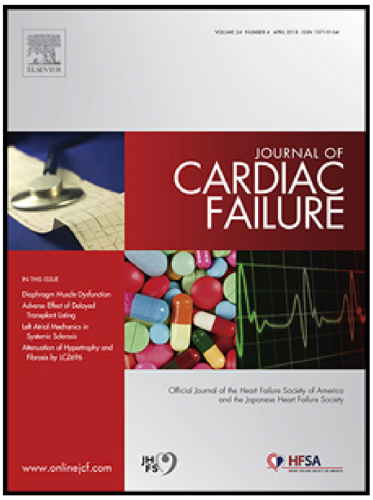

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PII: S1071-9164(18)30303-8
DOI: 10.1016/j.cardfail.2018.07.004
Reference: YJCAF 4153

To appear in: *Journal of Cardiac Failure*

Received date: 26 September 2017
Revised date: 2 June 2018
Accepted date: 5 July 2018

Please cite this article as: Jonathan Grinstein MD , Teruhiku Imamura MD , Eric Kruse BS, RDCS , Sara Kalantari MD , Daniel Rodgers BS , Sirtaz Adatya MD , Gabriel Sayer MD , Gene H. Kim MD , Nitasha Sarswat MD , Jayant Raihkelkar MD , Takeyoshi Ota MD, PhD , Valluvan Jeevanandam MD , Daniel Burkhoff MD, PhD , Roberto Lang MD , Nir Uriel MD , Echocardiographic Predictors of Hemodynamics in Patients Supported with Left Ventricular Assist Devices , *Journal of Cardiac Failure* (2018), doi: 10.1016/j.cardfail.2018.07.004

Echocardiographic Predictors of Hemodynamics in Patients Supported with Left Ventricular Assist Devices

Short title: Non Invasive Hemodynamic Assessment in LVAD

Jonathan Grinstein, MD[Θ]; Teruhiku Imamura, MD[*†]; Eric Kruse, BS, RDCS[*†]; Sara Kalantari, MD[*†]; Daniel Rodgers, BS[*†]; Sirtaz Adatya, MD[ξ]; Gabriel Sayer, MD[*†]; Gene H. Kim, MD[*†]; Nitasha Sarswat, MD[*†]; Jayant Raihkelkar, MD[*†]; Takeyoshi Ota, MD, PhD[*§]; Valluvan Jeevanandam, MD[*§]; Daniel Burkhoff, MD, PhD[#]; Roberto Lang MD[*†]; and Nir Uriel, MD[*†]

[Θ]MedStar Heart and Vascular Institute, Division of Cardiology, Washington D.C., *University of Chicago Medical Center, [†]Department of Medicine and [§]Department of Surgery, Chicago, IL. [ξ]Kaiser Permanente Advanced Heart Failure, Santa Clara, CA. [#]Columbia University, Division of Cardiology, New York, NY.

Corresponding Author:
Jonathan Grinstein, MD
Advanced Heart Failure and Cardiac Transplantation
MedStar Heart and Vascular Institute
Cardiology Division
110 Irving St, NW, Washington, D.C. 20010
Tel: (202) 877-8085; Fax: (202) 877-8032
Jonathan.S.Grinstein@medstar.net

Manuscript Word Count (Body Text, References and Figure Legends): 2954

Disclosures:
Dr. Uriel is a consultant to Medtronic and Abbott
Dr. Jeevanandam is a consultant to Abbott
Dr. Lang is a consultant and is on the Speaker's Bureau for Philips
Dr. Burkhoff is a consultant to Medtronic
All other authors have no relevant disclosures

ABSTRACT

INTRODUCTION: The assessment of hemodynamics in patients supported with left ventricular assist devices LVAD is often challenging. Physical exam maneuvers poorly correlate with true hemodynamics. We assessed the value of novel, echocardiographic (TTE) derived variables to reliably predict hemodynamics in patients supported with LVAD.

