CHEST

Management Strategies for Acute Pulmonary Embolism in the ICU

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TOPIC IMPORTANCE: Acute pulmonary embolism (PE) is a common disease encountered by pulmonologists, cardiologists, and critical care physicians throughout the world. For patients with high-risk acute PE (defined by systemic hypotension) and intermediate high-risk acute PE (defined by the absence of systemic hypotension, but the presence of numerous other concerning clinical and imaging features), intensive care often is necessary. Initial management strategies should focus on optimization of right ventricle (RV) function while decisions about advanced interventions are being considered.

REVIEW FINDINGS: We reviewed the existing literature of various vasoactive agents, IV fluids and diuretics, and pulmonary vasodilators in both animal models and human trials of acute PE. We also reviewed the potential complications of endotracheal intubation and positive pressure ventilation in acute PE. Finally, we reviewed the data of venoarterial extracorporeal membrane oxygenation use in acute PE. The above interventions are discussed in the context of the underlying pathophysiologic features of acute RV failure in acute PE with corresponding illustrations.

SUMMARY: Norepinephrine is a reasonable first choice for hemodynamic support with vasopressin as an adjunct. IV loop diuretics may be useful if evidence of RV dysfunction or volume overload is present. Fluids should be given only if concern exists for hypovolemia and absence of RV dilatation. Supplemental oxygen administration should be considered even without hypoxemia. Positive pressure ventilation should be avoided if possible. Venoarterial extracorporeal membrane oxygenation cannulation should be implemented early if ongoing deterioration occurs despite these interventions. CHEST 2024; 166(6):1532-1545

KEY WORDS: acute pulmonary embolism; obstructive shock; pulmonary embolism; pulmonary vascular disease; right ventricular failure; thromboembolic disease

Acute pulmonary embolism (PE) remains a serious and potentially life-threatening condition that has seen several advances in management, including the advent of surgical embolectomy, suction embolectomy catheters, catheter-directed fibrinolytics, and lower doses of fibrinolytics, all of which have improved options for the management of high-risk and intermediate-risk acute PE. Many of these advanced therapies are implemented after a multidisciplinary discussion among numerous subspecialists,

ABBREVIATIONS: CO = cardiac output; ECMO = extracorporeal membrane oxygenation; iNO = inhaled nitric oxide; IVF = IV fluid; LV = left ventricle; MAP = mean arterial pressure; PA = pulmonary artery; PE = pulmonary embolism; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RV = right ventricle; RVEDVI = right ventricular end diastolic volume index; RVSV = right ventricular stroke volume; SV = stroke volume

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and we believe that this collaborative process is at the crux of high-quality acute PE care. However, although these multidisciplinary conversations are ongoing and interventional suites are prepared for the patient, basic knowledge of the supportive care for acute PE remains mandatory. This review focuses on the central elements of care for all patients with high-risk and intermediate-risk acute PE, namely, fluid management, diuretics, vasopressor choices, mechanical ventilation, and extracorporeal life support.

Literature Search

Search Strategy and Methodology

The authors initially used Table 1 from the 1997 review by Layish and Tapson[1] to identify early articles about hemodynamic support with vasopressors in acute PE. We then searched each of those articles in PubMed and reviewed them for inclusion in our article. We also referenced the Similar Articles and Cited By sections of those article's abstracts on PubMed to identify additional references for inclusion. After this, we performed a general search strategy on PubMed using the terms *pulmonary embolism* and *vasopressor*. We filtered these results by original research articles to find informative studies (animal or human) that we missed with the initial search strategy. We also ran a second filter for *review article* to ensure no similar review articles were in the recent published literature.

Next, we reviewed the references section of a trial by Lim et al[21] to identify primary literature about IV fluids (IVFs) and IV diuretics in acute PE. We used a similar strategy as described previously to identify additional references for inclusion. After this, we performed a general search strategy on PubMed using the terms *pulmonary embolism* and *diuretic* or *pulmonary embolism* and *intravenous fluid* or a combination of all three. We ran similar filters as described previously.

All search strategies limited articles to those published in English. Any meta-analyses, systematic reviews, or narrative reviews were selected preferentially. These then were followed by randomized controlled trials, prospective studies in humans, retrospective studies in humans, prospective research in animal models, case series, and finally case reports. Our primary focus was on articles in the pulmonary, cardiology, and critical care literature; however, we did not filter for these specifically.

Evidence Review

Right Ventricle Pathophysiologic Features in Acute PE

The pulmonary circulation in health is a low-pressure and low-resistance circuit that is able to accommodate the same cardiac output (CO) as the systemic circulation at pressures that typically are less than one-fifth of the systemic circulation with a pulmonary vascular resistance (PVR) that is about one-eighth the systemic vascular resistance.[22] The healthy, thin-walled right ventricle (RV), with its typical crescent-shaped cavity, is adapted to this low-pressure pulmonary circulation. The RV is especially susceptible to failure in response to increases in vascular resistance, as is seen with acute PE. Although the left ventricle (LV) can maintain a normal stroke volume (SV) across a wide range of systemic resistances, the right ventricular SV (RVSV) precipitously declines in response to small changes in RV afterload (as determined by PVR, pulmonary arterial compliance, and impedance). The RV must increase its contractility to compensate for this increased afterload to maintain proper coupling between the RV and the pulmonary arteries (PAs).[23,24]

It is also important to note that both the RV and LV occupy the same pericardial space. The pericardium is fibrous and does not readily accommodate acute changes in RV size in response to increased afterload. The net result is ventricular interdependence such that elevated RV pressure causes the interventricular septum to bow into the LV. In the absence of right to left shunt, the LV inflow is the same as the RVSV and the RVSV is inversely related to the PVR.[25]

Ultimately, a failing RV leads to impaired LV filling by reduced RVSV, septal bowing, and increased pericardial pressure from the enlarging right heart (Fig 1). Furthermore, as the right atrial pressure increases, coronary venous congestion worsens LV diastolic function and further impairs LV filling.[26] The RV and LV also share the same interventricular septum, and the contraction of this septum accounts for approximately 20% of the LV ejection fraction.[27] Thus, the failing RV leads to LV failure, which ultimately culminates in reduced systemic BP.

