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ORIGINAL ARTICLE

Intermittent Occlusion of the Superior Vena Cava Reduces Cardiac Filling Pressures in Preclinical Models of Heart Failure

Navin K. Kapur[1] · Lara Reyelt[1] · Paige Crowley[1] · Lauren Richey[1] · John McCarthy[1] · Shiva Annamalai[1] · Sarah Newman[1] · Lena Jorde[1] · Sina Forotuanjazi[1] · Allen Razavi[1] · Tim Lenihan[1] · Daniel Burkhoff[1] · Richard H. Karas[1]

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Abstract

Congestion is a major determinant of clinical outcomes in heart failure (HF). We compared the acute hemodynamic effects of occlusion of the superior (SVC) versus the inferior vena cava (IVC) and tested a novel SVC occlusion system in swine models of HF. IVC occlusion acutely reduced left ventricular (LV) systolic and diastolic pressures, LV volumes, cardiac output (CO), and mean arterial pressure (MAP). SVC occlusion reduced LV diastolic pressure and volumes without affecting CO or MAP. The preCARDIA system is a balloon occlusion catheter and pump console which enables controlled delivery and removal of fluid into the occlusion balloon. At 6, 12, and 18 h, SVC therapy with the system provided a sustained reduction in cardiac filling pressures with stable CO and MAP. Intermittent SVC occlusion is a novel approach to reduce biventricular filling pressures in HF. The VENUS-HF trial will test the safety and feasibility of SVC therapy in HF.

Keywords Heart failure · Devices · LV unloading · Circulatory support · Hemodynamics

Introduction

Approximately 23 million individuals worldwide suffer from heart failure and account for over 1 million hospitalizations annually in the USA alone [1]. In patients with heart failure, poor heart function overloads the lungs with fluid and leads to shortness of breath. Recent data shows that elevated cardiac filling pressures predict short- and long-term outcomes in advanced heart failure [2, 3]. Diuretics improve these symptoms and heart function by reducing fluid overload. However, diuretics take time to work and may be ineffective in subjects with chronic heart failure. For this reason, a device-based approach to reduce fluid overload may quickly improve symptoms and heart function in subjects with congestive heart failure. No devices are currently FDA-approved for the purpose of rapidly reducing cardiac filling pressures and improving heart function in subjects with heart failure.

The Frank-Starling mechanism identifies preload as a major determinant of cardiac output reducing volume overload may improve cardiac output, or at least not diminish cardiac output, among patients with systolic heart failure in a volume-overloaded state [4]. The superior (SVC) and inferior vena cava (IVC) account for one-third and two-thirds of venous return to the heart, respectively. We postulated that temporary occlusion of the SVC may rapidly reduce intracardiac pressures without decreasing systemic blood pressure or cardiac output. We now compared the hemodynamic effects of acute SVC versus IVC occlusion and further tested a novel catheter-mounted SVC occlusion system (preCARDIA Inc.) in a swine model of congestive HF.

Methods

Experimental Protocol of Myocardial Infarction

Studies were conducted in adult, male Yorkshire swine. The study protocol was approved by the Institutional Animal Care

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✉ Navin K. Kapur
Nkapur@tuftsmedicalcenter.org

[1] Molecular Cardiology Research Institute and The CardioVascular Center, Tufts Medical Center, 800 Washington Street, Box # 80, Boston, MA 02111, USA

