Controlled Cross Circulation: Effects on Donor Hemodynamics

by

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ABSTRACT

Controlled cross circulation was performed in six pairs of dogs to assess hemodynamic changes in the donor dog. Cardiopulmonary bypass was performed for 45 minutes, with an aortic cross clamp time of 35 minutes. Anesthesia was maintained in the donor dog with 1.8% end-tidal isoflurane. Parameters before and after controlled cross circulation were compared using a Wilcoxon Signed Rank Test.

Donor left ventricular dP/dt max, pulmonary capillary wedge pressure, blood volume, systemic vascular resistance, heart rate, total protein, platelet count, and white blood cell count did not change significantly. Donor cardiac output, end diastolic volume, central venous pressure, stroke volume, mean arterial blood pressure, and packed cell volume all decreased significantly ($p<0.05$). Recipient blood volume and donor cardiac performance (LV dP/dt max/end diastolic volume) increased significantly ($p<0.05$).

These changes may have been caused by a net shift of blood volume from the donor to the recipient patients during cardiopulmonary bypass. It is speculated this shift occurred because of variation in delivered roller pump flow with changes in inlet tubing pressure. The increase in donor myocardial performance was presumably due to increased circulating catecholamines, elevated because of a baroreceptor response to hypotension. Hematologic changes are attributed to hemodilution from the prime solution in the extracorporeal circuit. Despite a statistically insignificant decrease in blood volume, myocardial performance was enhanced in the donor dog. Controlled cross circulation is analogous to the acute onset of an arteriovenous fistula. This indicates that the donor will be able to support the recipient for the duration of cardiopulmonary bypass if blood volume is maintained.

ACKNOWLEDGMENTS.

I would like to take this opportunity to thank my coinvestigators for their assistance in carrying out this project. I would also like to thank Megan Irby and Jeanette Baker for their technical support and willingness to learn completely new tasks necessary for the completion of this project.

A special thanks goes to Kate Savage for her endless support during the preparation of this manuscript and for her drive not to accept anything but complete understanding of the subject matter at hand.

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I would like to thank C. Walton Lillihei for his kindness and support when I had questions regarding the historical aspects of this technique and especially for his courage to ask "Why not?" when everyone else was asking "Why?"

Finally, I would like to thank all of the dogs that gave up their lives for the completion of this project. I hope that through their sacrifices I have gained a better understanding of the physiology of the cardiovascular system and that I might use that understanding to help other animals with cardiovascular disease.

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LIST OF ABBREVIATIONS

AV-Arteriovenous

BV-Blood volume

CCC-Controlled cross circulation

cm-centimeter

CO-Cardiac output

CPB-Cardiopulmonary bypass

CPI-Cardiac performance index

CVP-Central venous pressure

D-Diameter

E-Elastance

Fr-french

g-gram

HR-Heart rate

Hz-Hertz

Kg-Kilogram

L-Length

LV-Left ventricular

l-Liter

μl-microliter

MAC-Mean alveolar concentration

MAP-Mean arterial pressure

mEq-Milliequivalents

ml-Milliliters

mm Hg-Millimeters of mercury

n-Viscosity

Q-Flow

pCO2-Partial pressure of carbon dioxide

P-Pressure

PCWP-Pulmonary capillary wedge pressure

r-radius

SV-Stroke volume

SVR-Systemic vascular resistance

t-Time

TTC-Tetrazolium solution

U-Units

VED-End diastolic volume

V-Volume

INTRODUCTION.

A. Justification of study.

Controlled cross circulation (CCC) was the first consistently successful method for cardiopulmonary bypass (CPB) in humans.[1] Dogs were used as the research model. Physiologic parameters were evaluated in both populations, but myocardial performance was not assessed. Qualities of CCC including lower cost and more physiologic nature when compared with mechanical oxygenation may allow clinical application in veterinary medicine. A better understanding of its physiologic effects is imperative in order to maximize survival in both patients.

Controlled cross circulation is analogous to placental circulation.[1] Advantages of CCC over mechanical oxygenation include reduction of exposure of blood to air and extracorporeal surfaces and lower cost. Consequences of exposure of blood to extracorporeal surfaces include platelet sequestration, red blood cell lysis and thrombus formation by initiation of the clotting cascade.[2-5] Decreased blood-to-air contact surface area limits platelet sequestration and air microembolus formation.[3]

Controlled cross circulation is the most physiologic method for CPB.[6-8] Controlled cross circulation is analogous the acute onset of an arteriovenous (AV) fistula in the donor.[9] The physiologic effects of AV fistulas have been well described.[10-16] The primary alteration is an acute decrease in systemic vascular resistance (SVR) which results in decreased in mean arterial pressure (MAP). Shunting of blood increases venous return. Baroreceptors are stimulated by hypotension causing catecholamine release. Myocardial performance is enhanced through increased preload, decreased afterload, and increased myocardial

contractility due to circulating catecholamines.[17] Upon closure of the fistula, hemodynamic parameters rapidly return to control values, provided the duration of the fistula is short and myocardial failure has not ensued (<24 hours).[16]

B. Statement of hypothesis.

The purpose of this study is to describe the physiologic and hemodynamic effects of CCC in the donor to optimize the hemodynamic status of both patients. The null hypothesis tested is "controlled cross circulation will not affect myocardial performance and hemodynamics in the donor dog." It is hoped that the advantages of the decreased cost and more physiologic nature of CCC will make CPB more accessible in veterinary medicine.

LITERATURE REVIEW.

A. Historical perspective.

Cardiopulmonary bypass has been used for more than forty years in the surgical treatment of structural abnormalities of the human heart. In 1953, Gibbon was the first to successfully use CPB to close an atrial septal defect in an 18-year-old girl.[18] Lillihei and Morley began developing CCC in 1952, initially as an interim method to permit open heart surgery experience in dogs without the need for a conventional pump oxygenator, which was unavailable to them at the time.[1, 6] Survival in research dogs was far greater with CCC than with mechanical oxygenation, so it was soon implemented in humans for correction of congenital heart defects. From March of 1954 to July of 1955, CCC was the primary method used for CPB. Forty-five patients, paired with a parent which served as a donor, were operated upon using this technique, with 100% survival in the donor patients and 66% survival in the recipients, all of whom had previously inoperable conditions.[9, 19-21] In 1955, CCC was replaced by mechanical oxygenation because of convenience and safety.[1] In 1972, Pullen, at the University of California, compared CCC with conventional CPB in twenty dogs and suggested that CCC was cumbersome. The physiologic effects of the two procedures were not compared. Survival of CPB with CCC was 100%, with no postoperative deaths attributed to CCC.[22] A second study evaluating cross circulation was more recently performed.[23] In this study, cross circulation was not controlled, in that the donor and recipient were directly connected, with no roller pump interposed. In these dogs, flow was determined by the pressure differential between dogs and by the length and diameter of tubing. Conclusions of this study were that cross

circulation offered an inexpensive and physiologic means of instituting CPB. Further modifications of their technique were recommended.

Cardiopulmonary bypass creates a dry surgical field within the heart and perfuses or protects vital organs. Blood is redirected from the right atrium or venae cavae to a reservoir by gravity flow and is actively pumped through a mechanical oxygenator. It is returned to the arterial circulation to maintain mean arterial pressure at physiologic levels.[24] In CCC, the mechanical oxygenator is replaced by a biological oxygenator, the donor. Unoxygenated blood is delivered from the recipient's right atrium to the donor's femoral vein. Oxygenated blood is removed from the donor's abdominal aorta through the femoral artery and is directed to the recipient's aorta under pressure to maintain perfusion of the recipient's systemic circulation. With CCC there is minimal contact between blood and air, thus decreasing platelet sequestration[2] and air microembolus formation. There is minimal contact of blood with extracorporeal surfaces, thus decreasing red blood cell lysis and thrombogenesis, formed through activation of the coagulation cascade.[9, 19-21] Controlled cross circulation is the most physiologic method for CPB identified to date.[6-8]

Cardiopulmonary bypass has been used for correction of structural abnormalities of the heart in veterinary patients.[21, 22, 24-35] Cost, technical difficulty, fragility of canine red blood cells, and the diseased state of the myocardium in advanced cardiac disease have impeded progress of open heart surgery in dogs. Further dampening the surgical success is the tendency to use CPB as a treatment of last resort, after prolonged attempts at medical management

have proven unsuccessful. Consequently, open heart surgery is infrequently used in veterinary medicine.

B. Myocardial performance.

Myocardial performance is dependent on two properties of cardiac muscle. The first is fiber shortening in response to initial myocardial fiber length. This was observed by Roy in 1879 who showed that changes in venous pressure could alter the work of the heart.[36] In 1895, Otto Frank demonstrated in frog hearts that the greater the presystolic fiber length and tension, the greater the developed tension during systole. Starling published a series of papers describing output of the heart as a function of central venous pressure (CVP).[36] Dependence of myocardial contraction on presystolic fiber length (preload) became known as Starling's law of the heart.

The second property which affects cardiac performance is myocardial contractility.[36] Myocardial contractility is defined as the ability of myocardial cells to shorten under a given loading condition. Myocardial contractility was first described in the 1950's,[36] when it was discovered that the classic Frank-Starling curve of myocardial performance could be shifted by changes in myocardial contractility under the influence of epinephrine.

When assessing myocardial performance, initial fiber length and contractility must be considered. Assessment of myocardial contractility must be independent of preload, afterload, and heart rate, and be reproducible and correctable for variation in body size and ventricular dimensions.[37-40]

Afterload is defined as the aortic diastolic pressure against which the ventricle must contract. Ejection phase indices such as ejection fraction or rate of circumferential shortening are dependent on afterload, since they go to zero at infinite afterload. The rate of rise of left ventricular (LV) pressure (LV dP/dt max), based on the isovolumic phase of contraction, is an indicator of myocardial performance. It is measured immediately prior to opening of semilunar valves, thereby decreasing the effect of afterload. Instead, this index tends to be preload dependent, because of the Frank-Starling mechanism.[21, 38, 41]

Left Ventricular dP/dt max is a sensitive indicator of cardiac inotropic state. It is affected by changes in preload, afterload, and heart rate (HR).[41] The dependence of LV dP/dt max on preload is due to the effect of the Frank-Starling Law of the heart. Dependence of LV dP/dt max on inotropic state has been demonstrated by norepinephrine infusion while maintaining constant preload, afterload and HR.[42] At a constant initial fiber length, the rate of force development increases as a result of positive inotropic influences. Assessments of myocardial contractility based on LV dP/dt max can only be made if other hemodynamic variables are kept constant. Left ventricular dP/dt max rises until the aortic valve opens.[41, 42] When afterload is increased, semilunar valve opening occurs later in the cardiac cycle. A delay in LV ejection causes increased dP/dt max. Heart rate has also been shown to affect myocardial contractility through "homeometric autoregulation", independent of preload, afterload and inotropic state.[42] This results from the sequential increase in myocardial contractility with repeated stimulation of myocardial cells, known as the staircase phenomenon. [41] When limitations are taken account, LV dP/dt max has proven to be the most useful when

investigating directional changes of contractility in a single patient in response to acute interventions.[41]

If LV dP/dt max is corrected for preload, it can be used as an estimate of myocardial performance even when loading conditions cannot be controlled.[38, 41] Left ventricular dP/dt max/End Diastolic Volume (VED) is markedly sensitive to changes in inotropic state when preload and afterload cannot be controlled[38, 43, 44] The LV dP/dt max/VED relation is linear within the physiologic range, and the slope of this relationship is proportional to the contractile state.

The LV pump function can be assessed as a time varying elastance model.[45-48] This model relates LV pressure to LV volume at any phase of the cardiac cycle by a factor of E(t), the ventricular elastance.

$$P(t) = E(t)\,(V(t)-V0), \qquad \text{Equation 1.}$$

Where P(t) is LV pressure at time (t), V(t) is the LV volume at time t, and V0 is the "dead volume" of the ventricle, or minimum volume with which the ventricle is able to produce supra-atmospheric pressure. E(t) reaches a maximum , E(max) at time, T(max), defined as end systole. The end systolic pressure-volume relation is defined as follows:

$$PES = Emax\,(VES - V0)$$

E(max) is the end systolic pressure-volume relation; PES is the end systolic pressure, and VES is the end systolic volume. This is a sensitive estimate of

cardiac inotropic state, and is relatively insensitive to changes in loading conditions in isolated canine hearts, conscious dogs, and in man.[43] By differentiating Equation 1, the time derivative of LV pressure can be expressed relative to the LV elastance (E(t)), in the following equation:

LV dP/dt max=d(E(t) (V(t)-V0))/dt.

Left ventricular dP/dt reaches a maximum value, LV dP/dt max, during the isovolumic phase of contraction, when V(t) equals VED. Thus,

LV dP/dt max = (dE(t)/dtmax)(VED - V0). Equation 2.

This predicts that LV dP/dt max/VED should be a linear relationship, and the slope should be proportional to that of the left ventricular elastance, Emax. Since Emax is relatively load independent, LV dP/dt max/VED should also be load independent.[43]

Generally, multiple points are plotted to establish the slope of the LV dP/dt max/VED relationship. This calculation can be simplified by dividing LV dP/dt max by VED at each point and assessing a single cardiac contractility index.[38] This cardiac performance index (CPI) can be used to evaluate myocardial performance at each inotropic state and is an excellent estimate of myocardial performance when loading conditions cannot be controlled.

