Method of Preload Reduction during LVPVR Analysis of Systolic Function

Airway Pressure Elevation and Vena Cava Occlusion

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Background: A graded preload reduction during analysis of the left ventricular pressure-volume relationship (LVPVR) is required for derivation of end-systolic elastance (Ees) and preload recruitable stroke work (PRSW). The authors aimed to measure serial changes in these systolic function parameters before and during planned circulatory interventions using two different methods of preload alteration: a positive airway pressure plateau (APP) and inferior vena cava occlusion (IVCO).

Methods: In eight animals, measurements were made at 38°, 30°, 32°, 34°, and posthypothermia 38°C. In an additional eight animals, isoflurane, adrenaline, and aorta occlusion (balloon catheter occluder) were administered in series, each with a preintervention control measurement. Left ventricular volume was measured by conductance. Paired measurements of the systolic function parameters Ees and PRSW, each derived with two preload methods, were analyzed for bias.

Results: Circulatory alterations were achieved with the temperature, isoflurane, adrenaline, and aorta occlusion interventions. Measured changes in Ees and PRSW from control to intervention showed a strong correlation and no significant bias for APP in relation to IVCO. The APP-derived absolute values for Ees and PRSW demonstrated a consistent positive bias compared with IVCO.

Conclusion: The APP method for preload reduction during LVPVR analysis detected changes in Ees and PRSW during the circulatory interventions in this model that were not different than those detected using another preload reduction method, IVCO. APP and IVCO are not interchangeable methods for preload reductions during LVPVR absolute quantitation of systolic function, and each needs to be used serially.

A LOAD-INDEPENDENT means for assessing left ventricular (LV) function is vital to facilitate rational medical decision making concerning need for and effect of inotropic support in patients with circulatory dysfunction. Current bedside means for assessing LV function are highly influenced by loading conditions, that is, preload and afterload.[1] Analysis of the left ventricular pressure-volume relationship (LVPVR) is a robust method for quantitating LV function, which is strongly independent of the momentary loading conditions.[2] A controlled pre-load alteration is implemented for the analysis of the systolic function parameters end-systolic elastance (Ees)[3] and preload recruitable stroke work (PRSW).[4] It is the analysis of LV events over that range of loading conditions that makes these LVPVR systolic parameters strongly independent of prevailing preload or afterload.[5]

Clinical implementation of LVPVR analysis is limited by the high degree of invasiveness regarding data collection. The preload alteration maneuver that traditionally has been used for obtaining these contiguous heart cycle LV pressures and volumes over a range of preloads and afterloads is a balloon catheter occlusion of the inferior vena cava. To render LVPVR analysis more clinically applicable, less invasive means are needed for the controlled preload alteration and for the acquisition of LV pressure and volume data. Transient increased intrathoracic pressure delivered through an increase in airway pressure, in a range that is typical for positive pressure ventilation, has been shown to be able to cause preload reductions from beat to beat that allow derivation of Ees and PRSW.[6] We hypothesized that a positive airway pressure plateau (APP) could be used for controlled preload reduction to facilitate LVPVR analysis of Ees and PRSW over a range of LV function brought about by experimental means. We further hypothesized that these systolic function parameters derived from APP-generated preload reductions would have a consistent relationship over this range of ventricular function to the same parameters derived from paired measurements using the traditional transient inferior vena cava balloon occlusion (IVCO) method of preload reduction. We aimed to analyze the relationship of the systolic function parameters derived from the two different preload reduction methods, which were acquired in paired fashion before and during planned circulatory interventions.

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Methods

General Preparation

With approval from the ethical animal use committee of the University of Umeå and in conformity with the European Convention for the Protection of Vertebrate Animals used for Experimentation and other Scientific Purposes (Council of Europe No. 123, Strasbourg 1985), 16 female Swedish landrace (half-breed Yorkshire) pigs weighing between 31–44 kg (mean weight, 37.9 kg) were first premedicated with intramuscular azaperone, 2 mg/kg, and ketamine, 12 mg/kg, and then anesthetized

with intravenous pentobarbital, 15 mg/kg. Anesthesia was maintained with pentobarbital infusion, 15–20 mg·kg^{-1}·h^{-1}, and isoflurane 0.5–1% was administered during the surgical preparation. A tracheotomy was performed, and the pigs were ventilated (Siemens-Elema 900B, Stockholm, Sweden) to normocapnia and normoxia (Oscar, Datex-Ohmeda, Helsinki, Finland) with volume-regulated respirator settings and tidal volumes of 10 ml/kg, with minute ventilation and inspired oxygen titrated with the assistance of repeated blood gas measurements (ABL-5, Radiometer, Copenhagen, Denmark). With the goal of establishing and maintaining normovolemia in the anesthetized state, the pigs received intravenous fluids by protocol: acetated Ringer's solution, 10 ml/kg, during the first hour, then 4 ml·kg^{-1}·h^{-1} throughout the study period. Temperature was maintained between 38 and 39°C at the start of the protocol with the use of warmed intravenous fluids and a warming blanket. Intravascular catheters were placed through cutdowns into the jugular venous and the carotid artery systems bilaterally. A three-lumen central venous catheter (Arrow International, Reading, Pennsylvania) and a pulmonary artery catheter (Optimetrix, Abbott Critical Care Systems, North Chicago, Illinois) were placed *via* the jugular vein, and an arterial catheter was placed into the descending aorta. A 7-French LV pigtail combination tip manometer and dual field conductance catheter was placed through an 8.5-French introducer (Arrow International, Reading, Pennsylvania) in the carotid artery system into the left ventricle using fluoroscopic guidance. For the hypothermia series (eight animals), one conductance catheter was used (ANP/269, Sentron, Roden, The Netherlands), which had 11 electrodes with a 6-mm spacing. For the second group of eight animals, a second similar catheter (CA-71083-PN, CD Leycom, Zoetermeer, The Netherlands) was used, which had 12 electrodes, an 8-mm spacing between electrodes, and a shorter pigtail. An optimal position was obtained using a combination of fluoroscopic appearance and best conductance voltage (see conductance section in Methods below) signals in five channels. A 7-French balloon-tipped catheter (Fogarty arterial embolectomy catheter, Vascular Technology AB, Gothenburg, Sweden) was placed through the right atrium into the inferior vena cava (IVC) using fluoroscopic guidance with the balloon tip resting in a position such that during inflation it could occlude IVC inflow to the right atrium.

