Extra-Aortic Balloon Counterpulsation
An Intraoperative Feasibility Study

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Background—Current methods of counterpulsation or ventricular assistance have significant vascular and limb complications. The aim of this study was to determine the safety and performance of a new method of non-blood–contacting counterpulsation using an inflatable cuff around the ascending aorta (extra-aortic balloon [EAB]).

Methods and Results—In 6 patients undergoing first time off-pump coronary bypass surgery via sternotomy, the EAB was secured around the ascending aorta and attached to a standard counterpulsation console. At baseline and with 1:2 and 1:1 augmentation, hemodynamic and echocardiographic parameters of ventricular function and coronary flow were measured. High-intensity transient signals were measured using transcutaneous Doppler over the right common carotid artery. No complications occurred. With EAB there was no significant change in heart rate or blood pressure and no increase in high-intensity transient signals. There was a 67% increase in diastolic coronary blood flow (mean left-main diastolic velocity time integral 15.3 cm unassisted versus 25.1 cm assisted, \( P<0.05 \)). Measurements with transesophageal echocardiography at baseline and with 1:1 counterpulsation demonstrated a 6% reduction in end-diastolic area \((P=NS)\), a 16% reduction in end-systolic area \((P<0.01)\), a 31% reduction in left ventricular wall stress \((P<0.05)\), and a 13% improvement in fractional area change \((P<0.005)\).

Conclusions—EAB counterpulsation augments coronary flow and reduces left ventricular afterload. Further testing is warranted to assess the use of the EAB for chronic non-blood–contacting support of the failing heart. (Circulation. 2005;112[suppl I]:I-26–I-31.)

Key Words: aorta • balloon • heart-assist device • heart failure • cardiac output

Timed increase of the diastolic aortic pressure to augment coronary flow was first demonstrated by the Kantrowitz brothers in 1953.1 Further experimental work using pedicled diaphragm wrapped around the descending aorta stimulated to contract during diastole demonstrated the added benefit of decreased ventricular work by lowering left ventricular afterload.2

The intra-aortic balloon pump (IABP) has been used for the treatment of cardiogenic shock since 1968 and has been shown to be an effective tool for decreasing left ventricular afterload, improving global left ventricular function, and increasing diastolic coronary blood flow and myocardial perfusion pressure.3 The IABP is typically used after extensive myocardial infarction or after cardiac surgery for temporary support. This device is usually placed through the femoral artery and thus the patient is immobile, which can lead to a high incidence of leg complications.4

Long-term counterpulsation may provide extended physiological support to the heart and allow myocardial recovery to occur. Various mechanisms have been devised for long-term support in patients in chronic heart failure to avoid leg complications and to allow mobility. Clinical examples include inserting a regular intra-aortic balloon via a Dacron graft sewn to the iliac artery5 or subclavian artery6 or directly into the thoracic aorta7; an implantable transmural descending thoracic aortic counterpulsation device with an inflatable pocket8; and ascending aortomyoplasty using the right latissimus dorsi muscle.8

An extra-aortic balloon (EAB) (C-Pulse; Sunshine Heart, Inc) has been developed for ascending aortic counterpulsation, which may be suitable for implantation in selected patients with heart failure who require ventricular assistance as destination therapy. The EAB is a non-blood–contacting preshaped balloon and cuff that is wrapped and secured around the ascending aorta and connected via a gasline to a balloon pump console. The EAB is positioned immediately above the sinotubular junction of the aorta to maximize the cardiac counterpulsation effect (Figure 1). Intraoperative animal studies have confirmed improved coronary blood flow with EAB counterpulsation, with no adverse histological effect on the ascending aorta after approximately 30 minutes of exposure.9 The use of the device is contraindicated in patients with ascending aortic disease or intact aorto-coronary
grafts. Significant ascending aortic atheroma occurs in approximately 17% of patients undergoing cardiac surgery.

This study aimed to demonstrate the safety and feasibility of using EABs in humans and to test the primary hypothesis that the EAB would augment coronary flow and reduce left-ventricular afterload in human subjects. In addition, we sought to document whether the EAB would be associated with an increase in cerebral microemboli arising from the aorta.

Methods
The study protocol was approved by the regional ethics committee, and all patients gave written informed consent. Patients undergoing routine (non-urgent) first time off-pump coronary bypass surgery were recruited, provided they had no risk factors for stroke, no evidence of left ventricular impairment, and a normal chest x-ray.