METHODS: 102 Doppler-TTE images of the LVAD outflow cannula were obtained during simultaneous invasive right heart catheterization in 30 patients (22 HMII, 8 HVAD) supported with CF-LVAD either during routine RHC or during invasive ramp testing. Properties of the Doppler signal though the outflow cannula were measured at each ramp stage (RS) including the systolic slope (SS), diastolic slope (DS) and velocity time integral (VTI). Hemodynamic variables were concurrently recorded including Doppler opening pressure (MAP), heart rate (HR), right atrial pressure, pulmonary artery pressure, pulmonary capillary wedge pressure (PCWP), Fick cardiac output (CO) and systemic vascular resistance (SVR). Univariate and multivariate regression analyses were used to explore the dependence of PCWP, CO and SVR on DS, SS, VTI, MAP, HR and RS.

RESULTS: Multivariate linear regression analysis revealed significant contributions of DS on PCWP ($PCWP_{pred} = 0.164DS + 4.959$, $R = 0.68$). Receiver operator characteristic curve (ROC) analysis revealed that $PCWP_{pred}$ could predict an elevated PCWP ≥ 18 mmHg with a sensitivity (Sn) of 94% and specificity (Sp) of 85% (AUC 0.88). Cardiac output could be predicted by RS, VTI and HR ($CO_{pred} = 0.017VTI + 0.016HR + 0.12RS + 2.042$, $R = 0.61$). CO_{pred} could predict a CO ≤ 4.5 L/min with a Sn of 73% and Sp of 79% (AUC 0.81). SVR could be predicted by MAP, VTI and HR ($SVR_{pred} = 15.44MAP - 5.453VTI - 6.349HR + 856.15$, $R = 0.84$) with a Sn of 84% and Sp of 79% (AUC 0.91) to predict SVR ≥ 1200 Dynes-sec/cm^5.

CONCLUSIONS: Doppler-TTE variables derived from the LVAD outflow cannula can reliably predict PCWP, CO and SVR in patients supported with LVAD and may mitigate the need for invasive testing.

INTRODUCTION

Left ventricular assist devices (LVAD) have become a mainstay therapy for patients with advanced heart failure. Over 2000 durable LVADs are implanted each year in the United States (1). With improvements in technology and management, survival following LVAD implantation now exceeds 80% at 1 year and 70% at 2 years (1,2). Despite improvements in outcomes, inadequately treated heart failure remains a major hindrance for many patients leading to readmissions for heart failure management. Readmission rates approach 1.64 per patient-year of follow up with up to 25% of readmissions occurring because of cardiac or LVAD related problems (3,4).

Invasive assessment of both LVAD performance and intracardiac hemodynamics are often necessary during the index admission or following readmission. Right heart catheterization (RHC) and hemodynamic ramp tests can be performed to guide medical management (5,6). Non-invasive methods to reliably estimate intracardiac hemodynamics would allow for optimization of medical therapy and LVAD support without the added inconvenience and risk of invasive monitoring. Transthoracic echocardiography (TTE) in patients supported with LVAD has previously been shown to be effective in assessing right-sided flow and pressures and can be used as part of an algorithm to estimate left-sided filling pressures (7). Previous attempts to define hemodynamics using TTE involve time intensive protocols and heavily rely on the E/e’ ratio, which is poorly validated among patients with advanced heart failure and among patients supported with LVAD (8,9).

In the current study, we propose TTE parameters derived entirely from Doppler analysis of the LVAD outflow graft that are readily obtainable and can accurately predict pulmonary capillary wedge pressure, cardiac output and systemic vascular resistance.

METHODS

Patient Population

Consecutive patients undergoing simultaneous RHC with simultaneous transthoracic echocardiography TTE between October 2014 and October 2016 were enrolled into this analysis. To assess the reliabilty of TTE parameters under different loading conditions, a subset of patients underwent repeat TTE and hemodynamic measurements during stages of an invasive hemodynamic ramp protocol. Demographic information was extracted by chart review. All patients provided informed written consent and the institutional review board approved the study.

Right heart catheterization and Ramp Testing

RHC was performed via the right internal jugular vein using a 5 French Swan-Ganz catheter (Edwards Lifesciences, Irvine, CA). Therapeutic anticoagulation was maintained for the test with a target INR between 2 and 3. Measurements included central venous pressure (CVP), systolic, diastolic and mean pulmonary artery pressures (SPAP, DPAP, MPAP), and pulmonary capillary wedge pressure (PCWP).