Conductance-based Left Ventricular Volumetry

The conductance technique has been described in depth previously.[7,8] The conductance catheter (aforementioned) and signal conditioning amplifier (Sigma 5DF, CD Leycom, Zoetermeer, The Netherlands) were used to measure LV volume. Calibration to flow measured by another method, or the reference ratio (α) to the conductance-derived cardiac output (stroke volume

× heart rate), was calculated at the start of each intervention through comparison with an average of three thermodilution cardiac output measurements. Thermodilution cardiac output was measured using the thermistor-tipped pulmonary artery catheter and a cardiac output computer (WTI, Wetenskappelijk Technische Instituut, Rotterdam, The Netherlands). Offset assessments for parallel conductance volume (Vc) at zero positive end-expiratory pressure (PEEP) using the hypertonic saline method and blood conductivity (ρ) were also collected at the start of each intervention. These were recorded and analyzed using a commercial software package (PC Conduct, CD Leycom, Zoetermeer, The Netherlands). Parallel conduction measurements, the α reference ratio and ρ for each intervention, including at each temperature, were incorporated into the calibration of conductance signal to volume based on the following formula.[7]

In six of the eight animals in group 2, Vc was also measured at the start of the experiment twice, each at 5 and 10 cm H_2O PEEP. All circulatory waveforms, including all active segments from the conductance catheter, were recorded during measurement sequences on a digital signal acquisition and analysis software (Acqknowledge II, Biopac, Santa Barbara, California).

Graded Preload Reduction Procedure

Invasive preload reductions *via* IVCO were performed during brief apnea periods at zero airway pressure (ZEEP) by inflation of the IVC balloon for approximately 6 s. The APP maneuver for preload reduction was performed by first placing the animal at apnea and ZEEP briefly and then connecting the endotracheal tube to 15 cm H_2O positive pressure delivered by the ventilator (Evita 4, Dräger Medizintechnik Gmbh, Lübeck, Germany) for approximately 6–8 s so that successive decreases in LV pressures and volumes were observed and recorded. The inspiratory pressure increase time was set to 0.2 s, and the duration of inspiratory flow, or achievement of end-inspiration, was never more than 0.5 s. End-inspiration was reached well before the progressive LV volume and pressure reductions (the LVPVR analysis period) began. The same APP intervention with 15 cm H_2O was used for all subjects at all temperatures. When the end-systolic pressure and volume stopped decreasing from beat to beat or when 8 s total were reached, the positive airway pressure was released, and the subject was reconnected to the previous resting ventilator setting.

Temperature Exchange Apparatus

An extracorporeal venous-arterial, heat-exchanging circuit was connected to each subject in the first group of eight animals (group 1) before the start of data collection. The venous inflow to the circuit came through a heparin-coated, 21-French venous catheter (Pediatric ve-

nous cannula, Biomedicus, Minnesota) that was placed through the external jugular vein to the superior vena cava–right atrial junction using fluoroscopic guidance. This was connected by heparin-lined tubing (Medtronic Inc., Minneapolis, Minnesota) to a combination heat exchanger and gas-exchanging membrane (Maxima PRS oxygenator, Medtronic Inc., Minneapolis, Minnesota) distal to a centrifugal blood pump (Medtronic Biomedicus Centrifugal Blood Pump, Medtronic Inc, Minneapolis, Minnesota). An air–oxygen blend at low flows was connected to the oxygenator membrane. The arterial inflow from the circuit into the subject went through a heparin-coated, 18-French catheter (Fem-Flex II Duroflo, Edwards Lifesciences Corporation, Irvine, California) placed through the external carotid artery into the descending aorta with the assistance of fluoroscopy. The extracorporeal circuit was primed with 0.5 l of acetated Ringer's solution and 5,000 U of heparin. Activated clotting time (ACT) (Hepcon HMS, Medtronic Biomedicus, Minneapolis, Minnesota) was monitored, and addition heparin was given if the ACT decreased below 200 s. Temperature was measured using the pulmonary artery catheter tip thermistor. After the preparation was completed, a rest period for circulatory stabilization was observed. At the conclusion of the study period, the pigs were euthanized using a combination of intravenous pentobarbital bolus and then intravenous potassium bolus.

Aortic Balloon Catheter Occlusion

In the second group of eight animals (group 2), a Fogarty 7-French, balloon-tipped catheter (Fogarty arterial embolectomy catheter, Vascular Technology AB, Gothenburg, Sweden) was placed into the descending aorta at the level of the diaphragm with fluoroscopic guidance through an introducer placed in the femoral artery. Transient inflation of the balloon with 2 or 3 ml of fluid was designed to bring about increases in blood pressure through partial or complete aortic occlusion.

Measurement Protocol

Conductance calibration measurements were obtained before each intervention. At each predetermined measurement point, all signals were recorded from before the start of the preload reduction until after the subject had returned to resting circulation with maintenance mechanical ventilation. All graded preload reductions were performed during brief apnea periods at ZEEP. LV pressure and volume data were collected during each different preload reduction method with a 2-min rest period between measurements. For half of the animals, APP was always performed before IVCO, and *vice versa* for the other half. This was done to minimize possible systematic effect of one measuring sequence on the other, although our criteria for starting all measuring sequences was that there were no apparent effects from

a previous sequence that could be observed on minute-by-minute trending of blood pressures and heart rate. The LVPVR preload reduction sequences were later analyzed offline for Ees and PRSW (see LVPVR analysis section in Methods below).

Hypothermia

Eight animals (group 1) were studied with extracorporeal temperature regulation only and no other interventions. After initial LVPVR measurements at 38°C, temperature in the animals was decreased using the extracorporeal heat exchanger to 30°, 32°, 34°, and then 38°C, with LVPVR measurements recorded at each temperature using each preload reduction method. Half of the animals had their temperature decreased successively from 38° to 34°, 32°, 30°, and then 38°C. The temperature sequence for the other half was 38°, 30°, 32°, 34°, and then 38°C. Maximum flows in the extracorporeal circuit never exceeded 1.5 l/min during temperature manipulation. Once the target temperature was reached, the extracorporeal circuit was excluded from the subject (although recirculating within the external circuit), and the arterial and venous catheters were flushed with heparinized saline. Then, the LVPVR measurements with preload reduction sequences were performed. Temperatures were noted at the time of pressure and volume measurements.

Adrenaline, Isoflurane, Aortic Occlusion

Eight animals (group 2) were studied with interventions in series: isoflurane administration, adrenaline infusion, and aortic occlusion. A rest period was observed, and then a control measurement was collected before each intervention. After measurements were recorded for each intervention, a lengthy rest period was observed before the next control measurement and intervention. Isoflurane was administered to a dose of 1% end-expired. Adrenaline was infused in doses of 0.075 and 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ with paired measuring sequences at each dose. The animals rested for 60 min after the adrenaline infusion intervention and measurement were completed. Then, after a new control measurement, partial aortic occlusion was performed using a 7-French Fogarty catheter (Fogarty arterial embolectomy catheter, Vascular Technology AB, Gothenburg, Sweden) placed through a femoral artery 8-French introducer to increase mean arterial pressure (MAP) to a static point 20–40 mmHg above that for the control measurement. Once the stable blood pressure increase was achieved and general circulatory stability was demonstrated for several minutes, paired preload reductions and measurements were performed.

