Review

Mechanical Circulatory Support to Treat Pulmonary Embolism:

Venoarterial Extracorporeal Membrane Oxygenation and Right Ventricular Assist Devices

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Mechanical circulatory support may help patients with massive pulmonary embolism who are not candidates for systemic thrombolysis, pulmonary embolectomy, or catheter-directed therapy, or in whom these established interventions have failed. Little published literature covers this topic, which led us to compare outcomes of patients whose massive pulmonary embolism was managed with the use of venoarterial extracorporeal membrane oxygenation (VA-ECMO) or a right ventricular assist device (RVAD).

We searched the medical literature from January 1990 through September 2018 for reports of adults hospitalized for massive or high-risk pulmonary embolism complicated by hemodynamic instability, and who underwent VA-ECMO therapy or RVAD placement. Primary outcomes included weaning from mechanical circulatory support and discharge from the hospital. We found 16 reports that included 181 patients (164 VA-ECMO and 17 RVAD).

All RVAD recipients were successfully weaned from support, as were 122 (74%) of the VA-ECMO patients. Sixteen (94%) of the RVAD patients were discharged from the hospital, as were 120 (73%) of the VA-ECMO patients. Of note, the 8 RVAD patients who had an Impella RP System were all weaned and discharged.

For patients with massive pulmonary embolism who are not candidates for conventional interventions or whose conditions are refractory, mechanical circulatory support in the form of RVAD placement or ECMO may be considered. Larger comparative studies are needed. ***(Tex Heart Inst J 2020;47(3):202-6)***

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Pulmonary embolism (PE) may be responsible for as many as 180,000 deaths annually in the United States.[1] The prevalence of venous thromboembolism, which encompasses deep vein thrombosis and PE, is approximately 100 per 100,000 individuals in the U.S.[2] Pulmonary embolism occurs in approximately a third of cases of treated venous thromboembolism, and the associated 30-day mortality rate in these patients is as high as 12%.[2] In some patients who are not candidates for standard interventions or whose PE is refractory, mechanical circulatory support (MCS) may help; however, little published literature covers this topic. We searched existing reports to compare outcomes of patients whose massive PE was managed with the use of venoarterial extracorporeal membrane oxygenation (VA-ECMO) or a right ventricular assist device (RVAD).

Classification of Pulmonary Embolism

In the past, PE was classified primarily by using the Miller Index, which focused on the obstructive degree of filling defects in the pulmonary arteries and their segmental branches.[3] The American Heart Association has since established 3 classifications for acute PE: massive, submassive (intermediate-risk), and low-risk.[4,5] Massive PE involves sustained hypotension (systolic blood pressure <90 mmHg for at least 15 min or a need for inotropic support, caused only by PE), pulselessness, or persistent profound bradycardia. Submassive PE features either right ventricular (RV) dysfunction or myocardial necrosis without systemic hypotension. Low-risk PE is acute but lacks the adverse clinical markers that characterize massive or submassive PE.[4,5]

Pathophysiology of Pulmonary Embolism

Multiple mechanisms cause hemodynamic instability in patients who have massive PE. Increases in RV afterload increase RV wall tension and can lead to wall dila-

tion. In addition, PE can increase pulmonary vascular resistance by contributing to hypercoagulable states, chiefly through increasing systemic inflammation and the activation levels of thrombin and platelets.[6] Right ventricular dilation can shift the interventricular septum leftward,[7] thus compromising left ventricular (LV) preload and consequent cardiac output.[8] Impaired cardiac output in the presence of increased RV afterload decreases RV coronary perfusion pressure.[9] Elevated RV end-diastolic pressure can increase coronary venous pressure, ventricular wall stress, and oxygen demand.[9] Consequent coronary ischemia can cause RV infarction, RV failure, and worsening hemodynamic instability.[9]

Managing Massive Pulmonary Embolism

In addition to parenteral anticoagulation, 3 beneficial interventions for massive PE are systemic thrombolysis, pulmonary embolectomy, and catheter-directed therapy (CDT).[5]

In systemic thrombolysis, drugs such as urokinase, streptokinase, and tissue plasminogen activator are administered to convert plasminogen to plasmin, the active protease. Plasmin reduces clot burden by cleaving fibrin, the main structural component of PE.[10] In patients with massive PE who have no contraindications, systemic thrombolysis is a first-line therapy[11]; in a meta-analysis,[12] it lowered recurrence and mortality rates more than heparin administration alone did.