Cardiac output (CO) was calculated using the indirect Fick equation with an estimated oxygen consumption of 125 mL/min/m^2. Arterial oxygen saturation was measured from peripheral plethysmography and hemoglobin was measured from the venous blood gas. Mean arterial pressure (MAP) was defined as the opening pressure recorded using the Doppler technique and a manual sphygmomanometer. Systemic vascular resistance (SVR) was calculated from the MAP, CVP and CO. Heart rate (HR) was recorded from telemetry. Hemodynamic parameters were measured at each stage of the ramp study in the subset of patients who underwent ramp testing. Real-time echocardiographic imaging was performed simultaneously with hemodynamic image acquisition.

Our ramp protocols have previously been described (10,11). In brief, patients underwent hemodynamic assessment at their presenting speeds and then had their speeds reduced to a low speed of 2300 rpm (HVAD) or 8000 rpm (HMII). Speeds were then increased by an increment of 100 rpm (HVAD) or 400 rpm (HMII) until a maximum speed of 3200 rpm (HVAD) or 12000 rpm (HMII). Repeat hemodynamic assessments were performed at each ramp stage (RS) (Supplemental Table 1). Ramp testing was terminated early if the patient developed a suction event, ventricular arrhythmia or MAP > 120 mmHg.

Doppler Echocardiograpic Analysis

Limited echocardiography including pulse-wave Doppler acquisition of the outflow graft of the CF-LVAD was conducted at the time of right heart catheterization and at each ramp stage in the subset of patients who underwent ramp testing. Properties of the Doppler signal though the outflow graft including the diastolic slope (DS), systolic slope (SS) and velocity time integral (VTI) were measured and defined as previously reported (12-14). Briefly the DS was measured as the rate of change in velocity during the diastolic portion of the cardiac cycle and SS was measured as the maximum rate of change in velocity during the systolic portion of the cardiac cycle. VTI of the outflow cannula was measured over the entire cardiac cycle (from R wave to R wave on the surface electrocardiogram) (Figure 1). Individuals analyzing the Doppler signal were blinded to the hemodynamic data.

Statistical Methods

Data was recorded using a spreadsheet (EXCEL 2011, Microsoft Corp, Redmond, WA) and analyzed using SPSS statistical software v24.0 (SPSS,IBM, Armonk, NY). Normality was assessed using the Shapiro Wilk test. Univariate and multivariate linear regression analyses were used to explore the dependence of PCWP, CO and SVR on DS, SS, VTI, MAP, HR and RS. All parameters with a p value of < 0.0.5 on univariate analysis were included in the multivariate analysis after the confirmation that variance inflation factors of each variable were not significant (<2.0). Pearson correlation testing was performed to compare the measured parameter (PCWP, CO and SVR, respectively) to the predicted value ($PCWP_{pred}$, CO_{pred} and SVR_{pred}, respectively) following multi-regression analysis.

We also explored the sensitivity and specificity of each predicted value to discriminate whether PCWP was ≥ 18 mmHg, CO ≤ 4.5 L/min or SVR ≥ 1200 Dynes-sec/cm^5, respectively. True positive (TP), true negative (TN), false positive (FP) and false negative (FN) rates were determined at various thresholds for each parameter. The sensitivity and specificity of these parameters for detecting either an elevated PCWP, reduced CO or elevated SVR was calculated at each threshold and a receiver operating characteristic curve (ROC) of sensitivity versus (1-specificity) was created. To assess the reproducibility of the diastolic slope and systolic slope, all measurements were repeated by a second observer and inter-observer variability was assessed by intraclass correlation measurement.