LVPVR Analysis: Derivation of Ees and PRSW

A series of consecutive heart beats from the measurement period and controlled preload reduction was analyzed based on selecting the maximum number of beats

in sequence with end-systolic pressure-volume points that changed in an approximately linear relation to each other. End-systole was defined using the algorithm of iterative (we determined the number of iterations) tangent calculations from a line using the x intercept determined from the regression line for estimated end-systolic points (end-systolic points first determined using the tangent of x = 0 and the end systolic curve for each heart cycle for individual points).[5] End-diastole was defined either as the point 12 or 16 ms after the R wave onset, or the point 40 ms preceding the dP/dt_{max} greater than 500 mmHg/s, whereafter the end-diastolic position was confirmed manually during analysis so that it had the same relation in the heart cycle throughout the preload reduction sequence.[4] Where there was an obvious result on the P-V diagram that did not match the end-diastolic position, we systematically timed the point from the R wave on the electrocardiograph (ECG) so that the appropriate point on the P-V diagram was achieved. Ees was calculated as the slope of the linear regression of the end-systolic volume and pressure during preload reduction.[5] Stroke work (SW) for a heart cycle was calculated as the integral of measured LV pressure and volume during that cycle. PRSW was calculated as slope for the stroke work divided by the end-diastolic volume for successive beats during preload reduction.[4] The Ees and PRSW linear regression slopes were not accepted if the r value by least squares regression did not exceed 0.9.

Other Hemodynamic Measurements and Calculations

At the control measurement for each intervention, a thermodilution cardiac output (CO) was measured (average of three measurements). This was used to derive the α calibration value for conductance volumetry for that intervention, so the control CO value by conductance was calibrated to, or has the same value as, the thermodilution measurement. CO results were the stroke volume measured by conductance volumetry multiplied by the heart rate, detected from ECG. Thermodilution CO measurements were not collected during the interventions. Ejection fraction (EF) was calculated as (end-diastolic volume − end-systolic volume)/end-diastolic volume.

Statistics

Descriptive statistical analysis was performed for grouped measurements from each intervention and its control. Where there were multiple or graded interventions after a control measurement (temperature and adrenaline), analysis for differences during the intervention was conducted first using analysis of variance (ANOVA) and a test of simple contrasts. If a difference during the intervention was detected, then a paired *t* test was performed. Significant differences were defined as those where the paired *t* test *P* value was less than 0.05.

To test for differences in effects for APP and IVCO, the systolic function parameters with each method were used to provide a change (or ΔEes and ΔPRSW) from control to intervention. These ΔEes and ΔPRSW results were grouped for each systolic function parameter (Ees and PRSW) to allow analysis for bias.[9] Linear regression of the paired (both preload reduction methods) absolute values for Ees and PRSW and for ΔEes and ΔPRSW was performed. Variation in repeated measurements of Vc at different levels of PEEP was described using coefficient of variance ± SEM.

Results

General circulatory parameters for control measurements and the effects of temperature change and extracorporeal circulation in the first eight animals (group 1) are shown in table 1, and isoflurane, adrenaline in two doses, and aortic occlusion (group 2) are shown in table 2. The general circulatory effects of hypothermia interventions include decreases in heart rate, CO, SW, and dP/dt_{max} and increases in EF. Decreases in MAP occurred with isoflurane and adrenaline. MAP during aortic occlusion was an average of 27 mmHg above the control MAP measurement series, suggesting that LVPVR was analyzed during an acute increase in afterload. CO and EF decreased during isoflurane, increased during adrenaline, and did not change significantly during aortic occlusion. Adrenaline produced decreases in end-diastolic and end-systolic volumes with an increase in stroke volume (SV), whereas aortic occlusion produced increases in ventricular pressures and volumes with no change in SV and hence a decrease in EF.

Prospective preload alterations using IVCO and APP were collected and analyzed for all interventions. A typical example of the pressure-volume observations during these paired preload reduction sequences used for Ees and PRSW derivation is shown in figures 1 and 2. These figures display the entire preload alteration sequence, including the onset of the APP and IVCO and the portion that is selected for analysis of Ees and PRSW. From the combined animals in both groups (n = 16), LV pressure and volume measurements during control and intervention were analyzed for Ees and PRSW. Either Ees or PRSW, or both, could be calculated successfully for all 192 measuring sequences interventions. In 10 of 384 LVPVR analyses, a single Ees or PRSW could not be successfully calculated from the control or intervention measurement. Of 106 paired measurements for systolic function parameters using two preload methods, 96 paired measurements were available for analysis of change in systolic function from control to intervention. Ees and PRSW results with both preload reduction methods for each intervention (both groups of animals) are shown in figure 3 along with the control measurement

Table 1. General Circulatory Parameters, Group 1

	Control	T30	T32	T34	T38
Temp (°C)	38.1 ± 0.2	30.2 ± 0.3*	31.8 ± 0.1*	33.7 ± 0.1*	37.8 ± 0.1
HR (bpm)	127 ± 9	78 ± 2*	93 ± 6*	104 ± 7*	116 ± 4
MAP (mmHg)	86 ± 3	58 ± 3*	67 ± 3*	72 ± 2*	71 ± 4*
MPAP (mmHg)	23 ± 1	25 ± 1	26 ± 1	25 ± 2	27 ± 1
CVP (mmHg)	5 ± 1	6 ± 1	6 ± 1	5 ± 1	5 ± 1
CO (l · min^{-1})	5.9 ± 0.6	3.9 ± 0.3*	4.5 ± 0.3*	5.2 ± 0.3	5.3 ± 0.4
EDV (ml)	109 ± 16	97 ± 12	95 ± 13	96 ± 12	112 ± 12
EDP (mmHg)	9.3 ± 1.4	8.5 ± 1.6	8.7 ± 1.5	7.9 ± 1.8	9.4 ± 1.8
ESV (ml)	68 ± 13	49 ± 9*	50 ± 9*	52 ± 8*	72 ± 9
ESP (mmHg)	93 ± 3	53 ± 4*	65 ± 4*	72 ± 4*	83 ± 4*
SV (ml)	47 ± 4	51 ± 4	50 ± 5	50 ± 5	45 ± 4
EF (%)	45.5 ± 3.6	55.2 ± 3.3*	54.7 ± 3.4*	52.3 ± 2.9*	41.3 ± 2.0
SW (mmHg · ml)	3952 ± 441	2742 ± 322*	3141 ± 349*	3407 ± 385	3259 ± 359*
dP/dt max (mmHg · s^{-1})	1670 ± 105	1118 ± 63*	1369 ± 191	1523 ± 69	1234 ± 87*
α	0.48 ± .02	0.42 ± .02	0.45 ± .03	0.48 ± .03	0.51 ± .03
Vc (ml)	49.5 ± 2.4	49.2 ± 2.4	50.5 ± 2.4	52.2 ± 2.2	50.6 ± 1.8

Data are presented as mean ± SEM, n = 8. * $P < 0.05$ *versus* control.