Echocardiography allows an acceptable estimation of LV volume.[49, 50] To simplify calculations, the LV geometry is assumed to be elliptical with a length (L),

and major and minor diameters (D1 and D2), for calculation of LV volume from angiographic measurements.[51] The cube formula ($V=\pi/6*D^2*L$, where D is the echocardiographically estimated short axis dimension) can be used to estimate LV volume from the echocardiographic short axis dimension, given the following assumptions: a) the echocardiographic short axis dimension correlates well with the angiographic minor diameter, b) the major diameter is twice the minor diameter, and c) ventricular geometry does not change during systole versus diastole. [51] Because of eccentricity of the left ventricle, the ratio between major diameter and minor diameter actually varies from 1.2 to 3.2. A corrected cube formula was derived ($V=(7.0/2.4+D)/D^3$).[50] This estimate is accurate regardless of timing during the cardiac cycle and does not require determination of L, the ventricular length. This equation provides correlation between echocardiographic volumes and angiographic volumes, both at end diastole and end systole.

C. Cardiac output.

Cardiac output (CO), defined as the volume of blood ejected by the heart in a given period of time, is affected by preload, afterload, HR and inotropic state.[52] The heart must be able to make minute to minute adjustments in order to cope with changes in venous return and circulatory demand. Cardiac output is a product of stroke volume (SV) and HR. The four factors which affect SV are essentially the same as those which affect cardiac performance.[52] The first is preload, due to Starling's law of the heart. The second is inotropic state. The third is afterload which affects SV by restricting ventricular emptying. The fourth is HR which

influences the duration of the ventricular filling phase of diastole. Increased heart rate shortens the period of ventricular filling and decreases SV.

Heart rate is determined by the rate of impulse generation from the sinoatrial node and is influenced by the relative contributions of sympathetic tone, which increases HR and parasympathetic tone which decreases HR.[52] Temperature and metabolic activity of the sinoatrial tissue are directly related to HR. Ionic concentrations and pH will also affect HR.

Cardiac output is most frequently estimated using indicator dilution methods.[52, 53] Cardiac output is estimated from dilution of an indicator substance over a period of time. Ideal qualities of an indicator include adequate mixing in blood, minimal loss from circulation, and lack of toxicity. Commonly used indicators include iced injectate, indocyanin green, and radioactive pellets.

Thermodilution method is the most commonly used clinical estimate of CO.[52, 53] Estimates of cardiac output are performed using a multilumen catheter placed from the jugular vein into the right atrium and pulmonary artery. Iced injectate is administered through a proximal port into the right atrium. A temperature dilution curve is derived using a thermistor located in the pulmonary artery. A time-temperature curve is constructed which allows estimation of CO. Advantages of the thermodilution technique over other methods are simplicity, reproducibility, lack of recirculation, rapid repetition, safety, rapid indicator mixing in blood, and the lack of a need for blood withdrawal.[53] There is excellent correlation between thermodilution methods and other conventional methods of estimating CO.[54-56]

Sources of inaccuracy in the thermodilution technique include inconsistent technical performance, catheter or computer malfunction, respiratory effects on right ventricle, rewarming of the injectate, inaccurate measurement of patient or injectate temperature, inadequate temperature difference between patient and injectate, improper thermistor positioning, wrong volume of injectate, intracatheter septal defects, and insufficient mixing of injectate in blood. Random timing of injection relative to the respiratory cycle can result in inaccuracies of 40% on the left side of the heart and 70% on the right side of the heart. Many of these factors may be eliminated by insuring that all measurements are performed by the same technician, at the same point in the respiratory cycle.[53]

D. Pulmonary capillary wedge pressure.

The multilumen catheter properly placed in the pulmonary artery can be used to measure pulmonary capillary wedge pressure (PCWP). This is an estimate of left atrial pressure and is measured by inflating a small balloon, proximal to the distal port.[57] Elevations in PCWP indicate overhydration, or left heart failure, while decreases indicate dehydration, decreased BV, or increased in cardiac function.

E. Systemic vascular resistance and mean arterial pressure.

Resistance (R) is the drop in pressure through a length of tubing divided by the flow: $R = \frac{P1 - P2}{Q}$ where P is pressure and Q is flow. It is proportional to the viscosity of the fluid and the length of tubing, and inversely proportional to the fourth power of the radius of the tubing.[58] Very small decreases in radius will

markedly increase resistance, explaining the effect of peripheral vasoconstriction on SVR. Systemic vascular resistance opposes blood flow from the LV and can be calculated by dividing the difference between mean arterial pressure (MAP) and central venous pressure (CVP) by CO.[53, 58] SVR maintains arterial pressure with a given CO. With lower SVR more CO is required to maintain a given MAP.

Because resistance through the peripheral vasculature is equal to the pressure difference divided by the flow, the pressure difference is then equal to the product of CO and SVR (MAP-CVP=CO x SVR). Since CVP is usually small relative to MAP it is often ignored. Therefore, MAP is approximately equal to the product of CO and SVR.[58] Changes in CO and SVR will result in a corresponding change in MAP. Cardiac output may in turn be altered by changes in SV or heart rate.[52]

F. Blood volume.

For successful CCC, balanced blood flow between donor and recipient patients is imperative, because minor disparities can result in substantial blood loss from one patient to another over a period of time.[9, 19] Blood flow by occlusive roller pumps is affected by inlet tubing pressure.[59] This can result in imbalanced blood flow between patients. Therefore, blood volume monitoring in both patients is necessary.

Blood volume can be estimated from dilution of an indicator within the vasculature.[60] The indicator must be quickly and easily dispersed in the blood and remain long enough to be measured. The most commonly used indicator for blood volume estimation is Evan's blue. A known quantity of dye is injected and allowed

to disperse for ten minutes. Plasma is isolated from a blood sample by centrifugation. Spectrophotometric analysis determines the concentration of dye in the sample of plasma. Plasma volume is estimated from a curve created by plotting known concentrations of Evan's blue and calculated plasma volumes (Figure 1). Blood volume can be estimated from the plasma volume with the following equation: BV = Plasma volume x 100/(100-0.87 x Hematocrit).[60, 61] The correction factor of 0.87 accounts for plasma which is trapped between packed red blood cells in venous blood.

G. Effects of isoflurane on hemodynamics.

When assessing hemodynamics with a research model, it is important to consider effects of anesthetics used in the model. Studies have been performed to evaluate effects of isoflurane on the cardiovascular system.[39, 62-66] The minimum alveolar concentration (MAC) of isoflurane is 1.28%[67] to 1.5%.[68] Pagel's study showed that isoflurane had a similar effect on LV dP/dt max in both autonomically intact and autonomically blocked dogs.[66] The depressant effect (40-60%) was dose dependent. Isoflurane depresses sympathetic efferent nerve activity in dogs, resulting in a blunted response to baroreceptor stimulation.[69, 70] This effect is dose dependent. Cardiac output was not significantly affected in autonomically intact dogs at 1.25 MAC, but was significantly depressed (-20%) at 1.75 MAC. In autonomically blocked dogs, the depressant effect was more severe. Systemic vascular resistance was significantly decreased in autonomically intact dogs (-25%), and this effect was equal at 1.25 and 1.75 MAC. It was not significantly changed in autonomically blocked dogs. Coronary blood flow was increased (+30%) in

autonomically intact dogs at both 1.25 and 1.75 MAC. It was not changed in autonomically blocked dogs. [66] Other studies have confirmed the cardiodepressant effects of isoflurane, although these effects are favorable when compared with other inhalation anesthetics, and all of these effects are dose dependent. [39] Stevens et al. showed in humans that isoflurane demonstrated remarkably little change in circulatory effects when comparing one hour of anesthesia with five hours of anesthesia.[71] Since cardiovascular effects of isoflurane are dose dependent and unaffected by prolonged anesthesia, it is a reasonable anesthetic for a CPB research model.

H. Enzyme mapping for evaluation of myocardial ischemia.

Macroscopic myocardial ischemia can be delineated using an enzyme-mapping technique.[72, 73] Myocardial cells are enzymatically active and are rich in respiratory enzymes. Ischemic myocardial cells rapidly lose nonspecific dehydrogenase activity. This can be detected by incubating the myocardium in tetrazolium solution (TTC), a hydrogen ion acceptor for at least four hours. Normal myocardium reduces the colorless TTC to a red deposit on the surface, contrasting it with ischemic myocardium which lacks the red color. This can be used to grossly evaluate myocardium for presence of ischemia at a macroscopic level prior to development of these changes histopathologically.

INVESTIGATIVE PROCEDURES.

A. Specific objectives.

The objective of this study was to describe changes in cardiac performance and hemodynamic function in the donor dog following CCC. Cardiac performance was assessed using a CPI, LV dP/dt max, CO, and MAP. Other hemodynamic parameters measured included CVP, VED, PCWP, SV, BV, SVR, and HR. Blood volume was also calculated in the recipient dogs. Complete blood count parameters included packed cell volume, white blood cell count, platelet count and total protein. Blood gases were performed at regular intervals before and after CCC. After the donor dogs were killed, myocardial enzyme mapping was performed.

B. Investigative protocol.

1. Animal treatment.

The experiment was performed on six pairs of adult dogs of unknown age, obtained from the Nonclient Animal Facility at Virginia Polytechnic Institute and State University. Animals were determined to be healthy on the basis of physical examinations, complete blood counts and serum chemistry panels. Six males and six females were used. No attempt was made to match dogs on basis of gender. Dogs were placed in wire cages, and food was withheld for twelve hours prior to surgery. Animals were housed and maintained in accordance with the guidelines of The Humane Animal Care Committee.

2. Experimental design.

Mongrel dogs were used for donors. Beagles were used for recipients. Pairs had both major and minor cross-matches performed to assure blood compatibility, but blood typing was not performed. Anesthesia was induced by mask with isoflurane (5%).[a] Following intubation, dogs were ventilated[b] to maintain arterial pCO2 at 35 to 45 mm Hg. End tidal isoflurane concentration was measured in the donor dog and maintained at 1.8% using a calibrated infrared light absorption anesthetic analyzer.[c] Lead II surface electrocardiograms were monitored in both dogs.[d] Urine output was measured using a closed urinary collection system.

Donor and recipient dogs were instrumented as shown in figure 2. The donor dog was placed in right lateral recumbency. The left cervical region was aseptically prepared. The jugular vein was isolated by surgical cutdown and a Swan-Ganz catheter[e] was placed with the distal port within the pulmonary artery and the proximal port was left within the right atrium. The carotid artery was isolated by surgical cutdown and a 100 cm, 8 Fr, double lumen, fluid filled catheter[f] was placed with the distal port within the left ventricle and the proximal port was within the aortic root. All catheter positions were confirmed by obtaining characteristic blood pressure wave patterns. The donor dog was heparinized[g] using

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[a] "Isoflo" Abbott Laboratories, North Chicago, IL 60064. Order #5260-04-01.
[b] Ohmeda 7000 ventilator. BOC Healthcare, Madison, WI 53707-7550.
[c] "Datex Model 222"Puritan-Bennett Corporation, 265 Ballardvale St. Wilmington, MA 01887.
[d] "Propaq" Model 106, Protocol™ Systems Incorporated. Beaverton, OR 97006.
[e] Model #93A 131H 7P Thermodilution Catheter. Baxter Edwards Division. 17221 Red Hill Ave. Irvine, CA 92714.
[f] Model #DL-500. Cordis Corporation. PO Box 025700. Miami, FL 33102-5700.
[g] Elkins-Sinn, Incorporated, Cherry Hill, NJ 08003.

300 U/Kg sodium heparin. Heparinization was confirmed when activated clotting time was found to be greater than 400 seconds.[h,74-77].

The medial portion of the donor's right thigh was aseptically prepared. Large bore (12 Fr-16 Fr) cannulae[i] were placed in the femoral artery and vein by surgical cutdown. The reservoir[j] and tubing[k] were primed with 1 liter of 5% dextrose resulting in a reservoir level of 600 ml. The reservoir allowed an assessment of blood flow from the right atrium in the recipient dog.

The recipient dog was placed in right lateral recumbency. Arterial pressure was monitored using a 20 gauge, 2 inch, over-the-needle catheter[l] placed in the dorsal pedal artery. The medial right thigh was aseptically prepared. A 65 cm 5 Fr. fluid filled catheter[m] was advanced from the femoral vein to the right atrium in order to monitor CVP by surgical cutdown. Its position was confirmed by obtaining characteristic pressure wave forms. A left fourth intercostal thoracotomy was performed. The recipient dog was heparinized[g] using 300 U/Kg sodium heparin. The femoral artery was cannulated using a 19 cm, 12 Fr., arterial perfusion catheter.[n] An active 16 Fr left ventricular vent was placed.[o] A large bore (22 Fr-26 Fr) sump catheter[p] was placed within the right atrium. Connections

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[h] "Hemochron™" Model #400. International Technidyne Corporation, Edison, NJ.
[i] William Harvey® Extracorporeal Cannulae. Bard Cardiopulmonary Division. C.R.Bard Incorporated. 1425 South Village Way, Santa Ana, CA 92705.
[j] BCR-2000. Baxter Healthcare Corporation. Bentley Laboratories, Inc. Irvine, CA 92714.
[k] Tygon®. 6409-18 Masterflex. Cole Parmer Instrument Company. Barrington, IL 60010.
[l] "Angiocath™" Cat. #3828181 Becton Dickinson Vascular Access. Sandy, UT 84070.
[m] "Renal Double Curve" Cat. #5568-12. Diagnostic Product Division. Mallinckrodt, Incorporated. St. Louis, MO 63134.
[g] Elkins-Sinn, Incorporated, Cherry Hill, NJ 08003.
[n] Pediatric Arterial Perfusion Cannula. Cat.# 96820-012. Metronic Biomedicus Incorporated. 9600 West 76th St. Eden Prairee, MN 55344.
[o] "Argyle™" Cat. #888-590224. Sherwood Medical Industries. St. Louis, MO 63103.
[p] William Harvey® Extracorporeal Cannula. Bard Cardiopulmonary division. CR Bard, Inc, 1425 South Village Way, Santa Ana, CA 92705.

between donor and recipient patients, the reservoir and the roller pump were completed.