The decrease in mean arterial pressure (MAP) worsens the downward spiral of right-sided heart failure. The key

TABLE 1] Summary of Studies of Vasoactive Agents in Acute Pulmonary Embolism Sorted by Intervention and Then Comparator

Study	Model	Intervention	Comparator	Study Type	No.	Outcome
Schultz et al[2]	Porcine	Terlipressin	Control	Comparative	12	Terlipressin increased MAP and SVR and decreased mPAP and PVR, but decreased CO and increased serum lactate. Ex vivo terlipressin constricted mesenteric arteries and relaxed the PA.
Yu et al[3]	Leporine	Sodium nitroprusside	IVF	Comparative	20	Sodium nitroprusside reversed shock in 80% of rabbits compared with 0% receiving IVF. The mPAP and MAP also improved with sodium nitroprusside.
Dias-Junior et al[4]	Canine	Sodium nitrite	IVF	Comparative	26	Sodium nitrite increased cardiac index while reducing PVRI and SVRI compared with IVF. In nonacute PE, sodium nitrite decreased MAP and cardiac index.
Vlahakes et al[5]	Canine	Phenylephrine	None	Comparative	18	Phenylephrine increased CO, SV, systolic BP, and RV coronary driving pressure.
Wang et al[6]	Leporine	Phentolamine	IVF	Comparative	24	Phentolamine bolus improved MAP, mPAP, and survival compared with IVF. Phentolamine also decreased α-adrenergic receptor expression.
Hirsch et al[7]	Canine	Norepinephrine	Phenylephrine	Comparative	12	Norepinephrine improved RV blood flow, RV oxygen consumption, RV contractility, PVR, and CO when compared with phenylephrine.
Angle et al[8]	Canine	Norepinephrine	None	Exploratory	8	Norepinephrine infusion increased SV and CO without increasing PVR or sacrificing renal blood flow.
Rosenberg et al[9]	Canine	Norepinephrine	Isoproterenol	Comparative	29	Norepinephrine improved MAP, SVR, mPAP, and CO without improving survival. Isoproterenol increased mortality.
Molloy et al[10]	Canine	Norepinephrine	Isoproterenol	Comparative	6	Isoproterenol improved CO and RVSV and reduced PVR compared with norepinephrine.
Ducas et al[11]	Canine	Norepinephrine	Isoproterenol	Comparative	18	Norepinephrine infusion increased CO and systolic BP without affecting PVR, whereas isoproterenol increased CO and decreased PVR.
Ghignone et al[12]	Canine	Norepinephrine	IVF	Comparative	8	IVF decreased SV and MAP in the setting of increased RVEDP. Norepinephrine decreased RVEDP while increasing SV.
Lyhne et al[13]	Porcine	Milrinone, levosimendan, dobutamine	Milrinone, levosimendan, dobutamine	Randomized comparative	18	Milrinone and levosimendan increased CO, decreased PVR, decreased mPAP, and improved RV PA coupling. Dobutamine increased RVSW and RVESP.
Tanaka et al[14]	Human	Milrinone, dopamine, dobutamine	IVF	Comparative	24	Milrinone infusion decreased mPAP more than dobutamine, dopamine, or IVF. Milrinone also led to increased CO without decreased MAP or SVR.

(Continued)

TABLE 1] *(Continued)*

Study	Model	Intervention	Comparator	Study Type	No.	Outcome
Kerbaul et al[15]	Porcine	Levosimendan	IVF	Comparative	14	RV PA coupling and RV contractility were increased with levosimendan, whereas PA elastance, PA impedance, and RV afterload were decreased.
Boulain et al[16]	Human	Epinephrine	None	Case report	1	Epinephrine resolved shock in a patient with acute PE for whom IVF, norepinephrine, dobutamine, and systemic fibrinolytics failed.
Ducas et al[17]	Canine	Dopamine	Dobutamine	Comparative	24	Dopamine and dobutamine both increased HR, MAP, and CO while decreasing PVR without affecting the pulmonary pressure-flow relationship.
Jardin et al[18]	Human	Dobutamine	None	Exploratory	10	Dobutamine increased cardiac index and SV and decreased PVR.
Pagnamenta et al[19]	Canine	Dobutamine	None	Exploratory	10	Dobutamine infusion had no flow-independent effects on the PA, and only at high doses (20 μm/kg/min) resulted in a decrease in the mPAP.
Wolfe et al[20]	Canine	Amrinone	None	Exploratory	10	Amrinone bolus followed by an infusion increased MAP and CO while decreasing mPAP.