RESULTS

Baseline Characteristics

Thirty patients (22 HMII, 8 HVAD) underwent simultaneous right heart catheterization (RHC) with simultaneous transthoracic echocardiography (TTE) between October 2014 and October 2016. Baseline characteristics of the cohort are summarized in table 1. A subset of 10 patients underwent repetitive measurements during stages of a hemodynamic ramp study after the baseline RHC. In total, 102 measurements were obtained. Average age was 59.5 (range 44-76) and 73% were male. Patients who underwent hemodynamic ramp testing had similar characteristics as those who underwent isolated RHC although there was a trend towards a shorter duration of LVAD support among those who underwent ramp testing (10.4 ± 11.3 months vs. 24.4 ± 21.3 months, p = 0.06). Descriptive statistics of the variables used to predict hemodynamics are summarized in supplemental table 2.

Doppler Waveform Analysis and Hemodynamics

Univariate and multivariate analyses of variables predictive of PCWP, CO and SVR are shown in Table 2a, 2b and 3. A multivariate linear regression model showed significant contributions of DS to PCWP ($PCWP_{pred} = 0.164DS + 4.959$, R = 0.68) (Figure 2a, left). Receiver operator characteristic curve (ROC) analysis revealed that $PCWP_{pred}$ could predict an elevated PCWP ≥ 18 mmHg with a sensitivity of 94% and specificity of 85% (AUC 0.88) (Figure 2a, right). Multivariate linear regression modeling revealed that cardiac output could be predicted by RS, VTI and HR ($CO_{pred} = 0.017VTI + 0.016HR + 0.12RS + 2.042$, R = 0.61) (Figure 2b, left). ROC analysis revealed that CO_{pred} could predict a CO ≤ 4.5 L/min with a Sn of 73% and Sp of 79% (AUC 0.81) (Figure 2b, right). SVR could be predicted by MAP, VTI and HR ($SVR_{pred} = 15.44MAP - 5.453VTI - 6.349HR + 856.15$, R = 0.84) (Figure 2c, left). ROC analysis revealed that SVR_{pred} could predict an SVR ≥ 1200 Dynes-sec/cm^5 with a sensitivity of 84% and specificity of 79% (AUC 0.91) (Figure 2c, right). The inter-observer variability was low for the diastolic slope and systolic slope as represented by a high intraclass correlation coefficient for both variables (r = 0.94 and r = 0.92, respectively).

DISCUSSION

In this study we evaluated the accuracy of echocardiographic parameters to predict invasive hemodynamics. Our main findings are as follow: (1) PCWP can be assessed using the DS of the outflow cannula. (2) CO can be assessed using the RS, HR and the VTI of the outflow cannula. (3) SVR can be assessed using the MAP, HR and VTI of the outflow cannula.

Hemodynamic assessment of patients supported with LVAD allows for optimization of pump performance and guidance of medical management (5). Tailoring LVAD speed to the physiologic needs of the patients as assessed by invasive hemodynamic testing leads to improved survival and reduced readmission rates (15). Although invasive hemodynamic assessment can be safely performed in the majority of LVAD patients, it remains an invasive test that carries risk and inconvenient to the patients (16). Physical exam poorly predicts LVAD hemodynamics as traditional auscultatory and visual exam techniques are unpredictable and unstudied in the setting of continuous unloading of the left ventricle (17). Supplementary and accurate non-invasive methods of assessing LVAD hemodynamics are thus necessary in order to maximize LVAD performance while at the same time mitigating risk to the patient.

Doppler-TTE can be used to non-invasively assess flow patterns in both the native heart and LVAD circuit and can indirectly be used to assess intracardiac pressures and cardiac output. Estep et al. showed that Doppler-TTE can accurately predict right atrial pressure, right ventricular stroke volume and pulmonary vascular resistance. They also showed that a complex algorithm involving measurements of mitral inflow velocities, right atrial pressure, systolic pulmonary artery pressure and indexed left atrial volumes could accurately predict left sided filling pressures (7). The complexity of their algorithm, and the need for repetitive measurements, has limited widespread adoption of this technique (9). Flow through the LVAD outflow graft can similarly be assessed using Doppler TTE. Stainback et al. showed that the VTI of the outflow graft in patients supported with the Jarvik 2000 (Jarvik Heart, Inc., New York, NY) measured by pulsed-wave Doppler correlated with a non-invasive assessment of cardiac output from TTE-derived RV and LV cardiac output (18). To date, no group has validated outflow graft VTI with invasively measured cardiac output. With sonographer experience and dedicated training, our group has reported that the outflow graft can be successfully imaged in up to 95% of patients (19).

