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The left ventricular assist effect and biocompatibility study of a novel para-aortic counterpulsation device

C. SHI, D.-D. ZHOU, G. LIU, L. ZHANG, J.-J. MENG, Y. GENG, X.-G. LIU

Department of Cardiothoracic Surgery, First Affiliated Hospital of Bengbu Medical College, Bengbu City, Anhui province, China

Abstract. – OBJECTIVE: To evaluate the hemodynamic characteristics and biocompatibility of a new para-aortic counterpulsation device in animal experiment studies.

MATERIALS AND METHODS: Para-aortic counterpulsation device (PACD), a monoport device, consists of a blood chamber anastomosed to the descending aorta by means of a valveless graft and an air chamber connected to IABP machine. Hemodynamic parameters during the PACD-assisted beats were compared with those during the unassist beats. Acute heart failure was induced in all animals, and the hemodynamic effects of PACD were then reassessed.

RESULTS: We successfully induced heart failure in all cases, in conditions of which cardiac output (CO) and MAP decreased 17.6% and 27.7% respectively, and PCWP increased 57.7%. Hemodynamic indexes, cerebral and heart perfusion improved significantly after PACD assisting. PACD activation increased significantly CO and MAP 6.29% and 2.04% respectively. Both of SAP and DAP decreased significantly from 85.00 to 81.88 mmHg and 59.63 to 54.63 respectively, at the same time, MADP increased 19.4%, after PACD assist. The value of MDLMF, LMF and CSF was increased by 14.0%, 13.8% and 11.6% respectively. LCAF increased by 11.23%, after PACD assist. The PFH increased significantly in the first six hours. There was no statistically significant difference in the last two hours. When the acute animal experiments were completed, there were no infarct ischemic, thrombosis change in organs by Gross and histologic observation.

CONCLUSIONS: PACD with good biological compatibility significantly reduced the left ventricular afterload, increased diastolic arterial pressure and myocardial perfusion, improved heart function and cerebral perfusion.

Key Words:

Mechanical assist device, Heart failure, Counterpulsation, Circulation assist.

Abbreviations

PACD = Para-aortic counterpulsation device; CO = Cardiac output; IABP = Intra-aortic ballon pump; SAP = Systolic aortic pressure; DAP = Diastolic aortic pressure; LV = Left ventricular; BFH = Blood free hemoglobin; MAP = Mean aortic pressure; PCWP = Pulmonary capillary wedge pressure; MADP = Mean diastolic aortic pressure; MDLMF = Mean diastolic left main coronary blood flow; LMF = Left main coronary artery blood flow; CSF = Corosinuses blood flow; LCAF = Left carotid artery blood flow; MCO = Myocardial oxygen consumption.

Introduction

Mechanical assist is an efficient way to treat acute and chronic refractory heart failure (HF)[1,2]. Intra-aortic balloon pump (IABP) is now the assisting device used most extensively. It is especially effective in coronary patients with cardiogenic shock. Despite numerous advantages IABP possesses, certain disadvantages, including serious vascular complications and patients strictly confined to their beds[3]. These restraint its application in long term assisting of patients with advanced HF. In addition, the effect of IABP is limited in patients with severely low cardiac function, where systolic aortic pressure (SAP) is lower than 70 mmHg. The para-aortic counterpulsation device (PACD) has been proven capable of efficiently supporting patients with profound HF. Animal experiments have shown that PACDs with a similar volume to IABPs have a better counterpulsation effect. We have been dedicated to developing a new type of PACD and have completed some preliminary animal studies. Below is the report of its assist effect and biocompatibility of our PACD.

