Circulation: Heart Failure

ORIGINAL ARTICLE

Hemodynamic Effects of Mechanical Circulatory Support Devices in Ventricular Septal Defect

Results from a Computer Simulation Model

Mohit Pahuja, MD
Benedikt Schrage, MD
Dirk Westermann, MD
Mir B. Basir, DO
Arthur Reshad Garan, MD
Daniel Burkhoff, MD, PHD

BACKGROUND: Ventricular septal defect (VSD) is a lethal complication of acute myocardial infarction (AMI) and is often associated with cardiogenic shock. The optimal form of percutaneous mechanical circulatory support (MCS) for AMI-VSD is unknown.

METHODS AND RESULTS: We used a previously validated cardiovascular model to simulate AMI-VSD with parameters adjusted to replicate average hemodynamics reported in the literature, including a pulmonary-to-systemic blood flow ratio of 3.0. We then predicted effects of different types of percutaneous MCS (including intra-aortic balloon pumping, Impella, TandemHeart, and extracorporeal membrane oxygenation) on pressures and flows throughout the cardiovascular system. The simulation replicated all major hemodynamic parameters reported in the literature with AMI-VSD. Inotropes and vasopressors worsened left-to-right shunting, whereas vasodilators decreased shunting at the expense of worsening hypotension. All MCS devices increased forward blood flow and arterial pressure but other effects varied among devices. Impella 5.0 provided the greatest degree of pulmonary capillary wedge pressure reductions and decreased left-to-right shunting. Extracorporeal membrane oxygenation worsened pulmonary capillary wedge pressure and shunting, which could be improved by adding Impella or passive left ventricular vent. Pulmonary-to-systemic blood flow ratio could not be reduced below 2.0, and pulmonary flows remained high with all forms of MCS.

CONCLUSIONS: Although no form of percutaneous MCS normalized hemodynamics in AMI-VSD, pulmonary capillary wedge pressure and shunting were worsened by extracorporeal membrane oxygenation and improved by Impella. Accordingly, based on hemodynamics alone, Impella provides the optimal form of support in AMI-VSD. However, other factors, including team experience, device availability, potential for tissue ingestion, and clinical characteristics, need to be considered when choosing a percutaneous MCS device for AMI-VSD.

Key Words: arterial pressure ■ computer ■ hemodynamics ■ hypotension ■ myocardial infarction

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WHAT IS NEW?

- Pharmacological agents and mechanical circulatory support (MCS) devices are commonly used in patients with ventricular septal defect (VSD) and acute myocardial infarction (AMI). However, their hemodynamic effects are largely unknown in this setting but are expected to vary among devices.
- Our study is the first to predict the effects of different medications and MCS devices on hemodynamics and pressure-volume loops of both left and right ventricle in patients with AMI-VSD using a comprehensive cardiovascular model to explain the expected differential hemodynamic effectiveness of these different therapeutic approaches.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Clinicians should be aware that in patients with AMI-VSD no pharmacological or MCS devices normalizes hemodynamics.
- Therapy should improve total blood flow, pulmonary capillary pressure, and oxygen delivery and bridge to definitive VSD closure therapy.
- Extracorporeal membrane oxygenation (ECMO) increases VSD shunt flow and, as in cardiogenic shock without VSD, has the potential to increase pulmonary capillary pressures and increase left ventricular end-diastolic pressure.
- In contrast, percutaneous left ventricular assist provides the greatest degree of left ventricular unloading and reduction of pulmonary capillary pressure.
- A combination of ECMO and percutaneous ventricular assist provides the maximum support while also reducing pulmonary capillary pressure.

Ventricular septal defect (VSD), also referred to as ventricular septal rupture, is an infrequent but lethal complication of acute myocardial infarction (AMI). Over the past decades, the incidence of AMI VSD has progressively declined with the advent of thrombolytics and mechanical reperfusion therapy; nevertheless, it is estimated that VSDs occur in ≈0.3% of all ST-elevation AMIs.[1,2] AMI-VSD is associated with high mortality (40%–80%), which has remained unchanged for decades.[1,3,4] Particularly high mortality rates are encountered when AMI-VSD is associated with cardiogenic shock (CS).[5–8] Definitive therapy for hemodynamically significant VSDs is only achieved through surgical or percutaneous closure.[2,9–12] However, short-term therapy include hemodynamic stabilization, and preservation of end-organ function is often required.[2]

The cornerstone of medical management of AMI-VSD involves decreasing systemic arterial resistance to facilitate left ventricular (LV) ejection through the aortic valve which reduces the left-to-right shunting through the VSD and enhances forward flow while attempting to improve systemic blood pressure. However, in the setting of hypotension, vasoconstrictors, and inotropes are frequently used and often worsen shunt across the VSD. Mechanical circulatory support (MCS) devices are frequently used to augment forward cardiac output (CO) improving systemic perfusion and reducing shunting.

Intra-aortic balloon counterpulsation (IABP) is the most commonly used form of MCS in such patients.[1,13] Several case reports and small case series have reported the utilization of extracorporeal membrane oxygenation (ECMO) for hemodynamic support as a bridge to definite surgery.[8,11,14–17] LV assist devices, both percutaneous and surgical, have also been used as a bridge to recovery, transplant, or surgery.[18–24] There are increasing number of reports on the use of percutaneous LV assist devices, such as Impella and TandemHeart, as a bridge to surgery or transcatheter VSD closure.[9–12,25–27]

However, there are limited data on the hemodynamic effects of MCS in AMI-VSD. A summary of key studies found in the literature is provided in Table 1. Accordingly, there is a lack of information concerning which form of MCS provides the optimum support in AMI-VSD. Such information is unlikely to be forthcoming due to the low incidence and high acuity of AMI-VSD making clinical studies difficult, if not impossible, to conduct.

In view of these limitations, we used a previously validated comprehensive cardiovascular model[28] to compare the theoretical hemodynamic effects of different forms of MCS on hemodynamics in AMI-VSD.

