsible for part of the symptoms and signs of acute PE. Some investigators now consider this the pivotal event in PE (36).

Once a thrombus lodges in a PA, there is rapid and complex interaction of cellular and molecular events that cause release of procoagulants and vasoconstrictors plus anticoagulants and vasodilators. It seems likely that the body's ability to balance these opposing responses determines outcome. Table 2 (23,37,38) lists some of the humoral mediators involved in the response to acute PE. This table illustrates that the overall contribution of a mediator to the outcome of acute PE involves more than effects on the smooth muscles of pulmonary vessels. Table 3 shows an example of how certain cell types contribute to the coagulant and vasomotor balance after PE by releasing a variety of mediators. The following section summarizes current

(limited) knowledge about the most important of the cellular and molecular elements involved in the coagulant and vasomotor balance after acute PE.

Platelets

Platelet activation and aggregation are key events of both thrombus formation and vasoconstriction after acute PE. Platelet activity on the surface of an embolus remains increased despite the embolus having been formed at a site remote from the lungs (39). 5-hydroxytryptamine (HT), a powerful constrictor of the pulmonary vasculature (11), is released from the dense granules of activated platelets. 5-HT is removed and metabolized by the lung (40). An acute PE may reduce the functional size of the vascular bed, decrease uptake and metabolism of 5-HT (41), and increase the systemic concentrations of 5-HT (42). The reduced extraction and metabolism of 5-HT makes it difficult to predict how long after a PE that the PAP will be increased in humans. Both mechanical obstruction and pulmonary vasoconstriction are thought to reduce the metabolic capacity of the lung (11,41), which is probably an underappreciated entity in the pathophysiology of PE.

5-HT promotes platelet aggregation and adherence to activated endothelium, thereby increasing the local concentration of 5-HT and platelets (42). Platelets inhibit clot lysis in the lung (43). Because 5-HT also inhibits prostacyclin (PG-I₂) release from pulmonary endothelium, it may initiate and propagate a vicious cycle of increased platelet aggregation, decreased clot lysis, and vasoconstriction in the PA (41).

Thromboxane A₂ (Tx-A₂), another platelet product, causes pulmonary vasoconstriction (11), which contributes to mismatching of ventilation-perfusion. With increasing, PAP shunt vessels are opened (19). This causes hypoxia and further pulmonary vasoconstriction (44). Tx-A₂ also has proaggregatory effects on platelets that contribute to further release of 5-HT from platelets.

Adenosine diphosphate (ADP) is another compound that causes pulmonary vasoconstriction, recruitment of additional platelets, and activation of platelet G-protein, a class of second messengers. G-proteins activate membrane phospholipase, which causes arachidonic acid formation, mainly from phosphatidylcholine (45). Arachidonic acid is the substrate of cyclooxygenase and lipoxygenase, which yield vasoconstrictive prostanoids and leukotrienes, respectively.

Platelet-derived growth factor (PDGF) has several roles. It directly vasoconstricts, activates the release of other vasoconstrictors, and mediates vascular remodeling (46). It also inhibits further platelet activation (47) and aggregation through two or more independent negative-feedback loops (48-50), one of which involves the stimulation of PG-I₂ synthesis by PDGF.

Table 2. Examples of Mediators Affecting the Aggregatory-Pulmonary Vasomotor Balance After Pulmonary Embolism

	Prothrombotic/vasoconstrictive effect	Antithrombotic/vasodilative effect
Serotonin	Vasoconstriction (37)	Production of NO (37)
ADP	Vasoconstriction, platelet recruitment (37)	Production of NO (37)
Thrombin	Vasoconstriction (37) activates platelets (23)	Production of NO (37) and PG-I ₂ (23)
ACh	Vasoconstriction (23)	NO production (37)
Catecholamines	Vasoconstriction at normal PAP (23)	NO production (37), vasodilation at ↑ PAP
Leukotrienes	Vasoconstriction (23)	Production of NO (37)
Bacterial toxins, cytokines	Tissue factor expression (37)	NO production (37)
Shear stress	Endothelial cell damage (37)	Production of NO (37)
ROS	Inhibition of NO production (37)	Vasodilation (23), Production of PG-I ₂ (38)
NO	Inhibition of NO production (37)	Vasodilation, inhibition of platelet- and leukocyte activation (37), ↓ ROS (37), Inhibition of GPIIb/IIIa and several integrins (37), ↓ tissue factor (37)
AT-II	Inhibition of NO production (via ↑ ROS), ↑ ET-1, ↑ catecholamines (37)	Production of NO (37)
ET-1	Vasoconstriction, ↑ coagulability (↑ FVIII, ↓ AT, ↓ tPA) (37)	Release of NO and EDHF (37)
PDGF	Vasoconstriction (37), ↑ platelets (23)	Production of PG-I ₂ (23)
PAF	Vasoconstriction, ↑ platelet- and leukocyte adhesion to endothelium (37)	Production of NO (37)

Many humoral mediators and physical factors have opposing effects on hemostasis as well as vasomotor control. The information contained in the table is not comprehensive.