Surgical pulmonary embolectomy, which typically involves performing a median sternotomy, entering the pericardium, and establishing cardiopulmonary bypass, is associated with higher mortality rates than systemic thrombolysis.[13] Nevertheless, surgical embolectomy can improve survival prospects when thrombolysis is contraindicated or ineffective. A group of investigators[14] prospectively compared the outcomes of surgical embolectomy and repeat thrombolysis in patients refractory to initial thrombolysis and found a clear survival benefit from embolectomy.

Patients in whom thrombolysis has failed and embolectomy is contraindicated may benefit from CDT with or without thrombolysis for acute management.[11,15] The goal of CDT is to decrease RV strain and improve pulmonary vascular perfusion by minimizing the central clot burden.[16] Conventional CDT techniques include rotating pigtail fragmentation and rheolytic thrombectomy[17,18]; novel techniques include performing ultrasound-assisted thrombolysis and using clot-retrieval devices.[15] Mechanical-aspiration thrombectomy systems, such as the Indigo® system (Penumbra, Inc.), are being evaluated.[15] Catheter-directed therapy has improved survival prospects in patients with massive PE who were not candidates for the other first-line options.[16]

Mechanical Circulatory Support

Whether from extracorporeal membrane oxygenation (ECMO) or a ventricular assist device,[19] MCS may help patients who have refractory PE or contraindications to other therapies. Few published articles cover the outcomes of ECMO or (in particular) RV assist devices (RVADs) in managing massive PE.

Extracorporeal membrane oxygenation consists of venovenous or venoarterial (VA) circulatory support. Venovenous ECMO typically involves draining blood from large central veins through an outflow cannula into a peripheral oxygenator; oxygenated blood then returns through a femoral inflow cannula into the right atrium. In VA-ECMO, blood from the central veins is oxygenated and returned to the systemic arterial circulation through an inflow cannula.[19] In patients with RV failure from pulmonary hypertension, VA-ECMO advantageously bypasses the pulmonary circulation and decreases RV preload, improving RV function.[19]

Ventricular assist devices chiefly aid patients who have ventricular heart failure.[20] An RVAD can be used to treat postcardiotomy hemodynamic instability, as well as RV heart failure arising from myocardial infarction, pulmonary hypertension, or cardiac transplantation.[21] Implantation usually involves placing an inflow cannula in the right atrium and an outflow cannula in the pulmonary artery.[22] In 2012, a percutaneous RVAD, the Impella RP® System (Abiomed, Inc.), was approved for managing RV failure in patients undergoing heart surgery as well as those who had a myocardial infarction or transplanted heart.[23]

Methods

We systematically searched PubMed, Medline, Scopus, and nonindexed sources for English-language case reports, case series, and retrospective cohort studies, published from January 1990 through September 2018. We used the following syntax: (*emboli* OR *embolism* OR *pulmonary embolism* OR *massive pulmonary embolism*) AND (*assist device* OR *ventricular assist device* OR *RVAD* OR *LVAD* OR *Impella* OR *ECMO* OR *extracorporeal membrane oxygenation*). We then evaluated articles that were cited in the identified studies. Two investigators (AB and RA) screened the results to ensure adherence to the inclusion criteria: hospitalized adults with suspected or known massive or high-risk PE complicated by hemodynamic instability who underwent either VA-ECMO or RVAD placement.