CO = cardiac output; HR = heart rate; IVF = IV fluids; MAP = mean arterial pressure; mPAP = mean pulmonary artery pressure; PA = pulmonary artery; PE = pulmonary embolism; PVR = pulmonary vascular resistance; PVRI = pulmonary vascular resistance index; RV = right ventricle; RVEDP = right ventricular end diastolic pressure; RVESP = right ventricular end systolic pressure; RVSV = right ventricular stroke volume; RVSW = right ventricular stroke work; SV = stroke volume; SVR = systemic vascular resistance; SVRI = systemic vascular resistance index.

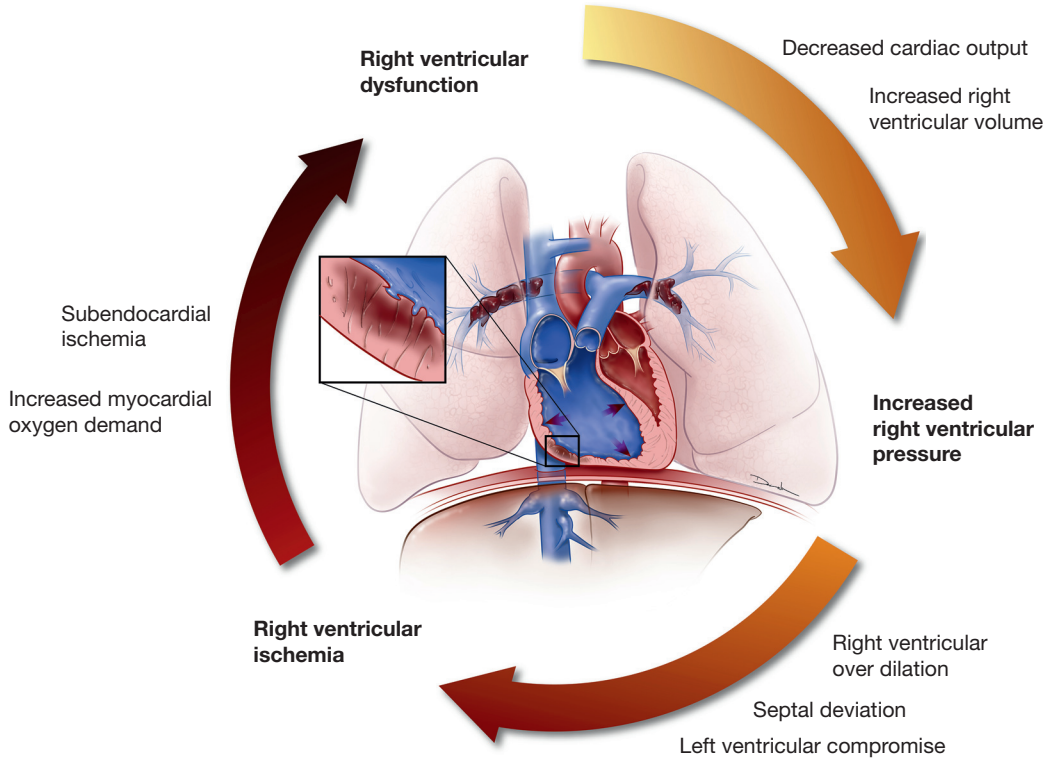

Figure 1 – *Diagram showing the cyclical mechanisms that drive right ventricular failure in acute pulmonary embolism. The terms that appear in boldface are the primary physiologic processes that define right ventricular failure, whereas the terms that do not appear in boldface are the underlying pathophysiologic processes that result in the bolded terms. This process is often referred to as the right ventricular death spiral, although it is notable that left ventricular function also is compromised in this model.*

to understanding RV physiologic features in acute PE is the equation:

RV diastolic coronary perfusion pressure = (diastolic arterial pressure) – (RV end diastolic pressure).

As the MAP is reduced because of the drop in CO and the RV end diastolic pressure increases because of increases in the RV volume, the net result is impaired RV coronary perfusion. As opposed to the left coronary artery, the right coronary artery is perfused in both systole and diastole; the high RV pressure in systole also impairs perfusion. This decrease in right coronary perfusion happens at the most inopportune time when the oxygen demand of the failing RV is increased. This imbalance between RV oxygen demand and oxygen delivery to the RV during its time of need leads to subendomyocardial ischemia, which worsens RV performance further. In addition to the mechanical obstruction of the pulmonary vascular bed in acute PE, hypoxic pulmonary vasoconstriction and the release of vasoactive mediators from platelets and fibrin-rich thrombi increases the PVR further.[28] Ultimately, the RV becomes uncoupled from the PA, which may lead to death.[24] Improvement in RV ventriculoarterial coupling depends on reduction in afterload, rather than adaptation of the RV.[29] While decisions are being made about potential interventions for acute PE, the pathophysiologic features described should inform management with an aim toward optimizing RV function (Fig 2), particularly because time is of the essence in acute PE.[30]

Hemodynamic Support in Acute PE

Although a wealth of literature describes vasopressors and inotropes in shock states, very little of the data are specific to acute PE. Human data are limited to case reports, case series, and retrospective reviews. Much of what we know about the pharmacologic approach to acute PE is from various animal models,[1] and differences among models may introduce untoward variability in the results.[31]

Animal studies support norepinephrine, which has both inotropic and vasoconstrictive properties, as the optimal choice for hemodynamic support during acute