Data was collected in the following manner. A four channel Maclab unit[q] was used for monitoring of left ventricular pressure, aortic root pressure, right atrial pressure and pulmonary artery pressure. Pressures were digitized and recorded directly to hard drive[r] using a Transbridge transducer amplifier manifold.[s] All transducers[t] were zeroed to the level of the right atrium, and were calibrated using a mercury manometer[u] prior to each experimental period. Transducers were again zeroed prior to critical measurements. Data were recorded at a frequency response of 30 Hz.

Arterial blood gas determinations were performed in the donor dog prior to time zero to establish an arterial pCO2 of 35 - 45 mm Hg. Blood was collected from the aortic root catheter. They were then performed three times at ten minute intervals for comparison between pre and post CCC values.

Blood volume determinations were performed in both dogs using Evan's blue[v] dilution using a previously described method.[60] Spectophotometric analysis of plasma samples was performed.[w] Absorbance was compared with the standard dilution curve (Figure 1). Because blood volumes were only compared within dogs, they were not expressed relative to body weight. Measurements of MAP, CVP, left ventricular pressure, PCWP and HR were performed in triplicate at ten

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[q] World Precision Instruments, Inc. 375 Quinnipiac Ave, New Haven, CT.
[r] Mac SE. Apple Computers. 5130 Parkway Plaza Blvd. Charlotte, NC 28217.
[s] Model# TBM-4. World Precision Instruments, Inc. 375 Quinnipiac Ave, New Haven, CT.
[t] Model BLPR. World Precision Instruments, Inc. 375 Quinnipiac Ave, New Haven, CT.
[u] Fisher Scientific Company. PO Box 4827 Norcross, GA 30091.
[v] Cat. #T-1824 E515. Fisher Scientific Company. Fairlawn, NJ.
[w] Milton Roy Spectronic 1001+. Fisher Scientific Company. Fairlawn, NJ.

minute intervals, and results were averaged. Cardiac output was measured three to five times at each of three ten minute intervals, and all of these values were averaged.[x] Measurement of cardiac output was performed by thermodilution method using a five ml injection of iced five percent dextrose. End diastolic and stroke volumes were estimated using transthoracic echocardiography[y] at pump speeds of 100, 200, 300, 400, 500, 600, 700, and 800 ml/min in order to achieve multiple points along the LV dP/dt max/VED relationship. These values were averaged to compare prebypass and post bypass end diastolic volumes. Corresponding left ventricular pressure tracings were monitored.

This was identified as time zero. Baseline data were collected. Cardiopulmonary bypass was initiated by opening the right atrial sump line from the recipient dog. When blood flow was seen in the right atrial sump line, the two head[z] roller pump[aa] was turned on at an initial speed of 50 ml/min/kg of recipient body weight. Ventilation was discontinued in the recipient dog for the duration of CPB. Pump speed was then adjusted between 400 and 1000 ml/min to maintain a MAP of 50 mm Hg in the recipient dog. An aortic cross clamp was placed proximal to the origin of the recipient's brachiocephalic trunk. Cold cardioplegia solution containing 35 mEq/l potassium chloride, 25 mEq/l sodium bicarbonate, 1 g/l dextrose and 87 mEq/l sodium chloride was infused into the aortic root using a

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[x] Cardiac Output Computer Model #COM-2. Baxter Edwards Division. 17221 Red Hill Ave, Irvine, CA 92714.

[y] "Accuson" Computed Sonography. Model#128 R/F. 1220 Charleston Rd. Mountain View, CA 94039.

[z] "Easy Load™" Model #7518-10. Masterflex®Cole-Parmer Instrument Company, Barrington, IL 60010.

[aa] Model #7523-00. Masterflex®Cole-Parmer Instrument Company, Barrington, IL 60010.

20 gauge over-the-needle catheter[bb], until electrical activity in the ventricle was abolished.[78, 79] This was repeated as necessary.

After 35 minutes of CPB, the aortic cross-clamp was removed. During the next ten minutes, the recipient was gradually weaned off of CPB by decreasing pump speeds, while spontaneous cardiac function returned. At 45 minutes, CPB was discontinued. Defibrillation was used as necessary using internal paddles.[cc] Cardiac output and pulmonary capillary wedge pressure was recorded during CCC, but not compared statistically.

Blood was obtained for complete blood counts from the dorsal pedal arterial access catheter in the recipient dog, and from the aortic root catheter in the donor dog following cardiopulmonary bypass. Data collection was repeated to evaluate the same parameters measured pre bypass. Heparin was reversed with protamine sulfate at 0.75 mg/100 U total heparin dose.[dd] Reversal was determined to be complete when activated clotting times were less than 110 seconds. The recipient dog was killed using an overdose of pentobarbital.[ee] The donor dog was maintained at a light plane of anesthesia for six hours to allow time for enzyme mapping changes to take place with oxymorphone[ff] boluses of 0.05 mg/Kg administered intravenously as needed and was then killed with an overdose of pentobarbital and had gross evaluations of cardiac anatomy performed. Myocardial enzyme mapping was performed as previously described[72] to evaluate gross evidence of myocardial ischemia. Transverse sections through the right and left

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[bb] "Angiocath™" Cat. #3828181 Becton Dickinson Vascular Access. Sandy, UT 84070.
[cc] Model #43100-A. Hewlett-Packard Company. Cardiology Business Unit. 1700 Parker St. McMinnville, OR 97128.
[dd] Elkins-Sinn, Incorporated, Cherry Hill, NJ 08003.
[ee] Beuthanasia®-Special. Schering-Plough Animal Health Corporation. Kenilworth, NJ 07033.
[ff] Pitman-Moore, Inc. Washington crossing, NJ 08650.

ventricles were incubated in a covered dish containing warmed TTC solution[gg] for 45 minutes. At the end of the incubation period, heart slices were placed in formal saline[hh] in a phosphate buffer solution.[ii] Dogs that spontaneously died had complete necropsies performed.

3. Calculated values.

Blood volume was calculated from the plasma volume with the following equation: BV = Plasma volume x 100/{100-(0.87 x Hematocrit)}.[60, 61] Combined BV was calculated as donor BV + recipient BV. Systemic vascular resistance was calculated as (MAP - CVP) x 79.9 / CO.[53] The correction factor of 79.9 is used for the conversion of SVR from mm Hg/ml/min to dynes x sec x cm^{-5}. Left ventricular dP/dt max was calculated from the left ventricular pressure tracing using Maclab software manipulations.[jj] Cardiac performance was calculated as LV dP/dt max / LV VED.[43]

4. Statistical analysis.

Means of prebypass values of CO, CVP, SVR, MAP, HR, SV, PCWP, CPI, LV dP/dt max, pO_2, pCO_2, pH and tCO_2 were compared with means of postbypass values within dogs with the Wilcoxon Signed Rank Test[kk]. Preoperative values of BV, hematocrit, platelet count, white blood cell count, and total protein were

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[gg] Cat. #T-413. Fisher Scientific Company. Fairlawn, NJ.
[hh] Cat. #SF 994. Fisher Scientific Company. Fairlawn, NJ.
[ii] Sodium Phosphate Monobasic, Sodium Phosphate Dibasic. Cat. S-468. Fisher Scientific Company. Fairlawn, NJ.
[jj] World Precision Instruments, Inc. 375 Quinnipiac Ave, New Haven, CT.
[kk] SAS Institute, Box 8000, Cary, NC 27511-8000

compared with postoperative values with the Wilcoxon signed rank test. Significance was established at $p<0.05$.

RESULTS.

A. General.

Controlled cross-circulation was performed in six pairs of dogs for 45 minutes. Hemodynamic and hematologic values are shown on table 1. Significant decreases in CO, VED, CVP, SV, MAP, total protein, and hematocrit were observed in the donor dog. Cardiac performance and recipient blood volume increased. Left ventricular dP/dt max, donor BV, combined BV, SVR, HR, arterial pO_2, arterial pCO_2, arterial pH, arterial tCO_2, platelet counts and white blood cell counts did not change significantly in the donor dog. Pulmonary capillary wedge pressure and cardiac output were elevated for the duration of CCC, but were not compared statistically with other time periods.

B. Mortality.

Five of six recipients were successfully weaned from bypass and resumed spontaneous cardiopulmonary function. In the sixth dog, spontaneous cardiac function began approximately three minutes prior to the discontinuation of bypass, but at the time of discontinuation of bypass, cardiac function had not recovered sufficiently to support the patient. The heart fibrillated multiple times, and cardiac arrest ensued. No abnormalities were found at necropsy. Two of the six donors spontaneously died approximately one hour after discontinuation of bypass (#3 and #4) after post bypass data had been collected. These two dogs had hemodynamic factors which were unique to them. Both dogs had the lowest prebypass MAP's, the greatest increases in SVR following CPB and had increases in LV dP/dt max

following bypass where all of the others had decreases in LV dP/dt max. Blood volume decreased in both dogs. No abnormalities were found at necropsy.

C. Cardiac output and blood pressure.

Cardiac output decreased significantly following CCC in the donor dog ($p=0.03$). The pre bypass mean was 2.87 ± 0.47 L/min (mean ± stdev). The post bypass mean was 1.80 ± 0.35 L/min (Figure 3.) Pulmonary capillary wedge pressure did not decrease significantly in the donor dog following CCC ($p=0.06$). (Figure 4.) The pre bypass mean was 5.28 ± 1.69 mm Hg. The post bypass mean was 2.15 ± 2.83 mmHg. Mean arterial pressure decreased significantly in the donor dog following CCC ($p=0.03$). The pre bypass mean was 81.10 ± 9.63 mm Hg. The post bypass mean was 55.90 ± 5.79 mm Hg (Figure 5.) Central venous pressure decreased significantly in the donor dog from a prebypass mean of 1.55 ± 0.72 mm Hg to a post bypass mean of -0.30 ± 1.59 mm Hg ($p=0.03$)(Figure 6.)

D. Heart rate.

Heart rate did not change significantly following CCC in the donor dog ($p=0.87$)(Figure 7.) The pre bypass mean was 124 ± 11.4 beats per minute. The post bypass mean was 125 ± 10.6 beats per minute.

E. Hematology.

Total protein did not change significantly following CCC in the donor dog($p=0.06$)(Figure 8.) The prebypass mean was 6.18 ± 0.57 g/dl. The post bypass mean was 4.42 ± 0.37 g/dl. Packed cell volume decreased significantly in

the donor dog following CCC (p=0.03)(Figure 9.) The pre bypass mean was 36.4 ± 3.25 %. The post bypass mean was 32.6 ± 4.66 %. The platelet count in the donor dog did not change significantly following CCC (p=0.12). The pre bypass mean was 258,000 ± 50,700 platelets/µl. The post bypass mean was 184,000 ± 56,700 platelets/µl. The white blood cell count did not change significantly in the donor dog following CCC (p=0.62) (Figure 11.) The pre bypass mean was 8,820 ± 1,840 leukocytes/µl. The post bypass mean was 6,680 ± 2,220 leukocytes/µl.

F. Cardiac performance.

Cardiac performance increased significantly in the donor dog from a pre bypass mean of 52.30 ± 36.00 mm Hg/sec/ml to a post bypass mean of 95.50 ± 60.70 mm Hg/sec/ml (p=0.03)(Figure 12.)

G. Systemic vascular resistance.

Systemic vascular resistance did not change significantly following CCC (p=0.31)(Figure 13.) The prebypass mean was 2,313 ± 494 dynes sec/cm^5. The post bypass mean was 2,545 ± 311 dynes sec/cm^5.

H. Blood volume.

Donor BV did not change significantly following CCC (p=0.31)(Figure 14.) The prebypass mean was 1,544 ± 237 ml. The post bypass mean was 1,420 ± 91 ml. Donor dogs one, two, three, and four showed decreased BV following CCC, while dogs five and six showed increases in BV of 224 and 177 ml respectively. Recipient BV increased significantly following CCC (p=0.03)(Figure 15.) The

prebypass mean was 1,010 ± 49 ml. The post bypass mean was 1,398 ± 138 ml. Combined blood volume did not change significantly following CCC (Figure 16.) The preoperative mean was 2,553 ± 258 ml. The post operative mean was 2,775 ± 131 ml.

I. Echocardiographic findings.

End diastolic volume in the donor dog decreased significantly following CCC (p=0.03)(figure 17.) The pre bypass mean was 33.8 ± 22.0 ml. The post bypass mean was 19.1 ± 7.4 ml. Stroke volume decreased significantly in the donor dog following CCC from a pre bypass mean of 23.5 ± 6.3 ml to a post bypass mean of 14.6 ± 3.1 ml (p=0.03)(Figure 18.)

J. LV dP/dt max.

Left ventricular dP/dt max did not change significantly following CCC (p=0.62)(Figure 19.) The pre bypass mean was 1,532 ± 278 mm Hg/sec. The post bypass mean was 1,423 ± 314 mm Hg/sec.