Results

The search revealed 113 articles, 90 of which were duplicates or irrelevant. Of the remaining 23, 7 did not meet the inclusion criteria. Sixteen studies, from the U.S., Canada, Austria, Czech Republic, Poland, France, Italy, Japan, and Australia, qualified for our review (Table I).[22-37] We divided the total of 181 patients into 2 groups: massive PE managed with the use of VA-ECMO (164

patients, from 4 retrospective cohort studies and a case report), and massive PE managed after RVAD placement (17 patients, from 10 case reports and a case series).

Of the 164 patients treated with VA-ECMO, 122 (74%) were weaned from MCS (Table II).[28,33-36] In the 4 cohort studies,[33-36] the patients' median days on MCS before weaning were 4, 5, 4, and unspecified. In all, 120 patients (73%) survived to hospital discharge; the 2 deaths were from refractory cardiogenic shock with multiorgan failure in the presence of recurrent PE.[33]

All 17 patients treated with RVADs were weaned from MCS after a mean 3.9 ± 1.9 days of support.[22-27,29-32,37] Their mean age was 48 ± 16.5 years. Sixteen (94%) then survived to hospital discharge; one elderly patient died of infection 28 days after RVAD removal and 10 days after release from intensive care.

TABLE I. Reports of Venoarterial ECMO and Right Ventricular Assist Devices Used to Treat Massive Pulmonary Embolism

Reference	Report Type	Pts. (n)	Age (yr), Sex	MCS Indication	MCS Type	Weaned from MCS (%)	Weaning Time (d)	Survived to Discharge (%)
Kaltenböck F, et al.[24] (1993)	CR	1	34, M	Failed embolectomy and ECC	RVAD (BVS 5000)	1	5	1
Konstantinov IE, et al.[25] (2007)	CR	1	27, M	Failed CPB	RVAD (BioMedicus)	1	2	1
Gregoric ID, et al.[26] (2008)	CR	1	21, F	Failed fibrinolysis	RVAD (CentriMag)	1	NA	1
Lango R, et al.[27] (2008)	CR	1	81, M	Failed CPB	RVAD (3M Sarns)	1	2	0 (died of infection, 28 d after RVAD removal)
Belohlavek J, et al.[28] (2010)	CR	1	51, M	Failed fibrinolysis and embolectomy	VA-ECMO	1	5	1
Geller BJ, et al.[29] (2012)	CR	1	48, M	Failed fibrinolysis	RVAD (TandemHeart)	1	6	1
Said SM, et al.[30] (2013)	CR	1	23, F	Embolectomy contraindicated	RVAD (CentriMag)	1	10	1
	CR	1	70, F	Embolectomy contraindicated	RVAD (CentriMag)	1	4	1
Kumar Bhatia N, et al.[31] (2017)	CR	1	47, M	First-line therapies contraindicated	RVAD (Impella RP)	1	2	1
Lodewyks CL, et al.[32] (2017)	CR	1	30, M	Failed fibrinolysis and embolectomy	RVAD (BioMedicus 540)	1	2	1
Corsi F, et al.[33] (2017)	RCS	17	51*; 6 M, 11 F	Initial intervention	VA-ECMO	10 (59)	4*	8 (47)
Salsano A, et al.[22] (2017)	CR	1	57, M	Failed embolectomy	RVAD (Stöckert)	1	4	1
Pasrija C, et al.[34] (2018)	RCS	20	47*; NA	Initial intervention	VA-ECMO	19 (95)	5.1*	19 (95)
George B, et al.[35] (2018)	RCS	32	56*; 17 M, 15 F	Initial intervention	VA-ECMO	21 (66)	4*	21 (66)
Elder M, et al.[23] (2018)	CS	5	51 ± 14.6; NA	Initial intervention	RVAD (Impella RP)	5 (100)	3.2 ± 2	5 (100)
Minakawa M, et al.[36] (2018)	RCS	94	62.1 ± 15.7; NA	Initial intervention	VA-ECMO	71 (76)	NA	71 (76)
Shokr M, et al.[37] (2018)	CR	1	52, F	Failed CDT with thrombolysis	RVAD (Impella RP)	1	5	1
	CR	1	72, M	Failed CDT with thrombolysis	RVAD (Impella RP)	1	4	1

CDT = catheter-directed therapy; CPB = cardiopulmonary bypass; CR = case report; CS = case series; ECC = extracorporeal circulation; F = female; M = male; MCS = mechanical circulatory support; NA = not available; RCS = retrospective cohort study; RVAD = right ventricular assist device; VA-ECMO = venoarterial extracorporeal membrane oxygenation

*Median

Data are presented as number, number and percentage, or mean ± SD, unless otherwise stated.