METHODS

The current article uses data available in the literature, as summarized in Table 1. Our study did not require Institutional Review Board approval because we utilized data from published case series as the basis for simulating the hemodynamics of AMI-VSD using a well-validated computational model. The details of the cardiovascular model used in this study have been provided previously,[28] including the kinetics of oxygen and carbon dioxide fluxes as blood moves from compartment-to-compartment through the circulation.[29] In brief, mechanical pump properties of each chamber were characterized using a time-varying elastance model. Pulmonary and systemic vascular beds were modeled by series of capacitances and resistances. A VSD was simulated by introducing a connection between left and right ventricles (RV), the flow through which (F_{VSD}) was determined by the equation governing flow through an orifice: $F_{VSD}=51.3\cdot r^2\cdot\sqrt{(\Delta P/1060)}$, where F_{VSD} is in units of L/min, r is the radius

Table 1. Hemodynamic Data Available From the Literature Regarding Hemodynamics of Acute Myocardial Infarction–Related Ventricular Septal Defects and Effects of Different Forms of MCS[6,8–10,17]

	Menon et al[6]; N=41/55		Thiele et al[13]; N=23		Tsai et al[17]; N=1		Rob et al[8]; N=7		La Torre et al[9]; N= 5		Gregoric et al[10] N=11	
Intervention	**IABP**		**IABP**		**ECMO**		**ECMO**		**Impella**		**Tandem Heart**	
Age, y	72±10		70±10		65		66.4 ± 8.5		61.8±2.2		53±15	
% Male	42		52		100		71.4		80		75	
	Pre-IABP	Post-IABP	Pre-IABP	Post-IABP	Pre-ECMO	Post-ECMO	Pre-ECMO	Post-ECMO	Pre-Impella	Post-Impella	Pre-TandemHeart	Post-TandemHeart
Heart rate, beats per minute	102±23	…	106±19	100±18	…	…	115±16	68±8.8	…	…	…	…
MAP, mm Hg	62±12	…	67±16	76±15	67±7.6	67±7.6	64±7.4	83±4.6	…	…	66±7	78±9
SBP, mm Hg	83±13	102±15	…	…	…	…	…	…	…	…	77±11	98±13
CVP/RAP, mm Hg	18±7	…	16±5	13±4	13±1.5	16±2	…	…	20.8±2.8	12.2±3.1	…	…
PA mean, mm Hg	…	…	32±6	27±5	…	…	…	…	…	…	…	…
PA systolic, mm Hg	48±17	…			49±3.1	43±6.2	…	…	74±18.2	38.6±12	…	…
PCWP, mm Hg	22±9	…	21±7	16±6	…	…	…	…	27.6±4.4	15.4±5.9	28.9±7	9±n/a
Qp:Qs	…	…	3.1±0.9	2.4±0.8	…	…	…	…	2.9±0.2	1.48±0.1	…	…
Sv O_2 (%)	…	…	…	…	…	91±4.7	…	…	88.8± 3	76±5.1	…	…
CI, L/(min·m^2)	…	…	1.8±0.6	2.1±0.7	…	…	…	…	1.9±0.4	3.1±0.6	…	4.8±1.8

CI indicates cardiac index; CVP, central venous pressure; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump pulsation; MAP, mean arterial pressure; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; Qp:Qs, pulmonary-to-systemic blood flow ratio; RAP, right atrial pressure; and SBP, systolic blood pressure.

of the orifice (in mm) and ΔP (in mm Hg) is the instantaneous pressure gradient between the LV and RV (ie, ΔP=LV pressure−RV pressure).

Four different forms of support were investigated: IABP, LV-to-proximal aorta pumping (as with Impella pumps), left atrial-to-femoral artery pumping (as with TandemHeart), and right atrial-to-femoral artery pumping (as with ECMO). Models for all forms of support have been described previously[30,31] and discussed further in the Data Supplement. Effects of drugs were simulated by modifying LV and RV contractility (inotropes), increasing systemic vascular resistance (vasopressors), or decreasing systemic vascular resistance (vasodilators).

Starting parameter values of the model were adjusted to simulate AMI-VSD hemodynamics based on the composite of limited hemodynamic data from several studies in the literature (Table 1)[6,9,10,13,17] using a custom designed patient hemodynamic fitting algorithm[28] and are detailed further in the Data Supplement.

Simulation results were illustrated as pressure-volume (PV) loops of RV and LV, aortic, pulmonary arterial, atrial, and ventricular pressure waveforms over time, average systemic, pulmonary, and pump flows, and arterial, venous, and pulmonary artery (PA) oxygen saturations. Regarding blood flow, there are 5 parameters to consider: blood flow through the aortic valve due to LV pumping (F_{AO}), flow provided by the MCS device (F_{MCS}), flow through the VSD (F_{VSD}), total blood flow to the body (F_{TOTAL}), and flow through the PA (F_{PA}). During MCS, F_{TOTAL} is the sum of F_{AORTA} plus F_{MCS}; in the context of ECMO plus an Impella venting strategy, the sum of the flows of the ECMO plus the Impella determine total flow to the body.

RESULTS

Starting with a simulation of LV dysfunction as encountered in CS, the impact of introducing VSDs of various sizes on right and LV PV loops and hemodynamics are summarized in Figure 1 and Table I in the Data Supplement. Increasing VSD size (from 10 to 30 mm at 5 mm increments) was associated with progressive abbreviation of the isovolumic contraction phase, increased total stroke volume, decreased systemic flow, and decreased pressure generation, all due to left-to-right shunting. Concomitantly, shunt flow, pulmonary flow, pulmonary capillary wedge pressure (PCWP), LV end-diastolic volumes, and the pulmonary-to-systemic blood flow ratio (Qp:Qs) increased. Also a result of shunting, the RV PV loop showed progressive clockwise tilt such that volume increased during early systole. Additional simulations showed that the relative effects of the different MCS options were independent of VSD size (data not shown); therefore, the remaining simulations were performed with a 16.5 mm VSD which, as detailed above, corresponds with average size reported in the literature.

