An Experimental Canine Model to Study Left Ventricular Function

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Abstract: An increasing number of patients with uni- or bi-ventricular heart failure underscores the importance of heart failure research. An isolation of the left or right ventricle would allow for an evaluation of the contralateral ventricular function, the change in hemodynamics, and the capability of each ventricle to deal with the volume challenge. This experimental canine model was developed at the laboratory of Cardiac Physiology at Massachusetts General Hospital, Harvard Medical School. The model allows an evaluation of left ventricular function with a tight control of the preload and evaluation of the contractility of the myocardium to create pressure and handle the volume overload. The left atrial pressure (LAP), left ventricular end diastolic pressure (LVEDP), left ventricular end-systolic pressure (LVES), and myocardial contractility (DP/DT) can be measured using catheters and micro-ultrasound devices. Using this model, a Frank-Starling Curve can be generated for any given circumstance.

This manuscript describes the technical aspect of such a model including; preparation of the canines, cannulation, and measurement of intra-cardiac pressures.

INTRODUCTION

Despite significant progress in the prevention and treatment of cardiovascular diseases [1], the prevalence of heart failure has been increasing in the United States and worldwide. Nevertheless, many patients who are optimally treated with pharmacotherapy continue to progress from asymptomatic left ventricular dysfunction to symptomatic and end-stage heart failure [2-8].

There has been a need for an easy and adjustable experimental model with and without heart failure to study myocardial and left ventricular function [9]. This model would allow studying of each ventricle's contractility separately.

DESCRIPTION OF THE MODEL

Canines are appropriate animals for this model; however, other larger animals such as sheep or pigs can be used. In this model we used canines (n = 14) to study the left ventricular function and the efficacy of priming with Hemoglobin Based Oxygen Carrying Solution (HBOC-201 Biopure, Cambridge, MA) to preserve the left ventricular contractility; however, this manuscript addresses the technical aspects of the model only.

After intubation and anesthesia with isoflurane 1.5-2.5%, arterial and venous catheters were inserted for hemodynamic measurements. A left thoracotomy was performed and the pericardium was opened and suspended to form a cradle to support the heart. Micromanometer-tipped catheters were inserted into the left atrium and the left ventricle for pressure measurements. The left carotid artery was cannulated as an arterial access for the cardiopulmonary bypass (CPB) machine. The right atrium and pulmonary artery were cannulated to control the preload of the left ventricle. The right heart was bypassed and venous blood from the right atrium was diverted to the pulmonary circulation and into the left atrium. Systemic anticoagulation was performed with 200 i.E./kg heparin. Lactated Ringer's solution and HBOC-201 were used as priming solution in the control group (n = 7) and study group (n = 7), respectively.

After reaching a steady state, hemodynamic parameters were measured. Pre-ischemic left ventricular function curves were generated by controlling the preload *via* the pulmonary artery. A starting preload of 500 ml was used and the preload was increased by 500 ml/min in a stepwise fashion to a maximum of 3500 ml. After the pre-ischemic measurements, cardiac output was adjusted to 1.75-2.25 L/min (75 ml/min/kg) *via* carotid artery cannulation. The total cardiopulmonary bypass was initiated, the aorta was cross-clamped, and systemic cooling to 22-23C was conducted. The aorta was clamped and crystalloid potassium cardioplegia was infused into the aortic root (20 ml/kg). The cardioplegia was repeated 30 min later (10 ml/kg). Perfusion at 22 °C was maintained for 60 minutes at a flow rate of 75 ml/min/kg. After 60 minutes of ischemic time, the aortic clamp was removed. The heart was electrically converted if spontaneous rhythm did not resume. After 40-50 minutes of rewarming and recovery, the left ventricle function was studied again. Fig. (**1**) demonstrates the technical design of such a right heart bypass on a canine.

The left atrial pressure (LAP), left ventricular end systolic pressure (LVESP), and left ventricular end diastolic pressure (LVEDP) can be measured pre- and post-ischemia. The cardiac contractility can be measured *via* micro-ultrasounds placed in the myocardium measuring the contractility as acceleration of the myocardium over time. These data were translated into numbers as an expression of

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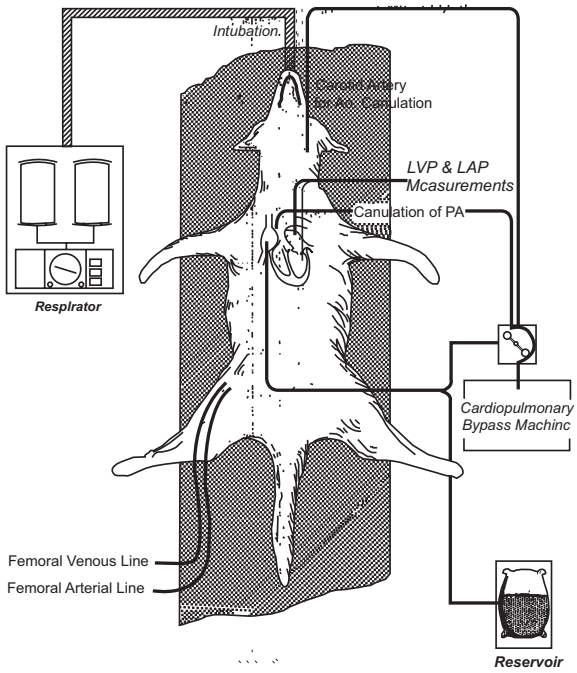