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and Use Committee (IACUC) at Tufts Medical Center. All experiments were performed according to the committee's guidelines. Animals were premedicated with Telazol (0.8 ml/kg, intramuscular). General anesthesia was induced and maintained with isoflurane (1–2%). All animals were intubated and mechanically ventilated (Harvard Apparatus Inc.) with room air and supplemented oxygen to maintain physiologic pH and oxygen saturation. Surface electrocardiography leads, an orogastric tube, peripheral 18 G venous catheters, and a rectal thermistor were placed in all animals. Heating pads were used as needed to maintain a core body temperature > 99 °F. Vascular access sheaths were then deployed into the right internal jugular vein (10Fr), left carotid artery (7Fr), and both femoral arteries (7Fr) and veins (10Fr). Unfractionated heparin boluses with a goal-activated clotting time of 300–400 s, continuous lidocaine infusion (1 mg/kg), and noradrenaline (0.16 mcg/min) were initiated in all animals. A 6Fr Judkins right coronary catheter (Boston Scientific) was engaged in the left coronary artery via the right femoral artery and baseline angiograms were recorded. A 3.0 × 8 mm angioplasty balloon (Boston Scientific) was deployed in the mid-LAD (left anterior descending artery) after the first diagonal branch with angiographic confirmation of LAD occlusion. After 120 min, the LAD balloon was deflated and coronary angiography was performed immediately after reperfusion and again after the end of the study protocol to confirm patency of the LAD.

Comparison of Acute IVC and SVC Occlusion Hemodynamics

Seven days after LAD occlusion and reperfusion, animals were returned to the catheterization laboratory for testing. Animals were intubated, anesthetized, and instrumented or hemodynamic analysis was performed as described above. After initial hemodynamic assessment, SVC venography was performed and a 32-cc endovascular balloon (Cook Medical) was deployed via the right internal jugular vein and inflated to occlude the IVC for up to 5 min, followed by a 15-min recovery period. The Coda balloon was then repositioned to occlude the SVC for up to 5 min. For the acute study, LV pressure and volume were recorded throughout the study protocol. For LV pressure and volume measurements, a 5Fr conductance catheter system (Sigma-M; CD Leycom, the Netherlands) deployed via the left carotid was used as we have previously described [5, 6]. Absolute LV volumes were measured by subtracting parallel conductance from total conductance volumes. Stroke volume is calculated as the difference in conductance volumes at +dP/dtmax and − dP/dtmin. LV stroke work was calculated as the product of peak LV peak systolic pressure and stroke volume.

Intermittent SVC Occlusion in a Model of Volume Overload Heart Failure

After 120 min of LAD occlusion as described above, the right and left renal arteries were occluded for 120 min with infusion of 10% hypertonic saline and 4 l of normal saline after reperfusion. The right and left renal arteries were then occluded in alternating fashion for 30 min in each artery for an additional 6 h. The preCARDIA SVC therapy system consists of two parts: a semi-compliant, atraumatic balloon occlusion catheter with tubing set and a pump console which enables controlled delivery and removal of fluid into the occlusion balloon. The preCARDIA catheter was introduced via the right internal jugular vein with a distal tip positioned in the right or left pulmonary artery and a proximal occlusion balloon positioned in the SVC. A fixed amount of 20% contrast in normal saline was delivered into the balloon at 0.5 ATM of pressure until occlusion of the SVC was achieved. SVC occlusion was confirmed by venography and demonstration of a pressure gradient between the right atrium (RA) and internal jugular (IJ) vein. The device was then programed to occlude the SVC for 5 min, followed by a 10-s period of volume removal (duty cycle) to re-establish flow through the SVC before the next occlusion phase. The duty cycle was then performed for up to 18 h of continuous pumping. Hemodynamic data was recorded during balloon inflation from a pulmonary artery catheter delivered via the right femoral vein.

Statistical Analysis

Results are presented as mean ± SD. For comparison of continuous variables between individual animal subjects, a pairwise student *T* test was performed. An unpaired student *T* test or one-way ANOVA was used to compare continuous variables between groups, with a Bonferroni correction performed. All statistical analyses were performed with GraphPad Prism (GraphPad Software, Inc., La Jolla, CA). An alpha-level of $p < 0.05$ was considered to indicate a significant effect or between-group difference.