ACh = acetylcholine; ADP = adenosine diphosphate; AT = antithrombin; AT-II = angiotensin II; EDHF = endothelium-derived hyperpolarizing factor; ET-1 = endothelin-1; FVIII = coagulation factor VIII; GPIIb/IIIa = glycoprotein IIb/IIIa; NO = nitric oxide; PAP = pulmonary artery pressure; PDGF = platelet-derived growth factor; PG-I₂ = prostacyclin; ROS = reactive oxygen species; tPA = tissue plasminogen activator; PAF = platelet activating factor.

Table 3. Factors Produced by Endothelial Cells Affecting the Aggregatory and Vasomotor Balance

	Pro	Anti
Coagulation	von Willebrandt factor Plasminogen activator inhibitor 1 Platelet activating factor Endothelin-1	Nitric oxide Tissue factor pathway inhibitor Heparan sulfate Antithrombin ADPase Thrombomodulin Tissue-plasminogen activator Prostacyclin
Vasoconstriction	Endothelin-1 Angiotensin-II Thromboxane-A ₂ Reactive oxygen species	Nitric oxide Prostacyclin EDHF Adenosine Adrenomedullin (34)

The endothelium has the potential to determine the aggregatory/vasomotor balance after Pulmonary Embolism. The mechanisms involved are incompletely understood. Unless otherwise specified, data are from Blaise (37).

EDHF = endothelium-derived hyperpolarizing factor.

Thrombin

Thrombus formation usually occurs in a systemic vein, often weeks before a PE occurs. Although the clot seems static when it embolizes, thrombin activity within the clot remains increased (51). Thrombin constricts smooth muscle directly (52) and indirectly (11), which is believed to contribute significantly to increased PVR. Additionally thrombin activates phospholipase A₂ and C in endothelial cells and platelets, which produces prostanoids that cause pulmonary

vasoconstriction and neutrophil activation (see below) (53,54). Thrombin also induces neutrophil and platelet aggregation (55). Fresh clot recovered from the PA 30 min after experimental PE was coated with platelets (13). The receptor for thrombin-platelet interaction is known (56) and is likely involved in both coagulation and inflammation (57). This suggests that thrombin receptor blockade may have therapeutic potential.

However, thrombin-induced events can lead to pulmonary vasodilation. Specifically, thrombin releases

PG-I₂ from human endothelial cells (58) and NO from pig PAs. The latter mechanism attenuates the increase in PVR after acute experimental PE (11).

Eicosanoids

Eicosanoids are products of arachidonic acid and are produced by leukocytes, platelets, and endothelial cells in response to a number of clot formation-induced stimuli. The cyclooxygenase pathway yields prostaglandins, including Tx-A₂ and PG-I₂; the lipoxygenase pathway yields leukotrienes. The enzymatic pathway for arachidonic acid metabolism depends on the cell type. Endothelial cells lack the lipoxygenase enzyme, and consequently, they cannot synthesize leukotrienes from arachidonic acid. However, intermediates of the lipoxygenase pathways are readily transferred from circulating leukocytes to endothelial cells, where they can be further metabolized to vasoconstrictors such as leukotriene C₄ (LTC₄) and leukotriene D₄ (LTD₄) (41,59).

Both TxA₂ (PA vasoconstrictor) and PG-I₂ (PA vasodilator) cause further activation, aggregation, and secretion of platelets (37), which seems counterintuitive and is another example of the complexity of the interaction of elements involved in PE and our incomplete understanding thereof.

Leukocytes

There is an impressive interplay between polymorphonuclear leukocytes (PMN), platelets, and endothelial cells that creates multiple positive feedback loops that alter the pathophysiology of pulmonary vasoconstriction after PE. Thrombin and platelet activating factor (PAF) are important activators of PMN (60,61). PAF is produced by both platelets and PMN (51) and activates both platelets and PMN (60). In rats, PAF causes release of endothelin (ET)-1, a strong pulmonary vasoconstrictor, from endothelial cells (62). PAF also inhibits NO production by these cells (62), which contributes to the increase in PAP. Other PMN products that have direct or indirect (11) pulmonary vasoconstrictive effects include Tx-A₂, leukotrienes (LTB₄, LTC₄, LTD₄, and LTE₄), and reactive oxygen species (ROS) (11,63). ROS are thought to be the main cellular mediators of organ damage after ischemia-reperfusion. Although controversial (64,65), both PMN depletion and monoclonal antibodies against PMN adhesion molecules (selectins and integrins) have been shown to prevent reperfusion pulmonary edema after PA occlusion (66,68). Proinflammatory cytokines generated during pulmonary ischemia-reperfusion (69) (e.g., tumor necrosis factor- α or interleukin [IL]-8) are chemotactic and contribute to organ damage after ischemia-reperfusion (69). A monoclonal interleukin-8 antibody injected IV prevented reperfusion lung injury in rabbits (70).