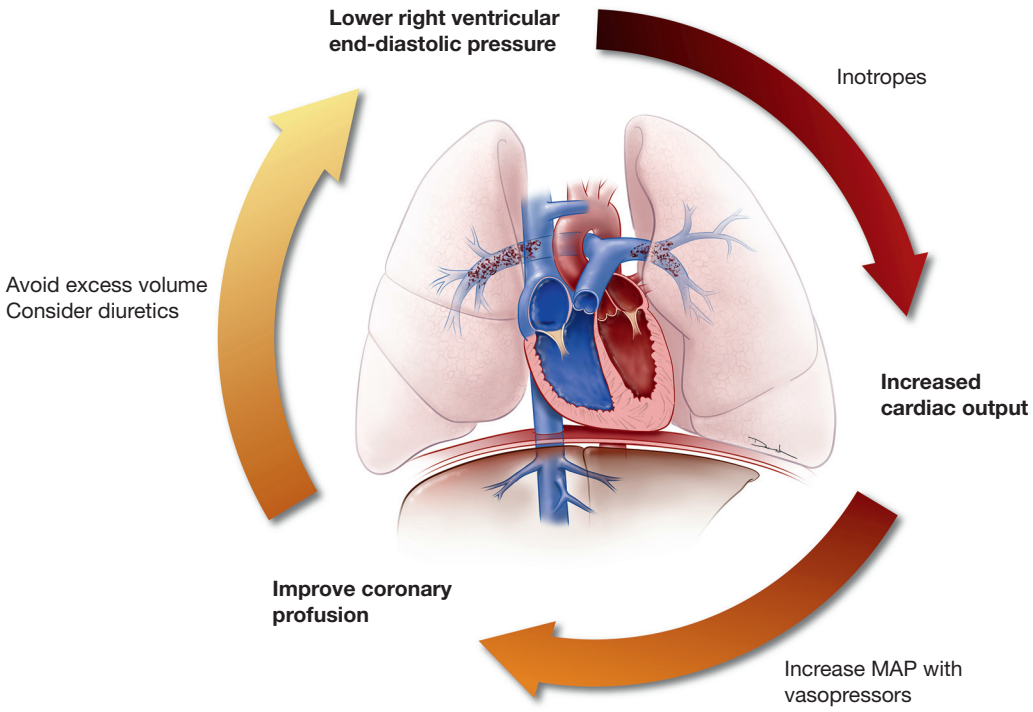

Figure 2 – *Diagram showing the cyclical mechanisms that improve right ventricular function after acute pulmonary embolism. The terms that appear in boldface are the primary physiologic processes that drive improved right ventricular function, whereas the terms that do not appear in boldface are the underlying management strategies that result in the bolded terms. We have maintained the same format as Figure 1 to illustrate how targeted management strategies can address each of the underlying physiologic principles that drive right ventricular failure in acute pulmonary embolism. We refer to this as the right ventricular cycle of recovery. MAP = mean arterial pressure.*

PE (Table 1).[2-20] Ghignone et al,[12] Ducas et al,[11] and Angle et al[8] observed improved hemodynamic results with norepinephrine compared with control treatment in canine models of acute PE. Vlahakes et al[5] observed similar improvements using phenylephrine, which does not stimulate inotropy directly, in a canine model of acute PA obstruction. They concluded that the benefits resulted from increased systemic BP and myocardial perfusion pressure, even without pharmacologic inotropy. However, when Hirsch et al[7] carefully compared both drugs in the same canine model of acute PE, they observed much more substantial increases in CO, decreases in PVR, and improvements in RV blood flow, oxygen consumption, and contractility with norepinephrine than with phenylephrine.

Indirect evidence in humans also suggests that phenylephrine may not be as beneficial as originally hoped. Rich et al[32] infused phenylephrine in patients with chronic pulmonary hypertension (PH). We must point out that chronic PH and acute PE are vastly different disease states, so drawing equivalencies between the two is challenging. Nevertheless, in the study by Rich et al, phenylephrine did increase RV coronary driving pressure (as predicted by Vlahakes et al[5]). However, it worsened RV function, presumably because of vasoconstriction of the RV coronary arteries or by PA vasoconstriction without the benefit of inotropy. Unfortunately, Rich et al did not test whether norepinephrine would cause the same vasoconstriction-mediated worsening in patients with chronic PH. Sympathomimetics, including norepinephrine and phenylephrine, directly vasoconstrict the PA, a property that is not shared by vasopressin.[33,34] Whether inotropy from norepinephrine compensates for the deleterious effect on PA in humans, as it seems to do in canines, is unknown.

Although α_1 sympathomimetics like norepinephrine and phenylephrine directly constrict both systemic and pulmonary arteries, arginine vasopressin[33,34] and terlipressin[2] (a precursor of lysine-vasopressin) limit vasoconstriction to systemic arteries and can dilate pulmonary arteries. Vasopressin is a good choice for augmenting the MAP in acute PE. Several acute PE animal studies have demonstrated improvements in mean pulmonary artery pressure, PVR, and RV ejection fraction among other metrics (Table 1). A more recent study by Schultz et al[2] demonstrated vasoconstrictive

properties of terlipressin on porcine mesenteric arteries and vasodilatory properties on pulmonary arteries, confirming the findings of Currigan et al[33] and Sugawara et al,[34] who both showed that vasopressin did not constrict pulmonary arteries, whereas it did constrict systemic arteries. An additional potential benefit of vasopressin is its potent role in renal efferent arteriole constriction.[35] This increases renal filtration and urine excretion, thereby decreasing blood volume.[36] Given the potentially harmful role of excessive intravascular volume in acute PE, this may be another explanation for the observed hemodynamic effects of vasopressin on the pulmonary circulation. In a porcine model of acute PE, terlipressin increased systemic BP and lowered PA pressure. Notably, however, terlipressin had the adverse effect of lowering CO, SV, and heart rate as well as increasing plasma lactate.[2]