Accordingly, the parameters of the simulation were adjusted to reproduce the average literature-based hemodynamic parameters in the presence of a 16.5 mm VSD as detailed in Table 2 and illustrated in Figure 2. Mean blood flow through the aortic valve was 3.8 L/min, mean flow through the VSD was 7.5 L/min, total pulmonary flow was 11.2 L/min, and the Qp:Qs was 3.0 (blood flows shown in yellow-highlighted boxes). As illustrated in Figure 2A, whereas central venous oxygen saturation was 67%, a

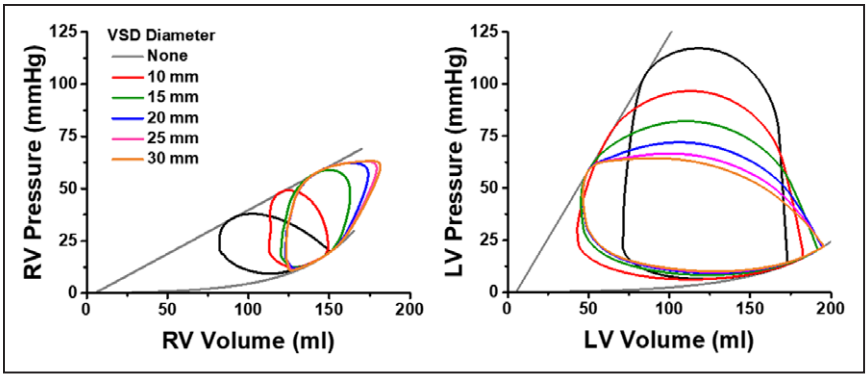

Figure 1. Right ventricular (RV) and left ventricular (LV) pressure-volume loops with cardiogenic shock state without ventricular septal defect (VSD), and with VSDs of sizes varying from 10 to 30 mm as indicated in the figure inset.

step-up in oxygen saturation is seen in the RV to 89%, consistent with values in the literature (Table 1).[9] Note the markedly reduced peak LV and aortic pressure and increases peak RV and pulmonary pressures compared with pre-VSD conditions (Figure 2D through 2G). Also, note that there is near equalization of right and LV pressures during the latter part of relaxation. The flow through the VSD (Figure 2H) is overwhelmingly left-to-right, as demonstrated in this case, a small degree of right-to-left flow occurs during the latter part of diastole as has been reported in the literature[32] and illustrated in the Doppler echocardiogram in Movie I in the Data Supplement.

Medical Therapies

Medical therapies commonly used in CS include inotropes, vasodilators, and vasoconstrictors: each alone or in certain combinations. Overall hemodynamic simulation results are summarized in Table 2, and the impact on RV and LV mechanics are illustrated in the PV loops of Figure 3.

Inotropes increased blood pressure and CO but markedly increased VSD flow and pulmonary pressures. As a result of increased pulmonary, systemic, and shunt flows, PCWP and central venous pressure (CVP) both increased. Thus, despite improved peripheral perfusion (Figure I in the Data Supplement), this approach did not improve the overall hemodynamic profile.

Reduction of afterload resistance with vasodilators can increase forward flow and reduce F_{VSD} and Qp:Qs but can reduce blood pressure. Accordingly, use of vasodilators may not be applicable. Addition of inotropes can counteract such effects to a certain extent (Table 2 and Figure 3B). Impact on flows and oxygen saturations are further summarized in Figures II and III in the Data Supplement.

Table 2. Hemodynamic Impact of Various Combinations of Medical Therapy, Including Vasodilation, Vasoconstriction, and Inotropic Stimulation

	Baseline	Inotrope	Vasodilator	Vasodilator +Inotrope	Pressor	Pressor +Inotrope
Flows, L/min						
Aortic	3.8	5.0	4.5	6.2	2.8	3.8
MCS	n/a	n/a	n/a	n/a	n/a	n/a
VSD	7.5	9.5	6.3	7.3	8.8	11.4
PA	11.2	14.4	10.8	13.4	11.6	15.1
Total body	3.8	5.0	4.5	6.2	2.8	3.8
Qp:Qs	3.0	2.9	2.4	2.2	4.0	4.0
Pressures, mm Hg						
CVP	18	20	16	18	17	18
PA (mean)	40	49	36	43	42	53
PCWP	26	31	23	26	28	34
Ao (mean)	61	71	50	57	70	84
Venous O_2 saturation, %	67	75	72	79	58	68
PA O_2 saturation, %	89	91	88	90	89	91

Percent changes in parameters are provided in Table III in the Data Supplement. Pressor, phenylephrine 75 μg/min; inotrope, dobutamine 7.5 μg/(kg·min); vasodilator, nitroprusside 3 μg/(kg·min). Ao indicates ascending aorta; CVP, central venous pressure; MCS, mechanical circulatory support; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; Qp:Qs, pulmonary-to-systemic blood flow ratio; RA, right atrium; and VSD, ventricular septal defect.