Results

SVC Occlusion Acutely Reduces Left Ventricular Filling Pressures

SVC occlusion was successfully performed in all 4 animals studied in the acute protocol. Acute IVC occlusion reduced left ventricular (LV) systolic and diastolic pressures, LV volumes, cardiac output, and systemic blood pressure. In contrast, SVC occlusion reduced LV diastolic pressure and volumes without affecting cardiac output or systemic blood pressure (Figs. 1 and 2).

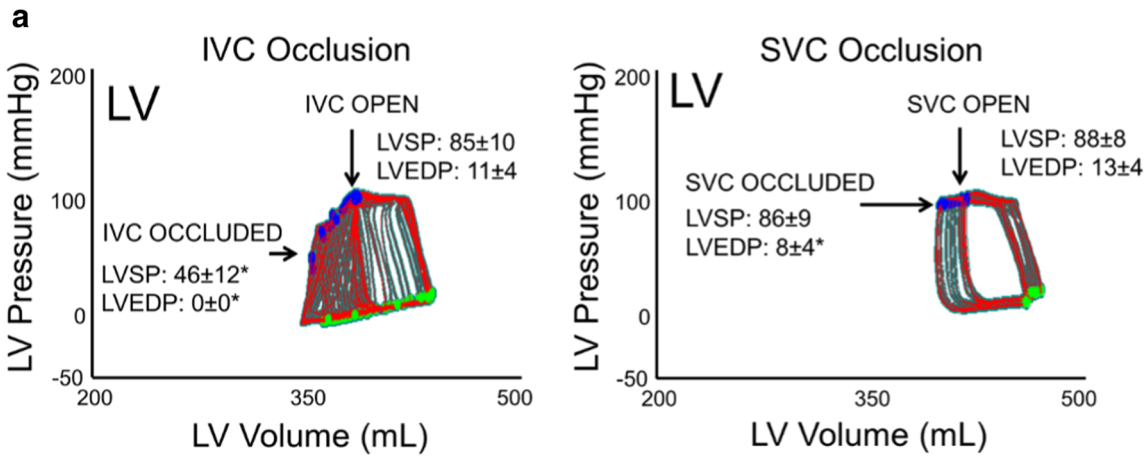

Fig. 1 SVC occlusion reduces lv diastolic not systolic pressure. Representative left ventricular pressure volume loops illustrate the effects of acute inferior (IVC) versus superior vena cava (SVC) occlusion in swine subjects 1 week after acute myocardial infarction induced by left anterior descending artery occlusion. *$p < 0.05$ comparing open versus occluded IVC or SVC ($n = 4$)

Prolonged SVC Therapy Provides a Sustained Reduction in Cardiac Filling Pressures

Volume loading after AMI increased biventricular filling pressures (Table 1; Fig. 3); preCARDIA device insertion and activation was successful in all 3 pigs. Two animals completed 18 h of therapy and one animal completed 14 h of therapy, which was terminated due to bradycardia and hypotension. At 6, 12, and between 14 and 18 h after initiation of SVC therapy, right internal jugular (IJ) venous pressure increased; RA, pulmonary capillary wedge pressure (PCWP), and mean pulmonary artery (PA) pressures decreased while cardiac output (CO) remained unchanged (Table 1; Fig. 4). Mean arterial pressure (MAP) remained above 60 mmHg during SVC therapy. Gross pathology showed no evidence of increased cerebral edema, no pulmonary emboli or cardiac damage, and no evidence of SVC damage or thrombosis due to the preCARDIA device.

Discussion

We report that compared with IVC occlusion, SVC occlusion rapidly decreases cardiac filling pressures without affecting cardiac output or systemic blood pressure and further report that prolonged therapy with the preCARDIA device to deliver intermittent SVC occlusion provided a sustained reduction in cardiac filling pressures. SVC therapy was well tolerated with stable mean arterial pressures and cardiac output and without evidence of damage to the SVC, lungs, heart, or brain. Future studies are required to determine the clinical utility of SVC occlusion as an approach to improve outcomes for patients with acute decompensated congestive heart failure.