Corresponding Author: Xue-gang Liu, MD; e-mail: xgliu99@126.com

Materials and Methods

PACD

The PACD (Figure 1) is a pneumatically driven device with a round, polyurethane chamber being the main part of counterpulsation and a moveable diaphragm separating the chamber into the blood space and the air space. The blood space, with a volume of 60 ml, connects to the aorta through a valveless vascular graft. The air space connects to the IABP console, providing power for counterpulsation through inflation and deflation. Like with IABP, PACD was ECG-triggered. With the occurrence of a dicrotic notch of aortic pressure waveform, the inflation of the air chamber was triggered to increase diastolic aortic pressure (DAP) and coronary perfusion. The deflation of the air chamber started before ventricular systole at the end of the diastolic period, to drive the blood filling to decrease left ventricular (LV) afterload. The fatigue resistance of polyurethane is much better than with IABP chambers. Also, the fact that the vascular graft matches better to the aorta avoids vascular complications, making it a potential choice for long term assisting.

Animals and Anaesthesia

The experiments were performed in 8 small fat-tail sheep weighing 44.9±2.5 kg. Food was withheld for 48 h and water was withheld for 24h before the operation. Anesthesia was induced with i.m. injection of 10 mg/kg ketamine hydrochloride (Heng Rui Medical Ltd, Jiangsu) and 0.5 mg/kg midazolam (NHWA Pharmaceutical Ltd, Jiangsu). The trachea was intubated with an 8-mm cuffed endotracheal tube. Tidal volume was 10 ml/kg. Respiration frequency was 18 times/min. Infusion of i.v propofol (Libang Pharmaceutical Ltd, Xian, China) and inhalation of isoflurane (Abbott Pharmaceutical Ltd, North Chicago, IL, USA) were adopted to keep anaesthesia levels.

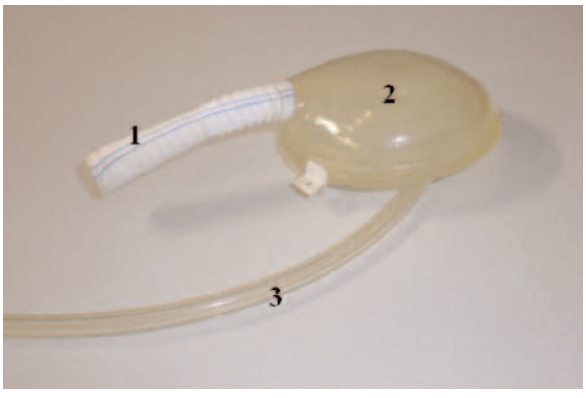

Figure 1. PACD. 1: vascular graft. 2: main part. 3: air chamber tubing.

Surgery

The right external jugular vein was surgically exposed and a three lumen catheter connected to an ECG monitor (Datex-Ohmeda S5/CCCM, Needham, MA, USA) and a cardiac output device (Edwards Life sciences VGS2, Irvine, CA, USA) were introduced to monitor the central venous pressure, right atrial pressure and pulmonary capillary wedge pressure (PCWP). Coronary artery retrograde perfusion tubing was inserted into coronary sinus through atrium dextrum to measure the cardiac returned blood volume. Arterial pressure tubing in the ascending aorta connected to a 16-channel physiological recorder (Biopac systems MP150 Inc, Goleta, CA, USA) to continuously record arterial pressure. Pressure tubing in the left ventricle was connected to a physiological recorder to continuously measure LV pressure. A 2.5mm ultrasonic flow meter probe (Transonic Systems INC, Ithaca, NY, USA) was put in the isolated left main coronary artery and connected to a 16-channel physiological recorder. After heparinization, the descending thoracic aorta was exposed and was sewn with 5-0 prolene sutures end-to-side the vascular graft which was connected to the PACD blood chamber. With the air chamber connected to the IABP console (Datascope 98, Datascope Corp., Montvate, NJ, USA), counterpulsation assist started following the successful construction of the HF model.

Acute LV Failure Model

LV failure was induced by multiple ligations of coronary arterial branches, starting from the peripheral segments of the left anterior descending (LAD) coronary artery, then, proceeding to the diagonal branches and finally to the proximal and midsegments of the LAD coronary artery. Hemodynamic changes were closely monitored. Lidocaine was administered intravenously to prevent ventricular arrhythmias.