Surgical Procedure
General anesthesia was provided using midazolam premedication, etomidate, neuromuscular blockade, isoflurane in oxygen, and low to moderate doses of fentanyl. Monitoring was according to the guidelines of the Australian and New Zealand College of Anesthetists. A 5-MHz transesophageal echocardiography (TEE) probe (Hewlett Packard) was placed after induction of anesthesia. After routine sterile preparation and sternotomy, significant diseases of the aortic root, valve, and ascending aorta were excluded by visual inspection, manual palpation, and TEE of the ascending aorta.

An EAB cuff was placed around the ascending aorta and securely sutured into position (Figure 1). The connector tubing was attached to a Datascopc 97 IABP console. The EAB was programmed to inflate at the dicrotic notch on the aortic pressure waveform and to deflate on the R wave of the ECG. The volume and timing was adjusted in 1:2 mode to optimize the augmentation of diastolic blood pressure as visually determined from the aortic pressure waveform on the Datascopc monitor. After a period of counterpulsation long enough to permit the required measurements, the EAB was removed and each patient underwent routine off-pump coronary bypass surgery using standard techniques. Conduits for grafting included the left internal mammary, radial artery, and saphenous vein, as appropriate. Patients were transferred to intensive care postoperatively, and then to the ward where they were followed-up until hospital discharge.

Hemodynamic and Carotid Doppler Measurements
Systolic, diastolic, and mean arterial pressures (via a right radial artery cannula) and central venous pressure (via a cannula introduced via the internal jugular vein to the superior vena cava) were monitored using transducers (Baxter) zeroed to the level of the midaxillary line. Heart rate was determined from the monitored ECG. A steady state was achieved before hemodynamic and echocardiographic measurements were performed, with no change in the patient position, fluid administration, or surgical stimulation during the measurement period. Hemodynamic measurements were made at baseline and with 1:2 and 1:1 EAB counterpulsation. The patients' hemodynamic condition were maintained for approximately 5 minutes between each set of measurements.

A Multi-Flow Doppler machine (DWL Elektronische Systeme GmbH) operated in the 2-MHZ pulsed wave mode was used to monitor the right common carotid artery. This was done during timed phases at baseline (after induction of anesthesia), placement of the EAB, counterpulsation, application of the side-biting clamp, and proximal aorto-coronary grafting. The data were stored for subsequent analysis. Artifacts attributable to mechanical noise or diathermy were removed from the data manually. High-intensity transient signals above a threshold of 12 decibels were counted.

Echocardiographic Measurements
Diastolic coronary flow was measured by positioning a pulsed-wave Doppler sample volume with narrow gating in the distal left main coronary artery in the mid-esophageal aortic valve short-axis view with the plane of the sector scan slightly superior to the aortic valve, adjusted to optimize the view of the distal left main and proximal left anterior descending coronary artery and to minimize the angle between the Doppler beam and the direction of coronary flow. Ventilation was suspended temporarily during Doppler recordings to minimize any cardiac movement. Recordings of 3 cardiac cycles at baseline and with 1:2 and 1:1 augmentation were recorded, and the average was taken for each mode. The diastolic coronary flow velocity integral was used as the primary measurement of diastolic coronary flow from the pulsed-wave Doppler waveform (Figure 2). Peak diastolic coronary velocity also was measured. To ensure comparable placement of the sample volume in the left main coronary artery and to avoid the effect of autoregulation on coronary flow, measurements were made with 1:2 augmentation, with comparisons between sequential assisted and unassisted beats. For other indices of cardiac function (eg, fractional area change), comparisons were made between baseline and 1:1 augmentation.

The transgastric mid-short axis view was used to measure left ventricular end-diastolic and end-systolic areas, endocardial and epicardial circumference, cavity dimensions, and wall thickness. Echocardiographic images were recorded on videotape and all measurements were made off-line by one independent sonographer. Three measurements taken from sequential cardiac cycles were made.

Figure 1. Schematic of the extra-aortic balloon wrapped around the ascending aorta (a, deflated; b, inflated), showing “thumb printing” effect on the greater curve of the ascending aorta.