K. Blood gases.

Arterial pH did not change significantly in the donor dog following CCC (p=0.87)(Figure 20.) The pre bypass mean was 7.30 ± 0.05. The post bypass mean was 7.29 ± 0.05. Arterial pCO_2 did not change significantly following CCC in the donor dog (p=0.625)(Figure 21.) The pre bypass mean was 38.7 ± 4.1 mm Hg. The post bypass mean was 39.0 ± 4.1 mm Hg. Arterial pO_2 did not change significantly following CCC in the donor dog (Figure 22.) The pre bypass mean

was 541.0 ± 70.9 mmHg. The post bypass mean was 525.0 ± 89.0 mm Hg. Arterial tCO_2 did not change significantly following CCC in the donor dog (p=0.125)(Figure 23.) The prebypass mean was 19.2 ± 1.9 mmol/liter. The post bypass mean was 18.8 ± 1.7 mmol/liter.

L. Weight ratios.

The donor to recipient weight ratios varied from 2.04:1 to 4.21:1, with an average of 2.94 ± 0.815 (mean ± sd, n=6). Donors which died had weight ratios of 2.48:1 (#3) and 4.21:1 (#4).

M. Enzyme mapping.

There was no evidence of myocardial ischemia in the hearts of those donor dogs which survived the entire procedure. There were, however abnormalities noted in the hearts of the dogs which spontaneously died. These abnormalities were characterized by areas of pallor in the middle of the myocardium, at multiple sites. Both of these dogs were defibrillated repeatedly during the resuscitation period.

Table 1 - Effects of Controlled cross circulation on donor hemodynamics (n=6).

Parameter	Pre Bypass	Post Bypass	P-value	Figure #
CO (L/min)	2.87 ± 0.47	1.80 ± 0.35	0.03*	3
PCWP (mm Hg)	5.28 ± 1.69	2.15 ± 2.83	0.06	4
MAP (mm Hg)	81.1 ± 9.63	55.9 ± 5.8	0.03*	5
CVP (mm Hg)	1.6 ± 0.72	-0.3 ± 1.6	0.03*	6
HR (Beats/min)	124 ± 11	125 ± 10	0.87	7
TP (g/dl)	6.18 ± 0.57	4.42 ± 0.37	0.06	8
PCV (%)	36.4 ± 3.2	32.6 ± 4.7	0.03*	9
PC (Platelets/µl)	258,000 ± 50,700	184,000 ± 56,700	0.12	10
WBC (cells/µl)	8,820 ± 1,840	6,680 ± 2,220	0.62	11
CPI (mm Hg/sec/ml)	52.3 ± 36.0	95.5 ± 60.7	0.03*	12
SVR (dynes x sec/cm^{-5})	2,313 ± 494	2,545 ± 311	0.31	13
Donor BV (ml)	1,544 ± 237	1,420 ± 91	0.31	14
Recipient BV (ml)	1,010 ± 49	1,398 ± 139	0.03*	15
Combined BV (ml)	2,553 ± 258	2,775 ± 131	0.31	16
VED (ml)	33.8 ± 22.1	19.1 ± 7.4	0.03*	17
SV (ml)	23.5 ± 6.3	14.6 ± 3.2	0.03*	18
LV dP/dt max (mm Hg/sec)	1,532 ± 278	1,423 ± 314	0.62	19
pH	7.296 ± 0.05	7.29 ± 0.05	0.87	20
pCO_2 (mm Hg)	38.7 ± 4.1	39.0 ± 4.1	0.87	21
pO_2 (mm Hg)	541.0 ± 70.9	525.5 ± 88.8	0.625	22
tCO_2 (mmol/liter)	19.2 ± 1.9	18.8 ± 1.7	0.125	23

Data are expressed as mean ± SD

CO = Cardiac output, PCWP = Pulmonary Capillary Wedge Pressure, MAP = Mean arterial pressure, CVP = Central venous pressure, HR = Heart rate, TP = Total protein, PCV = Packed cell volume, WBC = White blood cell count, CPI = Cardiac performance index, SVR = Systemic vascular resistance, BV = Blood volume, VED = End diastolic volume, SV = Stroke volume, LV dP/dt Max = Maximal rate of rise of left ventricular pressure.

* = significant difference ($p<0.05$)

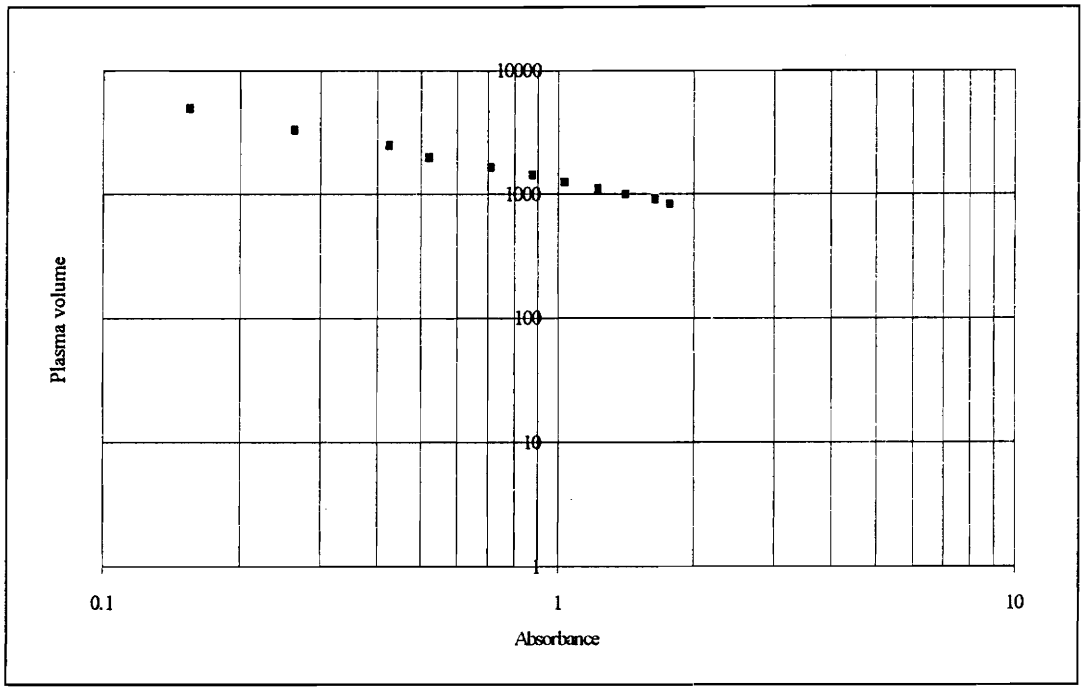

Figure 1 - Plasma volume estimated from plasma absorbance.

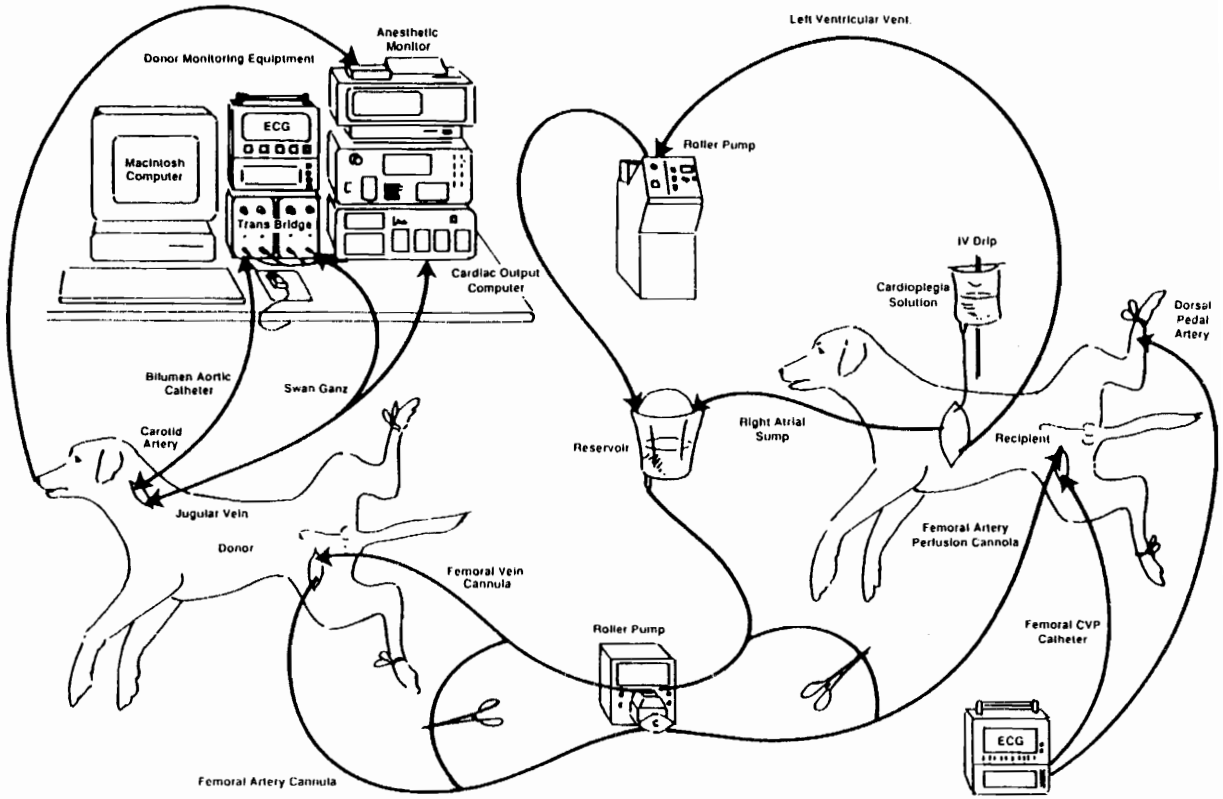

Figure 2 - Instrumentation for laboratory set-up.

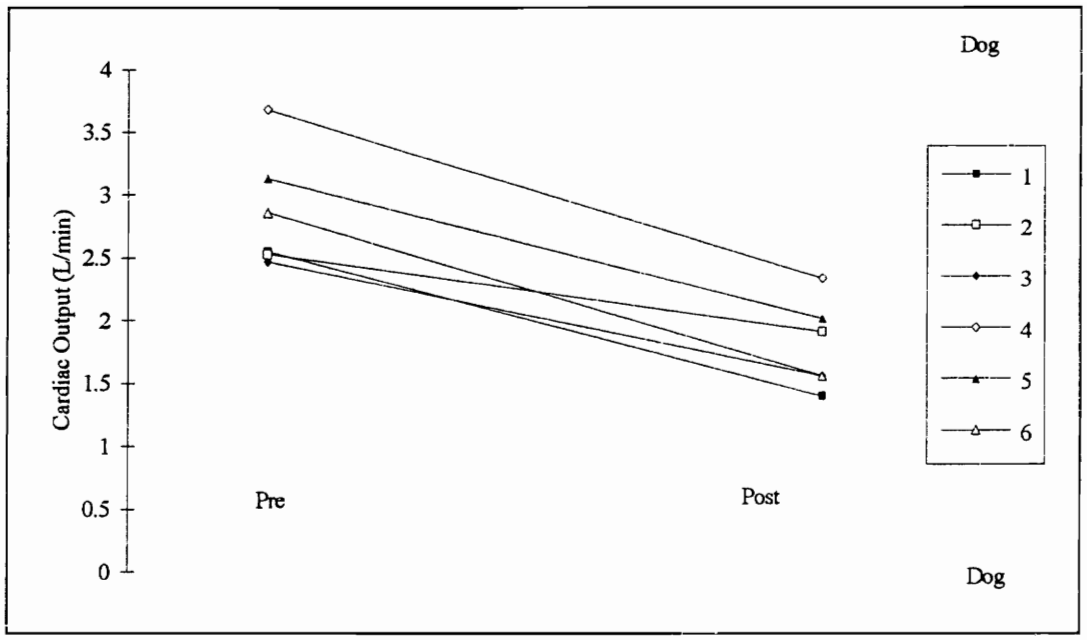

Figure 3 - Effect of controlled cross circulation on cardiac output in donor dogs.

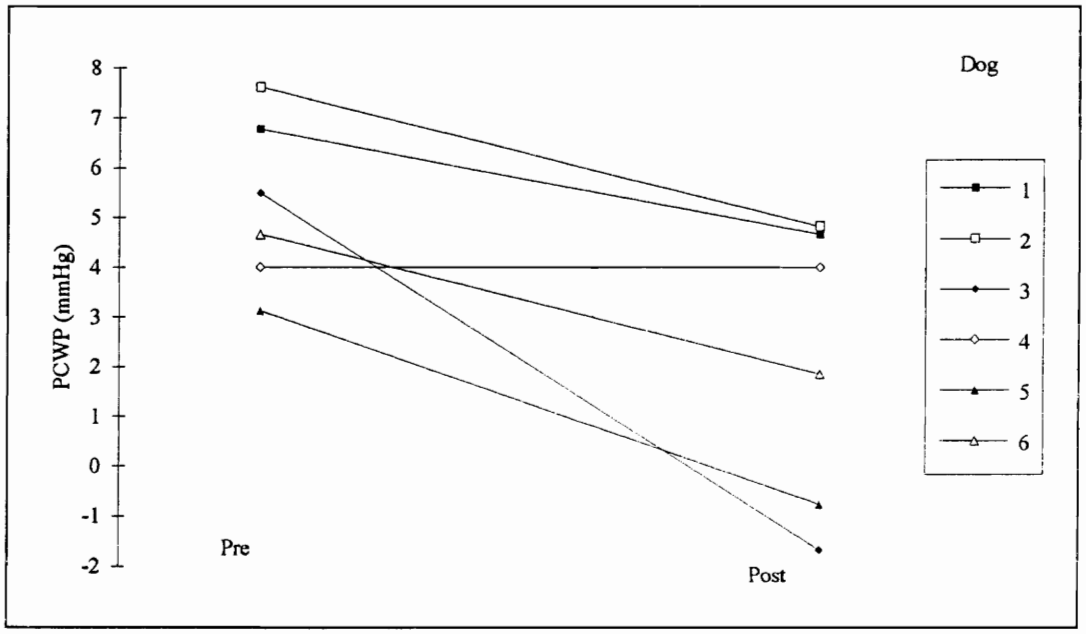

Figure 4 - Effect of controlled cross circulation on pulmonary capillary wedge pressure in donor dogs.

