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Invasive Left Ventricular Energetics During Enhanced External Counterpulsation

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Enhanced external counterpulsation (EECP) is a noninvasive technique that provides beneficial effects for patients with chronic, symptomatic angina pectoris. However, the direct left ventricular effects of EECP have not been studied invasively. We examined invasive right atrial pressure and left ventricular hemodynamics during EECP. Ten patients referred for diagnostic evaluation underwent left heart catheterization from the radial artery. At baseline and during EECP, left ventricular pressure and volume were measured using a micromanometer pressure-conductance catheter, along with recording of right atrial and central aortic pressures. Hemodynamics were recorded at different lower extremity cuff configuration and cuff inflation pressures. As cuff inflation pressure increased, EECP resulted in a dose-dependent increase in right atrial and aortic diastolic pressure ($P < 0.0001$). The increase in ventricular preload resulted in increased left ventricular volume. Maximum positive ($P = 0.0003$) and negative left ventricular dP/dt ($P < 0.0001$) increased. Left ventricular diastolic pressure decreased. There was a neutral effect on myocardial mechanical efficiency. In conclusion, EECP acutely increased right atrial and central aortic diastolic pressure. The increase in preload attenuated the reduction in left ventricular diastolic pressure resulting from systolic unloading. The increased preload counterbalanced the afterload reduction, resulting in a neutral effect on myocardial efficiency.

Keywords: external counterpulsation, hemodynamics, heart failure

INTRODUCTION

Enhanced external counterpulsation (EECP) is a noninvasive technique used for outpatients with refractory angina. The device utilizes 3 pairs of cuffs wrapped around the lower extremities that inflate sequentially during diastole. Clinical studies have shown that 35 daily 1-hour EECP treatment sessions increase the time to ischemia on exercise testing,[1–3] improve angina,[4] and enhance myocardial perfusion.[2,3,5,6] As demonstrated by 2- to 5-year follow-up studies, the effects on angina and quality of life are durable.[7–9]

Prior studies have used noninvasive techniques such as echocardiography,[10] finger plethysmography,[11] and radial tonometry[12] to demonstrate the hemodynamic effects of EECP: diastolic augmentation, systolic unloading, and afterload reduction. Invasive studies have proven challenging because the EECP cuffs obstruct the femoral arterial access site. Taguchi et al[13] performed right heart and radial artery catheterization during EECP, showing that EECP leads to diastolic augmentation, an increase in the cardiac index, and an increase in biventricular filling pressures. We previously reported that EECP augmented intracoronary diastolic pressure and flow in addition to left ventricular systolic

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unloading in a cardiac catheterization study via the radial artery.[14]

More recently, EECP has been studied in heart failure patients. Observational[15,16] and experimental[17] studies have shown that EECP is associated with improved exercise tolerance and quality of life in patients with left ventricular dysfunction. Although the systolic unloading is a beneficial hemodynamic effect for patients with left ventricular dysfunction, the increase in preload from compressing the lower extremity venous system may be problematic for individuals with congestive heart failure. It remains controversial whether high- versus low-pressure[18] during cuff inflation improves the clinical effects of EECP in heart failure patients. The relative contribution of each of the 3 sets of lower extremity inflation cuffs also remains unclear. Preliminary clinical studies indicate that patients with left ventricular dysfunction may still benefit from EECP; however, the degree to which left ventricular hemodynamics and preload are affected by EECP remains unclear.

In the present study, we invasively assessed right atrial pressure and left ventricular hemodynamics using a high-fidelity pressure-conductance (PC) catheter. We sought to examine changes in ventricular pressure, volume, contractility, work, and efficiency, which have not yet been evaluated during EECP. To determine the safety and efficacy of high- versus low-pressure cuff inflation and to determine the relative hemodynamic contributions of the different sets of external cuffs, we compared the effects of 4 different lower extremity cuff combinations at 5 different cuff pressures to determine how ventricular hemodynamic changes depending on the cuff pressure and location. Because of patient safety concerns with the expected increase in left ventricular preload, patients with decompensated heart failure were not enrolled in this study.

MATERIALS AND METHODS

Patient population

Outpatients referred for diagnostic right and left heart cardiac catheterization and coronary angiography were eligible for enrollment in this single-center, investigator-initiated study. This study population was completely different from our prior study of the effects of EECP on coronary hemodynamics.[14] Exclusion criteria included systolic blood pressure <90 mm Hg or >180 mm Hg; decompensated heart failure; femoral artery puncture within 1 week; severe aortic insufficiency; current atrial fibrillation; contraindication to radial arterial or internal jugular venous catheterization; and unstable angina, myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft surgery within the last month. All patients gave written informed consent before the procedure, and the protocol was approved by the Committee on Human Research.