Temp = temperature in degrees centigrade; HR = heart rate; MAP = mean arterial pressure; MPAP = mean pulmonary arterial pressure; CVP = central venous pressure; CO = cardiac output; EDV = end diastolic volume; ED = end diastolic pressure; ESV = end systolic volume; ESP = end systolic pressure; SV = stroke volume; EF = ejection fraction; SW = stroke work; dP/dt$_{max}$ = maximum of first derivative of pressure; α = α gain correction factor for conductance signal; Vc = parallel conductance correction factor.

for respective interventions. The hypothermia intervention had consistent negative effects on Ees and PRSW. Notably, during adrenaline at the lower dose, Ees did not increase in the setting of MAP decrease, whereas PRSW increased.

Change in Ees and PRSW from control to intervention (ΔEes and ΔPRSW) could be calculated from 55 and 56, respectively, measuring sequences. These ΔEes and ΔPRSW values were combined for all interventions and displayed in a correlation plot (fig. 4) to illustrate the raw data. No correlation analysis was performed for the APP–IVCO paired observations in figure 4 or for the absolute systolic function paired results displayed in figure 5. Ees

and PRSW results before and during interventions were successfully derived in eight of eight or seven of eight animals for all interventions except for aortic occlusion, where successfully analyzed control and intervention for PRSW numbered only six of eight (with eight of eight successfully calculated Ees values from the same LVPVR measurements). The reason for failure in calculating PRSW was inadequate beat-to-beat change in end-diastolic volumes, occurring most likely because of decreases in IVC flow and the balloon occlusion effect during thoracic aorta occlusion.

Bias analysis of the ΔEes and ΔPRSW during inotropic or afterload interventions demonstrates a small positive

Table 2. General Circulatory Parameters, Group 2

	C2 (n = 7)	ISO	C3 (n = 8)	AD1	AD2	C4 (n = 6)	AO
HR (bpm)	104 ± 8	90 ± 4*	91 ± 5	118 ± 7*	155 ± 9*	101 ± 7	102 ± 7
MAP (mmHg)	97 ± 7	70 ± 7*	99 ± 5	89 ± 5*	85 ± 5*	85 ± 6	112 ± 7*
MPAP (mmHg)	23 ± 1	20 ± 1*	22 ± 1	22 ± 1	23 ± 1	22 ± 1	26 ± 1*
CVP (mmHg)	6.6 ± 0.4	7.8 ± 0.5*	7.4 ± 0.5	5.9 ± 0.5*	5.0 ± 0.7*	5.3 ± 0.9	7.1 ± 1.3*
CO (l · min^{-1})	5.0 ± 0.5	3.7 ± 0.3*	4.5 ± 0.4	6.9 ± 0.5*	9.5 ± 0.5*	5.0 ± 0.5	5.6 ± 0.5
EDV (ml)	108 ± 9	111 ± 11	109 ± 11	103 ± 12	91 ± 11*	104 ± 6	107 ± 7
EDP (mmHg)	14.5 ± 1.4	12.3 ± 1.0*	13.9 ± 1.6	12.5 ± 1.6	10.4 ± 2.5	12.2 ± 1.4	15.6 ± 2.2*
ESV (ml)	65 ± 9	75 ± 11*	65 ± 10	50 ± 12*	39 ± 10*	61 ± 5	65 ± 5
ESP (mmHg)	109 ± 6	79 ± 6*	107 ± 5	97 ± 3*	98 ± 3*	97 ± 6	143 ± 11*
SV (ml)	48 ± 3	41 ± 2*	48 ± 2	58 ± 2*	61 ± 3*	48 ± 3	48 ± 3
EF (%)	45 ± 3	38 ± 3*	46 ± 3	60 ± 7*	69 ± 6*	46 ± 3	45 ± 4
SW (mmHg · ml)	4234 ± 369	2640 ± 254*	4225 ± 234	5077 ± 321*	6029 ± 162*	3893 ± 335	5281 ± 631
dP/dt$_{max}$ (mmHg · s^{-1})	1501 ± 199	856 ± 122*	1319 ± 139	1977 ± 232*	3189 ± 363*	1302 ± 229	2285 ± 506
α	0.54 ± 0.03		0.54 ± 0.04			0.54 ± 0.04	
Vc (ml)	74.6 ± 8.0		77.5 ± 9.1			78.3 ± 7.3	

Data are presented as mean ± SEM, n = 8. * $P < 0.05$ *versus* respective control.

C2 = Control before isoflurane; ISO = isoflurane 1% end tidal concentration; C3 = control before adrenaline; AD1 = adrenaline infusion 0.075 μg · kg^{-1} · min^{-1}; AD2 = adrenaline infusion 0.3 μg · kg^{-1} · min^{-1}; C4 = control before aorta occlusion; AO = aorta occlusion (see Methods text); HR = heart rate; MAP = mean arterial pressure; MPAP = mean pulmonary arterial pressure; CVP = central venous pressure; CO = cardiac output; EDV = end diastolic volume; EDP = end diastolic pressure; ESV = end systolic volume; ESP = end systolic pressure; SV = stroke volume; EF = ejection fraction; SW = stroke work; dP/dt$_{max}$ = maximum of first derivative of pressure; α = α gain correction factor for conductance signal; Vc = parallel conductance correction factor.
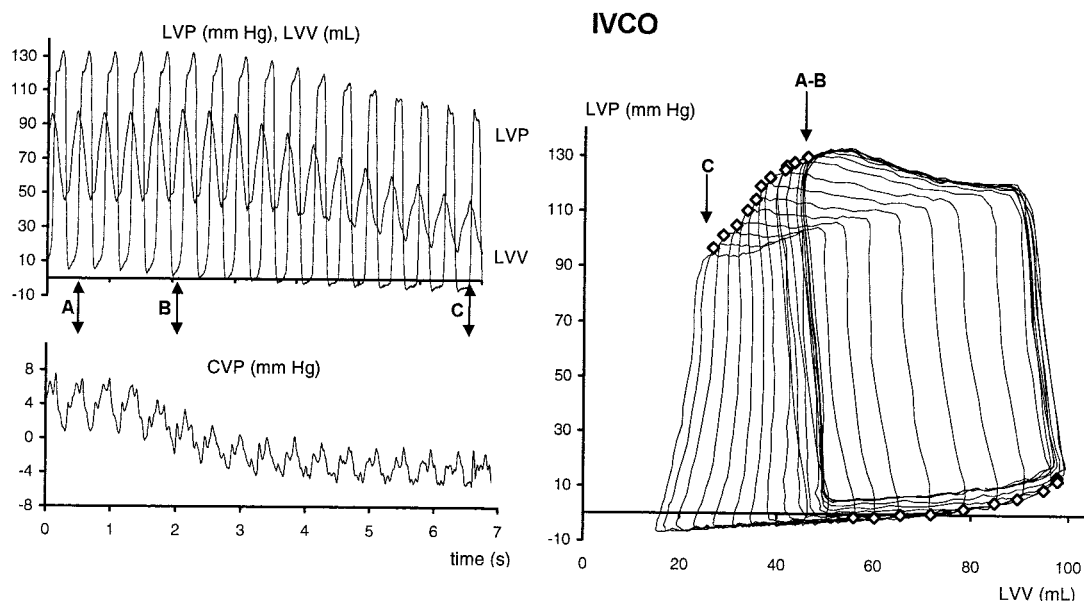
IVCO