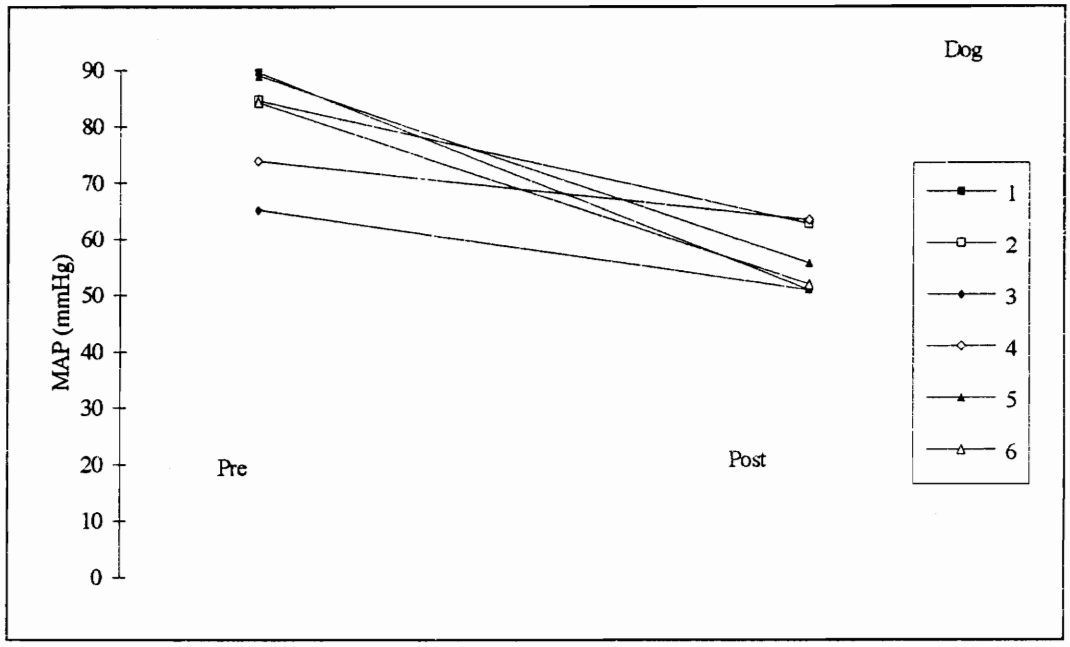

Figure 5 - Effect of controlled cross circulation on mean arterial pressure in donor dogs.

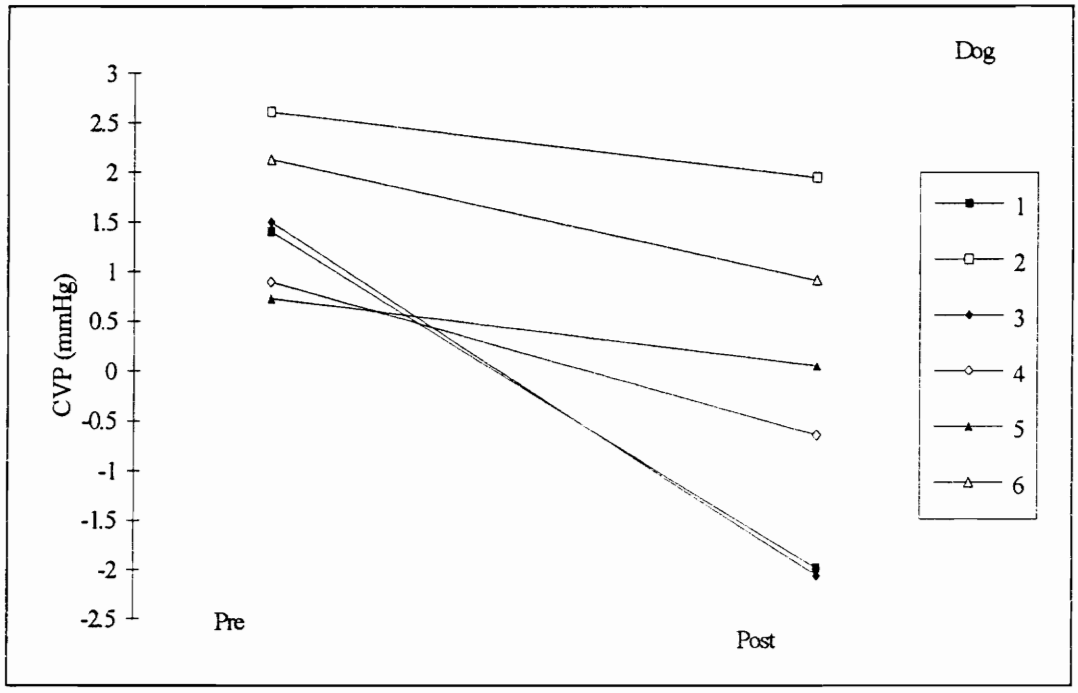

Figure 6 - Effect of controlled cross circulation on central venous pressure in donor dogs.

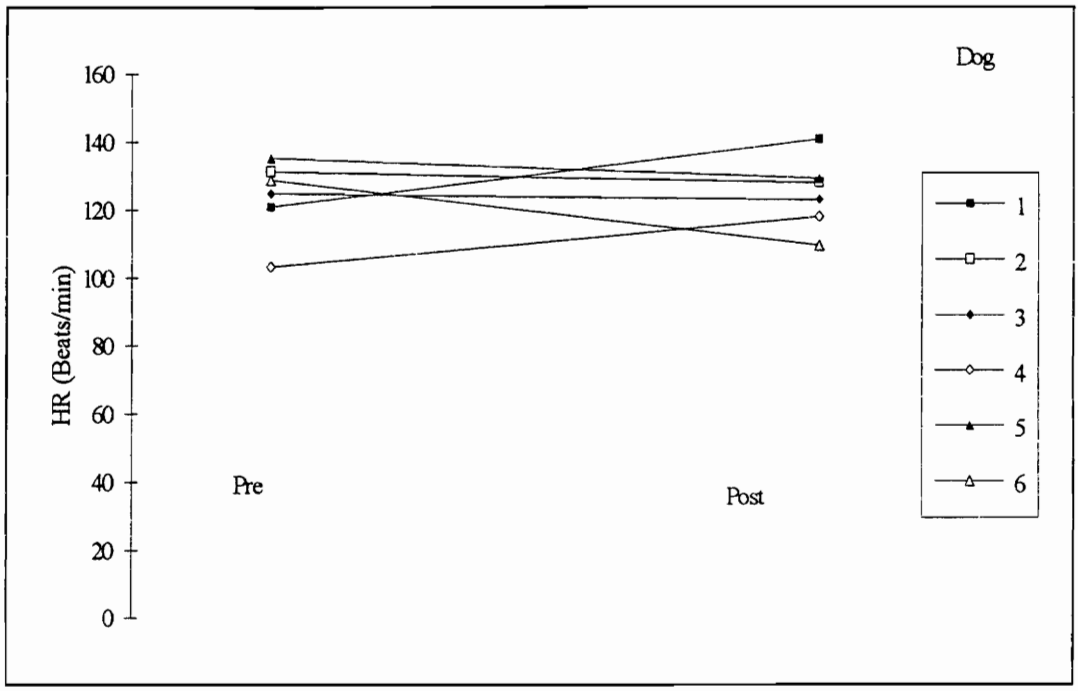

Figure 7 - Effect of controlled cross circulation on heart rate in the donor dog.

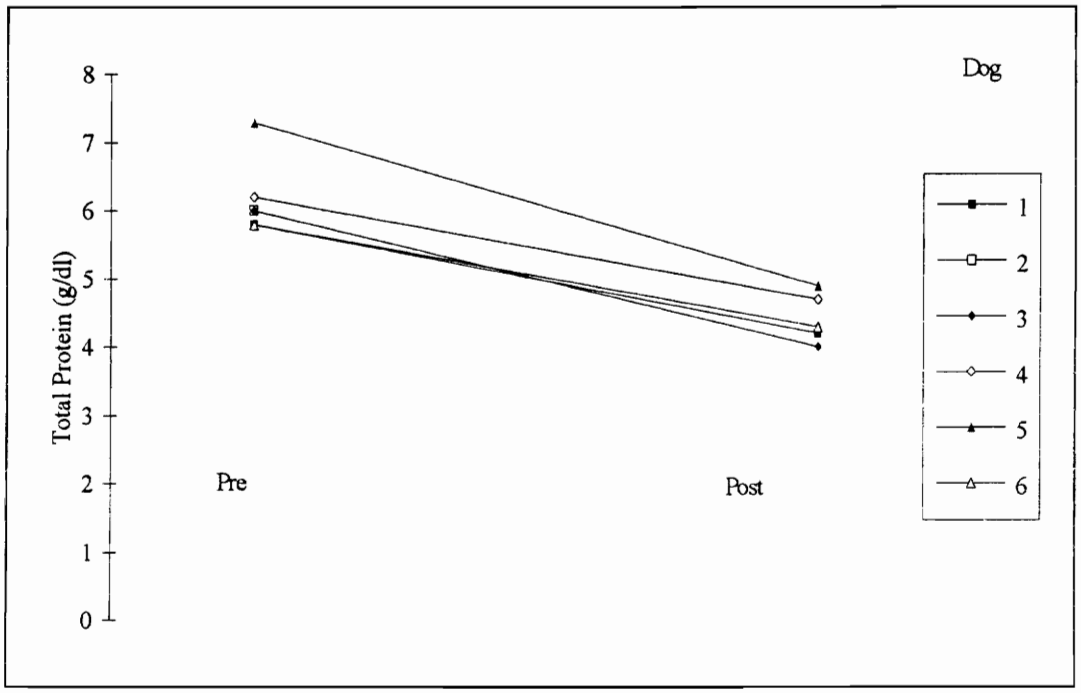

Figure 8- Effect of controlled cross circulation on total protein in the donor dog.

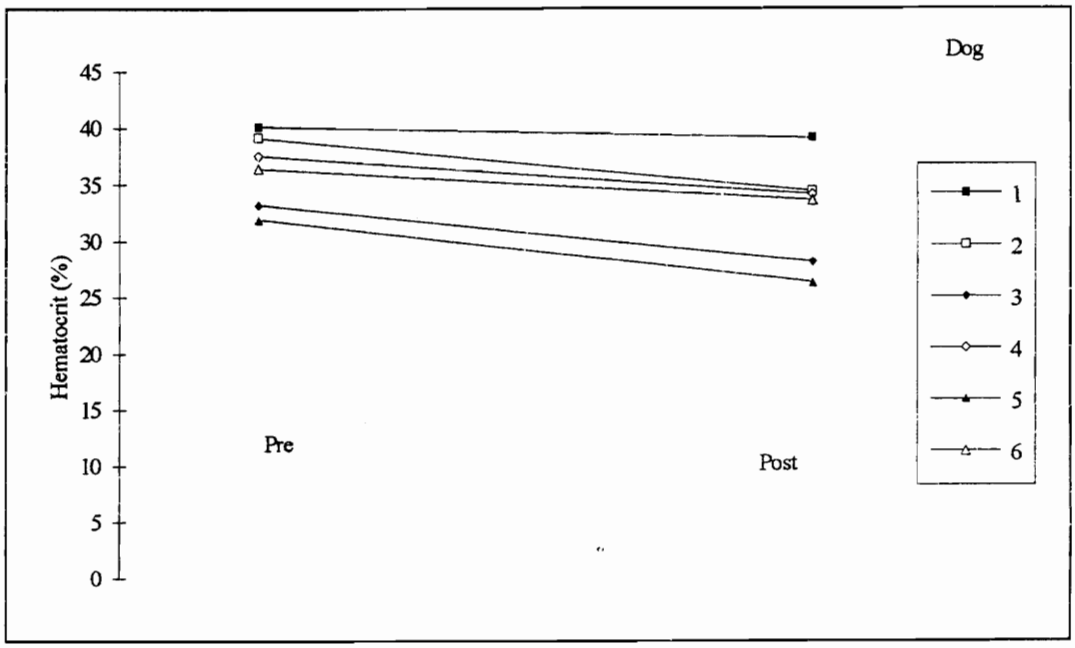

Figure 9 - Effect of controlled cross circulation on hematocrit in the donor dog.