Figure 2. Pulsed-wave Doppler recording from the left main coronary artery of a patient during 1:2 counterpulsation, showing the marked increase in diastolic velocity and velocity time integral in the augmented beat.
TABLE 1. Hemodynamic Parameters

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n=6)</th>
<th>1:1 (n=6)</th>
<th>1:2 (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>76 (1.2)</td>
<td>72 (1.1)</td>
<td>73 (1.6)</td>
</tr>
<tr>
<td>Central venous pressure, mm Hg</td>
<td>8 (0.5)</td>
<td>9.8 (0.5)</td>
<td>9.5 (0.6)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>112 (5.4)</td>
<td>112 (7.0)</td>
<td>103 (11.9)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>61 (1.3)</td>
<td>59 (2.4)</td>
<td>56 (2.9)</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>76 (2.4)</td>
<td>79 (2.0)</td>
<td>72 (4.8)</td>
</tr>
<tr>
<td>Peak diastolic augmentation pressure, mm Hg</td>
<td>...</td>
<td>94</td>
<td>93</td>
</tr>
</tbody>
</table>

Values listed are mean (SE).

at baseline and with 1:1 EAB augmentation. End diastole was defined as the largest left ventricular cross sectional area before ejection, and end systole as the smallest left ventricular area during systole.

The following formulas were used in calculations to characterize ventricular function:

Fractional area change (FAC) was calculated using end diastolic (EDA) and end-systolic area (ESA):

\[
FAC = (EDA - ESA) / EDA \times 100
\]

End-systolic meridional wall stress (SWS) was calculated using ESA, mean left ventricular posterior wall thickness (LVWT), and the systolic blood pressure (SBP):

\[
SWS = 0.668 \times \text{SBP} \times \text{ESA} / \text{EDA}^{1/2} \times \text{LVWT} \times (1 + \text{LVWT} / (2 \times \text{ESA})^{1/2})
\]

The rate corrected velocity of fiber shortening (Vcfc, circumference \( \times \text{s}^{-1} \)) was calculated using end diastolic and end systolic dimensions and left ventricular ejection time (LVET) and the R-R interval, measured from the Doppler recordings of coronary flow, using the aortic valve opening and closing clicks and the ECG signal:

\[
Vcfc = (EDD - ESD) / [(EDS)(LVET)(R-R interval)]^{1/2}
\]

The geometrical parameters defining the balloon (balloon curvature, length, and membrane throw) and the aortic diameter (measured with TEE) were entered into a solid model software program (Pro Engineer Wildfire, PTC Inc). Using the program’s analysis function, the predicted volume of the inflated balloon in each patient was calculated.

Statistical Analysis

Results are presented as mean (standard error) or mean and 95% confidence intervals (CI) about the mean. Wilcoxon signed rank tests were used to compare groups. All analyses were performed using the statistical software package SAS release 8.0 (SAS Institute Inc). Six patients provided more than 80% power to detect a 50% change in the primary outcome variable (diastolic coronary flow velocity integral), with level of significance set at 0.05 for the primary analysis assuming a standard deviation of 87%. All tests were 2-sided and all probability values are quoted without correction for multiple testing.

Results

Six patients were recruited into the study. None were excluded at the time of inspection of the aorta. The mean age was 54 years (range 41 to 71), height was 176 (± 7.0) cm, and weight was 86 (± 5.7) kg. All patients had 2- or 3-vessel disease and normal ventricular function. Three patients had significant left main stem disease (stenosis range 55% to 85%). All patients had the coronary bypass surgery completed off-pump. All received a left internal mammary graft to the left anterior descending artery, and either radial artery or saphenous vein aorto-coronary grafts were made to other target vessels. The median number of grafts per patient was 2. No patient experienced any postoperative complications.

Hemodynamic Outcomes

Systolic, diastolic, and mean arterial or central venous pressures were comparable at baseline and during counterpulsation (Table 1); heart rate tended to be lower during 1:1 counterpulsation than at baseline (72±1.1 versus 76±1.2, \( P=0.055 \)).

EAB counterpulsation significantly reduced LV ESA and SWS and significantly increased FAC and Vcfc (Table 2). There was a significant inverse correlation between wall stress and fiber shortening, demonstrating an improvement in ventricular function with a reduction in LV afterload in each patient with 1:1 augmentation compared with baseline (Figure 3a and 3b).

Transesophageal Echocardiography

The left main coronary artery could not be visualized adequately for Doppler assessment in 1 patient. In the remaining 5 patients, there was a mean increase of 84% in peak diastolic coronary flow velocity and a 64% increase in the diastolic velocity time integral (Table 3).

During counterpulsation, aortic internal diameter measured by M mode of the ascending aorta during early systole was 31±1.6 mm and in mid-diastole was 15±1.4 mm. The mean calculated displacement volume of the balloon was 20 mL (range 10 to 36 mL).

Transcutaneous Carotid Doppler

Data were successfully obtained in 5 patients (Table 4). There was no increase in the number of high intensity signals.