In the current paper, we report echocardiographic parameters that can reliably predict elevated PCWP, elevated SVR and reduced CO. Unlike previous methods which require multiple different image acquisitions from various chambers of the heart, our parameters can be obtained using a single pulsed-wave Doppler TTE image of the CF-LVAD outflow cannula which can be analyzed to provide the DS, SS and VTI. Together with readily available clinical information such as HR, MAP and LVAD speed (RS), we report new equations to predict absolute PCWP, CO and SVR. We also show that simplified equations that can be rapidly analyzed can quickly dichotomize high from low PCWP, CI and SVR.

Previously, our group utilized outflow graft VTI and DS as a marker of LVAD flow in the development of novel echocardiographic parameters to quantify aortic insufficiency (13). With the current study, we further enrich the use of these echocardiographic parameters to assess LVAD patients' hemodynamics to permit further optimization of medical therapy in the form of diuretics and afterload reduction.

LIMITATIONS

This is a single-center study and thus it is open to institutional and operator bias. Although our cohort size was modest at 30 patients, repeat measurements during sequential stages of invasive hemodynamic ramp testing was available for a subset of 10 patients which allowed for a more robust sample size (102 measurements) and also allowed for assessment of the parameters under variable loading conditions. Given that patients undergoing invasive ramp testing may have a unique clinical indication for this detailed testing, the possibility of a selection bias does exist. Hemodynamic assessments utilized the indirect Fick, which may be less accurate in LVAD patients, due to reliance on an assumed oxygen consumption and not a directly measured oxygen consumption (20). Unlike prior non-invasive assessments of hemodynamics in LVAD patients, our parameters are unique to LVAD physiology and validated in this patient population. A prospective validation study is needed to better assess these novel parameters.

CONCLUSIONS

TTE variables derived from pulsed-wave images from the LVAD outflow graft can reliably predict PCWP, CO and SVR in patients supported with LVAD. These parameters may mitigate the need for routine invasive testing and may be used, together with clinical assessment to tailor medical therapy in LVAD patients.

ACKNOWLEDGEMENTS

Dr. Uriel is a consultant to Medtronic and Abbott. Dr. Jeevanandam is a consultant to Abbott. Dr. Burkhoff is a consultant to Medtronic. All other authors have no relevant disclosures.

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TABLE AND FIGURE LEGENDS

Table 1: Baseline characteristics stratified by procedure type (ramp study versus isolated right heart catheterization).

	All Patients (n = 30)	Right Heart Catheterization (n = 20)	Hemodynamic Ramp (n = 10)
General Characteristics			

Age, years, mean ± SD	59.5 ± 9.4	59.8 ± 10.3	59.1 ± 7.9
Male, n (%)	22 (73)	16 (80.0)	6 (60)
Duration of LVAD, months ± SD	19.8 ± 19.6	24.4 ± 21.3	10.4 ± 11.3
Destination, n (%): BTT DT	 13 (43) 17(57)	 9 (45) 11 (55)	 4 (40) 6 (60)
Type of LVAD HMII HVAD	 22 (73) 8 (27)	 15 (75) 5 (25)	 7 (70) 3 (30)
Presenting Speed (RPM) ± SD HMII HVAD	 9127 ± 430 2700 ± 128	 9173 ± 471 2740 ± 152	 9029 ± 335 2633 ± 31
Origin of Cardiomyopathy			
Ischemic, n (%)	15 (50)	11 (55)	4 (40)
Nonischemic, n (%)	15 (50)	9 (45)	6 (60)
Hypertension, n (%)	18 (60)	12 (60)	6 (60)
Hyperlipidemia, n (%)	10 (33)	9 (45)	1 (10)
Atrial Fibrillation, n (%)	9 (30)	8 (40)	1 (10)
DM, n (%)	13 (43)	7 (35)	6 (60)
COPD, n (%)	6 (20)	2 (10)	4 (40)
PAD, n (%)	3 (10)	3 (15)	0 (0)
CVA, n (%)	5 (17)	5 (25)	0 (0)
S/p Sternotomy, n (%)	6 (20)	4 (20)	2 (20)

Table 2: A) Univariate and multivariate predictors of pulmonary capillary wedge pressure (PCWP). **B)** Univariate and multivariate predictors of cardiac output (CO).