Endothelium

The aggregatory and vasoactive balance after PE depends on endothelial cell well-being. When intact, the endothelium has anticoagulant and vasodilating activities. When disrupted, the endothelium exerts vasoconstrictive and procoagulant effects (71)(Table 3). At least four mechanisms for this endothelial action are recognized: (a) decreased release of antithrombotic molecules, most importantly PG-I₂ and NO (72); (b) decreased interaction of thrombin with thrombomodulin. In intact endothelium, this interaction leads to activation of Protein C and its cofactor Protein S, two vitamin-K dependent, native anticoagulants, both of which are located on the endothelial membrane. This interaction normally inhibits factors VIII (intrinsic pathway of coagulation cascade) and V (activation of prothrombin) (37); (c) heparins on the subendothelial matrix no longer bind effectively to antithrombin; consequently, prothrombin is not inactivated adequately (37); (d) endothelial cells usually release tissue plasminogen activator (tPA) at a constant rate. Endothelial damage decreases the concentration of this fibrinolytic compound (37).

Events occurring during PE that have a disruptive effect on the endothelium include increased PAP (23), high shear stress (37), absence of shear stress (73), hypoxia and ischemia (37), neutrophil activation (74), release of ROS (75), and the toxic effects of fibrin and its degradation products (76) among others. Consequences of endothelial disruption are listed in Table 4 (77). Ultimately, endothelial damage could lead to vasoconstriction and activation of the inflammatory system with further endothelial injury (37).

Interestingly, platelets have been reported to protect against pulmonary endothelial cell injury (78) through effects on hydrophilic platelet-derived factor(s) (78) or the adherence of platelets to endothelial gaps (79). It is unknown whether this occurs in the setting of PE.

Four endothelial-derived mediators contributing to the balance of vasoconstriction and vasodilation have been sufficiently studied in animal models of PE to warrant discussion, namely ET-1, NO, PG-I₂, and adrenomedullin.

The potent pulmonary vasoconstrictor ET-1 plays a crucial role in the vasoconstriction after an acute PE. ET-1 is released by a variety of chemical or physical stimuli present during PE, including norepinephrine, angiotensin II, hypoxia, shear stress, and thrombin (41). The systemic pressor effects of circulating ET are limited by extensive extraction of this compound during transit through the lung and by compensatory release of the endogenous vasodilators PG-I₂ and NO (41). Table 5 (80-87) gives an overview of the effects of stimulation and of antagonism of ET A and B receptors. ET-B receptors are present on pulmonary endothelial cells and are responsible for pulmonary clearance of ET-1 in dogs. In

Table 4. Effects of Endothelial Injury (77)

Impairs G-alpha-i proteins (a subtype of guanine-binding proteins, which leads to the production of NO in endothelial cells)
Decreases release of NO, prostacyclin, and endothelium-derived hyperpolarizing factor
Increases release of endoperoxides
Increases production of reactive oxygen species
Increases generation of endothelin-1
Decreases sensitivity of the vascular smooth muscle to NO, prostacyclin, and endothelium derived hyperpolarizing factor

NO = nitric oxide.

Table 5. Effects of Stimulation and Blockade of Endothelin (ET) Receptors

	ET-A receptor	ET-B receptor
Stimulation	Increased PVR (80, 82)	Increased PVR (82), decreased PVR during hypoxia (83), decreased PVR via NO-production (84), decreased SVR (85), vasoconstriction (pig skin) (86), decreases PVR in pulmonary hypertension (87)
Blockade	Decreased PVR (82, 87), decreased TXA ₂ and PGI ₂ (82)	Increased PVR (82, 87), decreased PGI ₂ /TXA ₂ -ratio (82), no effect (81)

PVR = pulmonary vascular resistance; TXA₂ = thromboxane A₂; PGI₂ = prostacyclin; NO = nitric oxide; SVR = systemic vascular resistance.
Note: some studies showed contradictory effects of the same intervention.

patients, abnormal ET-1 metabolism increases serum concentrations of this peptide after PE (80). There is a positive feedback mechanism between ET-1 and Tx-A₂ production. ET-1 activates the cyclooxygenase pathway, which enhances Tx-A₂ formation (80). As expected, cyclooxygenase inhibition decreases PVR after ET-A or ET-B receptor stimulation (11). Additionally, ET-1 exerts vasoconstrictive effects that are independent of its effects on Tx-A₂ formation (88). The precursor of ET-1, big ET, is released from the lungs after PE and causes coronary arterial vasoconstriction (89), which could aggravate the cardiodepression associated with acute PE. ET-1 also creates a prothrombotic and an antifibrinolytic environment through increase of factor VIII activity, decrease of antithrombin activity, and suppression of the release of tPA (37).