Fig. (1). Illustration of cannulation/cardiopulmonary bypass in our model. Right atrium served for venous cannulation, left carotid for arterial cannulation. Catheters were inserted into left atrium and ventricle. Right femoral artery was cannulated for monitoring of arterial pressure. Right femoral vein was cannulated for blood draws.

change in pressure in myocardium (mmHg/ms) at any given time. These data were correlated with increasing preload and cardiac output. Fig. (**2**) demonstrates the Frank-Starling Curves for both control and study group. Table **1** demonstrates the hemodynamic data collected using the right heart bypass in this model. The hemodynamic parameters and myocardial contractility were measured for each given preload. This model is adequate for acute studies and the canines were sacrificed following completion of the study.

COMMENT

This manuscript describes an easily reproducible animal model to isolate and study the function of the left ventricular. Using this model, the cardiac contractility, intracardiac pressures changes, ability of the myocardium to handle the increasing preload, and the impact of pharmacologic agents can be studied. It also allows Frank-Starling Curves to be generated under various circumstances.

Tamesue *et al*. [7] proposed a right heart bypass to evaluate the hemodynamic effects of a pumpless, implantable extracorporeal membrane oxygenation (ECMO) circuit between the right ventricle (RV) and left atrium (LA) in a chronic canine model with a RV pressure overload [7]. Melchior *et al*. [8] introduced rapid, quantified measurements of cardiac output (CO) following weaning from cardiopulmonary bypass (CPB). This novel technology has specific application in open heart surgery [9]. Breen *et al*. [10] developed a model to study the gas exchange in a canine model, in which cardiac output was controlled and measured. However, none of those models allow for an isolation of the left ventricle to study its function.

Nawa *et al*. [11] introduced a new experimental model for the total exclusion of the right heart in Mongrel dogs without using a cardiopulmonary bypass. A Y-shaped conduit was introduced into the superior and inferior venae cavae and the pulmonary artery. Thus, the right heart was bypassed and venous blood from the venae cavae was

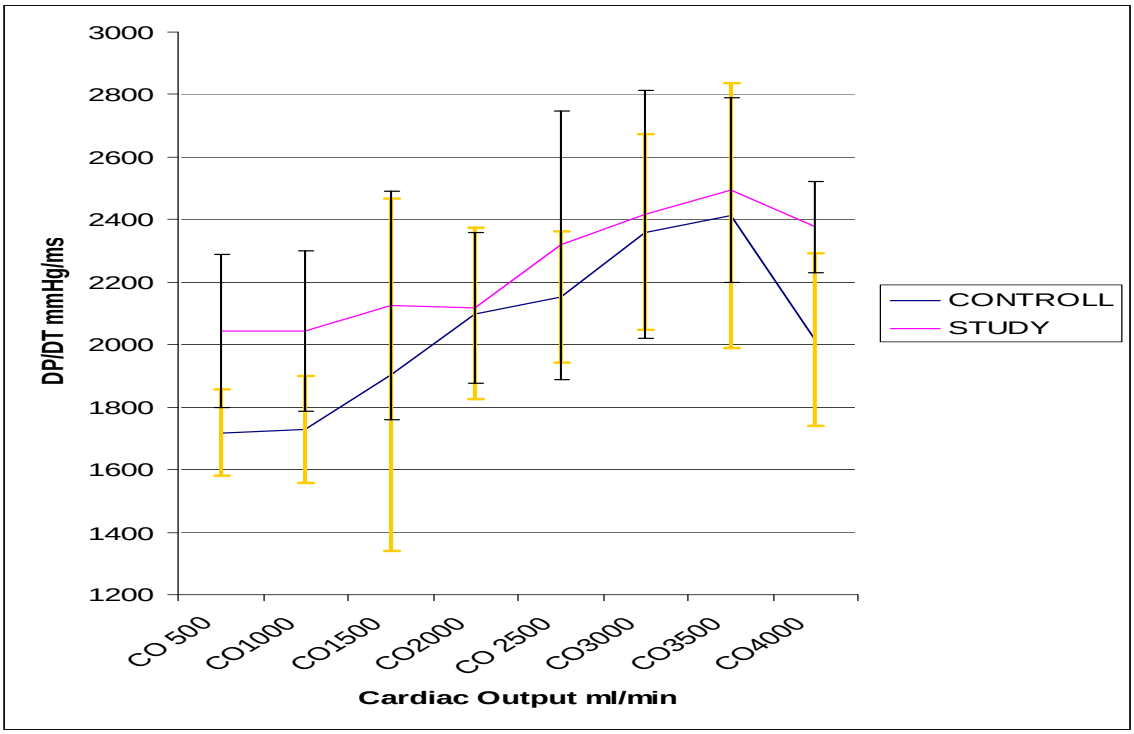

Fig. (2). Frank-Starling Curves for the canines in control (n = 7) and study (n = 7) group.