Cardiac catheterization

Right and left heart catheterization and coronary angiography were performed via the right internal jugular vein and the right radial artery, respectively. A 90-cm, 6-F MPA1 guiding catheter was advanced to the ascending aorta to measure aortic pressure using a fluid-filled pressure transducer. A 4-F pressure–volume, 12-electrode conductance catheter (CD Leycom, Zoetermeer, the Netherlands) with seven 10-mm spaced impedence segments was advanced through the guiding catheter to the left ventricle for left heart hemodynamic measurements recorded with the CFL 512 device (CD Leycom, Zoetermeer). All patients received 2 L/min of nasal cannula oxygen throughout the study period, and the level of conscious sedation was continued at a steady level throughout the study period.

EECP therapy

The model TS3 EECP device (Vasomedical, Inc, Westbury, NY) is composed of an air compressor, a computer module, 3 sets of cuffs, and a treatment table. This device was modified by removing the treatment table, enabling patients to lie on the cardiac catheterization laboratory table, with pressure hoses connecting to a portable air compressor unit on the EECP console. Before cardiac catheterization, the cuffs were wrapped around both calves and the lower and upper thighs (including the buttocks) of the patient. The EECP device inflates the cuffs with air and then deflates them, in a sequence that is synchronized with the patient's cardiac cycle. Pressure was applied sequentially from the calves to the buttocks, starting in early diastole. At the end of diastole, the compressed air was released rapidly from the cuffs to remove the externally applied pressure.

EECP was performed sequentially at 5 external cuff inflation pressure levels: 80, 160, 200, 260, and 300 mm Hg. Hemodynamics were recorded at baseline and then during each of these 5 pressure settings at 4 different cuff combinations: (1) calf cuffs only, (2) calf and lower thigh cuffs (termed 2-cuff low), (3) lower and upper thigh cuffs (termed 2-cuff high), and (4) all 3 cuffs. EECP was administered for 1 minute before hemodynamic measurements at each cuff type and pressure setting. At each setting, central aortic pressure using

the guiding catheter, left ventricular hemodynamics using the PC catheter, and right atrial pressure from the right internal jugular venous catheter were recorded. There was mild dampening of the aortic pressure from the 6-F guiding catheter with the inserted 4-F pressure–volume catheter; however, the degree of dampening was constant in each patient allowing for the accurate assessment of changes in aortic pressure during the study protocol. The same sequence of cuff combination and inflation pressure was used for every patient.

Combined PC catheter measurements

The micromanometer PC catheter apparatus consists of a PC catheter connected to a computer (CD Leycom CFL 512, Zoetermeer) and a power source. Under fluoroscopic guidance, the catheter is positioned along the long axis of the left ventricle with the electrode tip placed at the apex. Dual electric fields are generated using alternating currents of small amplitudes (frequency 20 kHz). The conductance between pairs of electrodes is measured and recorded by the computer. From the time-varying conductance, correlating volumes are calculated using a computer-programed algorithm. The data are analyzed offline by the Conduct NT software (version 2.8, CD Leycom, Zoetermeer, the Netherlands, Figure 1), yielding the following hemodynamic variables: stroke volume, tau, maximal positive and negative dP/dt, end-diastolic pressure, end-diastolic volume (EDV), end-systolic pressure, end-systolic volume (ESV), and stroke work.

Conductance catheter ventricular volumes were calibrated using ventricular volume measurements from echocardiography. Parallel conductance (Vc) for each patient was calculated using the PC catheter volume data in conjunction with left ventricular ejection fraction (LVEF) from transthoracic echocardiography using the equation Vc = EDVo − ((EDVo − ESVo)/LVEF). Individual patient volume data were adjusted in accordance with the calculated Vc's. Within-patient variability of Vc values is small[19]; therefore, relative changes of left ventricular volume data could be compared over a range of pressure settings.