The role of inotropes in acute PE is less clear. Inotropes like epinephrine, dopamine, and dobutamine (and the chronotrope isoproterenol) have been used to varying effect in animal models of acute PE and a few human studies (Table 1). In short, they seem to reduce PVR predominantly by increasing CO via increased heart rate, SV, or both. Whether this is beneficial in patients with acute PE is open for debate. On the one hand, increased CO should lead to increased right coronary perfusion; however, increased CO also requires increased oxygen consumption, which may offset the increased perfusion directly. Dobutamine is known for decreasing systemic vascular resistance and may lead to a precipitous drop in BP, leading to impaired right coronary perfusion. It is believed that the coadministration of a vasopressor with dobutamine may counteract this effect, but this has not been studied in sufficient detail for us to make an endorsement. Finally, an important adverse effect of inotropes is tachycardia and arrhythmias. With increasing heart rate, the time for passive ventricular filling decreases, which decreases effective SV as does atrial arrhythmias, which eliminate the atrial component of the SV.

More recently, inodilators (inotropes with vasodilatory properties) such as levosimendan, milrinone, and amrinone have gained increased attention in acute PE animal studies. These agents may have a role for improving RV-PA coupling and improving PA-specific metrics such as elastance or compliance. In a porcine model of acute PE, levosimendan improved RV-PA coupling by augmenting RV contractility and decreasing RV afterload.[15] Further study in humans beyond case reports is necessary before we can endorse widespread use of levosimendan in acute PE. For now, we urge caution in using inodilators in isolation because they cause peripheral vasodilation, which ultimately may decrease right coronary perfusion and potentially may worsen RV function.

Although we strongly urge against the use of phentolamine in acute PE, a recent animal study may lend some physiologic insight into the deleterious role of α-adrenergic signaling in RV dysfunction. In a leporine model of acute PE, α-adrenergic receptor expression was upregulated in the blood vessels of lungs with acute clot, and its expression was noted even in pulmonary vessels without clot.[6] Treatment with phentolamine (a nonselective α-adrenergic antagonist) abrogated some of this α-adrenergic receptor expression and improved pulmonary hemodynamics, thereby implicating α-adrenergic signaling in aggravating RV failure.

Based on the data we discussed, norepinephrine (typical dose range, 0.1-0.5 μm/kg/min) is a reasonable first option for the treatment of hemodynamically unstable acute PE, based on its ability to increase MAP and increase CO. However, if tachycardia or arrhythmia are problematic, phenylephrine (typical dose range, 0.1-1.5 μm/kg/min) is a viable option, provided it is not complicated by reflex bradycardia.[37] If hypotension persists, vasopressin (typical dose, 0.03 units/min) and vasopressin analogs may be beneficial, provided that CO is closely monitored or supported with inotropic agents.

Fluids and Diuretics in Acute PE

An abrupt increase in RV afterload and elevated RV end diastolic pressure may severely impair RV function during acute PE. This concept informs the approach to volume expansion in acute PE (Table 2).[21,12,38-43] Although, in healthy animal subjects, RV function increases as central venous pressure is raised from low to moderate levels,[44] even the normal RV will demonstrate dysfunction with excessive IV volume expansion.[45] Excessively increased RV end diastolic pressure overdistends the RV and compromises RV myocardial blood flow. Compromised coronary flow that is not mitigated by vasodilators results in decreased contractility of the RV. The fall in RV function occurs even in the absence of a pericardium, suggesting that it is the RV distention itself, and not external constriction, that compromises function.

Clinical data suggest that the potential benefits of fluid addition vs fluid removal are dependent on the baseline

TABLE 2] Summary of Studies of IVF and Diuretic Use in Acute Pulmonary Embolism Sorted by Intervention and Then Comparator

Study	Model	Intervention	Comparison	Study Type	No.	Outcome
Lim et al[21]	Human	Loop diuretic	Placebo	RCT	276	Loop diuretics decreased oligoanuria and normalized more sPESI parameters than placebo, but increased creatinine.
Ternacle et al[39]	Human	Loop diuretic	IVF	Retrospective	70	Loop diuretics decreased sPESI score, serum creatinine, oxygen need, and systolic BP when compared with IVF.
Schouver et al[40]	Human	Loop diuretic	IVF	RCT	46	Loop diuretics decreased HR, improved TAPSE, and normalized NT-proBNP and troponin faster than IVF.
Ferrari et al[41]	Human	Loop diuretic	IVF	RCT	60	Loop diuretics normalized NT-proBNP faster, but did not change troponin or RV dysfunction when compared with IVF.
Ghignone et al[12]	Canine	IVF	Norepinephrine	Comparative	8	IVF increased RVEDP resulting in RV failure, leading to decreased SV and MAP compared with norepinephrine.
Mercat et al[38]	Human	IVF	N/A	Uncontrolled, prospective, exploratory	13	IVF increased RAP and RVEDV, leading to increased cardiac index without increases in RVEF or PVRI.
Belenkie et al[42]	Canine	IVF	N/A	Uncontrolled, exploratory	10	IVF increased RV chamber size leading to leftward septal shift and decreased LVEDV and LVSW.
Molloy et al[43]	Canine	Isoproterenol, IVF, norepinephrine	Placebo	Comparative	24	Only dogs treated with norepinephrine survived $>$ 1 h and showed improved CO, MAP, PVR, and PVR to SVR ratio.