Of the many vasodilating and antithrombotic mediators released by healthy endothelium, PG-I₂ and NO are the most important (90-92). As well as dilating the PA, NO inhibits platelet adhesion and aggregation. Both occur via activation of the soluble guanylate cyclase in the platelet and vascular smooth muscle cytosol, which increases cyclic guanosine monophosphate concentrations (93). When these concentrations increase, the intracellular calcium ion concentration decreases. This causes vasorelaxation and inhibits fibrinogen binding to the glycoprotein IIb/IIIa receptor on the surface of the platelet membrane, which is required for platelet aggregation (93). Various vasoconstrictors released in the presence of a PE stimulate NO release by the pulmonary endothelium, including bradykinin, serotonin, adenosine, ADP, histamine, and thrombin (94). Others, including hypoxia (90) and ROS (11), inhibit NO release. Although the exact role

of NO in acute PE remains elusive, it is likely a key compound in the balance between vasodilation and vasoconstriction, as suggested by a case of successful treatment of cardiac arrest from acute PE by administration of inhaled NO (9).

Like NO, PG-I₂ is a potent pulmonary vasodilator and an inhibitor of platelet aggregation and activation (57,92,95). Unlike NO, PG-I₂ exerts its effects by increasing the intracellular cyclic adenosine monophosphate concentration. The half-life of PG-I₂ in blood is <5 min (96). A multicenter, randomized, controlled trial revealed that treatment with PG-I₂ increased survival of patients with primary pulmonary hypertension (PPH) (97), and this led the Food and Drug Administration (FDA) to approve IV PG-I₂ for the treatment of PPH. Analogues of PG-I₂ have been inhaled to treat PPH long term (98). A variety of substances released in response to PE cause the endothelium to release PG-I₂, including thrombin (11), arachidonic acid (99), and H₂O₂ (38). PG-I₂ decreases systemic 5-HT concentrations (42) and may also be a positive inotrope (100).

Adrenomedullin has limited structural homology with calcitonin gene-related peptide and amylin (101). This compound (adrenomedullin) is synthesized by both endothelial cells (102) and vascular smooth muscle cells (103). The principal physiologic action of adrenomedullin seems to be potent pulmonary vasodilation (104,105). Adrenomedullin is cleared by the lungs faster than it is produced (41). Systemic concentrations of adrenomedullin correlate positively with PAP and PVR (104,106), which may indicate a regulatory role for this compound. Adrenomedullin also has an antiapoptotic effect on endothelial cells (107). The

exact role of the above compounds in acute PE is undefined.

Ischemia Reperfusion

Whereas luxuriously perfused by a dual circulation under normal circumstances, pulmonary endothelial cells may suffer ischemia as a consequence of the hemodynamic (hypotension) and respiratory (hypoxia) perturbations associated with PE. When excluded from the pulmonary circulation, endothelial cells rapidly respond to the resultant loss of shear stress by almost instantaneous generation of ROS (73). Within seconds of ischemia commencing, endothelial nicotinamide-adenine-dinucleotide phosphate oxidase is activated, and superoxide anions are generated at the extracellular surface of the cell membrane (73). Approximately 15 s after the onset of ischemia, the intracellular Ca^{2+} concentrations increase because of release of Ca^{2+} from intracellular stores and by Ca^{2+} influx (73). This converts the enzyme xanthine dehydrogenase to xanthine oxidase, producing ROS upon reperfusion (108). After approximately 45 s of ischemia, increased NO generation is detected. This has been interpreted as an attempt by endothelial cells to restore blood flow to the ischemic area (73). However, vasodilation may not necessarily prevail. When previously ischemic areas are reperfused, ROS are produced predominantly by nicotinamide-adenine-dinucleotide phosphate-oxidase (109) and, to a lesser degree, by xanthine oxidase (110) (Fig. 2). The two most important mechanisms by which ROS are thought to contribute to pulmonary vasoconstriction are inhibition of NO release and endothelial damage (111). Nevertheless, the results of animal studies on the effect of ROS on pulmonary vascular tone are confusing and controversial. Both pulmonary vasodilation (81) and vasoconstriction have been reported in pigs (63). Infusion of superoxide dismutase into sheep after a PE (thrombin induced) attenuated the increase in PVR independently of Tx-A_2 effects (11). Allopurinol, a xanthine oxidase inhibitor, attenuates the increase in vascular permeability associated with ischemia-reperfusion of the PA in rabbits (112). Inhaled NO prevented ischemia-reperfusion-related hypoxemia in patients after lung transplantation (113).