The left ventricular end-systolic pressure–volume relationship (ESPVR, or end-systolic elastance, Ees) was measured by calculating the peak isovolumetric pressure (P_{max}) at the EDV estimated by a curve-fitting method from an isovolumetric ventricular pressure curve.[20] The single-beat ESPVR was the slope of the line drawn from the P_{max} point tangential to the end-systolic upper left corner of the pressure–volume loop. The P_{max} was the mean of applying this method to 10 beats, excluding all ectopic and postectopic beats. The x intercept of the single-beat ESPVR line defined the ventricular volume at zero pressure (Vo). Potential

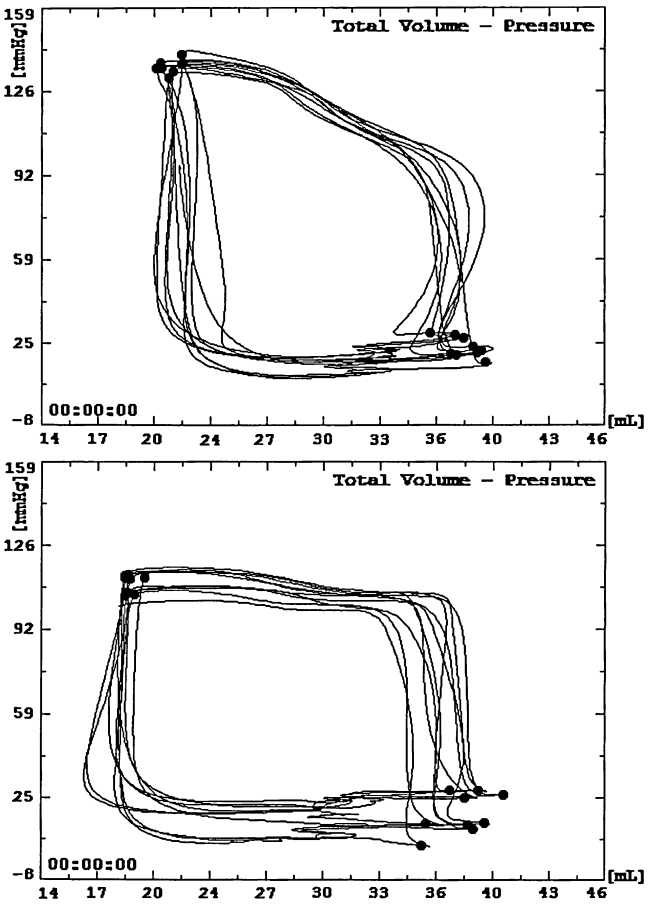

FIGURE 1. Representative left ventricular pressure–volume loops at baseline (A) and during 3-cuff, 300–mm Hg EECP (B). Note the reduction in LVEDP and the reduction in end-systolic pressure due to systolic unloading.

work was calculated as the area within the triangle from Vo and the points of aortic valve closure and mitral valve opening on the pressure–volume loop. Stroke work was calculated as the area within the pressure–volume loop. The pressure–volume area includes the area within the pressure–volume loop plus the triangular area formed by the Vo x axis point, the point of aortic valve closure, and the point of mitral valve opening. The pressure–volume area is the sum of external and stroke work. Mechanical efficiency was defined as the ratio of stroke work to pressure–volume area.

Statistical analysis

Data are presented at baseline as mean values with standard deviations for continuous variables. Mean changes and 95% confidence intervals were calculated at each cuff setting between baseline and the 300–mm Hg pressure setting. A generalized estimating equation linear regression model was constructed to independently determine changes from cuff settings and

pressure, using an exchangeable correlation structure and robust standard errors. P values <0.05 were considered significant. All analyses were performed using STATA version 9.2 (StataCorp, College Station, TX).

RESULTS

Patient population

Ten patients were enrolled. Seven patients were men, and the mean age was 56 ± 8 years (range 44–69 years). Indications for cardiac catheterization included the following: pre–lung transplant evaluation (n = 3), post–heart transplant surveillance evaluation (n = 2), diastolic heart failure (n = 2), and atypical chest pain (n = 2). Nine patients had a history of dyslipidemia, 6 had hypertension, 2 had diabetes mellitus, and none had renal insufficiency. Three patients had significant coronary artery disease, and 2 had been diagnosed with clinical heart failure. All patients had normal left ventricular systolic function with LVEF ≥50%. None had clinically significant peripheral vascular disease.