TABLE 2. Echocardiographic Left Ventricular Characteristics at Baseline and 1:1 Augmentation (n=6)

<table>
<thead>
<tr>
<th></th>
<th>Baseline, Mean (SE)</th>
<th>1:1, Mean (SE)</th>
<th>Absolute Change, Mean (95% CI)</th>
<th>% Change, Mean (95% CI)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDA, cm²</td>
<td>19.6 (1.29)</td>
<td>18.4 (1.10)</td>
<td>-1.2 (-2.96 to 0.40)</td>
<td>-6 (-15 to 3)</td>
<td>0.107</td>
</tr>
<tr>
<td>LVESA, cm²</td>
<td>10.1 (1.13)</td>
<td>8.3 (0.75)</td>
<td>-1.8 (-2.90 to -0.69)</td>
<td>-16 (-26 to -6)</td>
<td>0.009</td>
</tr>
<tr>
<td>FAC, %</td>
<td>49 (4)</td>
<td>55 (4)</td>
<td>6 (3 to 9)</td>
<td>13 (5 to 21)</td>
<td>0.004</td>
</tr>
<tr>
<td>Vcfc, circ ( \times \text{s}^{-1} )</td>
<td>1.3 (0.67)</td>
<td>1.6 (0.69)</td>
<td>0.3 (0.13 to 0.41)</td>
<td>26 (4 to 47)</td>
<td>0.004</td>
</tr>
<tr>
<td>Wall stress, 10³ dyn/cm²</td>
<td>153 (31.6)</td>
<td>99 (15.28)</td>
<td>-54 (-96.4 to -11.52)</td>
<td>-31 (-43 to -20)</td>
<td>0.022</td>
</tr>
</tbody>
</table>

LVEDA indicates left ventricular end-diastolic area; LVESA, left ventricular end-systolic area; FAC, fractional area change; Vcfc, rate corrected velocity of fiber shortening; and CI, confidence interval.
compared with baseline across the different phases of the procedure.

Discussion
This study is the first investigation in humans of an external aortic balloon counterpulsation device. In 6 patients with normal left ventricular function and no aortic pathology undergoing off-pump first time coronary bypass grafting, external aortic counterpulsation of the ascending aorta augmented diastolic coronary blood flow with no adverse events, no perioperative complications, and no evidence of increased embolization. In addition, left ventricular afterload was reduced.

Comparison to Published Data on Intra-Aortic Balloon Counterpulsation
The augmentation in coronary flow documented in this study is comparable to published data on the efficacy of intra-aortic balloon counterpulsation. The 64% increase in the diastolic velocity time integral was within the range (54% to 87%) reported with the IABP, as is the 16% reduction in ESA and the 13% increase in FAC. Our results were obtained with an average displacement of the aorta in the present study of 20 mL, which is half the balloon volume used in the studies of the IABP. This difference in efficiency may be attributable to the location of the counterpulsation device. In previous experimental studies by Furman et al, it was shown that diastolic counterpulsation is more effective at the level of the ascending aorta, for a number of reasons:

1. The closer the diastolic pulse wave generation is to the aortic valve, the more accurately counterpulsation can be timed to ventricular systole without conflict between the ventricular wavefront progressing distally from the aortic valve and the assist wave progressing proximally. Thus, proximity to the aortic valve allows better synchrony of the cardiac cycle to counterpulsation.
2. Pulse propagation is minimized, reducing counterpulsation efficiency loss.
3. Displacement of blood away from the ascending aorta at end diastole is maximized, leading to a greater fall in central aortic end diastolic pressure.

Similarly, a porcine model has demonstrated that a balloon catheter placed in the ascending aorta significantly increased graft flow in both internal mammary and venous conduits, whereas a descending aortic balloon did not.

Mechanisms of Action of Counterpulsation Effect
Counterpulsation may lead to an improvement in left ventricular systolic function by a reduction in the central aortic end-diastolic pressure and afterload, as well as an increase in diastolic coronary blood flow. Figure 3 clearly shows the predictable relationship between fiber shortening and wall stress in each patient, with a leftward shift in each case with counterpulsation ($r=-0.68, P=0.015$). It is likely that left ventricular systolic function improved as a consequence of reduced afterload (end-systolic wall stress) rather than because of an increase in myocardial contractility. Afterload reduction may also alleviate ischemia by reducing myocardial oxygen demand. Nevertheless, an acute improvement in

| TABLE 3. Measures of Coronary Blood Flow From Pulsed-Wave Doppler (n=5) |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | Baseline        | 1:2:1 Unassisted | 1:2:1 Assisted | % Change Unassisted |
| Peak diastolic velocity, cm/s | 50.4 (16.0) | 52.4 (14.7) | 95.9 (33.3) | 84% |
| Diastolic velocity time integral, cm | 16.4 (9.4) | 15.3 (7.2) | 25.1 (12.4) | 64% |