Reducing preload is a cornerstone of heart failure therapy. Existing decongestive therapies to reduce cardiac filling pressures include diuretics, ultrafiltration, and vasodilator therapy. None of these therapies have provided clear clinical benefit and are associated with worsening renal function or hypotension [7–9]. For this reason, new approaches to reduce cardiac filling pressures quickly and safely may improve patient symptoms, shorten hospital length of stay, and reduce cardiac work thereby limiting the progression of heart failure. Since preload is governed by venous return through the IVC or SVC, we first sought to determine the hemodynamic effects of obstructing one or the other conduit. We observed that IVC occlusion rapidly reduced cardiac filling pressures, but also severely reduced total cardiac output and systemic blood pressure. These findings are consistent with multiple reports that employ IVC occlusion as a research method to establish end-systolic pressure and volume relationships in the heart [5, 6, 10]. Additionally, IVC occlusion creates a gradient of high pressure in the abdomen and low pressure in the right atrium. As a result, renal, hepatic, and intestinal vein pressures may increase and further impair urine output, hepatic function, and drug absorption which may exacerbate congestive heart failure.

In contrast to IVC occlusion, SVC occlusion reduced cardiac filling pressures without decreasing cardiac output or systemic blood pressure. SVC occlusion may be superior to IVC occlusion as an approach to reduce cardiac filling pressures because it targets only one-third of cardiac preload as opposed to two-thirds. By reducing intracardiac filling pressures without negatively affecting systemic blood pressure or cardiac output, SVC occlusion reduces cardiac workload, oxygen consumption, and promotes rapid decongestion of both the pulmonary and systemic venous circuits [11–13]. Furthermore, by reducing LV volume, SVC occlusion may improve myocyte cross-bridge cycling thereby sustaining cardiac output. SVC occlusion also reduces right heart pressures and therefore may increase LV capacitance by shifting the interventricular septum towards the right heart [14, 15].