CO = cardiac output; HR = heart rate; IVF = IV fluid; LVEDV = left ventricular end diastolic volume; LVSW = left ventricular stroke work; MAP = mean arterial pressure; N/A = not applicable; NT-proBNP = N-terminal pro-brain natriuretic peptide; PVR = pulmonary vascular resistance; PVRI = pulmonary vascular resistance index; RAP = right atrial pressure; RCT = randomized controlled trial; RV = right ventricle; RVEDP = right ventricular end diastolic pressure; RVEDV = right ventricular end diastolic volume; RVEF = right ventricular ejection fraction; sPESI = Simplified Pulmonary Embolism Severity Index; SV = stroke volume; SVR = systemic vascular resistance; TAPSE = tricuspid annular plane systolic excursion.

status of the patient with acute PE. A small series of patients with moderately severe acute PE (low cardiac indices and high clot burden, but not vasopressor dependent) showed a beneficial effect of modest (0.5 L) IVF administration despite RV end diastolic volume indices (RVEDVIs) well above normal.[38] IVF administration increased the RVEDVI even further, yet increased cardiac index and decreased PVR. Notably, those with a normal baseline RVEDVI showed the greatest increase in cardiac index after IVF administration. Those with RVEDVIs two or more times normal showed nearly no increase in cardiac index, raising the possibility that they were approaching the point at which fluid addition would be detrimental.

Conversely, a retrospective analysis of patients with intermediate-risk acute PE who received either diuresis or IVF disclosed increased BP and improved creatinine in the former group.[39] However, both groups showed normal BP and normal mean creatinine level before treatment. In addition, those who received diuresis harbored significantly higher RV to LV ratios, suggesting that they were in the group most likely to benefit from diuresis. A prospective but nonrandomized study that allowed clinicians to choose between diuresis and administration of 0.5 L of saline reported that those selected for diuresis showed more rapid normalization of brain-type natriuretic peptide and troponin, but no difference in clinical outcome.[40] However, the influence of the selection criteria themselves, rather than the effect of treatment, is unclear. A randomized open-label study comparing diuresis with a 0.5-L saline infusion likewise reported more rapid decrease in brain-type natriuretic peptide after diuretics, but no difference in RV function measured by echocardiography or in clinical outcome.[41]

A well-performed randomized double-anonymized trial of patients with intermediate-risk acute PE who received either IV furosemide (80 mg once) or placebo disclosed resolution of oliguria more frequently among those who received diuretics at 24 h (91% vs 59%) and 48 h (95% vs 76%).[21] However, tachycardia resolved less frequently in the diuretic group (87% vs 96%) and creatinine increases were much more common (8.3% vs 0.7%). Other overall outcomes were the same between groups.

The decision to administer or to remove fluid during acute PE is nuanced. Modest amounts of fluid are reasonable in the absence of evidence for severe RV distention and dysfunction. However, large fluid resuscitation boluses may overdistend the RV and compromise its myocardial perfusion. Likewise, if CT imaging suggests severe RV dysfunction (eg, increased RV to LV ratio, reflux of contrast into the inferior vena cava, RA enlargement) or echocardiography demonstrates RV dysfunction, then diuresis, rather than fluid administration, may be wise. Assessment of volume responsiveness potentially is useful when deciding about administration of IVFs; however, the best method by which to do this is beyond the scope of this review.

Pulmonary Vasodilators in Acute PE

Part of the mechanism underlying the abrupt rise in PA pressure with acute PE is pulmonary artery constriction through neurogenic and humoral signaling.[46-49] It stands to reason that pulmonary vasodilators may alleviate the increased PA pressure and RV afterload both by counteracting this vasoconstrictive process and by increasing the nonobstructed cross-sectional area for blood flow. Despite the wealth of data supporting pulmonary vasodilators in pulmonary arterial hypertension and chronic thromboembolic PH, high-quality data in acute PE are scarce.

Perhaps the simplest of pulmonary vasodilators is supplemental oxygen. In the recently published Air vs Oxygen for Intermediate Risk Pulmonary Embolism (AIR) trial, fixed-dose supplemental oxygen was compared with ambient air in normoxic patients with acute PE with RV dysfunction on echocardiography who were receiving standard anticoagulation.[50] A notable, although nonsignificant, trend toward improvement in the primary end point (RV to LV ratio) with supplemental oxygen was observed, and several of the secondary end points were significant. Because the trial enrolled slowly owing to the COVID-19 pandemic, it was underpowered, likely biasing results toward the null hypothesis. A larger trial of this therapy is warranted.

Although IV nitric oxide donors (nitroglycerin, nitrite, and nitroprusside) are common in animal models, their use in humans is limited by systemic hypotension, particularly in patients with high-risk acute PE. Unlike systemic nitric oxide, the use of inhaled nitric oxide (iNO) has shown some promise.