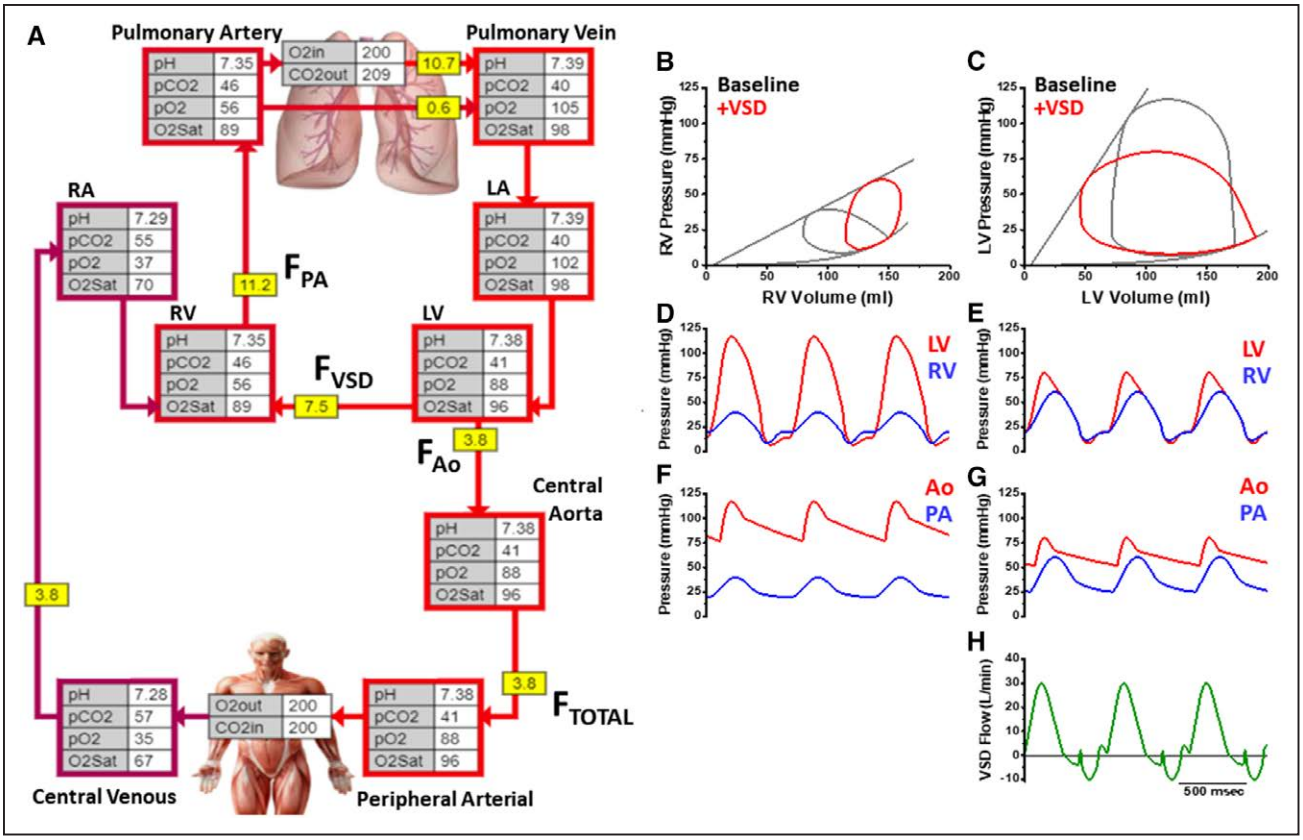

Figure 2. Hemodynamic profile in a patient with ventricular septal defect simulation.
A, Blood gas analysis and flow in different chambers of the heart, pulmonary and systemic circulation in a simulation of a patient with ventricular septal defect (VSD). Blood flows shown in yellow-highlighted boxes. F_{AO}, 2.0 L/min. O_2in and CO_2out are both relevant for the lungs and extracorporeal membrane oxygenation (ECMO) gas exchanger. **B**, Pressure-volume (PV) loops of the RV in a patient before and after simulated introduction of a 1.6 cm VSD shunt that resulted in a flow of 7.5 L/min. **C**, PV loops of the LV in a patient before (gray) and after (red) simulated introduction of a VSD shunt of 7.5 L/min. **D** and **E**, Pressure tracing in LV (red) and RV (blue) before and after VSD simulation. **F** and **G**, Pressure tracing in aorta and pulmonary artery before and after VSD simulation. **H**, Flow through the VSD during systole and diastole. CO_2in indicates carbon dioxide flux into the blood equivalent to total body CO_2 production; CO_2out, carbon dioxide flux out of the blood; F_{AO}, flow through aorta; F_{MCS} (ECMO), flow through ECMO; F_{PA}, flow through pulmonary artery; F_{TOTAL}, flow through peripheral arterial system; F_{VSD}, flow through VSD shunt; LA, left atrium; LV, left ventricle; MCS, mechanical circulatory support; O_2in, oxygen flux into the bloodstream; O_2out, oxygen flux out of the blood equivalent to total body oxygen consumption; O_2sat, oxygen saturation ; RA, right atrium; and RV, right ventricle.

Pressors can increase systemic blood pressure but can increase shunting and reduce systemic perfusion and thus reduce mixed venous saturation (Table 2, Figure 3C, and Figure IV in the Data Supplement). Inotropes can counteract these detrimental effects, but such a combination was the least effective at improving overall hemodynamics (Figure V in the Data Supplement). Estimated drug effects in relation to doses are summarized in Table II in the Data Supplement.

Impact of MCS

Overall results of MCS simulations are summarized in Table 3, Figure 3, and Figures VI through XII in the Data Supplement. By way of overview, venous blood oxygen saturations increased in proportion to blood flow to the periphery and mixed venous oxygen saturation (after mixing of blood returning from the veins with shunted blood from the LV) increased in proportion to the amount of flow through the VSD.

Intra-Aortic Balloon Counter Pulsation

With IABP, balloon deflation during systole reduces effective arterial afterload, thus facilitating ejection through the aortic valve. The increase in total blood flow to the body was 0.5 L/min (from 3.8 to 4.3 L/min), similar to what is seen on an average in CS with[13] or without[33] a VSD. Accordingly, there was only a small rise in mixed venous oxygen saturation. There was a decrease in flow through the VSD with a concomitant decrease in Qp:Qs from 3.0 to 2.6, also very similar to the average reported in the literature.[13] There were only small effects on PCWP and CVP. The impact of IABP on the PV loops (Fig. 4A) was also relatively subtle, mainly illustrating the reduction of peak LV and RV pressures. Additional details provided in Figure VI in the Data Supplement.

RA-to-Arterial Circulatory Support (ECMO)

ECMO support, consisting of pumping blood from the RA to the arterial system (at a rate of 3.6 L/min) through an oxygenator markedly improved total blood flow (to

Table 3. Comparison of Hemodynamic Parameters in the Presence of a VSD Without and With Different Form of Percutaneous Mechanical Circulatory Support

Prototypical Device			ECMO*	TandemHeart	Impella CP	Impella 5.0	ECPELLA* (CP)	ECPELLA* (5.0)	ECMO*+LV Vent
Configuration	Baseline	IABP	RA→Art	LA→Art	LV→Ao	LV→Ao	RA→Art+LV→Ao	RA→Art+LV→Ao	RA→Art+LV→Art
Flows, L/min									
Aortic	3.8	4.3	2.0	1.6	1.2	0.4	0.0	0.0	1.6
MCS	n/a	n/a	3.6	3.5	3.6	4.9	3.5/3.5†	3.5/4.6†	2.0/1.5†
VSD	7.5	6.8	10.0	7.5	6.6	6.2	8.5	7.1	8.0
PA	11.2	11.0	12.0	12.5	11.5	11.5	12.0	11.7	11.6
Total body	3.8	4.3	5.5	5.0	4.9	5.4	7.0	8.0	5.1
Qp:Qs	3.0	2.6	2.2	2.5	2.3	2.1	1.7	1.5	2.3
Pressures, mm Hg									
CVP	18	18	16	17	18	18	17	18	17
PA (mean)	40	39	43	38	39	38	41	38	41
PCWP	26	25	29	23	24	24	26	23	27
Ao (mean)	61	67	77	74	73	78	93	107	75
Venous O_2 saturation, %	67	70	86	75	73	75	88	90	85
PA O_2 saturation, %	89	88	97	89	89	89	96	96	95