Preliminary Measurement of Biocompatibility

Peripheral venous blood specimens were collected 2 hrs before the surgery, and 2 hrs, 4hrs, 6hrs and 8hrs after the surgery. Blood free hemogolobin (BFH) concentration was determined by UV spectrophotometry. After the assist proce-

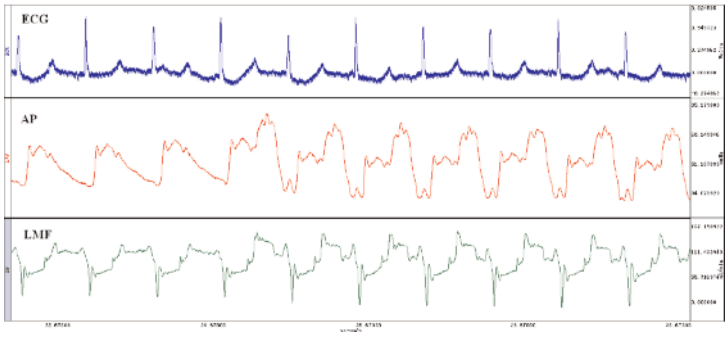

Figure 2. Aortic pressure curves left main coronary artery blood flow waveform traces before and after the mechanical assist. Upon counterpulsation, SAP and DAP decreased while MDAP increased; Coronary perfusion increased. AP: Aortic pressure. LMF: left mean coronary artery flow.

dure was done, gross specimens of all animals were observed and some were selected for histological study to investigate morphological variations under the microscope.

Statistical Analysis

Data collected with the physiological recorder and physiological flow meter were analyzed by BIOPAC's AcqKnowledge 4.1. To minimize deviations, hemodynamic parameter data was only collected after remaining stable for at least 10 min. Collecting period spanned at least 5 min. Comparisons between variables were made by repeated measures ANOVA. Comparisons involving only two groups were done by paired *t*-test. Data was presented as s±. A p-value < 0.05 was considered statistically significant.

Results

Acute HF Model Construction

All acute HF animal models were successfully constructed. Hemodynamic parameters in animals were significantly different before and after ligation of anterior descending branches and circumflex branches (Table I). After HF, CO and mean aortic pressure (MAP) respectively decreased by 17.6% (p<0.01) and 27.7% (p<0.01); PCWP increased by 57.7% (p<0.01).

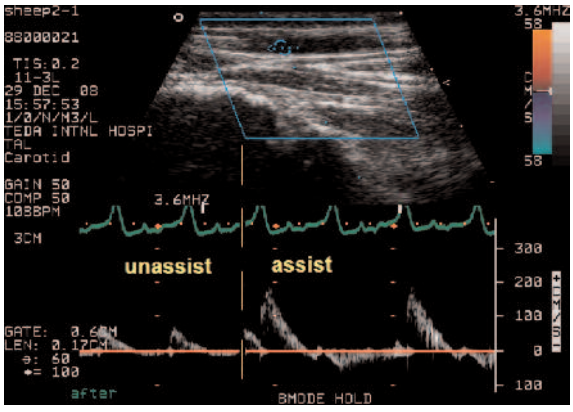

Figure 3. Measurement of left carotid artery blood flow changes before and after the counterpulsation assist with Color Doppler Ultrasound (CDU). Left carotid artery blood flow increased significantly after the counterpulsation assist.

Hemodynamic Parameter Changes in HF Animals with Assistance

All hemodynamic parameters were improved significantly in animals with the assistance of PACD (Figure 2; Table II). CO increased by 6.3% (p<0.01). MAP increased significantly by 2.04%. Systolic aortic pressure (SAP) decreased from 85.00±13.83 to 81.88±14.68 mmHg (p<0.01. Diastolic aortic pressure (DAP) decreased by 8.39%. Mean diastolic aortic pressure (MADP) increased by 19.4% (p<0.01).