Table 2a. Linear regression analyses to predict PCWP

	Univariate analysis		Multivariate analysis		VIF
	B (95% CI)	**p value**	**B (95% CI)**	**p value**	
Diastolic Slope	0.164 (0.129-0.199)	<0.001*	0.159 (0.119-0.200)	<0.001*	1.32
Systolic Slope	-0.05 (-0.008--0.002)	0.005*	-0.001 (-0.004-0.001)	0.32	1.10
Outflow VTI	0.072 (0.022-0.123)	0.006*	-0.003 (-0.046-0.040)	0.89	1.21
MAP	0.103 (-0.002-0.209)	0.055			
HR	0.073 (-0.014-0.160)	0.099			
Ramp Stage	-0.236 (-0.865-0.392)	0.46			

Table 2b. Linear regression analyses to predict CO

	Univariate analysis		Multivariate analysis		VIF
	B (95% CI)	**p value**	**B (95% CI)**	**p value**	
Diastolic Slope	-0.005 (-0.012-0.002)	0.17			
Systolic Slope	0.000 (-0.001-0.000)	0.55			
Outflow VTI	0.021 (0.014-0.028)	<0.001*	0.017 (0.009-0.024)	<0.001*	1.16
MAP	-0.008 (-0.024-0.009)	0.36			
HR	0.019 (0.006-0.032)	0.005*	0.016 (0.005-0.027)	0.004*	1.01
Ramp Stage	0.20 (0.110-0.289)	<0.001*	0.120 (0.036-0.204)	0.006*	1.16

Table 3: Univariate and multivariate predictors of systemic vascular resistance (SVR).

Table 3. Linear regression analyses to predict SVR

	Univariate analysis		Multivariate analysis		VIF
	B (95% CI)	**p value**	**B (95% CI)**	**p value**	
Diastolic	0.213 (-1.989-2.414)	0.85			

Slope					
Systolic Slope	0.043 (-0.119-0.204)	0.60			
Outflow VTI	-6.034 (-8.154--3.914)	<0.001*	-5.453 (-6.792--4.115)	<0.001*	1.01
MAP	15.74 (11.86-19.62)	<0.001*	15.44 (12.70-18.18)	<0.001*	1.00
HR	-6.427 (-10.29--2.570)	0.001*	-6.349 (-8.580--4.118)	<0.001*	1.00
Ramp Stage	-8.657 (-37.70-20.39)	0.56			

Supplemental Table 1: Relationship of ramp stage (RS) to Heartmate II and HeartWare HVAD speed.

Supplemental Table 2: Descriptive statistics for the variables used in the predictive analysis.

Figure 1: Measurement of velocity time integral (VTI) from R to R wave, systolic slope (SS) and diastolic slope (DS) from pulsed-wave Doppler TTE signal.