Fig. 1. Representative example of the pressure–volume events of an inferior vena cava occlusion (IVCO) preload reduction is demonstrated. The onset of IVCO balloon inflation is marked *A*. The beginning and end of the heart cycle sequence from which end-systolic elastance (Ees) and preload recruitable stroke work (PRSW) are derived are marked *B* and *C*, and these cycles have end-diastolic and end-systolic points marked on the corresponding pressure–volume curves to the right. The simultaneous CVP curve is included to help illustrate the timing of vena cava occlusion and the onset of left ventricular pressure and volume reduction.

bias for parameters derived from the APP preload reduction method in relation to IVCO (see fig. 4). For ΔEes, the bias for APP in relation to IVCO was -0.08 ± 0.41 (SD), and for ΔPRSW, the bias for APP in relation to IVCO was 1.89 ± 18.3 (SD). This is the main result, demonstrating a strong relationship of APP-derived Ees

and PRSW changes during circulatory interventions in relation to the same measurements acquired using IVCO, although with an apparent larger difference from mean bias values during the measurements involving larger changes from control to intervention. There are fewer measurements of large changes in systolic function pa-
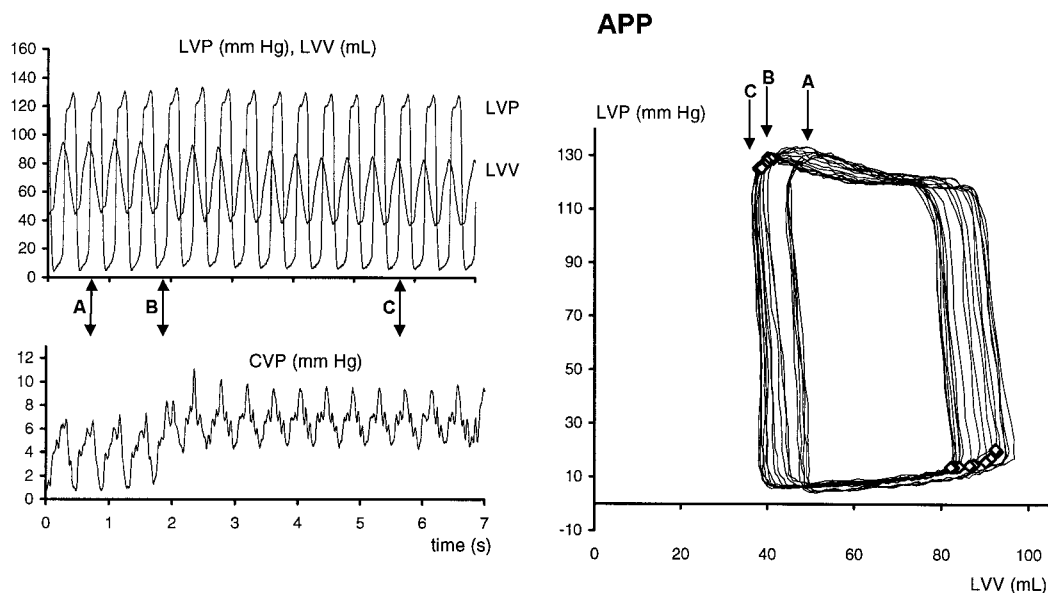
APP

Fig. 2. Figure represents the heart pressure and volume events that ensue after the institution of 15 cm H$_2$O CPAP. The onset of CPAP is marked *A*. The beginning and end of the heart cycle sequence where left ventricular pressure-volume relationship (LVPVR) is analyzed for systolic function parameters are marked *B* and *C*, and these cycles have end-diastolic and end-systolic points marked for the period between *B* and *C* on the corresponding pressure–volume curves. The CVP curve illustrates the timing of CPAP start in relation to the start of left ventricular pressure and volume reduction (see Results text). Note the relatively small change in end-systolic pressure between *B* and *C*, whereas end-systolic volume increases, occurring after an increase in systolic pressures during the period where lung inflation has occurred but before progressive end-systolic and end-diastolic pressure and volume decreases have begun (*B*).
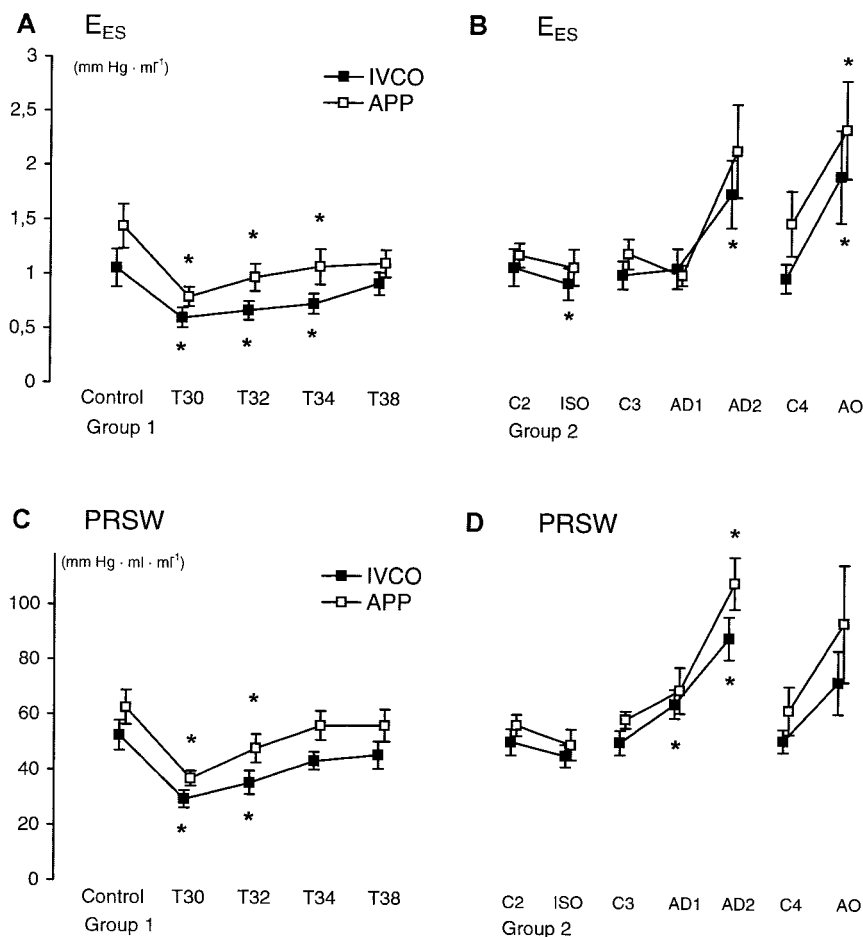
A E_{ES}