Hypoxia

Many of the classical pathophysiologic events after PE have their origin in hypoxia or culminate in hypoxia. The mechanisms by which hypoxia develops after PE include formation of very low and very high ventilation-perfusion units as a result of vascular obstruction and vasoconstriction, intracardiac shunting through a patent foramen ovale, intrapulmonary shunts secondary to atelectatic areas of lung, respiratory failure caused by increased work of breathing that is related to bronchoconstriction and to a decrease in lung compliance (edema,

lung infarcts, and loss of surfactant), and decrease in cardiac output that results in decreased mixed venous oxygen saturation (16). There are links between the above-described molecular pathophysiology and hypoxia. For instance, after hypoxia, ET-1 is released (27), voltage-sensitive K^+ channels are inactivated (27), and 5-HT is released from pulmonary neuroendocrine cells (27), all of which can contribute to hypoxic pulmonary vasoconstriction. As described above, hypoxia causes both generation of ROS and endothelial damage, which cause pulmonary vasoconstriction. Interestingly, hypoxic monocytes express tissue factor and plasminogen-activator-inhibitor-1, whereas tPA and urokinase are down regulated (114). This indicates that hypoxia itself can cause both pulmonary vasoconstriction and a prothrombotic and antifibrinolytic state.

Intrinsic Fibrinolysis

In well controlled experiments, roughly 50% of a PE clot dissolved in nonheparinized dogs after 3 h, and 70% dissolved after 6 h (13). If these data are applicable to humans, which may or may not be the case, it is difficult to understand why clot dissolution for brief periods of time does not recanalize the pulmonary vasculature sufficiently to reduce the increased PVR present after a PE. One explanation for this discrepancy might be that the clot causes an insult (e.g., RV infarction) that is not improved by recanalization of the PA. Another explanation may be that emboli that cause a PE in humans might not be fresh, unlike those in the animal study (13). Aging of thrombi before their embolization increases the time required for resolution of the clot (13). Angiographic studies in humans show incomplete clot resolution weeks after the PE occurred (115). Another explanation might be that as pulmonary vasoconstriction occurs, a greater degree of clot resolution would have to occur for adequate recanalization. Finally, despite avid clot resolution, fibrin formation persists on the clot surface at 12 h (13). Unless anticoagulation is effective, re-thrombosis of the PA may occur (11).

Therapeutic Options

Successful therapy for acute PE restores the ratio of RV O_2 supply and demand to normal or near normal. Figure 1 illustrates the pivotal position of RV- O_2 supply and demand, given that many events during acute PE reduce the RV- O_2 supply:demand ratio. Most importantly, RV pressure overload increases both RV size and pressure, which increases RV wall stress and O_2 consumption. It also decreases right coronary perfusion pressure. If ischemia develops, RV output decreases, culminating in RV failure and death (Fig. 1). Thus, the need to increase right coronary artery perfusion pressure is paramount. In a comprehensive review, Layish and Tapson (116) recommended the