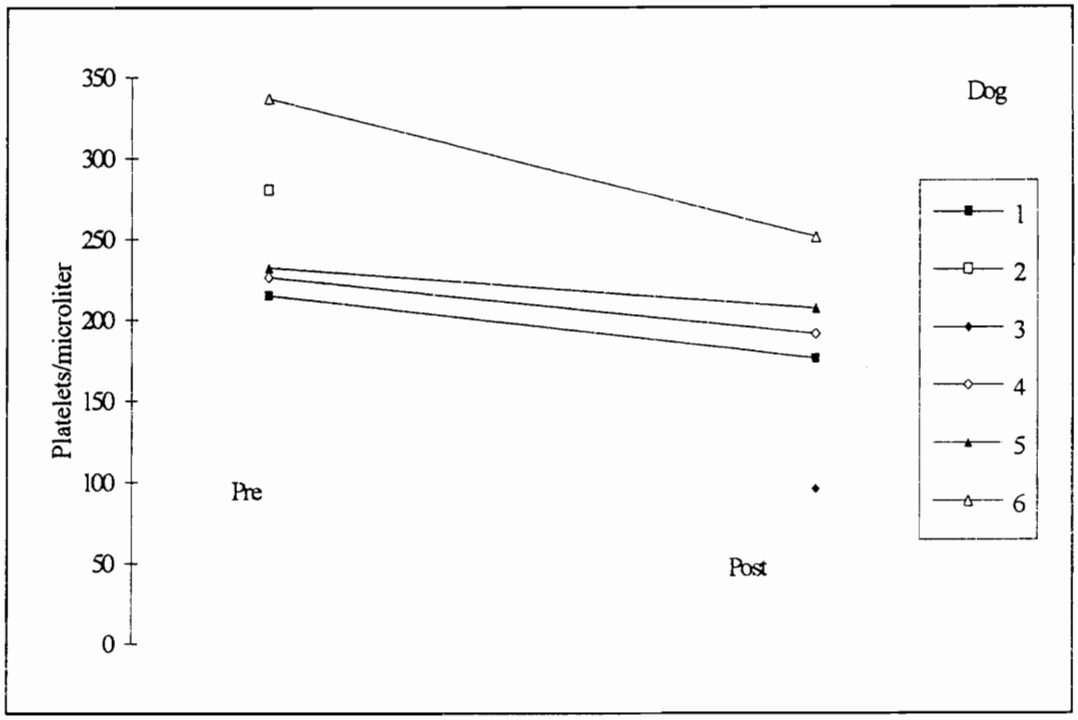

Figure 10 - Effect of controlled cross circulation on platelet count in the donor dog.

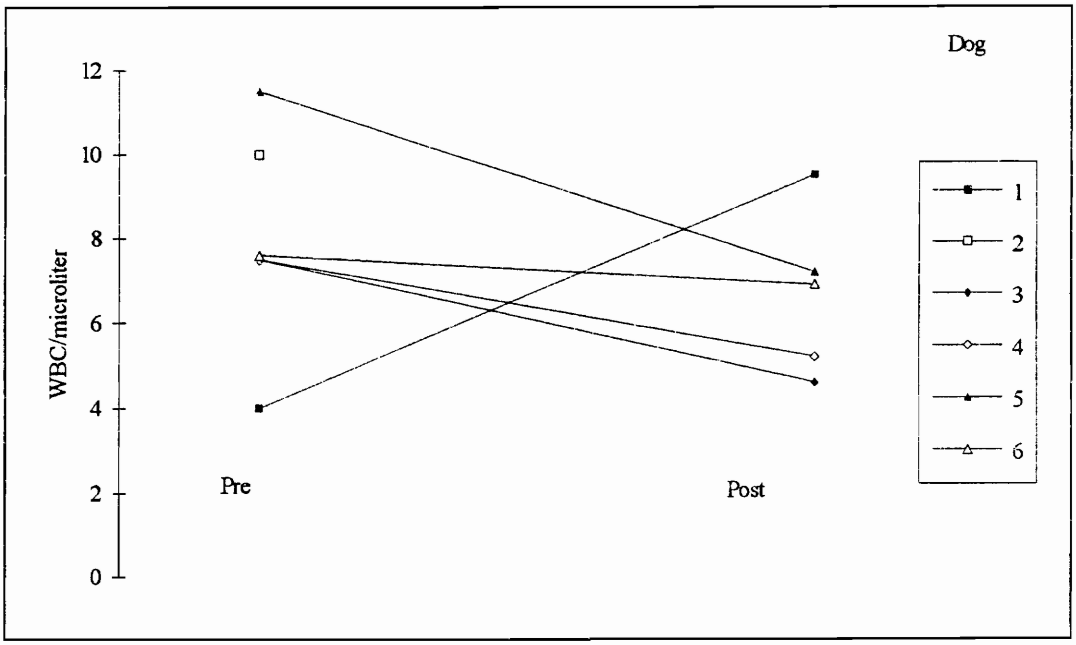

Figure 11 - Effect of controlled cross circulation on white blood cell count in the donor dog.

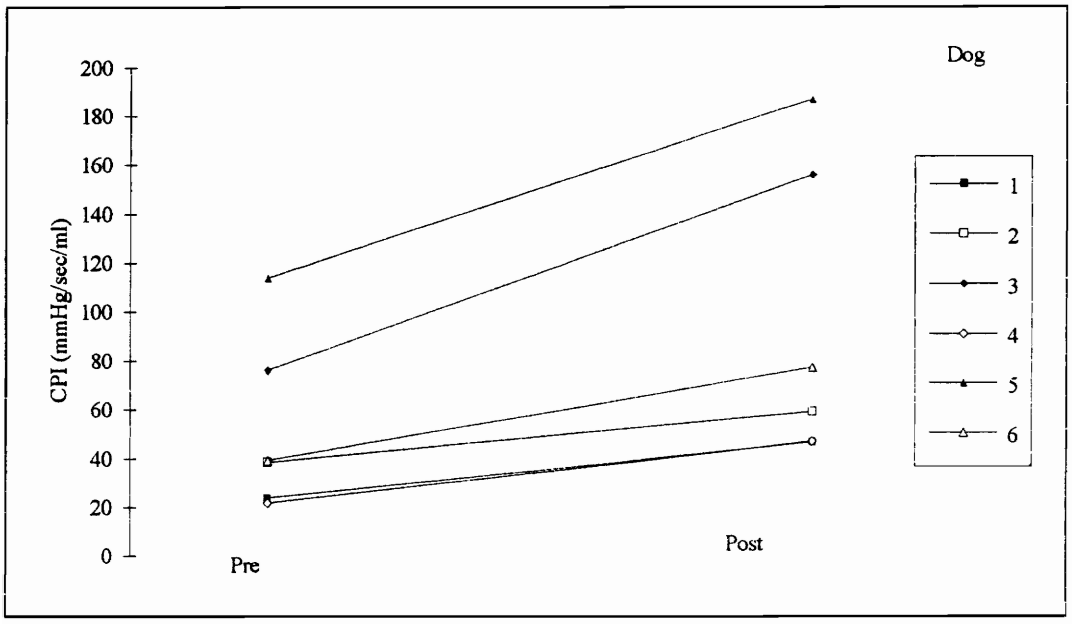

Figure 12 - Effect of controlled cross circulation on cardiac performance in the donor dog.

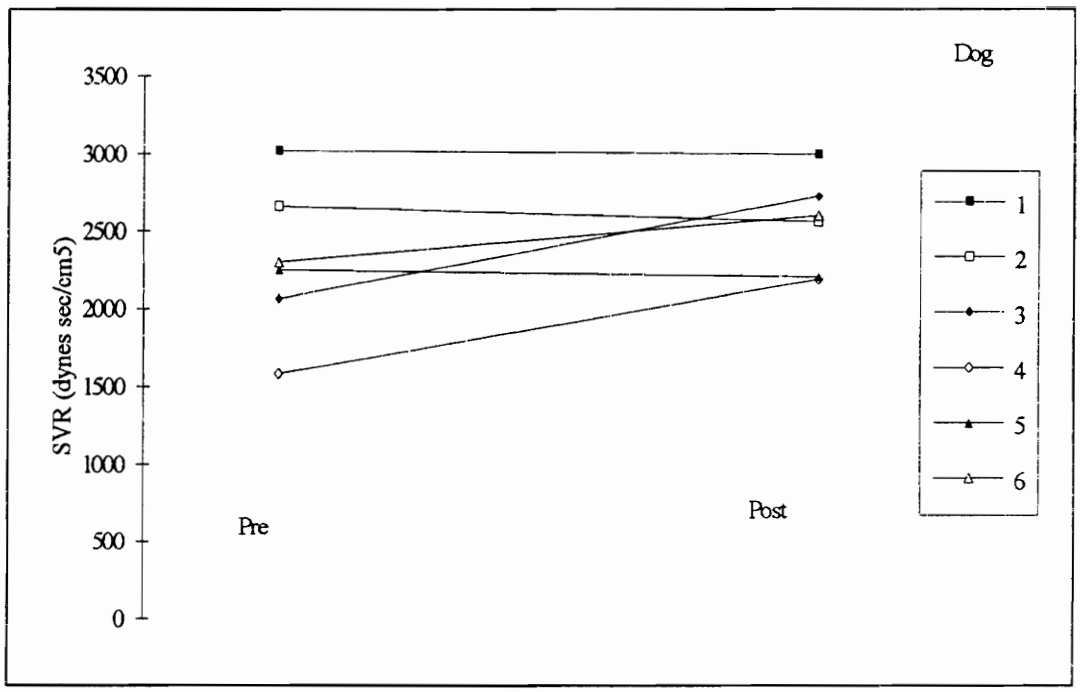

Figure 13 - Effect of controlled cross circulation on systemic vascular resistance in the donor dog.

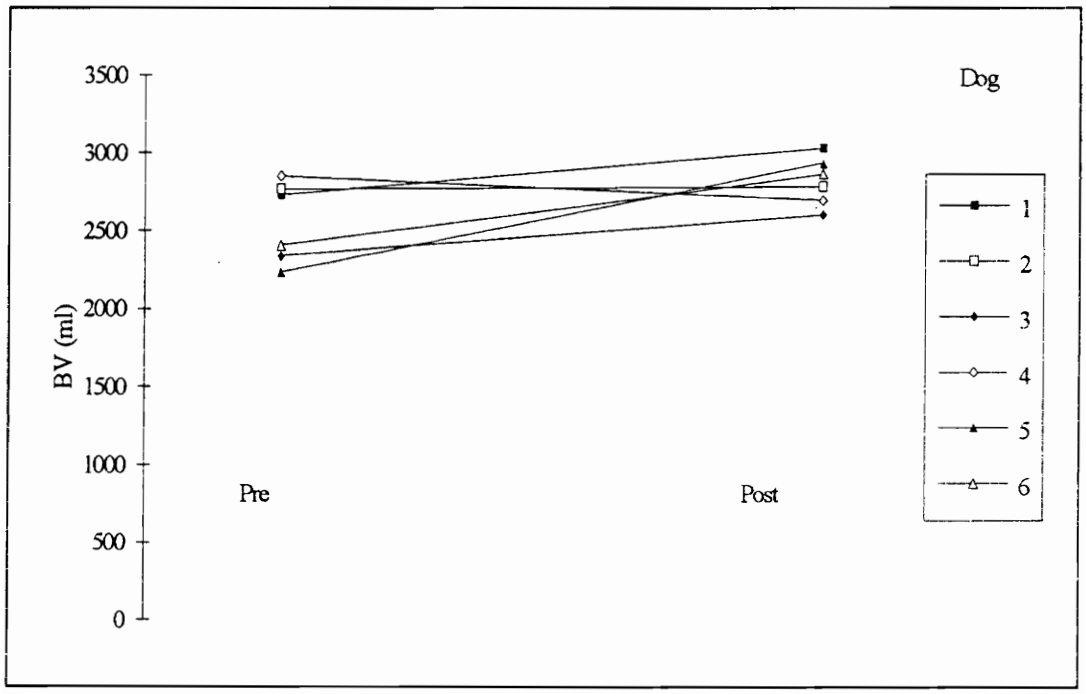

Figure 14 - Effect of controlled cross circulation on donor blood volume.

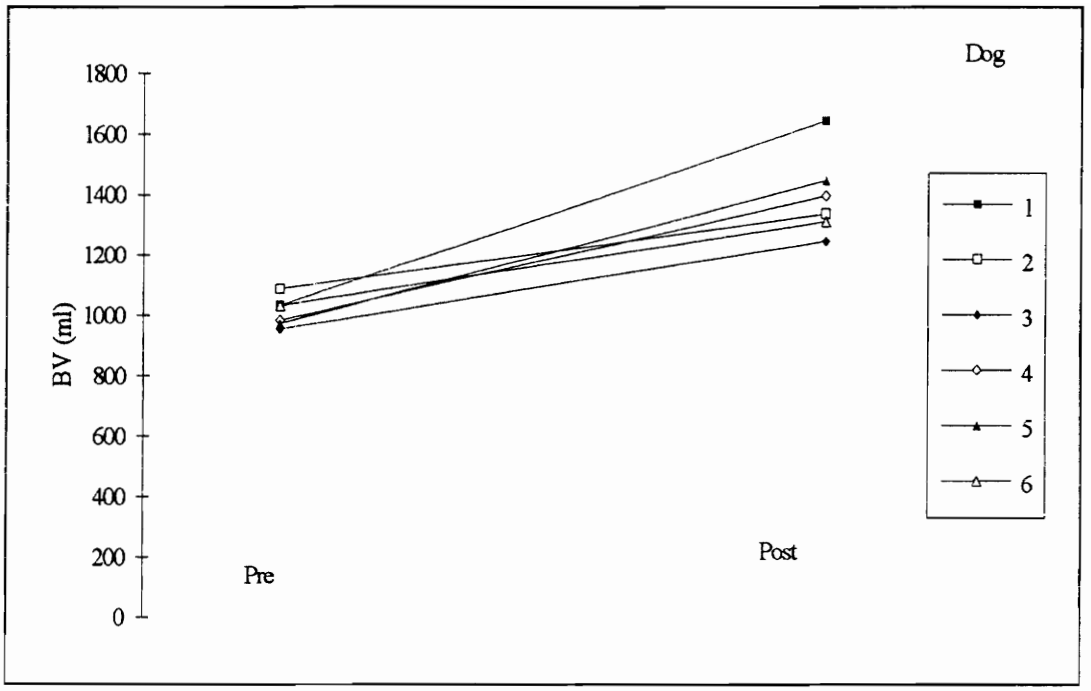

Figure 15 - Effect of controlled cross circulation on recipient blood volume.