B E_{ES}

C PRSW

D PRSW

Fig. 3. Figure shows mean end-systolic elastance (Ees) and preload recruitable stroke work (PRSW) (± SEM) during different interventions, where * denotes a significant (*P* < 0.05) difference in systolic function measurement compared with control. For group 1 (*A* and *C*), T30, T32, T34, and T38 represent temperatures 30°, 32°, 34°, and posthypothermia 38°C, although for one half the animals, temperatures were not achieved in that order (see Methods section). For group 2 (*B* and *C*), C2, C3, and C4 represent control measurement before each intervention, and these measurements are connected to the intervention measurement by a line. Mean values for the group ± SEM are displayed. Iso = isoflurane 1% end-tidal concentration, AD1 = adrenaline dose 0.075 μg·kg^{-1}·min^{-1}, AD2 = adrenaline dose 0.3 μg·kg^{-1}·min^{-1}, AO = aortic balloon occlusion.

rameters. The bias plot suggests that while during large changes in PRSW there is no clear difference in distance from the bias line, during Ees there is a suggestion that responses during Ees changes of larger magnitude diverge more negatively and positively from the average difference for all paired measurements. The largest changes in Ees (and in MAP) and the largest variation between Ees measurements with APP and IVCO occurred during aortic occlusion (see figs. 4 and 5 with ΔEes and ΔPRSW pairs marked A). When the raw data for Ees and PRSW are shown (see fig. 5), the majority of pairs for APP and IVCO show a higher value for the APP-derived parameters. Bias analysis for these absolute Ees and PRSW values during one measurement sequence demonstrates a positive bias (x = 0.26 ± 0.39 and x = 10.5 ± 16.4 SD, respectively) for the APP method, although figure 5 contains no information about the response of systolic function performance measurement during a circulatory intervention (see fig. 3).

Measurements of parallel conductance at the start of each protocol were collected for six animals at 0 PEEP, 5 cm H_2O PEEP, and 10 cm H_2O PEEP. Minimal variation for repeated measures of Vc at the different PEEP levels was noted, with coefficient of variance of 3.31 ± 0.78% (n = 6).

Discussion

These results demonstrate that, in an anesthetized animal model presumed to have relatively intact heart–lung interactions and with experimentally produced changes in LV systolic function and afterload conditions, an airway pressure elevation facilitates derivation of Ees and PRSW values with serial changes that are not significantly different from those derived from vena cava occlusion. This assessment of the performance of APP as a preload reduction method for LVPVR analysis provides new information about the effectiveness of a minimally invasive means of graded transient preload reduction for LVPVR systolic function analysis. This was demonstrated during both for LV dysfunction and during increased inotropic states, which is important because the clinical application of LV systolic function quantification is relevant in settings where the circulation is disturbed, and LV function can be outside of a person's usual resting range. Analysis of LVPVR using IVCO in subjects with LV dysfunction has been described.[3]

Experimental Changes in Systolic Function and Afterload

The interventions designed to alter systolic function were successful in bringing about significant changes in
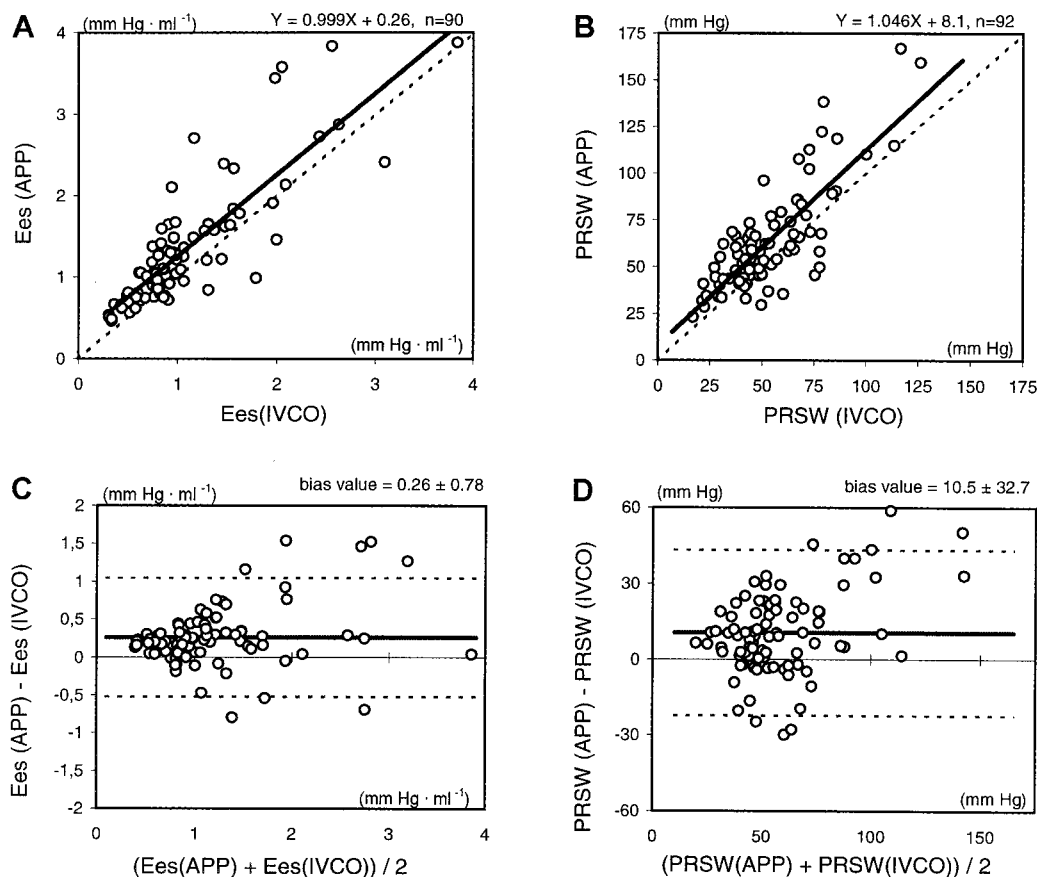
Fig. 4. The correlation plots in *A* and *B* demonstrate the raw data for differences in the paired measurements (ΔEes and ΔPRSW) for all groups and interventions. The equation for the regression line is demonstrated for each in *A* and *B*. The lower panels show a bias plot of the differences between control and intervention measurement (ΔEes in *C*, and ΔPRSW in *D*), with these differences paired for each of the two preload reduction methods. The solid line represents the mean difference between measurements using the two methods, and the hatched line represents 2 SD from that mean difference.