Right heart hemodynamics

Mean baseline hemodynamics are presented along with the mean changes, P values, and 95% confidence interval at each cuff setting between baseline and 300–mm Hg pressure settings (Table 1). We reported the P values across cuff settings with a cutoff of $P < 0.05$ as statistically significant. As cuff pressure increased, there was an increase in heart rate (baseline 71 ± 12 bpm) in each of the 4-cuff settings. With increasing cuff inflation pressure, right atrial pressure significantly increased in the 3-cuff setting (Table 1; Figure 2A). The 3-cuff setting had the greatest increase in heart rate and right atrial pressure.

Systemic hemodynamics

EECP resulted in significant aortic diastolic pressure augmentation (Table 1). There was a stepwise increase in diastolic augmentation as the cuff settings varied from 1-cuff up to the 3-cuff setting. Mean aortic pressure also increased as cuff pressure was increased, in all 4 cuff settings. The greatest increase in mean aortic pressure was observed for the 2-cuff high and 3-cuff settings. In this study cohort, systolic unloading was observed only in the 2-cuff high setting.

Left ventricular hemodynamics

Using the PC catheter, left ventricular end-diastolic pressure (LVEDP) was reduced in both the 2-cuff high and 3-cuff settings, with no change in LVEDP with the 1-cuff and 2-cuff low settings (Table 2; Figure 2B). The

TABLE 1. Systemic hemodynamics. The mean changes in the hemodynamic pairwise values from baseline to 300 mmHg inflation pressure are shown. P-values are from the repeated-measures generalized estimating equation linear regression model including each of the six levels of inflation pressure (0–300 mmHg).

Variable	Base ± SD	1 Cuff Mean change (95% CI)	P	2 Cuff Low Mean change (95% CI)	P	2 Cuff High Mean change (95% CI)	P	3 Cuff Mean change (95% CI)	P
Heart rate, bpm	71 ± 12	1.2 (−0.6 to 3.0)	0.0007	2.0 (0.3 to 3.8)	<0.0001	3.0 (2.0 to 3.9)	<0.0001*†	3.7 (1.6 to 5.7)	<0.0001*†
Right atrium, mmHg	10 ± 5	−0.5 (−1.5 to 0.6)	0.17	1.1 (−0.4 to 2.6)	0.01*	2.1 (−0.1 to 4.3)	0.12*	4.0 (1.7 to 6.4)	<0.0001*†‡
Aortic systolic, mmHg	133 ± 26	5.5 (1.4 to 9.6)	<0.0001	1.5 (−5.7 to 8.6)	<0.0001	−2.0 (−12.7 to 6.9)	<0.0001	4.1 (−3.2 to 11.4)	<0.0001*†
Aortic mid diastolic, mmHg	116 ± 21	9.6 (6.1 to 13.2)	<0.0001	17.6 (11.0 to 24.2)	<0.0001*	23.7 (14.3 to 33.1)	<0.0001*	31.3 (23.5 to 39.1)	<0.0001*†‡
Aortic mean, mmHg	107 ± 18	6.8 (3.5 to 10.1)	0.0002	8.7 (5.3 to 12.1)	<0.0001*	27.3 (16.9 to 37.7)	<0.0001*†	15.9 (11.2 to 20.4)	<0.0001*†

*if $P < 0.05$ for tests vs 1 cuff.
†if $P < 0.05$ for tests vs 2 cuff low.
‡if $P < 0.05$ for tests vs 2 cuff high.

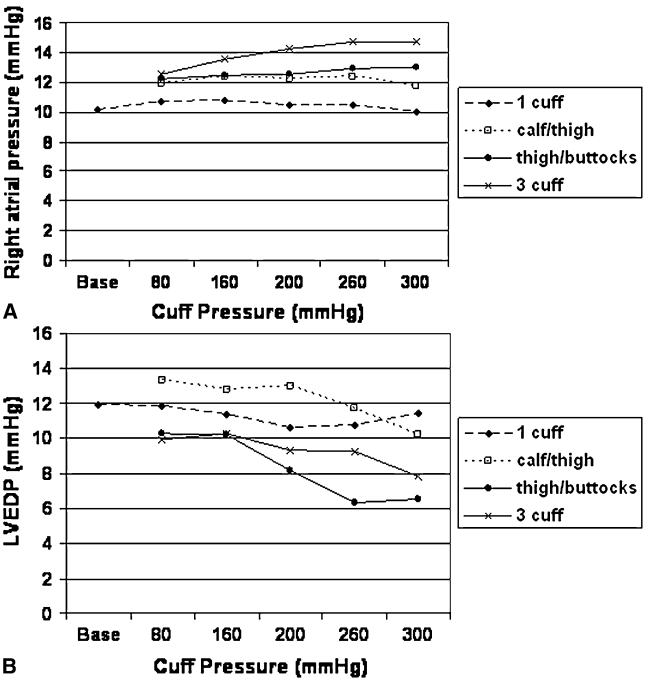

FIGURE 2. Mean right atrial pressure (A) and LVEDP (B) by cuff setting and inflation pressure.

greatest reduction in LVEDP was observed in the 2-cuff high setting.