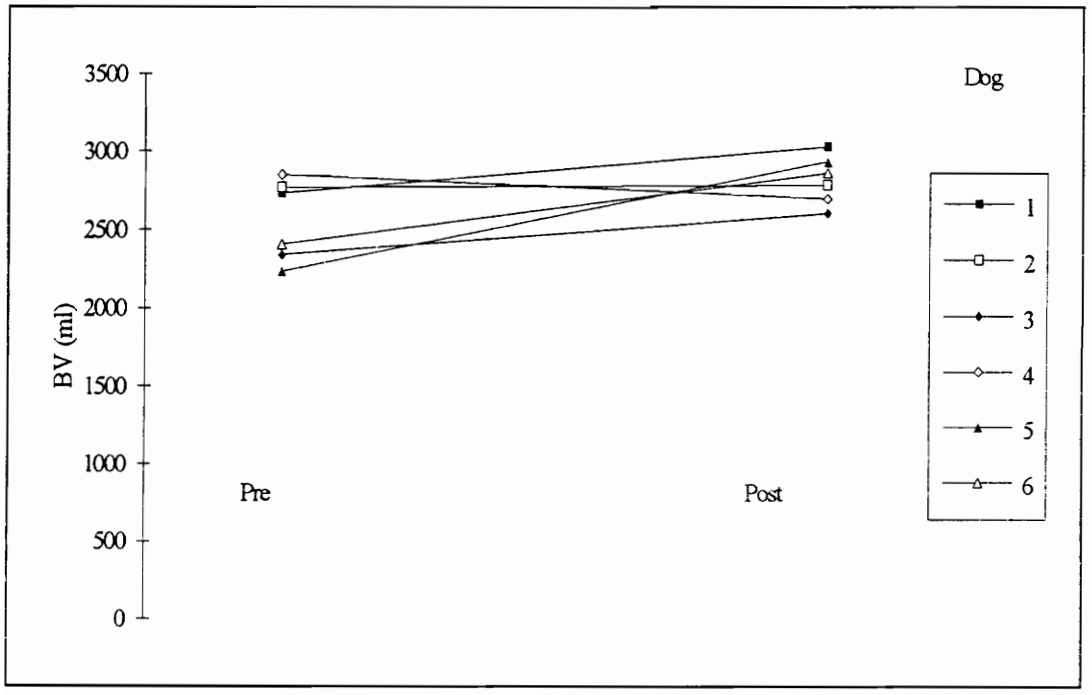

Figure 16 - Effect of controlled cross circulation on combined blood volume.

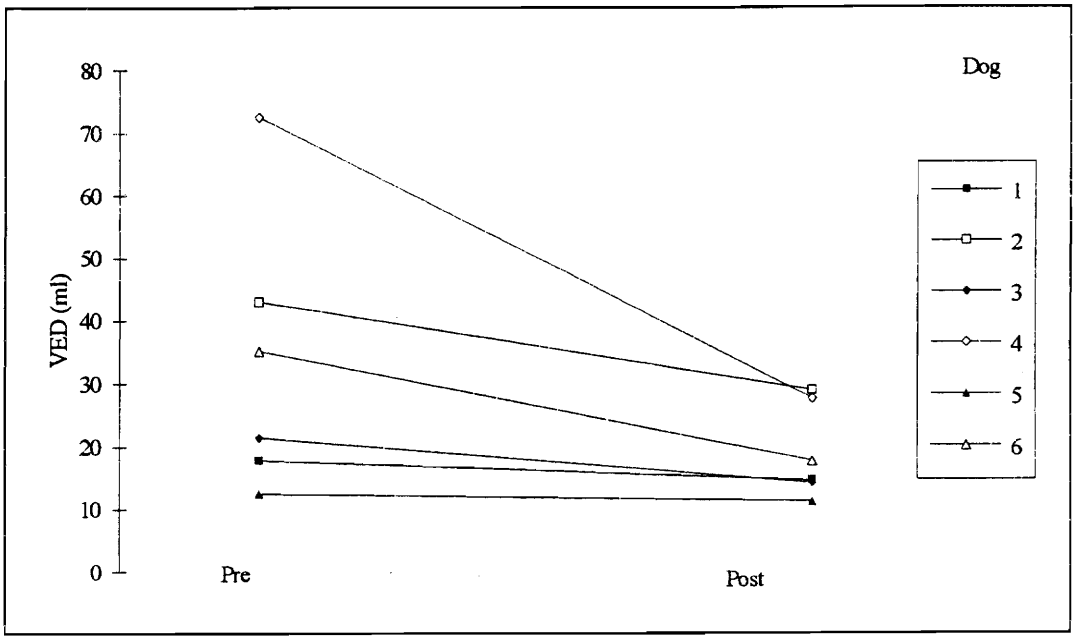

Figure 17 - Effect of controlled cross circulation on end diastolic volume in the donor dog.

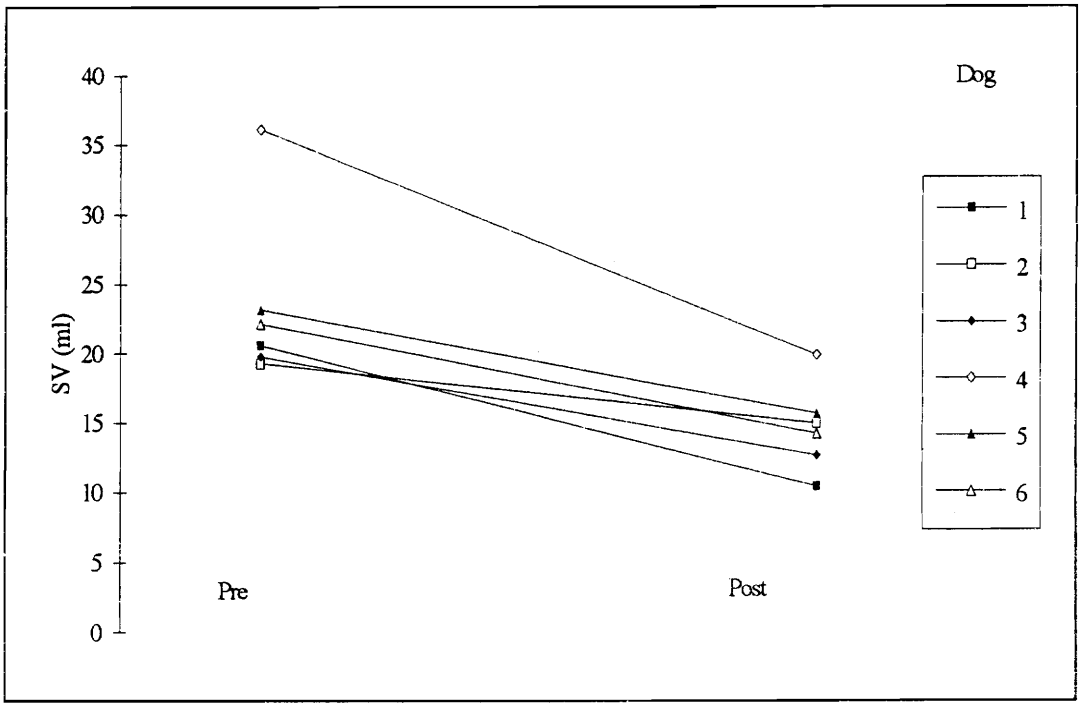

Figure 18 - Effect of controlled cross circulation on stroke volume in the donor dog.

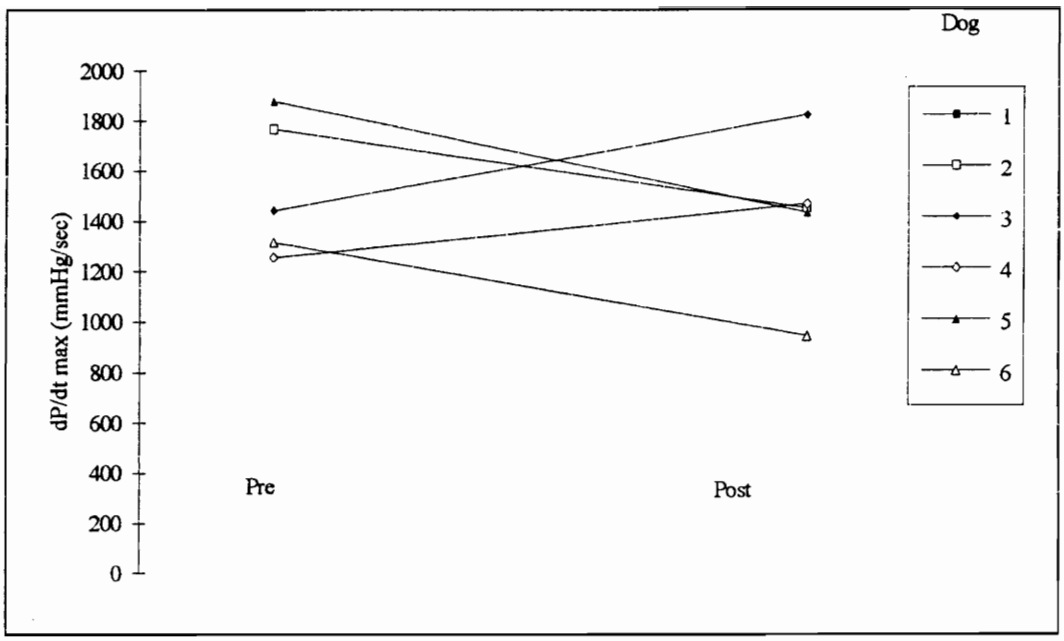

Figure 19. Effect of controlled cross circulation on LV dP/dt max.

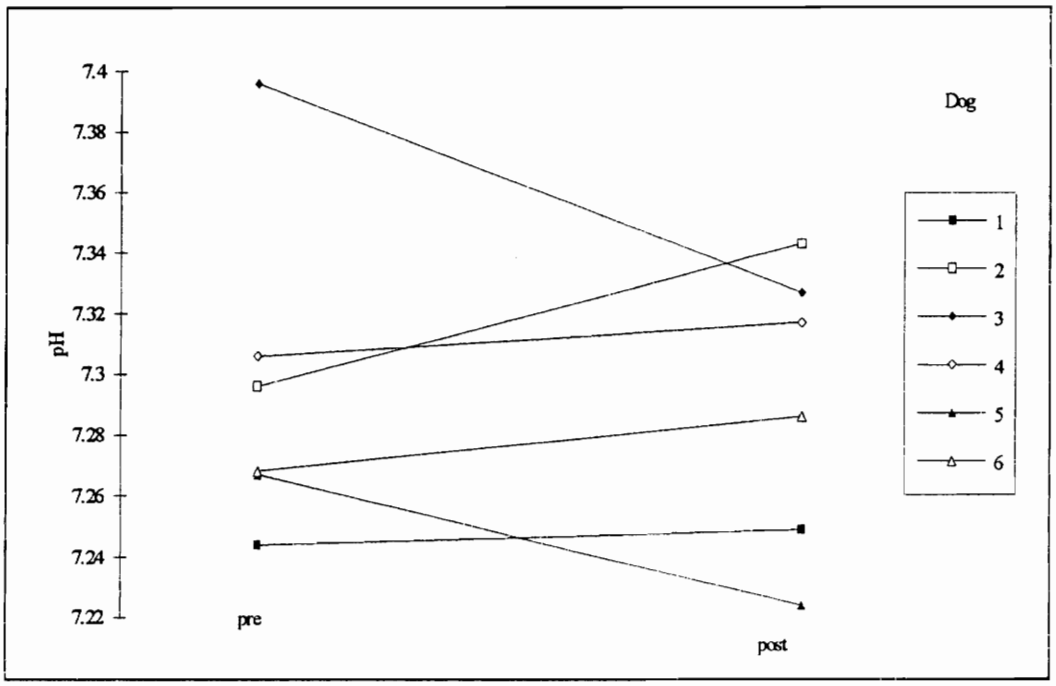

Figure 20 - Effect of controlled cross circulation on arterial pH in the donor dog.