at least one of the systolic function parameters in every case, although in several of the lesser degree interventions, there was a significant change in one of the parameters (Ees or PRSW) but not the other (see fig. 3). Also, statistical significance was reached for systolic function changes in isoflurane and adrenaline for one but not the other of the preload reduction pairs, and in all three cases for IVCO but not APP, respectively. Small numbers of pairs and relatively large variation between individual measurements potentially can explain lack of significant changes in Ees or PRSW for APP measurements during group 2 isoflurane Ees, adrenaline high-dose Ees, and adrenaline low-dose PRSW, where effects were expected or have previously been described.[10] Temperatures of 30° and 32°C brought about decreases in all groups of systolic function parameters, although there was a significant difference for Ees at 34° and PRSW was not different from control. Adrenaline even in the higher dose led to an increase only in the IVCO group for Ees, although an increase in PRSW was noted even at the lower dose. Ees decreased significantly during the modest dose of isoflurane, and PRSW remained

unchanged. Ees increased during aortic occlusion whereas PRSW did not.

Controlled Preload Alteration in LVPVR

The APP and the IVCO are interventions that progressively change pressure and volume conditions in the heart within generally predetermined ranges, although the absolute pressure and volume effects of the two methods clearly differ.[6] The goal of the APP is not to generate the same absolute pressure and volume events as IVCO. Rather, it is the resulting relationship of pressure and volumes from beat to beat, or the slope measurement of Ees and PRSW, that is of interest. The goal of the preload reduction interventions is to delineate LVPVR over a progressive series of preloads,[3–5] and in this, both methods were successful.

Limits of Standardized Airway Pressure Plateau

The preload reduction sequence APP was standard for all animals and not adapted for individuals or to particular interventions. A minimum amount and duration of positive airway pressure is necessary to bring about a
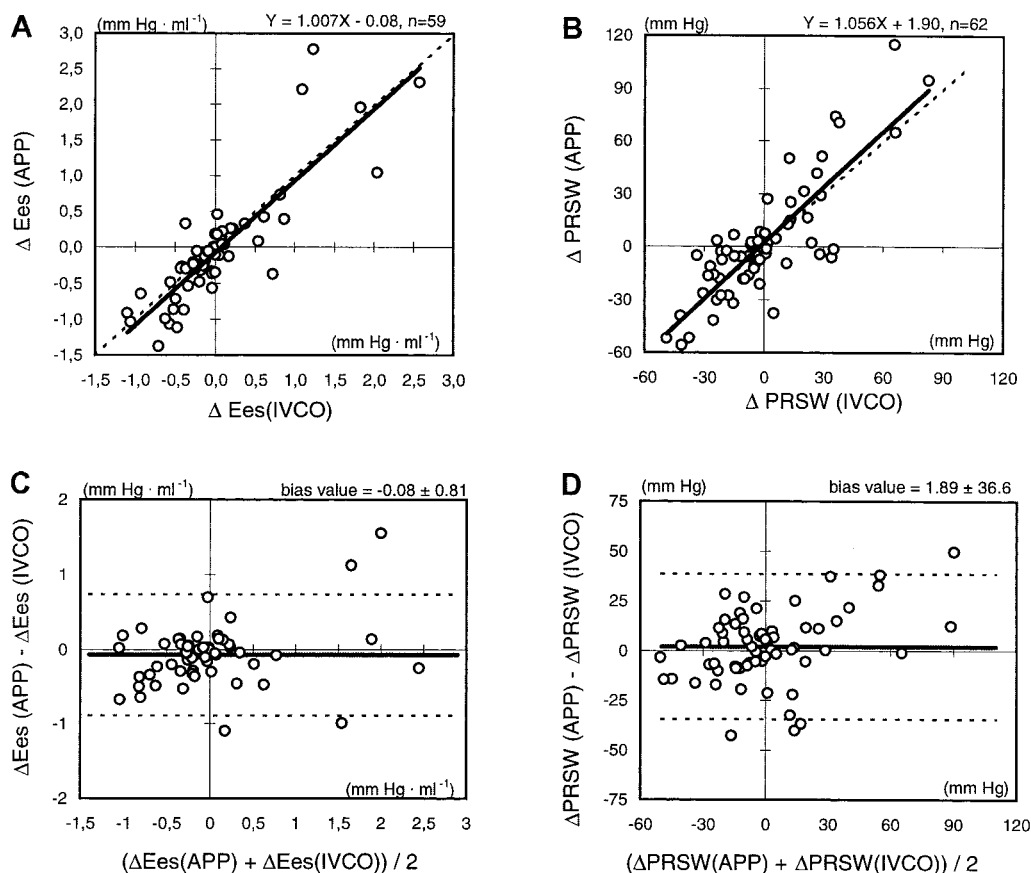
Fig. 5. *A* and *B* show the correlation plots for the absolute values for the paired measurements using the two different preload reduction methods (Ees-APP *vs.* Ees-IVCO, and PRSW-APP *vs.* PRSW-IVCO). A regression line has been plotted for each systolic function group of paired measurements. In *C* and *D*, bias plots are shown that demonstrate a positive bias value (solid line) for APP with ± 2 SD shown by the hatched line. A larger variation from the mean bias is the apparent value at the higher absolute measurement ranges.

clear beat-to-beat preload reduction that allows Ees and PRSW calculation. For Ees calculation, the presumption is that reductions in end-systolic volume (and pressure) occur when beat-to-beat preload reductions occur. Theoretically, this end-systolic pressure relationship may be problematic when, at low volumes, there are not significant beat-to beat decreases in volume, *e.g.*, when end-systolic volume is near zero. Thus, the Ees linear relationship does not hold at extremes of low preload, as has been previously described.[11] In the few measurement sequences where Ees could not be calculated, PRSW could be calculated.