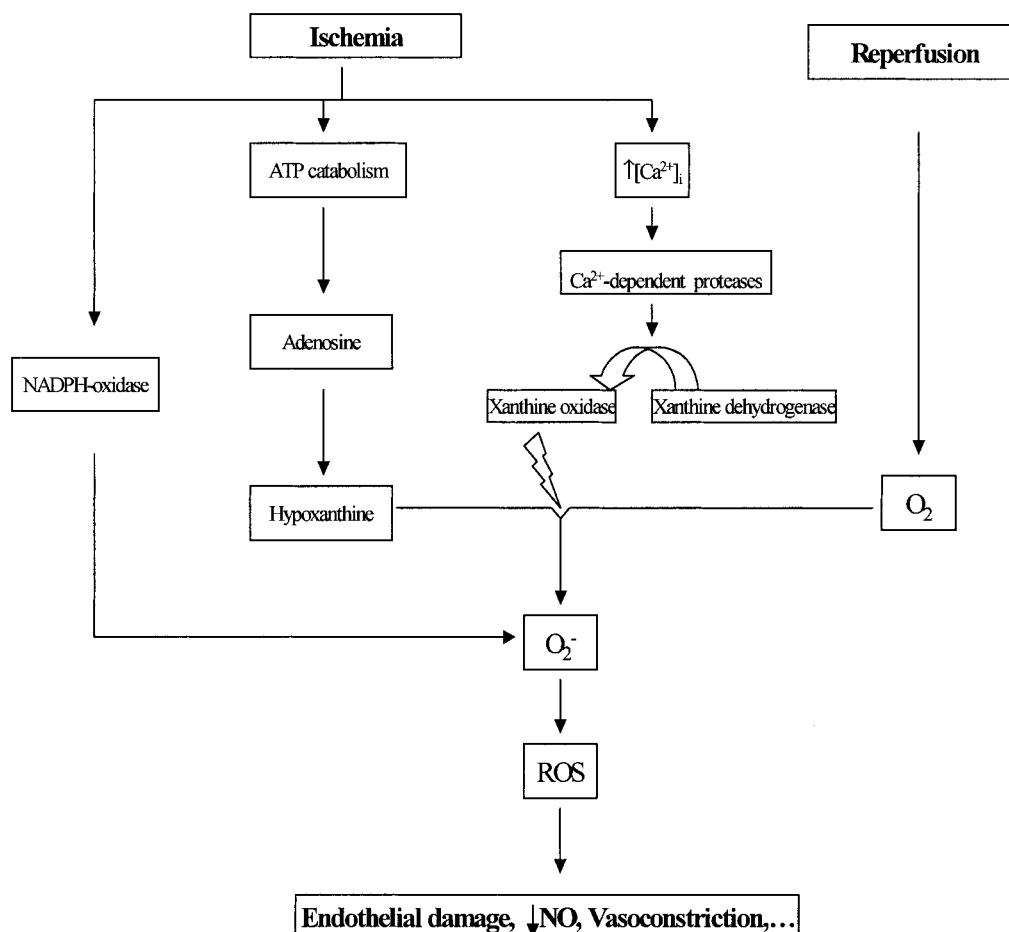


Figure 2. Reactive oxygen species are generated both during ischemia (nicotinamide-adenine-dinucleotide phosphate [NADPH]-oxidase) and upon reperfusion (Xanthine-oxidase, NADH-oxidase). Quantitatively the NAD(P)H-oxidase seems to be the more important mechanism (96).

use of catecholamines in hemodynamically unstable patients except for isoproterenol, which decreases PVR and increases cardiac output, whereas decreasing systemic blood pressure and coronary perfusion pressure. The net result is a worse outcome (23). The recommendation to administer catecholamines seems justified for several reasons: (a) when PAP are increased, all catecholamines except norepinephrine decrease PVR (Table 1) (23,31); (b) norepinephrine improves circulation after PE despite its effects on PVR (116,117); and (c) in models of RV failure with constant RV afterload, phenylephrine reverses the RV failure by increasing right coronary artery perfusion pressure (30).

Additional goals of therapy include minimizing hypoxia, maintaining RV preload and stroke volume, and maintaining left ventricular (LV) preload, LV stroke volume, and systemic perfusion, all of which would increase mixed venous oxygen saturation. This would reverse the pathophysiologic downward spiral but can be quite challenging to accomplish. It seems reasonable to increase the fraction of inspired oxygen (FIO₂), and to attempt to improve the matching of

ventilation and perfusion (inhaled vasodilators) (8,9,118-121) and to increase cardiac output if the shunt fraction is fixed (inotropes) (8,30,116), whereas decreasing PVR without reducing systemic perfusion pressure. The latter would be an ideal scenario but is very difficult to achieve unless pulmonary recanalization or selective pulmonary vasodilation can be accomplished. All three major pathophysiologic derangements of acutely increased PVR, (mechanical obstruction, neurogenic, and humoral vasoconstriction) are amenable to treatment. Mechanical obstruction is relieved by thrombolysis and anticoagulation (reviewed in detail elsewhere (122,123)) embolectomy or catheter extraction-fragmentation (2).

Embolectomy

Before cardiopulmonary bypass and deep hypothermic circulatory arrest became available, surgical embolectomy was considered a last-ditch effort because of the associated frequent perioperative mortality. Even today, patients are usually not considered candidates for embolectomy until they are *in extremis*.

Because circulatory shock and cardiac arrest increase perioperative mortality (124-126), it is not surprising that mortality associated with pulmonary embolectomy is still 16%-46% (126,127). However, survivors usually recover to a New York Heart Association Class 1 or 2 functional status (124,125). Thrombolysis does not seem to increase the risk of surgery (125). Embolectomy is usually an emergency procedure and presents a challenge to all team members involved. Anesthetic goals include preserving the RV-O₂ supply:demand ratio by optimizing ventilation, fluid management, and inotropic support. Transesophageal echocardiography (TEE) should be used to guide fluid and inotropic therapy because TEE allows visual estimation of RV function and estimation of PAP. Catheter embolectomy-fragmentation is an alternative to surgery that usually leads to at least partial recanalization of the PA. However, the associated mortality is comparable to that associated with surgery (128). Another interesting alternative to surgery is pharmacomechanical thrombolysis by intraembolic infusion of small-dose thrombolytics and fragmentation of the clot with a catheter or rotational device (129). Regardless of the approach, insertion of an inferior vena cava filter should be considered to prevent further embolization because recurrent PE and the associated mortality are frequent (128). Just as mechanical obstruction alone does not account for all the negative effects of a PE, treating the mechanical obstruction alone may not ensure a good outcome (8).