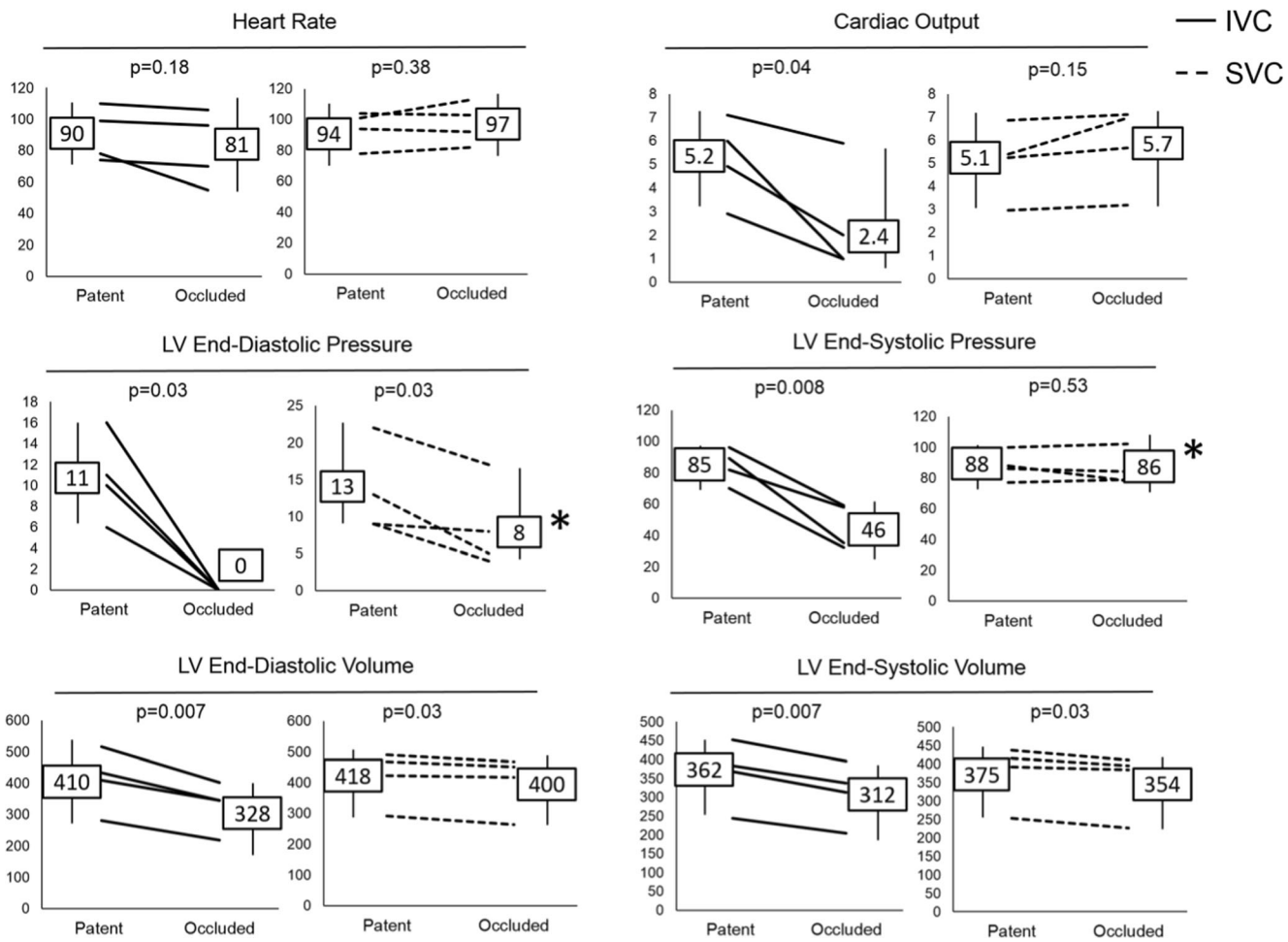

Fig. 2 Acute hemodynamic effects of SVC occlusion in heart failure. Line plots illustrate pairwise analysis of the hemodynamic changes observed with IVC versus SVC occlusion in swine subjects 1 week after acute myocardial infarction induced by left anterior descending artery occlusion. *$p < 0.05$ comparing patent versus occluded IVC or SVC ($n = 4$)

Finally, since SVC occlusion reduces central venous pressure, renal perfusion may improve, thereby leading to earlier decongestion of patients with acutely decompensated heart failure [16–18]. Future studies are required to determine whether application of SVC therapy benefits patients with other preload-dependent conditions such as heart failure with preserved ejection fraction, pulmonary hypertension with right heart congestion, or valvular regurgitation.

To begin studying the potential clinical utility of the SVC occlusion concept, we recently reported that acute SVC occlusion is safe and feasible in patients with heart failure [19]. In this proof-of-concept study, short-term SVC balloon

Table 1 Hemodynamic effects of SVC therapy

	Baseline	Post-AMI + volume loading	SVC therapy			End of study (SVC patent)
			6 h	12 h	13–18 h	
Heart rate (beats/min)	74 ± 8	89 ± 8	75 ± 3*	90 ± 11	95 ± 4	98 ± 2
Mean arterial pressure (mmHg)	84 ± 4	85 ± 8	67 ± 9	59 ± 2*	64 ± 10*	70 ± 4*
Internal jugular vein pressure (mmHg)	3 ± 2	5 ± 4	20 ± 10*	17 ± 4*	17 ± 2*	5 ± 1
Right atrial pressure (mmHg)	11 ± 2	16 ± 3†	12 ± 3*	13 ± 2*	11 ± 2*	17 ± 2
Mean pulmonary artery pressure (mmHg)	17 ± 4	26 ± 2	23 ± 2	18 ± 2*	19 ± 4*	25 ± 2
Pulmonary wedge pressure (mmHg)	11 ± 3	18 ± 3†	12 ± 3*	10 ± 2*	9 ± 2*	14 ± 1*
Cardiac output (l/min)	3.9 ± 0.9	3.7 ± 0.7†	3.7 ± 0.6	3.7 ± 1	4.4 ± 1.5	5.4 ± 1.5