Table 1. Hemodynamic Data Pre- and Post Ischemic

	Pre-Ischemic	Post-Ischemic
CO 500 ml		
Art pressure	86 ± 5	83 ± 2.9
LVP	89 ± 5.4	85 ± 7
DP/DT mmHg/ms	1718 ± 157	1495 ± 463
LVEDP	6.3 ± 1.7	12 ± 4.6
LAP	5.9 ± 1.8	10 ± 3.8
CO 1000 ml		
Art Pressure mmHg	87 ± 6	84 ± 6
LVP mmHg	90 ± 6	90 ±8
DP/DT mmHg/ms	1903 ± 170	1587 ± 437
LVEDP (mmHg)	6 ± 1.7	14.6 ± 11
LAP (mmHg)	6 ± 2	11.3 ± 6
CO 1500 ml		
Art pressure (mmHg)	89 ± 7	88 ± 9
LVP (mmHg)	90 ± 9.5	91 ± 8.5
DP/DT mmHg/ms	1996 ± 250	1727 ± 565
LVEDP (mmHg)	7.9 ± 1	15 ± 5.9
LAP(mmHg)	6.9 ± 1.6	13 ± 5.6
CO 2000 ml		
Art pressure (mmHg)	88 ± 6	86 ± 8.9
LVP(mmHg)	88 ± 7.6	91 ± 9
DP/DT mmHg/ms	2098 ± 275	1671 ± 607
LVEDP (mmHg)	8.9 ± 0.9	22 ± 13
LAP (mmHg)	8 ± 1.7	18 ± 8.3
CO 2500 ml		
Art pressure (mmHg)	89 ± 7.3	87 ± 5.7
LVP (mmHg)	93 ± 8.5	91 ± 4
DP/DT (mmHg/ms)	2154 ± 210	1872 ± 580
LVEDP (mmHg)	9.9 ± 3	22 ± 16
LAP (mmHg)	9 ± 2.1	19 ± 9
CO 3000 ml		
Art pressure (mmHg)	88 ± 5.6	86 ± 7.6
LVP (mmHg)	93 ± 7.5	91 ± 2.3
DP/DT (mmHg/ms)	2358 ± 313	1430 ± 468
LVEDP (mmHg)	11.9 ± 3.2	23 ± 5.3
LAP (mmHg)	11 ± 2.6	20 ± 6.8

diverted into the pulmonary circulation *via* the conduit [11]. This model might have clinical or experimental value in the pediatric population and allows studying the role and importance of the right ventricle. Our right heart bypass model has been used to study the efficacy of HBOC-201 as a priming solution in cardiopulmonary bypass [12, 13]. Using this model, Frank-Starling Curves can be generated in an experimental model and may serve as a cornerstone to study the ventricle function.

Mabuchi *et al*. [15] studied the right heart bypass model in an animal model by clamping the pulmonary artery. The pulmonary circulation was thereby supplied entirely by the artificial heart and the systemic circulation by the natural heart. This model enabled studies of long-term effects of an artificial right heart on systemic circulation [15].

Our model would allow studying the impact of ischemia after cross clamping in cardiopulmonary bypass. It is already a known principle that global ischemia diminishes LV and RV function [14]. Kitano *et al*. [16] evaluated the post-ischemic right ventricular function during left heart bypass using volumetric analysis with a conductance catheter in canines. Using the conductance catheter, the volumetric status of the right ventricle was assessed. Right ventricular pressure-volume curves were created in the presence of a left heart bypass and compared with measured parameters in the absence of the left heart bypass. The study was performed to evaluate the impact of the decompression of the left ventricle and correcting the septal shift (Bernheim effect) during a left heart bypass. A correction of the Bernheim effect would provide a better diastolic compliance and systolic performance because of unloading of unproportional afterload of the right ventricle. The authors concluded that a left heart bypass improved the overall right ventricular performance, particularly at higher end-diastolic pressures in canines with post-ischemic cardiac dysfunction [16].

Isolation of one or the other ventricle allows for accurate study of the opposite ventricle as well as the impact of various agents on myocardial contractility. It also allows for studying the ability of the left ventricle to deal with volume challenge without major changes in intracardiac pressure.

CONCLUSION

This model can serve as an experimental model to evaluate the left ventricular function and detect the ability of the left ventricle to deal with volume challenge. It allows for a direct measurement of myocardial function and the impact of various inotropic agents on myocardial function. Furthermore, hemodynamic change of hemodynamic and intracardiac pressure changes can be used to create pressure volume curves.

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