Appreciation of the importance of PA vasoconstriction as a consequence of PE is relatively new and so are the therapeutic approaches. One clinical scenario in which one of the novel therapeutic strategies may be applied is a patient with acute (<2 h) PE who is either not responding to or has a contraindication to one of the established treatment regimens. For example, decreasing systemic pressure and increasing PAP (8) or frank cardiac arrest (9), despite maximal conventional therapy, has prompted clinicians to successfully consider the use of currently not established therapies to try to reduce PA vasoconstriction. Only four alternative therapies have reportedly been tested or tried for the treatment of acute PE: Aspirin, inhaled NO, inhaled PG-I₂, and stellate ganglion blockade.

Antiplatelet Strategies

Platelets are a key element in the development of pulmonary vasoconstriction. Antagonizing platelet activity attenuates the acute increase in PVR and the degree of hypoxia associated with acute PE (130). Potential targets for antiplatelet strategies are some of the agonists involved in platelet activation, including thrombin, ADP, Tx-A₂, 5-HT, norepinephrine, and epinephrine (131).

Aspirin is a potent inhibitor of Tx-A₂-induced platelet aggregation but a very weak inhibitor of platelet aggregation induced by other agonists, such as ADP and thrombin. Aspirin does not prevent α granule release in response to a strong platelet agonist nor does aspirin inhibit shear-induced platelet aggregation (132). The PE prevention trial (133) was a large prospective trial (>13,000 patients) that sought to determine if small-dose aspirin prevented deaths from PE. The results were intriguing but controversial because of methodological problems, such as new sample size calculation, subgroup analysis, and *post hoc* analysis of selected end-points. It was also concluded that aspirin offered no additional benefit over low-molecular-weight heparin administration alone. Consequently, the use of aspirin in high-risk patients cannot be recommended at the present time.

NCX 4016, a NO-releasing aspirin, had a more pronounced antithrombotic activity than aspirin in two different animal species, largely because of multiple inhibitory effect on platelets, including inhibition of Tx-A₂ release and liberation of NO (134). Its antithrombotic activity takes 5 to 6 days to fully develop, but a vasodilating action is observed *in vitro* 1 min after administration of the drug, and the effect lasts for 30 min (135). Other potentially beneficial effects of NCX 4016, possibly related to NO-release, include inhibition of cytokine release, inhibition of transcription factors (nuclear factor κ B), reduced expression of adhesion molecules (GP IIb/IIIa, selectins), and inhibition of lymphocyte activation (135). NCX 4016 has not been tested in the setting of PE.

Other antiplatelet drugs target the low affinity ADP receptor (ticlopidine and clopidogrel) and the GP IIb/IIIa receptor of platelets (abciximab, eptifibatide, and the "fibans" [tirofiban, sirafiban, orbofiban, and lami-fiban]). Eptifibatide and abciximab may also inhibit thrombin generation (136). These drugs also have not been tested for the treatment of acute PE.

Triflavin, a polypeptide purified from snake venom, belongs to a family of Arg-Gly-Asp-(RGD)-containing peptides termed disintegrins. In one study (137), both the release of 5-HT and the formation of Tx-A₂ from aggregating platelets in the aorta were significantly inhibited by triflavin. Triflavin markedly reduced the adhesion of platelets to the subendothelium of the aorta *in vitro*. Again, this drug has not been used or tested in acute PE.

Heparin and low molecular weight heparin inhibit thrombin and factor Xa. This decreases platelet activation by thrombin, which in turn reduces the release of platelet-derived mediators. Reduced release of platelet-derived mediators, plus prevention of clot propagation, may be important reasons why heparin is well established in the treatment of PE (122).

Inhaled Vasodilators

Theoretically, an inhaled vasodilator will improve ventilation-perfusion matching by dilating only those arterioles that are adjacent to ventilated alveoli. The main concern when using vasodilator therapy is the potential for decreasing systemic perfusion pressure and aggravating RV dysfunction. The ideal vasodilator would be specific for the pulmonary circulation. At least two inhaled drugs meet this criterion and have potential in the treatment of acute PE.

The first such drug, inhaled NO, is probably beneficial in the treatment of acute PE. It selectively reduces PAP, improves gas exchange by better matching ventilation and perfusion, and by its antiplatelet effects (118). Several case reports describing the beneficial effects of inhaled NO for the treatment of acute PE have been published (8,9,119,120), but there has been no systematic collection of outcome data at present. Consequently, the use of NO in acute PE still must be viewed with the same caution that any promising but experimental therapy deserves. Risks and side effects of this therapy have been reviewed in detail elsewhere (138,139).

The second such drug, inhaled PG-I₂, reduces PAP and PVR but allows return of hemodynamic variables to pretreatment levels soon after the drug is discontinued (121). Although still investigational, it seems that the role for inhaled PG-I₂ (30–50 ng · kg⁻¹ · min⁻¹) for the treatment of acute PE might be similar to that of inhaled NO (121). Experience with this drug in the setting of acute PE is limited (5).