For both peak diastolic velocity and VTI: baseline versus unassisted, $P=NS$; unassisted versus assisted, $P<0.05$. |
myocardial function attributable to an enhancement of intrinsic myocardial contractility from improved coronary perfusion is possible, but none of the patients had unstable angina or signs of ongoing ischemia. Most studies of IABP have shown an increase in coronary blood flow, although in patients with significant coronary stenoses this has not been a consistent effect.\textsuperscript{20,21}

Safety of EAB Counterpulsation
This study did not demonstrate any acute adverse effects of extrinsic compression of the aorta by a preshaped balloon. Care was taken to exclude any significant aortic root or valve pathology or any obvious atheromatous change in the ascending aorta. The fact that there was no increase in the number of high-intensity signals in the common carotid artery and no postoperative neurological complications suggests that there was no increase in clinically significant emboli related to EAB counterpulsation during the study. The “thumb print” deflection by the EAB of the anterior ascending aortic wall minimizes strain, and there is no direct contact of opposing endothelial surfaces; these factors may reduce the risk of trauma to the aortic wall. The long term effect of EAB counterpulsation on the histology of the ascending aorta is currently under investigation in a preclinical model.

Limitations
This study was limited to the acute intraoperative setting, with each patient acting as their own control. As an initial safety and feasibility study, only patients with normal left ventricular function and no evidence of ongoing ischemia at the time of operation were included. Extrapolation of these data to patients with impaired ventricular function or acute ischemia is not possible. The hemodynamic effect of EAB counterpulsation in the populations in whom this technology may be indicated (eg, patients waiting for cardiac transplantation and those with intractable ischemia or heart failure) is currently under investigation. Published IABP data would suggest that this subgroup of patients obtains greater hemodynamic benefit from counterpulsation.\textsuperscript{3}

Estimation of coronary blood flow by TEE is relatively imprecise, and underestimation of the blood flow velocity is likely because of non-parallel Doppler sampling. The percentage change in coronary flow velocity, however, is more relevant to this study than the absolute values, and the position of the sample volume in the left main coronary artery did not change between successive beats. Some patients had left main coronary stenosis, which may have influenced the peak diastolic velocity measured, although previous studies have shown a similar percentage increase in the coronary flow velocity with counterpulsation compared with those without left main stem stenosis.\textsuperscript{14} In this study, the relative increase in peak flow velocity or velocity time integral in those patients with or without left main stem disease was not significantly different. The effect of autoregulation of coronary flow from a reduction in afterload was obviated because measurement of coronary flow in successive augmented and nonaugmented beats was in the 1:2 mode. It is possible that coronary flow was reduced in unassisted beats, which may have exaggerated the change in coronary flow in assisted beats when expressed as a percentage. As shown in Table 3, however, there was no significant difference between baseline coronary flow (before counterpulsation) and the unassisted beats, suggesting that the increase in flow was caused by the mechanical efficacy of counterpulsation. Measurement of reduction in afterload and end-systolic wall stress was made by comparing the areas in 1:1 mode versus baseline, which could have resulted in a change in the hemodynamic state, although there was no significant difference in blood pressure or heart rate at these different stages.

Clinical Implications
This study has demonstrated the feasibility and potential value of extra-aortic counterpulsation using a balloon wrapped around the ascending aorta intraoperatively in patients with normal left ventricular function. The intended use of this device, however, is for long-term implantation in patients with poor left ventricular function and intractable heart failure or ischemia as a less invasive alternative to a left ventricular assist device. The EAB has the advantages of assisting heart function without blood contact, the implantation procedure does not require cardiopulmonary bypass, and the device can be turned on and off safely without the need for anticoagulation. Left ventricular assist devices have proven successful as bridge-to-transplant therapy, and more recently have been shown to have survival benefit when used as destination therapy.\textsuperscript{22} There is increasing evidence that severe myocardial dysfunction may be reversible with long-term ventricular assistance,\textsuperscript{23–25} and the use of an EAB as a method of assisting the failing heart compared with other pharmacological and mechanical modalities warrants further definition.

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