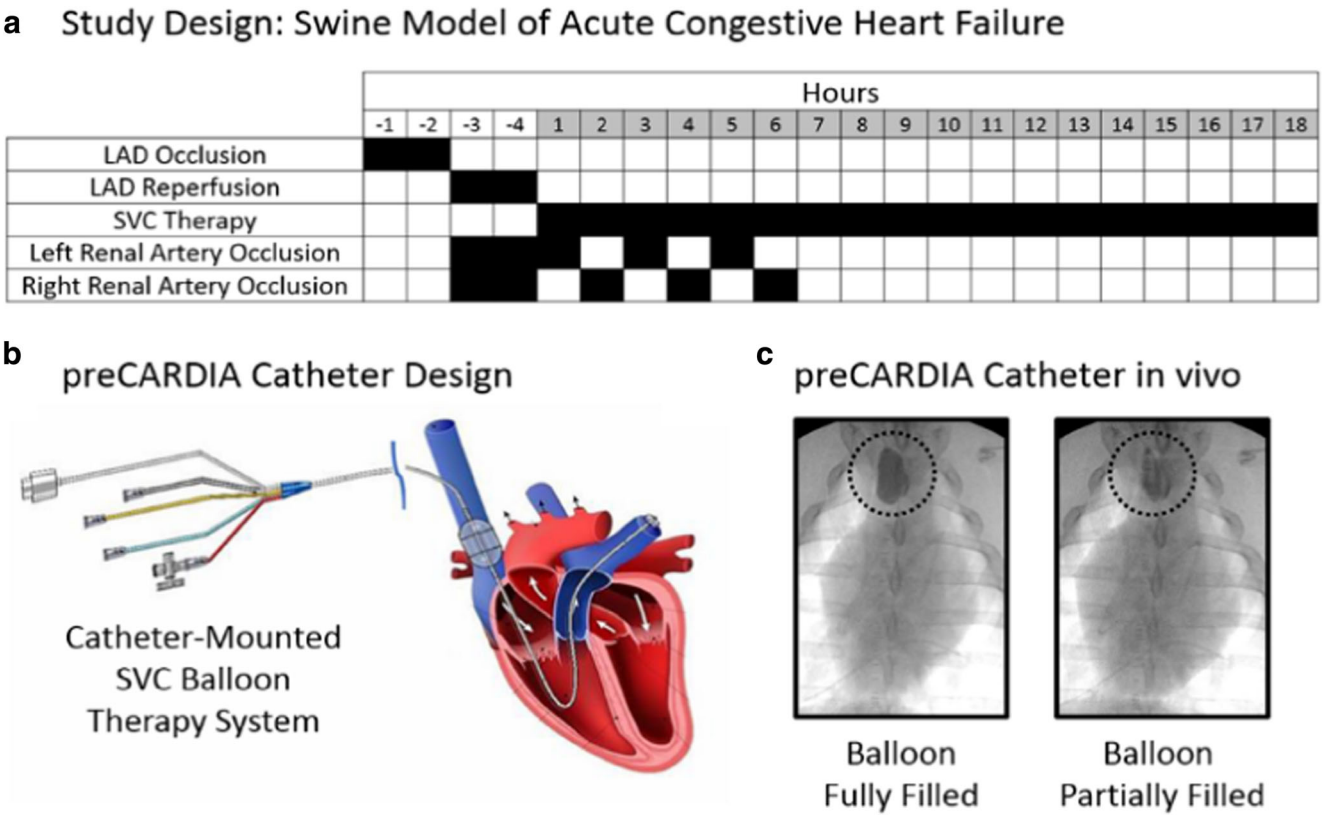

Fig. 3 Study protocol of SVC therapy in a model of heart failure. **a** Experiment design to test the hemodynamic effects of intermittent SVC occlusion in swine subjects with acute heart failure induced by left anterior descending artery occlusion followed by volume loading and intermittent renal artery occlusion ($n = 3$). **b** Illustration of the preCARDIA device with a balloon occlusion catheter, infusion pump, and hemodynamic monitoring console. **c** Fluoroscopic images illustrate the SVC balloon fully filled to achieve SVC occlusion and partially filled to allow for SVC patency throughout the period of SVC therapy

occlusion was performed in eight patients with systolic heart failure. Similar to our findings in the acute animal study above, 5 or 10 min of SVC occlusion reduced biventricular filling pressures without decreasing systemic blood pressure