Cardiac and Cerebral Blood Flow Perfusion Changed After the Assist

With the assist of PACD, cardiac and cerebral blood flow perfusion increased significantly (Figures 2, 3, Table III). Mean diastolic left main coronary blood flow (MDLMF), left main coronary artery blood flow (LMF) and corosinuses blood flow (CSF) each increased significantly, from 89.00±8.09 (ml/min), 66.63±7.78 (ml/min), 122.75±15.06 (ml/min) to 101.50±6.41 (ml/min),

Table I. Hemodynamic changes after HF induction (n=8, $\bar{x}$±s).

	CO (L/min)	PCWP (mmHg)	MAP (mmHg)
Baseline	3.86 ± 0.24	6.50 ± 1.10	93.75 ± 4.06
HF	3.18 ± 0.34	10.25 ± 2.43	67.75 ± 11.94
p	0.005	0.006	<0.001

Hemodynamic parameters in animals were significantly different before and after ligation of coronary artery.

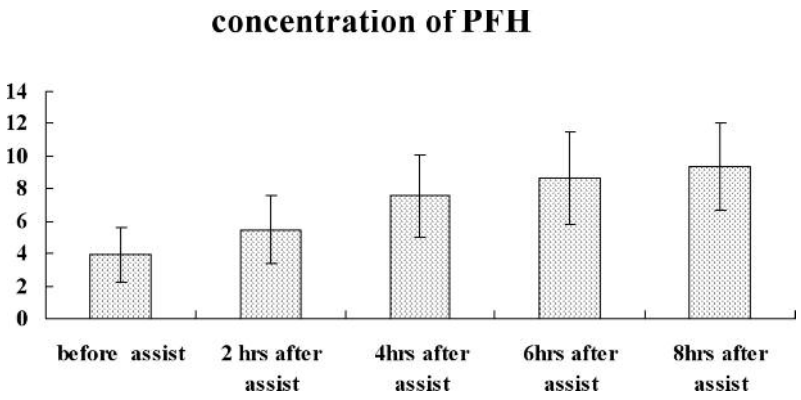

Figure 4. Changes in PFH levels.

75.88±8.03 (ml/min), 137.13±15.78 (ml/min). Left carotid artery blood flow (LCAF) increased significantly from 187.88±23.67 to 208.00±19.88 (ml/min).

Biocompatibility

With the assist of PACD, plasma free hemoglobin (PFH) level increased gradually. In the first 4 hrs with the assist, PFH level increased significantly ($p<0.01$); between 4 to 6 hrs after the assist, PFH level increased significantly ($p<0.05$); in the last 2 hrs, PFH level did not change significantly ($p>0.05$) (Figure 4). After the assist, no infarction, ischemia, necrosis or thrombus were observed in any organs (Figures 5 and 6). No thrombus was observed in PACD blood chamber.

Discussion

In many patients, HF causes and predisposing factors will eventually lead to deterioration of cardiac function in most patients, resulting inevitably to the drug ineffective refractory end-stage[4]. Treatment mostly relies on circulatory assist and heart transplantation. Counterpulsation assist is the most widely adopted mechanical assist method. Our study, as well as other research and clinical experiments have proven that counterpulsation assist plays a role in improving cardiac function, decreasing ventricular pressure and increasing coronary flow[5].

Our results show that all hemodynamic parameters were improved significantly after the

Table II. Comparison of hemodynamic measurements in HF animals before and after the assist (n=8, $\bar{x}\pm s$).

	HF	After Assist	*p*
CO (L/min)	3.18 ± 0.34	3.38 ± 0.28	<0.001
MAP (mmHg)	67.75 ± 11.94	69.13 ± 10.95	0.02
SAP (mmHg)	85.00 ± 13.83	81.88 ± 14.68	0.001
DAP (mmHg)	59.63 ± 12.00	54.63 ± 12.39	<0.001
MDAP (mmHg)	65.0 ± 12.3	77.6 ± 11.6	<0.001

All hemodynamic parameters were improved significantly in animals with the assistance of PACD

Table III. Cardiac and cerebral blood flow perfusion changes before and after the HF assist (n=8, $\bar{x}\pm s$).