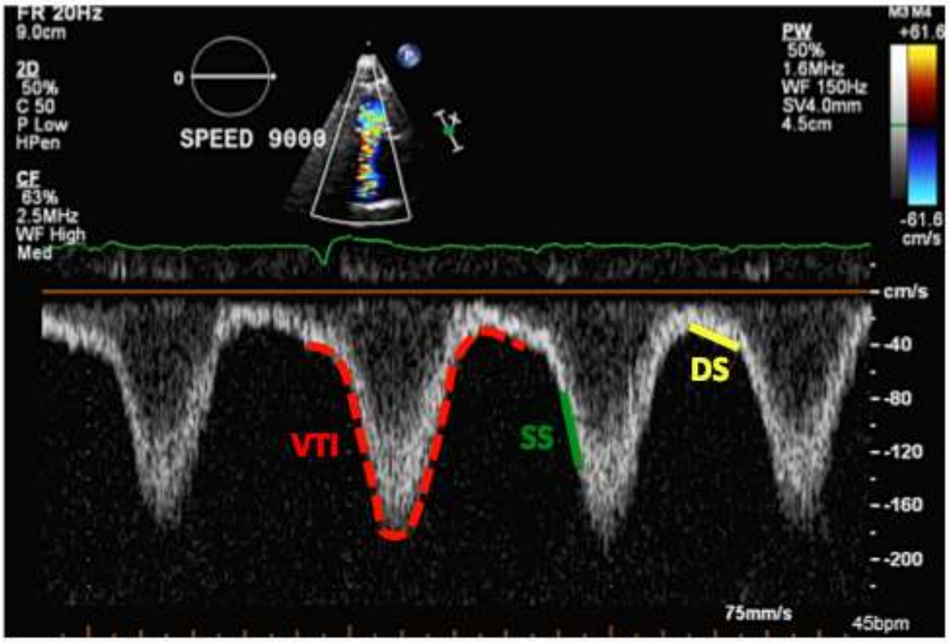
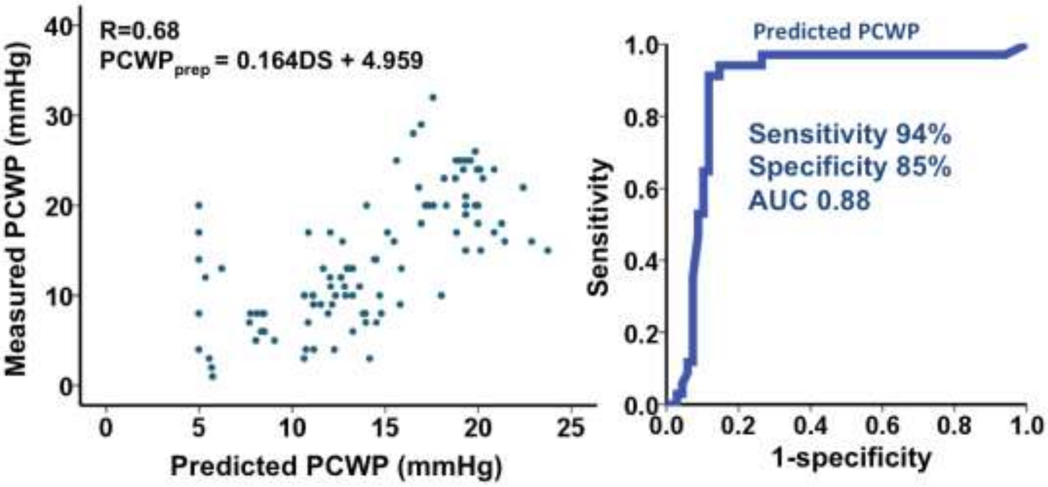
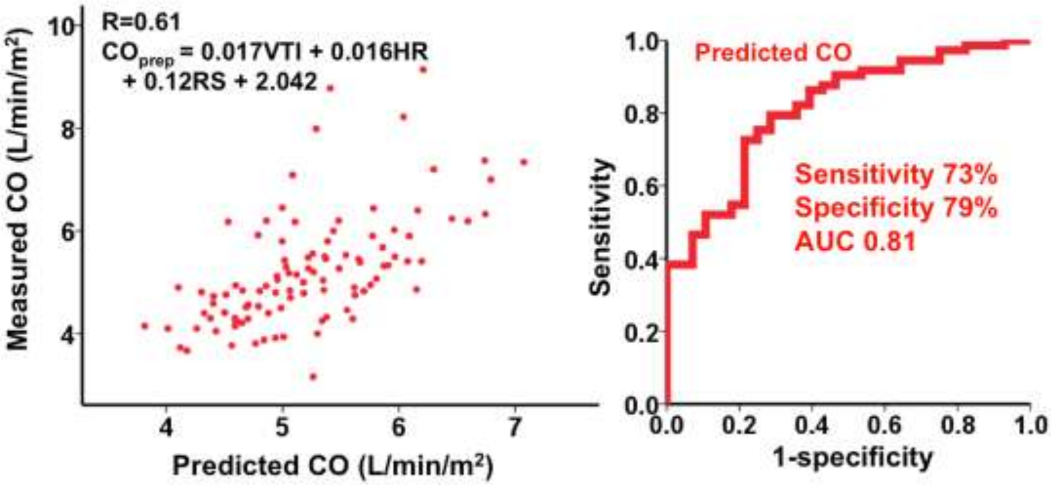
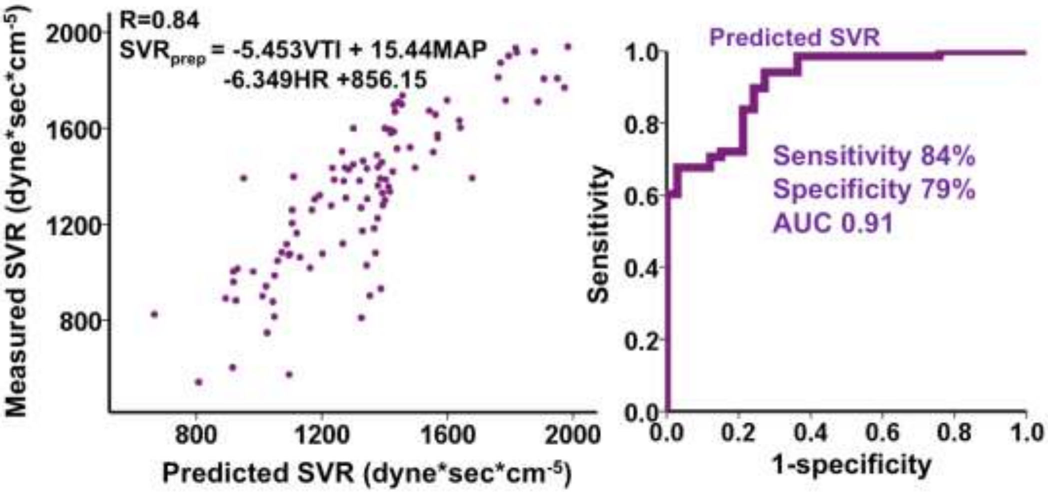