TABLE II. Comparison of Mechanical Circulatory Support Devices for Managing Massive Pulmonary Embolism

MCS Method	No. Treated	Age (yr)	Weaned from MCS	Weaning Time (d)	Survived to Hospital Discharge
VA-ECMO[a]	164	51, 51,[b] 47,[b] 56,[b] 62.1 ± 15.7	122 (74)	5, 4,[b] 5.1,[b] 4,[b] unspecified	120 (73)
RVAD	17	48 ± 16.5	17 (100)	3.9 ± 1.9	16 (94)
Impella RP	8	53 ± 7.2	8	3.4 ± 0.8	8 (100)
Other	9	43 ± 20.5	9	4.4 ± 2.6	8 (89)

MCS = mechanical circulatory support; RVAD = right ventricular assist device; VA-ECMO = venoarterial extracorporeal membrane oxygenation

[a]Because of inconsistent data presentation among reports, ages and weaning times for each report are shown.

[b]Median

Data are presented as number, mean ± SD, or number and percentage, unless otherwise stated.

Various RVADs were used to treat patients: the Impella RP® System and BVS® 5000 Bi-ventricular Support System (both Abiomed, Inc.), the Stöckert Centrifugal Pump and TandemHeart® pVAD (both LivaNova PLC), the BioMedicus and BioMedicus 540 Centrifugal Pump (both Medtronic, Inc.), the CentriMag™ Circulatory Support System (Abbott), and the 3M Sarns™ Centrifugal System (3M Health Care).

The 8 patients (mean age, 53 ± 7.2 yr) who had an Impella RP spent a mean 3.4 ± 0.8 days on MCS and survived to hospital discharge.[23,31,37] The 9 patients with other RVADs spent a mean 4.4 ± 2.6 days on MCS; one died before hospital discharge.

Discussion

The choice of intervention for managing massive PE depends on patient comorbidities and contraindications.[11] Mechanical circulatory support may help unsuitable candidates or patients who do not improve. However, using MCS—particularly RVADs—to manage massive PE has not been well studied.[19]

Our evaluation indicates that cardiac output generated by VA-ECMO may have been lower than that of the various RVADs, resulting in inadequate RV unloading. In the RVAD patients, the direct mechanical assistance to the affected ventricle may have decreased myocardial oxygen demand and accelerated recovery of cardiac function.[38] Whereas the VA-ECMO patients may have had suboptimal LV function (lower preload and higher afterload) that contributed to RV dysfunction through increased LV wall stress and impaired coronary oxygenation,[38] the RVAD patients may have had superior oxygen supplies to the systemic and coronary circulations. The RVAD recipients may have benefited from inpatient rehabilitation with ambulation, an option not typically afforded VA-ECMO patients. The Impella RP recipients generally had better outcomes, perhaps because its percutaneous placement avoids the complications associated with surgical device placement and concomitant thrombolytic therapy.[23] Finally, in the absence of objective data gleaned from the reports included in our analysis, the Impella patients appear to have had fewer comorbidities and less complicated hospital courses than the other patients.

Limitations. Limitations of this review include the small number of RVAD recipients, the quality of the available studies, and the unavailability of information on potential confounding factors such as patient comorbidities and preoperative hemodynamic measurements.

Conclusion

We conclude that MCS, whether VA-ECMO or RVAD placement, may help patients with massive PE who are poor candidates for conventional interventions or whose PE is refractory. However, large randomized controlled trials are needed to determine which treatment is more effective.

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