Ao indicates ascending aorta; Art, peripheral artery such as femoral artery; CVP, central venous pressure; ECMO, extracorporeal membrane oxygenation; ECPELLA, ECMO and Impella; IABP, intra-aortic balloon pump pulsation; LA, left atrium; LV, left ventricle; MCS, mechanical circulatory support; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; Qp:Qs, pulmonary-to-systemic blood flow ratio; RA, right atrium; and VSD, ventricular septal defect.

*Includes an oxygenator in the circuit.

†First number is the flow through the ECMO circuit; second number is the flow through the MCS device.

5.5 L/min) but increased flow through the VSD to 10.0 L/min. The addition of blood oxygenation substantially increased oxygen saturation in all compartments of the circulation (Figure VIIA in the Data Supplement). There were meaningful increases in arterial pressures but, as a result of the increased flow through the VSD and the increased afterload pressure on the LV, pulmonary pressures (including PCWP) all increased. Initiation of ECMO results in rightward shift of the LV PV loop towards a higher end-diastolic pressure and upward with increased peak LV pressure (Figure 4B). The increased pulmonary arterial pressures also result in rightward and upward shifts of the RV PV loops. These ECMO simulations are with a flow at 3.6 L/min. As ECMO flow is increased, there are further increases in total CO, mean arterial pressure (MAP), VSD flow, PA flow, decreased systemic blood flow (Figure VIIB in the Data Supplement, with ECMO flow 5.0 L/min), and decreased arterial pulse pressure signifying increasingly less aortic valve opening which can increase risk of development of an aortic root thrombus (as shown in Figure 5). The combination of ECMO with different LV venting strategies will be discussed below. Additional details provided in Figures X and XI in the Data Supplement.

LA-to-Arterial Circulatory Support (TandemHeart)

Pumping blood at a rate of 3.5 L/min (typical flow achieved with this form of support) from the left atrium to the arterial system increased MAP by ≈14 mm Hg (Table 3, Figure 4C), an amount similar to that reported in the literature (Table 1).[10] PCWP decreased by ≈4 mm Hg, and this was also associated with a similar decrease in mean PA pressure. As a result of the increased arterial pressure, flow through the aortic valve was decreased while flow through the VSD was not significantly altered; total blood flow to the body was significantly increased. In contrast to ECMO, with LA-to-arterial, there was a leftward shift of the LV PV loop (Figure 4C); like ECMO, peak LV pressure increased because of the increased afterload pressure on the LV. The RV loops also shifted leftward in response to the decreased afterload pressure on the RV. With increased pump flow, there are further increases in total CO, MAP, PA flow, and decreased flow through the VSD and aortic valve and decreased arterial pulse pressure signifying increasingly less aortic valve opening (as shown in Movie II in the Data Supplement). Additional details provided in Figure VIII in the Data Supplement.

LV-to-Aorta Circulatory Support (Impella)

Direct pumping of blood from the LV to the aorta decreased flow through the aortic valve, increased total flow to the body, and significantly decreased flow through the VSD with little effect on PA flow. There was an increase of MAP and a decrease of PCWP, whereas PA pressure was minimally affected. LV PV loops (Figure 4D) shifted leftward towards lower filling pressures and volumes, whereas peak LV pressure increased only slightly. Similarly, the RV PV loops also shifted slightly

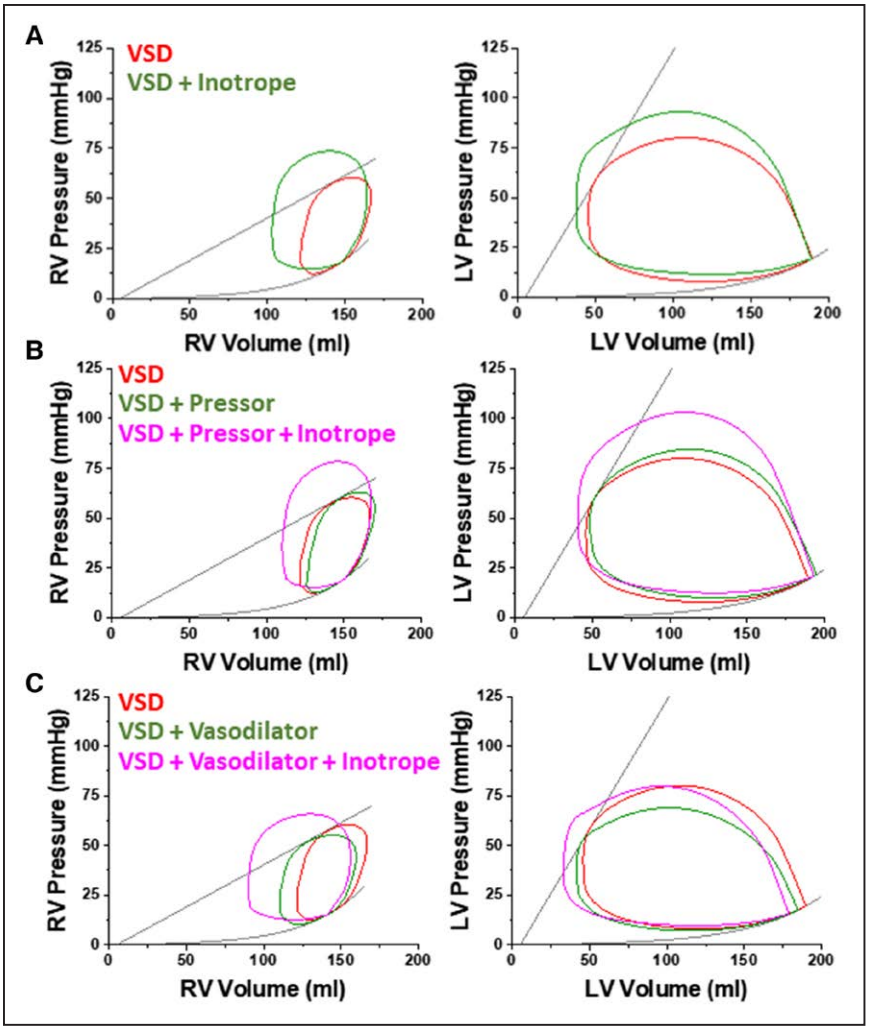

Figure 3. Demonstrates prototypical pressure-volume loops of the right ventricle (RV) and left ventricle (LV) in patient with ventricular septal defect (VSD) with different medical therapy.
Loops in red are baseline in each panel. Other simulations as follows: (**A**) with inotrope (green); (**B**) with pressor (green) and with pressor+inotropes (pink); (**C**) with vasodilator (green) and with vasodilator+inotrope (pink).