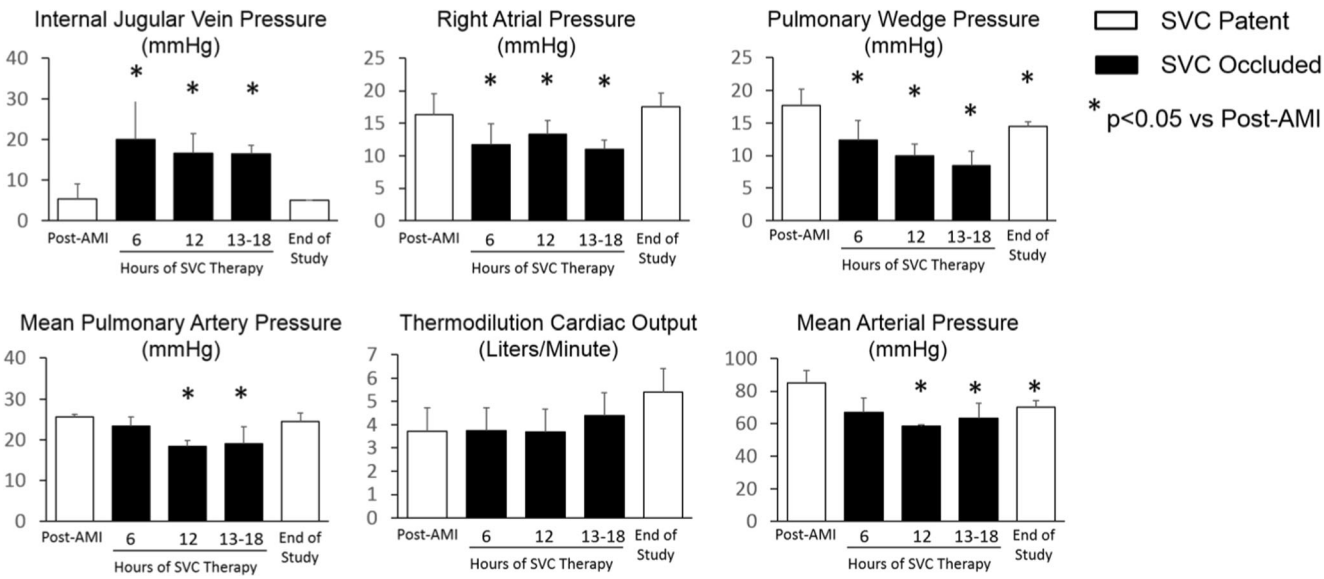

Fig. 4 Hemodynamic effects of SVC therapy in a model of heart failure. Bar graphs illustrate the hemodynamic effects of SVC therapy (intermittent SVC occlusion with the preCARDIA catheter) for up to 18 h with reduced cardiac filling pressures, increased internal jugular vein pressure, and stable cardiac output (*$p < 0.05$ versus baseline; $n = 3$)

or cardiac output. SVC occlusion was well tolerated without adverse events at 7 days of follow-up. This first clinical experience introduces transient SVC occlusion as a potentially new therapeutic approach to rapidly reduce cardiac filling pressures in heart failure; however, the impact of intermittent SVC occlusion and release over a prolonged period of time was unknown.