Maximum positive and negative dP/dt increased during EECP in the 2- and 3-cuff settings (Figure 3). There was a modest prolongation of tau, the time constant of left ventricular isovolumic relaxation, during the 2-cuff high and 3-cuff settings. Left ventricular end-systolic and end-diastolic volumes increased during the 2- and 3-cuff settings. The greatest increase in left ventricular end-diastolic and end-systolic volumes occurred with the 2-cuff low and 3-cuff settings.

The single-beat method for calculating Ees, a measure of contractility, decreased slightly only during the 2-cuff high setting. There were no significant changes in ventricular–arterial coupling (Ea/Ees) during EECP. Stroke work decreased significantly only with the 2-cuff high setting. Myocardial efficiency (stroke work/pressure–volume area) decreased slightly during 2-cuff EECP and had no significant change during 3-cuff EECP (Figure 4).

DISCUSSION

This invasive pressure–volume study of EECP demonstrates the direct changes in hemodynamics and systolic heart function that occur during EECP. Our findings both expand our current understanding of EECP therapy and lend support to previous work. Cuff inflation leads to aortic diastolic pressure augmentation, whereas cuff deflation results in systolic unloading. We observed that EECP acutely raises right atrial pressure, leading to increased preload to the left ventricle. Load-dependent contractility, measured by maximum positive dP/dt, increased during EECP. Maximum negative dP/dt increased as aortic diastolic pressure is augmented. The slight prolongation of the time constant tau during EECP suggests that EECP does not result in a load-independent measure of diastolic function. During the 3-cuff setting that promoted the greatest increase in preload, the reduction in LVEDP is attenuated. The 2-cuff high setting resulted in the greatest increase in maximum positive dP/dt along with the greatest reduction in LVEDP and left ventricular stroke work. Overall, left ventricular myocardial efficiency was unchanged: the increase in ventricular preload counterbalanced the beneficial hemodynamic effects of systolic unloading.

Hemodynamic changes during EECP have been studied through various modes. The technology of noninvasive finger plethysmography has been used to show that EECP results in systolic unloading and diastolic augmentation, the ratio of which is linked to a decrease in anginal status and adverse clinical events.[21] Taguchi et al[13] further confirmed these results by studies through right heart cardiac catheterization. His group has also showed that EECP increased preload measured by right atrial and pulmonary capillary wedge pressure changes. Using left heart catheterization via the radial artery, we have demonstrated that EECP resulted in left ventricular systolic unloading, increased diastolic coronary artery pressure, and increased coronary blood flow.[14]

The results from our current study further clarify the acute effects of EECP on left ventricular preload, contractility, lusitropy, and mechanical efficiency. By adjusting the cuff settings and inflation pressure, we were able to measure changes in ventricular function as preload, contractility, and systolic unloading were varied in a dose–response fashion. The traditional 3-cuff EECP system clearly increases right atrial pressure via lower extremity venous compression. This increased venous return resulted in increased ventricular volume. Although 3-cuff EECP promoted significant systolic unloading, the decrease in LVEDP was only modest as the systolic unloading was counterbalanced by increased venous return. In contrast, the 2-cuff high EECP mode (without calf cuff inflation) resulted in less venous return, the greatest decrease in LVEDP, the greatest increase in maximum positive dP/dt, and the greatest reduction in stroke work.

We had interest in the performance of the 2-cuff low mode, which could have application for hemodynamic

TABLE 2. Pressure-volume catheter hemodynamics. The mean changes in the hemodynamic pairwise values from baseline to 300 mmHg inflation pressure are shown. *P*-values are from the repeated-measures generalized estimating equation linear regression model including each of the six levels of inflation pressure (0-300 mmHg).