	Before Assist	After Assist	*p* value
MDLMF (ml/min)	89.00 ± 8.09	101.50 ± 6.41	<0.001
LMF (ml/min)	66.63 ± 7.78	75.88 ± 8.03	<0.001
CSF (ml/min)	122.75 ± 15.06	137.13 ± 15.78	<0.001
LCAF (ml/min)	187.88 ± 23.67	208.00 ± 19.88	<0.001

All hemodynamic parameters were improved significantly in animals with the assistance of PACD

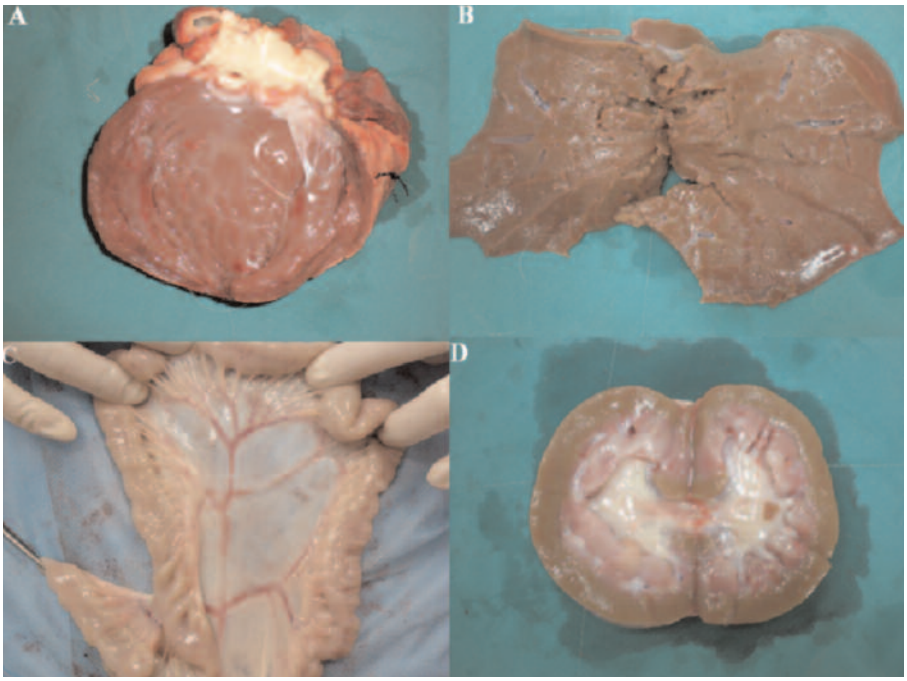

Figure 5. General observation of animal organs. There were no infarct ischemic, thrombosis change in organs of experimental animals, and was no thrombosis in mesenteric arterial system by the general observation.

counterpulsation assist. Two direct results of the counterpulsation assist are elevated DAP and decreased LV pressure overload. MADP is a critical indicator for counterpulsation effect. Unlike other tissue and organs, 75% of hemoperfusion in the heart came from diastole. Thus, it is direct-