For PRSW calculation, the SW must decrease for successive beats along with end-diastolic volume decreases. If the end-systolic pressure and volume decrease successively during the preload reduction maneuver but for some of the beats the SW does not decrease, then Ees can be calculated, but not PRSW. This was the case for several preload reduction sequences that did not allow PRSW calculation. The APP preload reduction may have been too small in those instances to bring about a stepwise reduction in SW, and a higher positive airway pressure may have been required to bring about a pre-

load reduction that allowed PRSW calculation. This demonstrates that Ees and PRSW describe different aspects of systolic function and can vary significantly from each other. PRSW is recognized as a more consistent and stable parameter of systolic function when multiple parameters have been examined for concordance with another established reference method.[12] It is a common experience in clinical medicine that small airway pressure elevations have minimal effects on arterial blood pressure and LV pressures and volumes, whereas larger airway pressure elevations can have a large effect on the circulation, leading to marked decreases in blood pressure, an obvious connection to LV pressures and volumes. There was no attempt to apply a range of higher experimental airway pressure interventions or define a maximal tolerable APP in this context. Rather, we have tried to show that a minimal airway pressure could produce the necessary preload effects and thereby minimize potential or possible side effects of higher airway pressures, such as lung hyperinflation or changes in autonomic tone in response to dramatic general circulatory changes. An optimal APP preload reduction could be designed for each subject and each measuring se-

quence through trial and error, starting in the lower airway pressure ranges and increasing airway pressures until an optimal preload reduction was observed. Because the goal in this study was to compare the APP with the IVCO intervention at rest, no trial and error stepwise variation in airway pressures that potentially could disturb the resting circulation was tried. Instead, one relatively minimal APP procedure was used. Despite the simplified form of the APP used in these subjects, it was still successful in generating the data required for systolic performance analysis.

Effects of the Interventions on Measured Systolic Function

The hypothermia model included temperature regulation and exposure to an extracorporeal circuit. Reduced LV systolic function was the result of hypothermia[13,14] and generalized inflammatory effects of exposure to the extracorporeal circuit (ECC).[15,16] The range and extent of LV dysfunction was large. Differences in systolic performance were observed between the initial prehypothermia LVPVR measurements and the immediate posthypothermia measurements at the same temperature (38°C), which may have been caused by a combination of posthypothermia contractile dysfunction[17] and inflammation over time from intermittent ECC exposure. Isoflurane, in combination with pentobarbital, produced modest reversible changes in LV function that are in ranges presumably common in clinical medicine, where patients with circulatory dysfunction are treated with anesthetic agents. That relatively low doses of a potent inhalational agent can cause significant changes in myocardial function with presence of barbiturates has been suggested in previous studies.[18]

LVPVR Assessment Methodology

The methods for volume and pressure data acquisition and analysis were chosen to implement direct LVPVR assessment with future intentions toward less invasive clinical implementation of similar or equivalent methods. For clinical application, LV catheterization is impractical because of its high degree of invasiveness, although conductance catheters have been used in settings where left heart catheterization is occurring for other reasons.[3,19] Other less invasive means of continuously assessing LV volumes are being investigated, including noninvasive LV conductance[20] and other means for acquiring indices of or surrogates for LV volume that demonstrate utility for LVPVR analysis of systolic function.[21] A minimally invasive transient preload alteration method that is predictable, reproducible, and nonthreatening as far as lasting circulatory effects is also necessary for implementation LVPVR analysis and routine Ees and PRSW measurement outside of the catheterization laboratory or cardiac surgery suite.

The conductance volumetry method was chosen anal-

ysis because of its continuous nature and ease of application in the acute large animal model. The conductance method is recognized for reliability in quantitating relative changes in LV volume, even if absolute calibration, particularly for parallel conductance signal, is difficult to verify in the whole animal preparation.[22] During the hypothermia sequence, calibration for parallel conductance and gain (α) were performed at each temperature. The lowest temperature was 30°C, and now performance problems resulting from temperature in this range were suspected in either the conductance apparatus or LV tip manometry. The tip manometer was calibrated at the start of each protocol at 21°C. With respect to the effects of aerated or less aerated lung tissue surrounding the heart during measurement sequences, one could suspect that LV parallel conductance differences could occur as the result of increased lung aeration during APP, and that this may account for some or much of the absolute differences between LVPVR measurements from the paired preload reduction sequences. Lung volumes were static, either at end-inspiration or end-expiration, for APP and IVCO, respectively. The results from Vc measurements at the start of each protocol in eight animals showed that there were no differences between Vc measured at 0 PEEP, 5 cm H_2O PEEP, and 10 cm H_2O PEEP. One can conclude from this that the events that led to absolute differences in LVPVR measurements between the two different preload reduction methods were not related to parallel conductance. Again, parallel conductance differences merely change the volume offset and not the stroke volume signal from conductance. Ees and PRSW should be resistant to differences in Vc whether the Vc has been measured accurately or not. Volume offset (Vc) and calibration (α and ρ) were measured for all interventions in all animals to have as accurate conductance volume measurements as possible. But, Ees and PRSW results are valid even if only the relative volumes are consistently measured. Further concern for the possibility of Vc changes during a preload reduction sequence or even during each heart cycle[23,24] is difficult to confirm or refute because there is no generally accepted reference method for LV volume measurement *in vivo*. With the advent of new methodologies, including magnetic resonance imaging (MRI), a more refined evaluation of actual LV volumes can be made,[25] although in this experiment MRI was not available.

In summary, this study has described a strong relationship between changes in systolic function measured using LVPVR analysis and two different preload reduction methods, one of which, APP, is new in this context and is minimally invasive. The range of the changes in systolic function was determined by the experimental interventions in this animal model, which were designed to replicate systolic function events common to intensive care and perioperative medicine. The model in an

anesthetized adult pig allowed testing *in vivo*, where the cardiopulmonary system at rest was considered to be intact. The results suggest that APP is not interchangeable with IVCO for LVPVR analysis because of a systematic positive bias, but that the absolute differences in serial measures were not different, during the circulatory interventions involving the inotropic and afterload increases and decreases measured in this investigation. This method for preload alteration presents a possibility for making the preload alteration aspect of LVPVR analysis simpler and less invasive. Further testing is required to see if APP has utility for LVPVR analysis in patients, starting first in patients with relatively intact heart–lung interactions.

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