Variable	Base ± SD	1 Cuff Mean change (95% CI)	*P*	2 Cuff Low Mean change (95% CI)	*P*	2 Cuff High Mean change (95% CI)	*P*	3 Cuff Mean change (95% CI)	*P*
LVEDP, mmHg	11.9 ± 10.4	−0.9 (−3.3 to 1.4)	0.13	−1.9 (−4.6 to -0.7)	0.09	−5.9 (−8.6 to −3.1)	<0.0001†	−3.4 (−6.4 to −0.4)	0.05†
Positive dP/dt, mmHg/s	1305 ± 202	0.8 (−45 to 46)	0.24	17 (−37 to 71)	0.004	501 (−16 to 118)	<0.0001†	67 (8 to 126)	0.0003†
Negative dP/dt, mmHg/s	−1325 ± 287	−38 (−106 to 30)	0.47	−11 (−93 to 71)	0.02	80 (−22 to 184)	<0.0001	50 (−50 to 149)	<0.0001
Tau, ms	38.6 ± 9.2	−0.9 (−3.2 to 1.3)	0.11	−1.5 (−3.3 to 0.4)	0.14	6.3 (−10.2 to 22.7)	0.004	2.1 (−3.2 to 7.4)	0.04
Ees, mmHg/mL	8.1 ± 6.7	−0.9 (−2.9 to 1.0)	0.72	−1.3 (−4.8 to 2.2)	0.53	−2.8 (−5.8 to 0.1)	0.036†	−1.6 (−3.7 to 0.6)	0.10
Ea	5.6 ± 3.7	−0.2 (−1.2 to 0.8)	0.002	−0.9 (−2.4 to 0.6)	0.59	−1.2 (−2.8 to 0.5)	<0.0001	−0.9 (−2.1 to 0.2)	0.06
Ea/Ees	0.46 ± 0.59	0.03 (−0.08 to 0.14)	0.07	−0.02 (−0.18 to 0.13)	0.88	0.11 (−0.04 to 0.26)	0.16†	−0.01 (−0.14 to 0.13)	0.80†
End-systolic volume, mL	15.6 ± 6.9	3.7 (−3.2 to 10.6)	0.10	12.2 (4.0 to 20.4)	0.0002*	4.1 (−0.4 to 8.7)	0.002*	8.4 (−4.7 to 21.5)	<0.0001*†‡
End-diastolic volume, mL	48.6 ± 19.7	4.6 (−4.1 to 13.2)	0.63	10.3 (1.3 to 19.3)	0.0008*	4.5 (−1.8 to 10.8)	<0.0001*	8.3 (−1.7 to 18.3)	0.002*†
SW	3683 ± 1850	258 (−222 to 738)	0.30	88 (−404 to 580)	0.63	−154 (−798 to 490)	0.0002	−163 (−777 to 451)	0.18
SW/PVA	0.93 ± 0.42	−0.02 (−0.08 to 0.04)	<0.0001	−0.03 (−0.08 to 0.03)	0.0088	−0.08 (−1.13 to −0.03)	0.0020†	−0.02 (−0.07 to 0.04)	0.46

*If $P < 0.05$ for tests vs 1 cuff.
†If $P < 0.05$ for tests vs 2 cuff low.
‡If $P < 0.05$ for tests vs 2 cuff high.

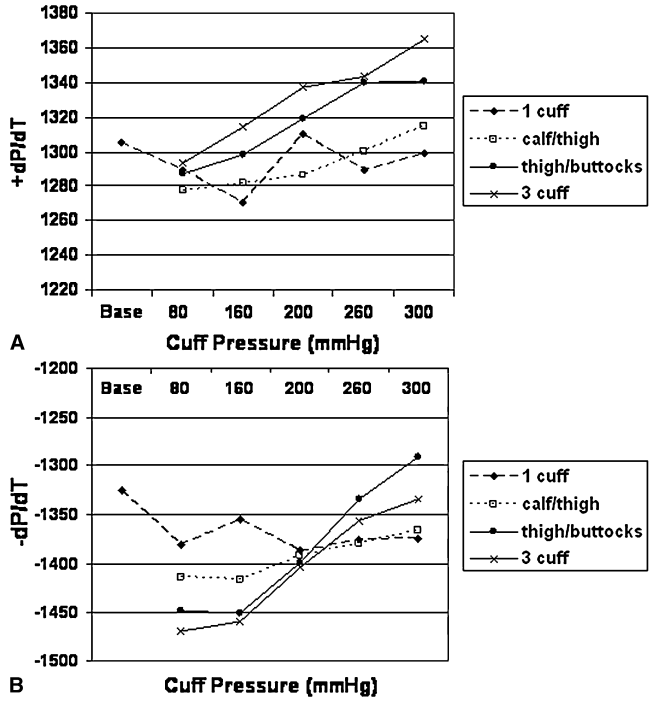

FIGURE 3. Maximum positive (A) and negative d*P*/d*t* (B) by cuff setting and inflation pressure.