A phase 2, double-masked, randomized controlled trial of iNO (50 parts per million) vs placebo in 76 patients with intermediate-risk acute PE yielded provocative, but not definitive, results.[51] In the group treated with iNO, normalization of troponin and echocardiography-

assessed RV function (the composite primary end point) was not significantly more common than in the placebo group. However, a post hoc analysis disclosed that the iNO group showed less echocardiographic evidence of RV hypokinesis and dilation. The American Heart Association did not make any recommendation for iNO use,[52] and the European Society of Cardiology made a guarded recommendation.[53]

The inhaled prostacyclin analog (iloprost) was used in two small case series, one to several days after presentation with intermediate-risk acute PE.[54,55] The patients treated with iloprost showed improved RV function over 3 to 90 days, although the improvement may have been the result of the normal rate of recovery, rather than the effect of iloprost. In a small single-masked randomized controlled trial of intermediate-risk acute PE randomized to IV epoprostenol vs placebo, epoprostenol did not improve RV dilatation or any other measured variables of RV function.[56] However, the patients were relatively healthy at baseline, which may have biased the results toward the null hypothesis.

In summary the administration of oxygen in acute PE with RV dysfunction is a low-risk procedure with potential therapeutic benefit. The addition of iNO is a reasonable consideration as rescue therapy in patients with ongoing RV dysfunction despite hemodynamic support, appropriate volume status, and supplemental oxygen administration.

Mechanical Ventilation and Sedation in Acute PE

Although invasive mechanical ventilation occasionally is required in the management of patients with acute PE, often in the case of severe hypoxemia or altered mentation or to facilitate procedures, ideally it is avoided because of the potential hemodynamic consequences. Hypoxemia in acute PE largely is mediated by ventilation-perfusion mismatch, and thus can be overcome with supplemental oxygen. High-flow oxygen therapy or noninvasive mechanical ventilation are the preferred methods and usually can provide adequate oxygenation to a target oxygen saturation of $> 90\%$.[53] In patients for whom mechanical ventilation is deemed necessary, the focus should be on avoidance of hypotension as well as worsening of hypoxemia, hypercarbia, and acidosis during and immediately after the intubation process.

Induction of Anesthesia: Patients with RV failure are prone to peri-intubation hemodynamic collapse. In a series of patients undergoing surgical pulmonary embolectomy, 29% of patients required vasopressors and 19% of patients experienced hemodynamic collapse necessitating CPR during induction of general anesthesia and intubation.[57] During induction, avoidance of worsening hypoxemia and hypercarbia is paramount, because both conditions can cause pulmonary vasoconstriction and can increase RV afterload.[58] Preoxygenation should be optimized; consider placement of a preinduction arterial line and ensure adequate venous access by central line or peripheral IV lines, with vasopressors immediately available to maintain MAP, and thus RV perfusion pressure. In general, evidence for induction strategies in acute PE specifically is limited. Etomidate likely is the most hemodynamically neutral induction agent in terms of effects on systemic vascular resistance and myocardial contractility and is preferred for use in patients with PH undergoing rapid sequence induction along with a paralytic.[59] Propofol has been associated with higher rates of peri-intubation cardiovascular instability in critically ill patients and should be used cautiously.[60,61]

Mechanical Ventilation: Positive pressure ventilation poses physiologic challenges to the failing RV. During a positive pressure breath, a reduced gradient for venous return ensues and RV preload falls.[62] The application of positive end-expiratory pressure accentuates this response throughout the respiratory cycle.[58] PVR is related to lung size, particularly at the extremes of lung volume, and the balance of circulation between the alveolar and extraalveolar vessel compartments.[63] Further increases in PVR mediated by swings in lung volume can raise RV afterload acutely and can precipitate a cycle of reduced RVSV leading to decreased LV preload and CO, with ensuing hypotension and shock.[58] Thus, as soon as mechanical ventilation is initiated, tidal volumes should be maintained at 6 to 8 mL/kg ideal body weight to avoid overdistention, and positive end-expiratory pressure should be applied cautiously.[53]

Extracorporeal Membrane Oxygenation for High-Risk Acute PE

For patients with cardiogenic shock resulting from acute RV failure because of acute PE, venoarterial extracorporeal membrane oxygenation (ECMO) can be offered for hemodynamic support.[64] Although venoarterial ECMO does not reduce the clot burden within the pulmonary arteries, it provides hemodynamic support, and thus time for clot resolution to occur.