Figure 2: A) *Left*: Performance of predicted pulmonary capillary wedge pressure (PCWP) derived from the diastolic slope (DS) compared to measured PCWP. *Right*: Receiver operating characteristic curves (ROC) of predicted PCWP to predict a PCWP ≥ 18 mmHg. **B)** *Left*: Performance of predicted cardiac output (CO) derived from the ramp stage (RS), velocity time integral (VTI) and heart rate (HR) compared to measured CO. *Right*: ROC of predicted CO to predict a CO ≤ 4.5 L/min. **C)** *Left*: Performance of predicted systemic vascular resistance (SVR) derived from the mean

arterial pressure (MAP), velocity time integral (VTI) and heart rate (HR) compared to measured SVR. *Right*: ROC of predicted SVR to predict an SVR ≥ 1200 Dynes-sec/cm^5.


R=0.68
PCWP$_{prep}$ = 0.164DS + 4.959
Measured PCWP (mmHg)
40
30
20
10
0
0
5
10
15
20
25
Predicted PCWP (mmHg)
Predicted PCWP
Sensitivity 94%
Specificity 85%
AUC 0.88
Sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.2
0.4
0.6
0.8
1.0
1-specificity


R=0.61
CO$_{prep}$ = 0.017VTI + 0.016HR + 0.12RS + 2.042
Measured CO (L/min/m^2)
10
8
6
4
4
5
6
7
Predicted CO (L/min/m^2)
Predicted CO
Sensitivity 73%
Specificity 79%
AUC 0.81
Sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.2
0.4
0.6
0.8
1.0
1-specificity


R=0.84
SVR$_{prep}$ = -5.453VTI + 15.44MAP -6.349HR +856.15
Measured SVR (dyne*sec*cm^{-5})
2000
1600
1200
800
800
1200
1600
2000
Predicted SVR (dyne*sec*cm^{-5})
Predicted SVR
Sensitivity 84%
Specificity 79%
AUC 0.91
Sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.2
0.4
0.6
0.8
1.0
1-specificity