leftward towards preloads, but peak RV pressures did not change. All of these effects were quantitatively larger when simulating the effect of device pumping at a rate of 4.9 L/min (eg, Impella 5.0) compared with when simulating the effects of a device pumping 3.6 L/min (eg, Impella CP). The impact of a 4.9 L/min device on flows and oxygen saturations are summarized in Figure IX in the Data Supplement.

Combination of RA-to-Arterial and LV-to-Aortic Circulatory Support (ECMO and Impella)

The increased afterload, LV filling, and PCWP associated with ECMO can be offset by combining it with an LV unloading strategy, such as offered by an Impella (Table 3, Figure 4E). The combination of 2 devices provides the greatest degree of overall circulatory support while simultaneously unloading of the LV. Compared with ECMO alone, total blood flow to the body is increased, blood flow through the aortic valve is markedly reduced (or eliminated), and flow through the VSD is decreased. There are further increases in arterial pressure, loss of arterial pulse pressure, and reductions of PCWP. Addition of LV-to-aorta pumping resulted in leftward shifts of both LV and RV PV loops. All of these effects on hemodynamics and PV loops were quantitatively larger with an LV-to-aorta pumping 4.9 L/min compared with a 3.6 L/min pump. Additional details are provided in Figure X in the Data Supplement.

Combination of RA-to-Arterial (ECMO) With a Passive LV Vent

An alternate means of dealing with LV loading caused by ECMO is the insertion of a passive LV vent that is connected to the venous port of the ECMO circuit; the cannula is inserted surgically through the LV apex via a mini-thoracotomy procedure[34] (Table 3, Figure 4F). We explored the impact of a passive LV vent with flow through the vent of 2.0 L/min. In comparison to ECMO alone, total blood flow to the body was decreased, as were flows through the aortic valve and through the VSD. MAP and, importantly, PCWP were decreased compared with ECMO alone. In comparison to ECMO and Impella (ECPELLA), the major hemodynamic differences were that total blood flow to the body and MAP were both lower with the LV vent. Shifts of the LV and RV PV loops were similar to those observed with

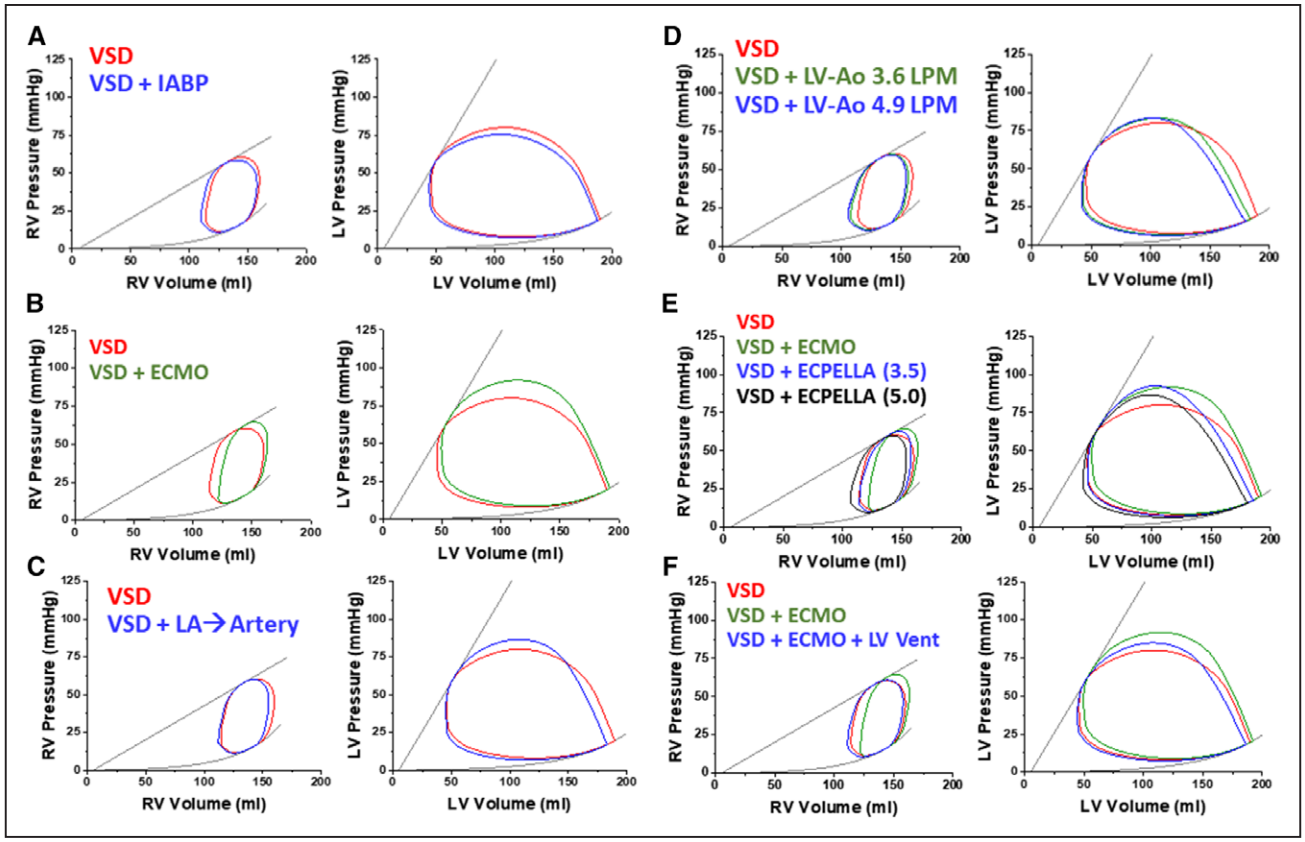

Figure 4. Comparison of prototypical pressure-volume loops of the right ventricle (RV) and left ventricle (LV) in a ventricular septal defect (VSD) patient with different mechanical circulatory support devices.