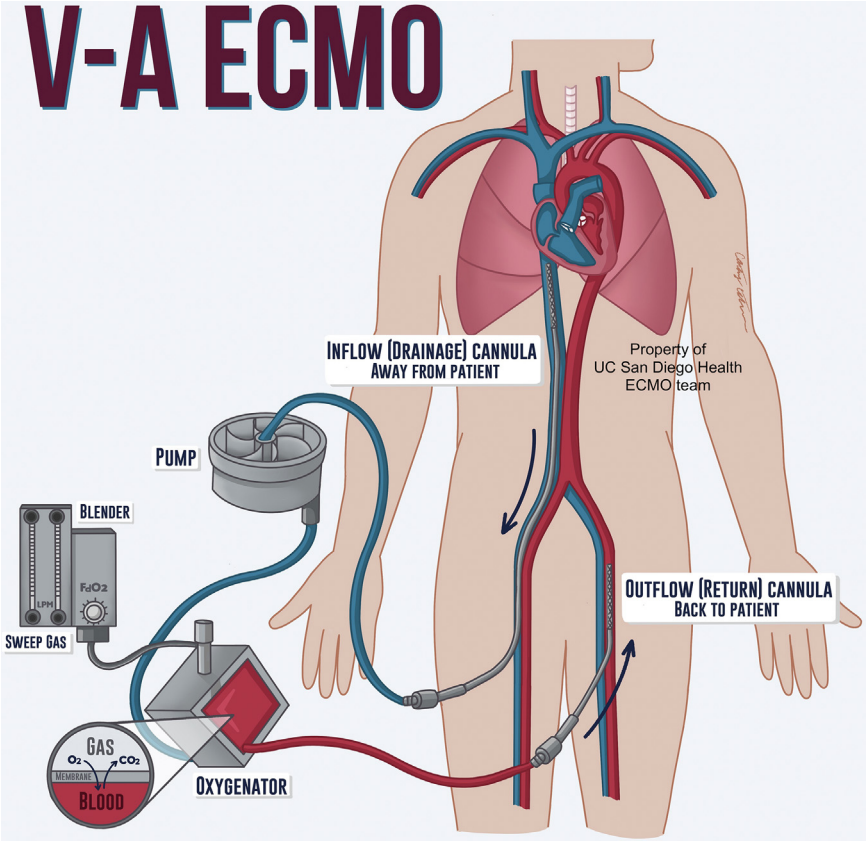

Figure 3 – *Diagram showing our preferred cannulation strategy for venoarterial ECMO in acute pulmonary embolism. ECMO = extracorporeal membrane oxygenation; V-A = venoarterial. (Reprinted with permission from the UC San Diego ECMO Team)*

Venoarterial ECMO supports the failing RV by reducing preload and RV distension and increasing right coronary perfusion (Fig 3). Venovenous ECMO should not be initiated for acute PE because it returns blood to the venous system and thus does not decrease RV preload or distension. Because of more mobile ECMO circuits, cannulation can be carried out anywhere in the hospital, and teams can be deployed to other hospitals who do not have in-house capabilities.[65] Venoarterial ECMO also can be placed during CPR (extracorporeal

TABLE 3] Summary of Suggestions for Management of Right Ventricular Failure Resulting From Acute Pulmonary Embolism

Hemodynamic support with vasopressors • Norepinephrine is a reasonable first choice for hemodynamic support. • Consider vasopressin as an adjunct vasopressor. • Provided BP is well supported, an inodilator could be added to improve inotropy and PA RV coupling.
Fluid management • In the absence of severe RV dilatation, cautious use of IVFs may be helpful with ongoing monitoring of their efficacy. • Consider IV loop diuretics particularly if evidence exists of RV dysfunction or volume overload.
Respiratory management • Supplemental oxygen administration is a low-risk procedure that may have benefits, regardless of the presence of hypoxemia. • Caution against positive pressure ventilation because of deleterious effects on RV filling. • If mechanical ventilation is necessary, use conservative positive end-expiratory pressure and low to moderate tidal volumes. • Caution against use of hemodynamically active agents that cause hypotension during induction for intubation (eg, propofol). Avoid hypotension after intubation.
Advanced therapy • Consider venoarterial ECMO (even in the absence of mechanical ventilation) as a bridge to an intervention in a patient who continues to deteriorate as a result of progressive RV failure.

ECMO = extracorporeal membrane oxygenation; IVF = IV fluid; PA = pulmonary artery; RV = right ventricle.

CPR), although survival outcomes are low (20%-40% for most ECMO indications) and cannulation must occur within 1 h of CPR.[66] The median time to cannulation in this study was 51 min, and one must wonder if the low survival rates would have been improved by faster cannulation. Although the prior extracorporeal CPR study included only one patient with a known PE as the cause of cardiac arrest, another recent systematic review focused exclusively on the population with acute PE. In 301 patients with high-risk acute PE, 65% of those undergoing cannulation for ECMO during CPR survived; however, they had a sixfold higher odds of death compared with patients with acute PE who survived CPR and subsequently underwent cannulation because of persistent shock.[67] Eighty-eight percent of those who survived were neurologically intact during follow-up. No increased risk of death was observed among patients who received systemic fibrinolysis before venoarterial ECMO cannulations compared with those who did not.

Administration of fibrinolytics is not a contraindication to ECMO cannulation, nor is the presence of ECMO cannulas a contraindication to administration of fibrinolytics.[67] Although anticoagulation goals are controversial for venoarterial ECMO, we use our institutional therapeutic anticoagulation goals for acute PE regardless of the presence or absence of venoarterial ECMO cannulas.[68] Catheter-based therapies and surgical embolectomy also can be performed safely in venoarterial ECMO. An analysis of the Extracorporeal Life Support Organization's database from 2010 through 2020 found 802 patients with high-risk acute PE requiring venoarterial ECMO.[69] The survival in this cohort was 53%. Although not statistically significant, a trend toward improved survival was observed among those who received embolectomy or catheter-based lysis while receiving ECMO (70%), compared with those who received ECMO alone (52%) or in whom ECMO was started after prior unsuccessful interventions (52%). The median duration of venoarterial ECMO time was 4.75 days. In the entire cohort, 40% experienced bleeding complications and a 5% rate of intracranial hemorrhage occurred; neither complication occurred more frequently among those who received advanced interventions while receiving ECMO. Although venoarterial ECMO is expensive and limited to large institutions, it should be considered in patients with acute PE and cardiogenic shock resulting from RV failure as a bridge to recovery with anticoagulation alone or thrombectomy.

Future Directions

In summary, the pathophysiologic processes that underlie RV failure in acute PE are abrupt, profound, and difficult to reverse. We have summarized our suggestions for acute PE management in Table 3.

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