support while femoral vascular sheaths are in place. This mode could have utility, for example, during cardiac catheterization via the femoral artery. However, the 2-cuff low mode had lower levels of diastolic augmentation and did not reduce LVEDP or stroke work. There was only a modest increase in maximal positive dP/dt, suggesting that the 2-cuff low setting provided relatively little hemodynamic support.

The decrease in left ventricular work and increase in contractility of the heart indicate that EECP may be helpful for patients with ischemic heart failure. This supports the findings of a preliminary pilot study which showed that patients with left ventricular

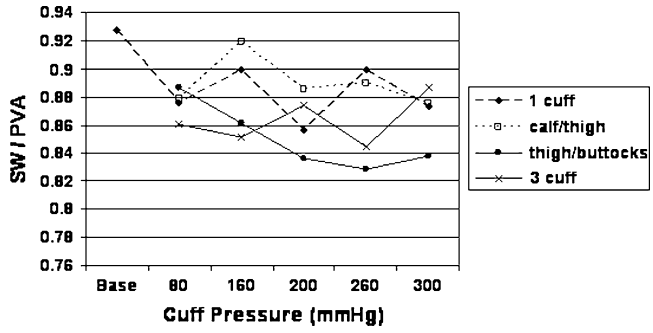

FIGURE 4. Myocardial efficiency (stroke work divided by the pressure–volume area) by cuff setting and inflation pressure.

dysfunction and associated angina benefited from an EECP regimen with reductions in angina class and improvement in quality of life.[21] The Prospective Evaluation of EECP in Heart Failure (PEECH) trial was the first EECP heart failure trial that included a control group and had mixed results.[17] The study population included patients with both ischemic and nonischemic heart failure. Although exercise tolerance increased to a greater degree in patients receiving EECP therapy, changes in peak VO_2 were not significant when compared with the control. Other improvements were noted as well, including New York Heart Association (NYHA) classification and quality of life, suggesting that EECP may be a viable therapy for heart failure patients.

A recent study reported that external counterpulsation delivered to heart failure patients at a lower cuff inflation pressure yielded lower mortality rates compared with treatment at higher inflation pressures.[18] In our study, higher inflation pressures resulted in significantly higher preload to the right atrium (Figure 2A). However, higher cuff inflation pressure also resulted in greater systolic unloading, thereby lowering left ventricular diastolic pressures (Figure 2B) and greater left ventricular contractility (Figure 3A). Our data have direct clinical implications for treating heart failure patients with external counterpulsation. For those with volume overload, lower inflation pressure external counterpulsation may be safer, as this will limit the increase in venous return. However, for euvolumic heart failure patients, higher pressure counterpulsation may yield greater hemodynamic effects to the left ventricle, resulting in increased contractility and systolic unloading.

Our study included several limitations. The sample size of this study was small and included patients neither with a diagnosis of decompensated heart failure nor with active myocardial ischemia. These groups may have had a different hemodynamic response to EECP. We also did not include any patients with peripheral vascular disease, in whom arterial pressure transmission may be decreased due to arterial occlusive disease. Our study population did not include those with impaired left ventricular systolic function. We may not be able to generalize our hemodynamic results to those with heart failure. Lastly, we did not vary the sequence of cuff pressure and settings during the study, possibly contributing to a systematic bias in the study results.

CONCLUSIONS

Invasive left ventricular hemodynamic assessment during EECP demonstrates significant aortic diastolic

pressure and contractility augmentation and reduction in left ventricular diastolic pressure. Venous compression results in increased preload, leading to increased ventricular volume and a neutral effect on myocardial mechanical efficiency. These hemodynamic changes are dependent upon both the cuff inflation pressure and the pattern of the inflation cuffs used. Low-pressure inflation up to 160 mm Hg may be harmful in volume-overloaded heart failure patients, as this setting results in increased preload without sufficient afterload reduction. Application of EECP in patients with heart failure may be improved by selecting cuff and inflation ranges to maximize systolic unloading while minimizing increases in preload.

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