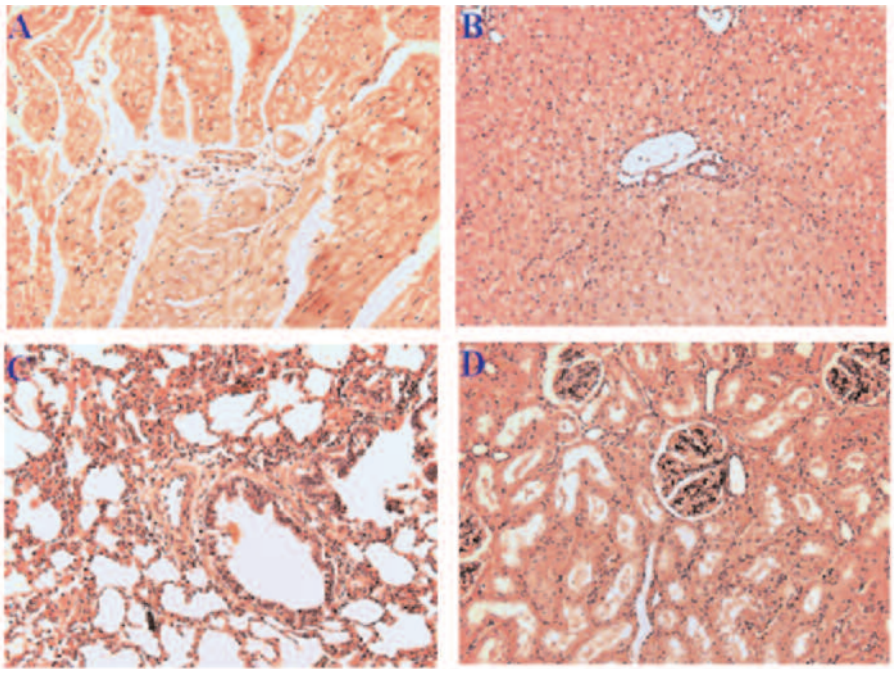

Figure 6. Microscopic histopathological observation of animal's organs (hematoxylin-eosin staining ×100). There were no organ infarction, edema, intravascular thrombosis and other pathological changes in microscopic histopathological observation.

ly associated with the length of diastole and the level of MADP. PACD increases the blood supply of coronary artery to improve cardiac pump function through elevating aortic diastolic pressure. In our study, MADP increased significantly, while myocardial blood perfusion increased because of the elevated diastolic pressure. This proved that counterpulsation assists improving myocardial blood perfusion. PACD has a good result in circulatory assists; therefore, has a positive effect in improving cardiac function, eventually improving hemoperfusion of the surrounding tissue and organs. The significant increase of CO and MAP indicated the efficient circulatory assist and the remarkably improved cardiac function.

SAP and DAP decreased significantly with the assist of PACD. This significantly lowered the cardiac afterload, which led to the decrease of myocardial oxygen consumption (MCO). PACD assist significantly increased MADP and cardiac perfusion, leading to myocardial oxygen supply increase. The consumption and supply of myocardial oxygen plays an important part in the occurrence and development of heart failure. Our study shows parameters related to oxygen consumption including SAP and DAP decreased significantly; parameters related to oxygen supply including PADP and LMF increased significantly. This indicates that PACD increases oxygen supply while reducing MCO, remarkably elevating the rate of MCO and myocardial oxygen supply, blocking the vicious circle of heart failure, and eventually reversing the cardiac function to increase CO and the perfusion of surrounding tissues. In our study, CO and LCAF both increased significantly with the assist of PACD. Counterpulsation assist increased CO, improved perfusion of surrounding tissues, and further validated that PACD significantly improved MCO and myocardial oxygen supply, improved cardiac function, and eventually elevated perfusion of important organs such as the heart and brain.

The blood chamber of our improved PACD connected to the aorta through a valveless vascular graft, therefore, barring the risk of hypostasis or even thrombus, especially where the blood chamber attaches to the thin diaphragm. *In vitro* fluid experiment showed that the 60 ml PACD, with the afterload of 100 cm H_2O had an ejection fraction of over 90%. Such a high ejection fraction decreased the left-over blood in the chamber at the end of the ejection. The whirling that arises in the filling and ejecting process facilitates the flushing away of coagulating blood, which reduces the chance of thrombosis and thromboembolism. Meanwhile, we tried to reduce the length of vascular graft and found the PFH peak after 8 hrs of assist reached only 9.36±2.68 mg/dl. Throughout the whole assisting process, the PFH always fell in animal physiological tolerance[6]. Moreover, pathological observation of the post-experimental organs and microscopic morphology reviewed no pathological changes, such as thrombosis, embolic infarction or organ infarction. Surface modification of materials and hemodynamic characters mentioned above enabled PACD to have a relatively high biocompatibility, therefore could be used to long-term circulatory assist of HF patients.

Conclusions

PACD significantly decreases LV afterload, increases DAP and myocardiac perfusion and improves cardiac function and cerebral perfusion. It has a remarkable assist effect and relatively better biocompatibility, thus could provide a long-term, safe and efficient circulatory assist for refractory HF patients.

Acknowledgements

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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