Loops in red are baseline in each panel. Other simulations as follows: (**A**) intra-aortic balloon pump pulsation (IABP; blue); (**B**) extracorporeal membrane oxygenation (ECMO; green); (**C**) left atrium (LA) to arterial pump (blue); (**D**) with LV-to-aorta at 3.5 L/min (green) and at 5.0 L/min (blue); (**E**) ECMO (green), ECMO+pLVAD at 3.5 L/min (blue), ECMO+pLVAD at 5.0 L/min (black); and (**F**) with ECMO (green) and with ECMO+passive LV vent (blue). ECPELLA indicates ECMO and Impella.

ECPELLA; however, peak LV pressure decreased (instead of increased) with the LV vent. Additional details are provided in Figure XI in the Data Supplement.

DISCUSSION

The infrequent incidence and acuity of disease[1] render the conduct of clinical studies of AMI-VSD between different forms of MCS difficult if not impossible. It is under such conditions that computational models have the potential to provide insights into physiologically based clinical decision making, allowing for direct comparison of treatment strategies without variability introduced due to differences in baseline hemodynamics and clinical conditions among patients.

The cardiovascular model used in this study[28] has accurately replicated the hemodynamics of a wide range of pathological conditions and has predicted and explained the hemodynamic impact of specific types of therapeutic interventions including many forms of MCS.[29,31,35–37] In the present study, the model successfully replicated the hemodynamic profile of an average AMI-VSD patient based on information in the literature. The model also replicated the known impact of pharmacological therapies, at least on a directional basis; no quantitative clinical data are available to perform direct comparisons. The model could equally well have simulated patients with different degrees of shock, but for the purpose of identifying basic principles, we focused on 1 profile and explored a wide range of MCS options. It was notable that to achieve that average hemodynamic profile, the size of the VSD (16.5 mm diameter) was very close to the median size reported in 2 separate studies.[24,38]

The first important insight provided by the model results was that no form of MCS was capable of normalizing hemodynamics in the setting of VSD; flow through the PA is always markedly elevated. This may occur because of increased left-to-right shunting through the VSD or due to increased right-sided venous return from increased systemic flow in the presence of left-sided support provided by the MCS device (Table 3). Thus, the benefit of MCS is to shift flow from going through the VSD and diverting it to the periphery, as evidenced by a change in Qp:Qs.

Different form of MCS provided different degrees of improvements in blood pressure and CO individually and in combination. In terms of potency of improv-

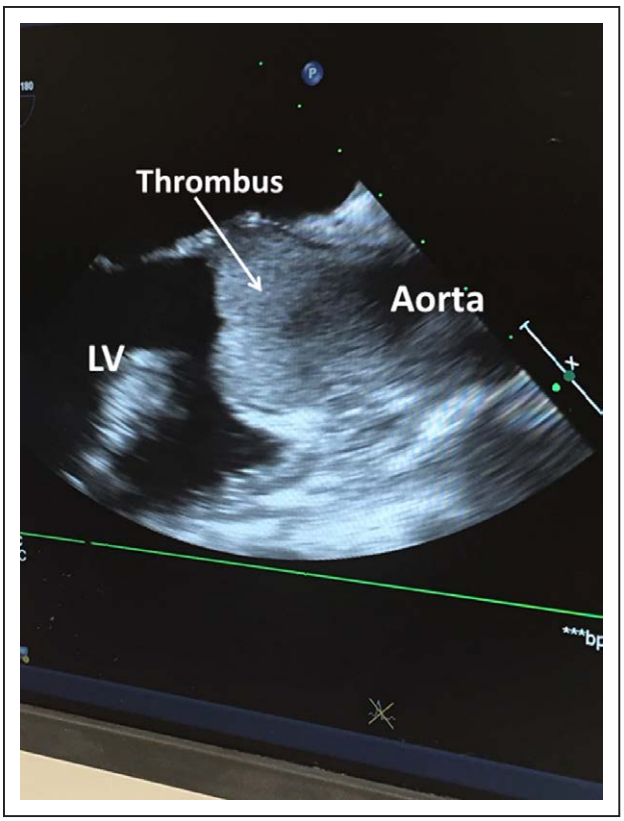

Figure 5. Patient with ventricular septal defect and extracorporeal membrane oxygenation with closed aortic valve and an aortic thrombus.
LV indicates left ventricle.

ing these indexes, the following order was revealed: ECMO plus LV-to-aortic pumping > high flow LV-to-aorta pumping (eg, Impella 5.0) > ECMO > LA-to-arterial pumping (eg, TandemHeart) > LV-to-aorta pumping using a 3.6 L/min device (eg, Impella CP) > ECMO with an LV vent > IABP. However, the impact on PCWP and VSD flow differed most among the approaches. PCWP decreased with LV-to-aorta pumps, and ECPELLA decreased minimally with IABP and increased with ECMO alone. Flow through the VSD was decreased most by LV-to-aorta pumps followed by IABP; lesser effects were noted with LA-to-arterial and ECMO plus LV vent; all other approaches increased flow through the VSD. VSD flow was increased most by ECMO alone. Key findings are summarized graphically in Figure XII in the Data Supplement.