To address this issue, we next tested the impact of prolonged therapy with intermittent SVC occlusion in a swine model of congestive heart failure. To observe meaningful changes in venous pressures, we employed persistent and intermittent renal artery occlusion combined with volume loading, which elevated right and left heart filling pressures after acute myocardial infarction. The preCARDIA device was then introduced and SVC therapy was applied for up to 18 h with a duty cycle of 5 min occlusion followed by 30 s of SVC release. In one animal, spontaneous sinus bradycardia and hypotension were observed after 14 h of SVC therapy and failed to resolve after termination of SVC therapy. No damage to the SVC, RA, right ventricle (RV), brain, or lungs was observed in this animal. A large anterior wall myocardial infarction due to the LAD ischemia and reperfusion injury was documented at autopsy. In all 3 animals, SVC occlusion increased IJ pressure and reduced RA, mean PA, and PCWP pressures. CO remained stable throughout the study period with a trend towards increased CO compared with post-AMI values.

One potential concern with SVC occlusion is the impact of elevated jugular vein pressure on cerebral function. In the clinical proof-of-concept, no neurologic deficits were identified during or for up to 7 days of follow-up after transient SVC occlusion. In this preclinical study, gross anatomic examination did not identify any cerebral damage despite prolonged SVC therapy. These findings support the potential neurologic safety of this approach and require further validation in a clinical study.

Based on these preclinical data combined with the proof-of-concept clinical results, the VENUS-HF early and feasibility study will now study the effect of the preCARDIA system in patients with congestive heart failure, reduced ejection fraction, and without evidence of cardiogenic shock. If successful, completion of the VENUS-HF EFS trial will inform development of a pivotal trial testing the clinical utility of SVC therapy as a new approach to quickly and effectively reduce cardiac filing pressures, stabilize cardiac function, and improve the timing and degree of decongestion for patients with acute heart failure. Future studies will determine the long-term effect of SVC occlusion on cardiac function.

Our study has several limitations. First, the number of animals studied is small. To establish safety, feasibility, and potential efficacy, a larger, more intensive study is required. Second, we only tested SVC therapy for up to 18 h and were unable to assess the impact of therapy on renal function, neurohormonal activation, or autonomic function. To identify any durable benefit in terms of improved symptoms, cardiac function, or diuretic responsiveness, a more prolonged therapy is required.

In conclusion, we report the first preclinical proof-of-concept results with transient SVC occlusion as a potentially new therapeutic approach to rapidly reduce cardiac filling pressures in heart failure. No prohibitive safety signal was identified and further testing to establish the clinical utility of transient SVC occlusion for heart failure is required.

Clinical Relevance

Congestion during acute heart failure remains a major independent predictor of clinical outcomes. We now report the preclinical test results of a novel approach to rapidly reduce cardiac filling pressures by employing a balloon-mounted catheter system (preCARDIA Inc.) that intermittently occludes venous return via the superior vena cava. The VENUS HF Trial will test the feasibility of this approach in patients with acute congestive heart failure.

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Compliance with Ethical Standards

The study protocol was approved by the Institutional Animal Care and Use Committee (IACUC) at Tufts Medical Center. All experiments were performed according to the committee's guidelines. No human studies were carried out by the authors for this article.

Conflict of Interest NKK receives institutional grant support and consulting and speaker honoraria from Abiomed Inc., Abbott Inc., Boston Scientific Inc., Medtronic Inc., and MD Start. NKK, RHK, and DB have equity and receive consulting honoraria from Precardia. TL and JM are employees of MD Start and Precardia.

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