Receptor Antagonism

The central role of thrombin in thromboembolism and the recent discovery of the thrombin-receptor open up new possibilities for the prevention and treatment of many diseases, including PE. A report of a thrombin receptor gene knockout-mouse suggests that blockade of both subtypes of thrombin receptors on human platelets should protect from thrombosis and from PE (140). Mice devoid of the thrombin receptor do not bleed spontaneously (141). Giving birth to their offspring is not associated with excessive hemorrhage in these animals. In monkeys, administration of a thrombin receptor antagonist prevented arterial thrombosis without altering hemostatic variables (activated partial thromboplastin time and bleeding time) (142). The role of these compounds in the prevention and treatment of PE is still to be determined.

Tx-A₂ receptor antagonism is reported to decrease the increase in PAP that occurs in response to PA stimulation with Tx agonists, but there is no effect on the increase in PAP associated with administration of 5-HT, norepinephrine, and other pulmonary vasoconstrictors (141). Tx-A₂ receptor blockade was less effective than inhibiting Tx-A₂ production (aspirin and

nonsteroidal antiinflammatory drugs) (143). Ridogrel blocks both the production of Tx-A₂ and its receptor and has some promise for the treatment of acute myocardial infarction. Currently, there is no role for Tx-A₂ receptor antagonism in acute PE.

5-HT receptor antagonism could be another logical strategy. 5-HT stimulates 17 different receptors (27). Ketanserin inhibits the 5-HT_{-2A} receptor, which attenuates hypoxia and pulmonary hypertension in dogs before (144) and after (145) PE. In humans, the 5-HT_{1D/B} receptor is believed to mediate pulmonary vasoconstriction, whereas in the rat, the 5-HT_{-2A} receptor serves this function (27). In the absence of baseline vascular tone, the 5-HT_{-2A} receptor mediates pulmonary vasoconstriction in humans. When PA-tone in humans is increased, the 5-HT_{1D/B} receptor is thought to mediate vasoconstriction (27). The administration of ketanserin to patients with mild symptoms from small PE caused only a minor improvement of hemodynamic variables and gas exchange. Whether this disappointing response was caused by specificity of the drug for the wrong receptor or suboptimal patient selection is unknown. Interestingly, ketanserin increased mixed venous oxygen tension without altering cardiac index. Of all the etiologies that contribute to hypoxia after PE, mixed venous desaturation is considered to be one of the two most important factors by some authors (1). This could explain the improvements in gas exchange seen in that study (146). The understanding of 5-HT receptors and their role in acute PE is evolving, and more effective 5-HT receptor antagonists can be expected to emerge, but there are none currently.

Sympathectomy

It has been postulated that an acute PE stimulates a sympathetically mediated pulmonary vascular reflex (29). PAs at rest have a very low baseline tone. For humoral mediators to cause pulmonary vasoconstriction, an initial increase in baseline tone is required (27). The sympathetic nervous system may be responsible for this initial increase in tone in small, muscular PAs. Why sympathectomy has been successful in humans (6,7) and in animals (26) for the treatment of PE cannot be satisfactorily explained by the above concept, given that it would require a prophylactic sympathectomy to protect against PE, is still unknown. Since the initial treatment of severe PE often involves thrombolysis or anticoagulation, the use of a thoracic epidural catheter to produce a sympathectomy would be unwise because of the potential for an epidural hematoma. Instead, a stellate ganglion block is probably more appropriate. This block has been used sporadically in patients in extremis after a massive PE and has provided rapid, dramatic improvement of symptoms (6,7). Relief of bilateral chest pain, decrease of the

respiratory rate from 40 to 18 per min, relief of dyspnea and orthopnea, reversal of cyanosis, and of circulatory shock occurred within minutes. This interesting therapeutic modality deserves further study.

Summary

Events during acute PE are complicated and difficult to distinguish from one another. A comprehensive understanding of PE in humans remains elusive, which is in part because of the inability to prospectively study early events in humans. *In vitro* work and animal models of experimental PE have contributed significantly to recent advances in our understanding the pathophysiology of this disease. Promising therapeutic strategies are on the horizon, but are difficult to test systematically in these critically ill patients. Acute PE remains the paragon of a disease for which prevention is infinitely better than treatment.

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Erratum

In the April 2003 supplement of abstracts presented at the 25th Annual Meeting of the Society of Cardiovascular Anesthesiologists held in Miami Beach, Florida, April 26-30, 2003, please note that in abstract SCA122, the order of authors was incorrect. The corrected order is: Jungwirth B, Eckel B, Kochs EF, Blobner M, Mackensen GB. Please contact the SCA headquarters office for the corrected abstract.