One discrepancy between the model predictions and limited data in the literature was the impact of LV-to-aorta, IABP, and LA-to-arterial pumping on PCWP. Clinical reports, summarized in Table 1, indicated much larger changes than seen in the simulation.[9,13,26] However, as detailed further below, the model predicts acute hemodynamic effects, whereas the timeframe between baseline and follow-up measurements in the clinical reports is not provided. Accordingly, reported large differences between pre- and post-MCS conditions most likely reflect influence of changes in medical therapies, renal function, and overall volume status occurring over longer timeframes. Nevertheless, model predictions are consistent with physiological principles; in the presence of recycling of flow through the PA, the only way to reduce PCWP in the setting of VSD is to substantially increase flow out of the LV or LA to the systemic arterial system using MCS. However, although shunt flow may be decreased, this will also result in increased total systemic flow which, in turn, increases venous return and thus maintains high flows through the pulmonary circuit and maintains relatively high PCWP (as illustrated in Table 3). Therefore, reductions in PCWP (and CVP for that matter) are predicted to be achieved mainly through management of volume status.

It is, therefore, noteworthy that model-predicted changes in total body flow and Qp:Qs were, in all cases, very similar to those reported in the literature. Qp:Qs is less subject to changes in volume status than are filling pressures.

As per the recent European Society of Cardiology Guidelines in patients with persistent CS and VSD, it is a class IIa recommendation (level of evidence C) to use short-term MCS as a bridge-to-recovery or surgery[39]; however, the guidelines do not specify a preferred form of support. In the current US guidelines, there is no comment on the level of evidence about the role of short-term MCS device for patients with AMI-VSD, whether occurring with or without CS. Based on the current results, LV-to-aorta and LA-to-arterial approaches would be favored when employing a single-device strategy due to primary effect of decreasing PCWP and unload the LV; higher flow devices provide greater degrees of unloading and improvement of total systemic flow. Although ECMO as a single device may provide the greatest improvement in blood pressure, this is achieved at the expense of increased PCWP, intracardiac pressures, and myocardial oxygen demand, which may impede ventricular recovery. One clinical feature that favors use of an ECMO approach is significant hypoxemia. Peripheral oxygen delivery though peripheral ECMO, however, creates the potential for differential hypoxemia where different vascular beds may remain relatively oxygen-poor depending on their location with respect to the reinfusion cannula. We also found that with increased ECMO blood flow (in the range from 3.6 to 5.0 L/min), total systemic, VSD shunt and pulmonary flows all increased, but there were no significant changes in CVP or PCWP. Thus, the main findings related to filling pressures are not critically dependent on ECMO flow in this range; this applies to ECMO alone or in combination with an Impella or LV vent unloading strategy. As in CS in general,[36,40,41] ECMO-supported patients should be monitored for signs of aortic valve closure, which may result in aortic root thrombus formation (as shown in Figure 5) and lack of reduction

or increases of PCWP in which case simultaneous use of a mechanical LV venting strategy (eg, ECPELLA) is indicated.

Surgical and percutaneous VSD repair are definitive treatment options[4,38,42,43] but are also associated with high mortality. Although ST-segment–elevation myocardial infarction guidelines recommend emergent surgical repair even in hemodynamically stable patients,[44] such procedures are associated with high early mortality.[1] Repair within 7 days has been associated with 54.1% mortality compared with 18.4% for elective procedures after 7 days after myocardial infarction.[45] Clinical stabilization and evolution of the infarcted cardiac tissue allow for a better tissue suturing substrate and more effective repair.[2] Better survival may also be because of selection and survival bias; patients who survive for >7 days before surgical repair likely have less severe hemodynamic compromise and preservation of end-organ function and are more likely to survive surgery. Mortality rates are similarly high with percutaneous closure approaches, with a similar inverse relationship between the timing of the procedure and mortality.[4,38,43] Thus, efforts to establish the most effective means of hemodynamically stabilizing patients with AMI-VSD may allow a greater number of survivors to an elective repair procedure.

Limitations

Results derived from computational models are subject to limitations which have been discussed previously.[35] Among these is that such models only account for short-term hemodynamic effects without accounting for intermediate (hours-to-days) physiological responses, such as changes in vascular tone, volume status (in the face of potentially improved renal function while on support), and heart recovery. Such factors may account for some of the differences noted between model predictions (Table 4) compared with those observed clinically (Table 1). In the clinical reports, with the exception of 1 study that provided daily measurements,[13] only single pre- and post-MCS measurements[6,9,10,17] are provided, and the timing of those measurements are either not specified or vary significantly among patients. Despite the limitation of the simulations and the potential limitations of the hemodynamic measurements in the clinical setting, there were important aspects where the model provided valuable predictions. Importantly, the advantage of modeling is the ability to directly compare hemodynamic effects of different strategies on equal ground.

Conclusions

In summary, the cardiovascular model used successfully replicated the average hemodynamics of patients reported in the literature and illustrated the limitations of medical therapies. Although ECMO, LV-to-aorta, and LA-to-arterial pumping can provide similar total blood flow to the periphery, ECMO can markedly increase VSD flow whereas this is decreased by LV-to-aorta and LA-to-arterial pumping. ECPELLA provided the greatest increase in flow to the body and blood pressure, but because of offsetting effect, PCWP or flow through the shunt may not be changed. No form of MCS normalizes hemodynamics in VSD (Table 3); no matter the approach, flow through the pulmonary circuit remains high and Qp:Qs does not normalize. Therefore, the goal of MCS should be to optimize total blood flow and oxygen delivery to the body, achieve adequate blood pressure, and minimize PCWP and CVP to bridge patients to a definitive VSD closure procedure. The choice of MCS device(s), either alone or in combination, should, therefore, include device availability, team familiarity, and structural issues in the infarcted ventricle including extent of ventricular damage (ie, friability of anterior free wall or posterior damage) and presence of LV thrombus.

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Correspondence

Mohit Pahuja MD, Division of Cardiology, Department of Internal Medicine, Detroit Medical Center/Wayne State University Medical School of Medicine, 4201 St Antoine, Suite 5A, Detroit, MI 4820. Email mohit.pahuja2@wayne.edu

Affiliations

Division of Cardiology, Department of Internal Medicine, Detroit Medical Center/Wayne State University Medical School of Medicine, Detroit, MI (M.P.). Department of Cardiology, University Heart Centre Hamburg Eppendorf, Hamburg, Germany (B.S., D.W.). Division of Cardiology, Department of Medicine, Henry Ford Health System, Detroit, MI (M.B.B.). Division of Cardiology, Department of Medicine, Columbia University Medical Center, New York, NY (A.R.G., D.B.). Cardiovascular Research Foundation, New York, NY (D.B.).

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