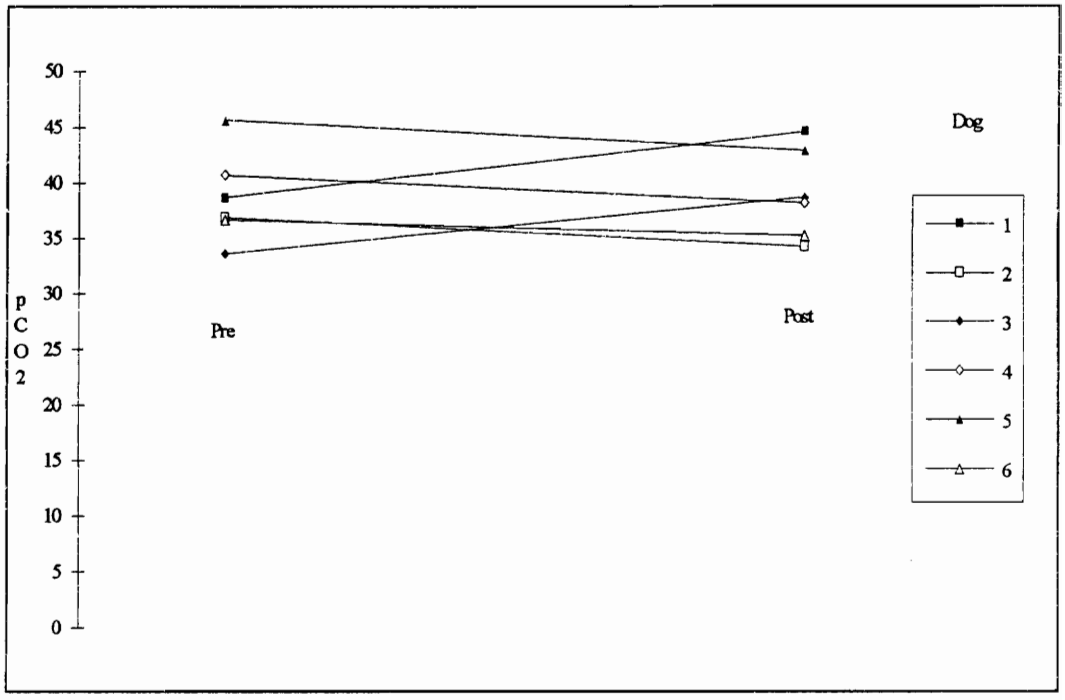

Figure 21 - Effect of controlled cross circulation on arterial pCO_2 in the donor dog

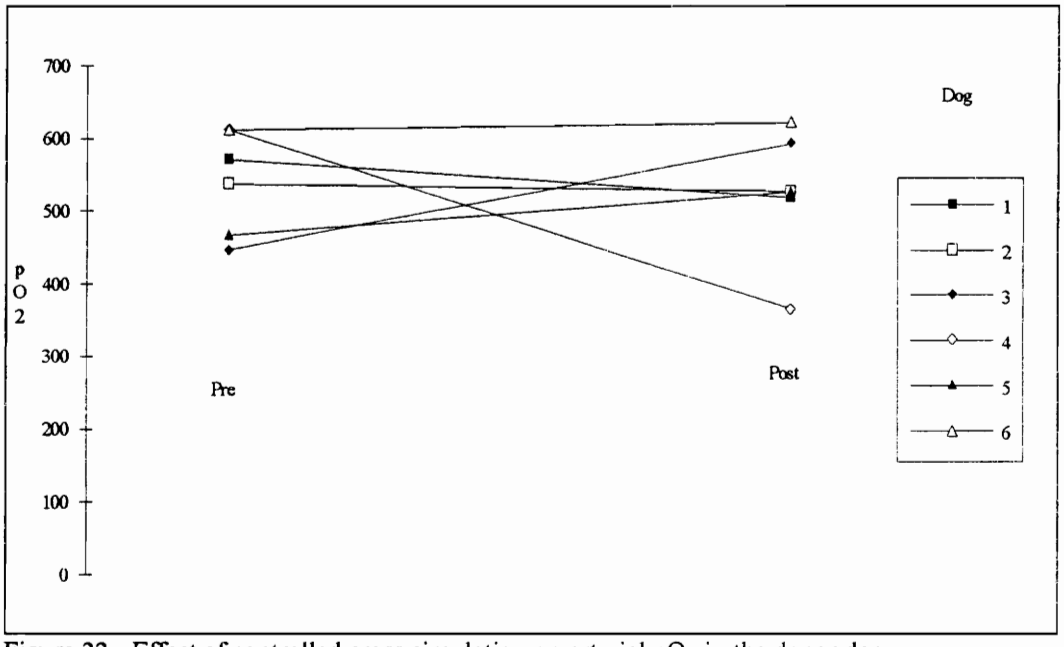

Figure 22 - Effect of controlled cross circulation on arterial pO_2 in the donor dog.

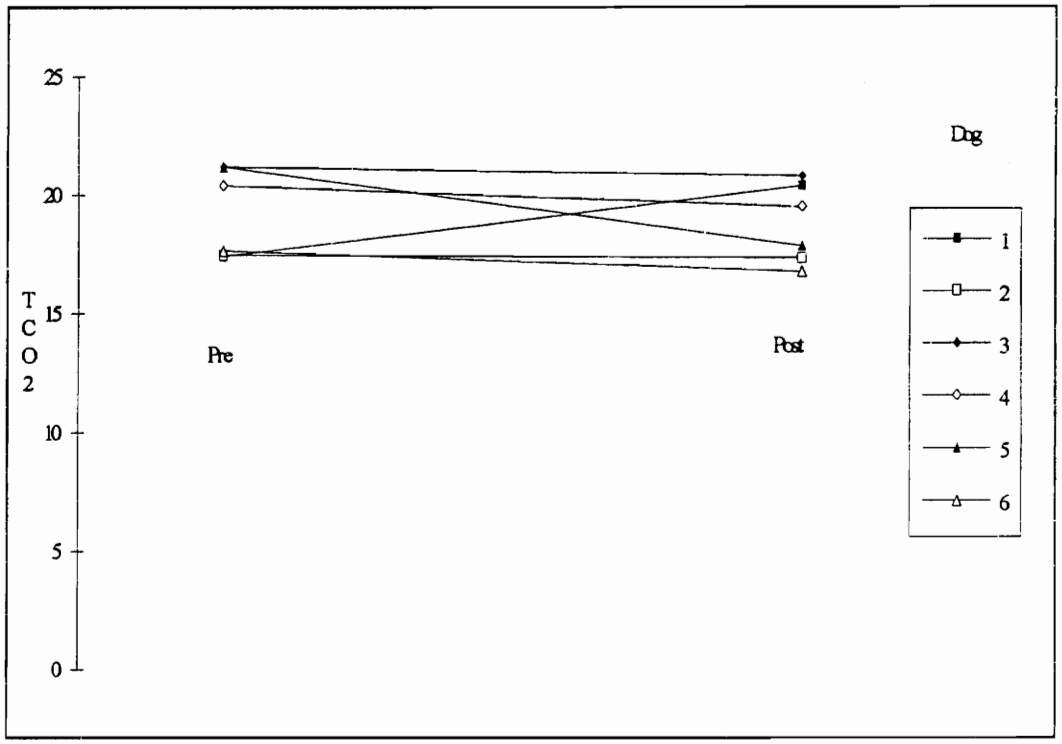

Figure 23 - Effect of controlled cross circulation on arterial tCO_2 in the donor dog.

DISCUSSION.

A. General.

The data indicate that CCC resulted in significant changes in hemodynamics in the donor dog. Cardiac output, LV VED, CVP, LV SV, MAP, total protein and hematocrit decreased significantly. Left ventricular CPI and recipient BV increased significantly. Left ventricular dP/dt MAX, donor BV, SVR, HR, arterial pO_2, arterial pCO_2, arterial pH, arterial tCO_2, platelet count and white blood cell counts did not change significantly. Myocardial performance was enhanced presumably due to a catecholamine response to CCC. There appeared to be a marked shift of blood from donor to recipient dogs.

B. Blood volume.

Blood volume increased significantly in recipient dogs. This is unexpected because cardiopulmonary bypass is typically associated with a marked decrease in BV in cardiac patients.[80-84] Reasons given for blood volume loss following cardiopulmonary bypass include redistribution of plasma volume into extravascular spaces, increased diuresis, blood sequestration and hemorrhage. Since fluids were not administered during CCC, increases in recipient BV suggest a blood volume shift from the donor dog. There was a documented blood volume loss in four of six donor dogs. Dogs number five and six had increases in blood volume estimated. All donors showed decreases in VED, CVP and SV, as well as decreases in cardiac output and mean arterial pressure. These decreases were seen in the two dogs which showed blood volume increases following CCC. The fact that there was consistently decreased preload in all donor dogs, including the two dogs which had

increases in measured BV suggests that blood volume calculation in these two dogs was erroneous. Given the increases in blood volume in recipient dogs five and six, along with the decreased donor preload in dogs five and six, increases in BV in these two donor dogs is very unlikely. Possible explanations for the erroneous BV measurement include laboratory error in the measurement of packed cell volume, the presence of residual Evan's blue dye in the injection cap, inadequate mixing of the Evan's blue dye solution and the injection of the wrong volume of Evan's blue dye solution.

If BV actually increased in donor dogs five and six, the presence of decreased preload with increased BV can be explained if venous capacitance decreases. Changes in venomotor tone limit the value of preload assessment as a means of evaluating postoperative hypovolemia.[81]

An alternate theory explaining the decreased donor dog LV preload is that increased myocardial performance resulted in decreased VED, CVP and PCWP. This is unlikely because CO, SV, and LV dP/dt max should have increased. Cardiac output and stroke volume, in fact, decreased, further supporting the theory of blood loss from the donor dog.

A second alternate theory is that hemodilution due to the priming solution in the extracorporeal circuit may have resulted in decreased oncotic pressure and subsequent loss of plasma volume into extravascular spaces. This should have resulted in decreased recipient BV. Recipient BV increased in all cases.

Massive rapid exchange transfusion with homologous blood has been documented to result in blood volume sequestration.[85-87] This has been simulated in the dog using AV fistula models. Three to seven minutes after an exchange of

incompatible plasma, arterial pressure falls precipitously, and measured BV volume can decrease markedly. Again, this is unlikely because an increase in recipient BV was observed in every case. In addition, major and minor cross matches were performed to assure compatibility.

The blood volume shift from donor to recipient dogs was likely due to variation in delivered flow by occlusive roller pumps with changes in inlet tubing pressure.[59] Exchange pump imbalance is a problem that plagued early studies of controlled cross circulation.[ll] Roller pumps can generate pressures that are less than one half of atmospheric pressure in the inlet tubing segment, before the inlet tubing collapses. When inlet pressure falls, actual flow will be less than that indicated by the pump because of tubing collapse. This is due to impaired elastic recoil of the tubing segment, operating at subatmospheric pressure. Failure of complete reexpansion will result in a pump output that is proportional to the cross-sectional area of inlet tubing. The result is a pulsatile flow with momentary reversal of blood flow at the end of each roller stroke. The actual flow is reduced below that indicated on the flow meter on the roller pump, because the flow meter is dependent only on the rotational speed of the rollers, not the actual flow. Reduction to one half of the meter reading can occur before total collapse of the tubing is seen. No inlet tubing collapse was seen in the present study.

Because inlet pressure falls at higher pump speeds, potential for errors in recorded flow increases at higher flow rates. Altering outlet tubing pressure has no effect on delivered flow because tubing expansion has markedly less effect on flow than does tubing collapse. [59]

[ll] Personal communication: Dr. C. Walton Lillihei, May 12, 1994.

The recipient to donor roller pump head was subjected to an inlet pressure of approximately 0 mm Hg (CVP in the recipient), while the donor to recipient roller head was subjected to an inlet pressure of approximately 70 mm Hg (MAP in the donor). The recipient to donor pump head was subjected to substantially lower pressures in the inlet segment. This makes it more likely that at high pump speeds, the recipient to donor segment was experiencing subatmospheric pressures and subsequent tubing collapse. This collapse may have resulted in lower delivered blood flow in the recipient to donor tubing segment, without any indication, because the flow meter was reading only the rotational speed of the pump head. Stiffer tubing, with less tendency to collapse at subatmospheric pressure, and the use of lower pump speeds would decrease the shift of blood from the donor to recipient patient.

The mean increase in BV in recipient dogs was 388.31 mls. This corresponds to 8.63 mls/min total BV shift from the donor to the recipient dog. With pump speeds of 500 mls/min common, this would require a decrease in flow of only 1.7% in the recipient to donor segment relative to the donor to recipient segment. With variations of 9%-33% reported in hemodialysis machine roller pumps[59] variations of the proportions found in this study are feasible.

C. Cardiac output.

Cardiac output decreased significantly in all donor dogs. Since CO is the product of SV and heart rate, and HR did not change, the decrease in CO was due to a decrease in SV. This, in turn, was likely due to the decrease in BV.

D. Mean arterial pressure and systemic vascular resistance.

Mean arterial pressure decreased significantly. Mean arterial pressure is approximately equal to a product of CO and SVR. Because SVR did not change significantly, the decrease in MAP was likely due to the decrease in CO. Systemic vascular resistance is the difference in pressure through the peripheral vasculature divided by the flow through the vasculature. Since MAP, CVP and CO all decreased, SVR did not change significantly. In addition to pressure and flow determinants, systemic vascular resistance is also a function of blood viscosity. Dilution with prime solution can result in a marked decrease in systemic vascular resistance.[58]

E. LV dP/dt max.

Controlled cross circulation had a variable effect on LV dP/dt max. Left ventricular dP/dt max is subject to changes in preload, afterload, and inotropic state, all of which were changing in all dogs. With decreased preload, LV dP/dt max should have decreased in all dogs. It increased only in dogs which spontaneously died following CPB. Both dogs that died had increased SVR, which effectively increased afterload. Increased afterload increases LV dP/dt max by delaying semilunar valve opening. Left ventricular dP/dt max will continue to rise until the semilunar valve opens.[41, 42]

When LV dP/dt max was corrected for preload the effect of loading conditions was eliminated. Left ventricular dP/dt max / VED showed a significant increase in cardiac performance. This increase was presumably due to catecholamine release secondary to baroreceptor response.

F. Hematologic changes.

Hematologic changes were also found. There were decreases in hematocrit, total protein, and platelet counts in all patients measured. Decreases in hematocrit and total protein were likely due to hemodilution. The mean combined BV was 2,553 mls. The extracorporeal circuit was primed with 1,000 mls of heparinized saline. This could account for a decrease of approximately 30% in hematocrit and total protein. Platelet counts have been shown to decrease secondary to CPB, due to factors other than hemodilution. These include platelet destruction, saturation of reactive sites in the extracorporeal circuit, aggregation due to the presence of damaged blood factors, and sequestration in the liver.[2-5] Platelet counts dropped an average of 29% in donor dogs. Thrombocyte counts in perfusions lasting less than forty-five minutes have been reported to drop 58%[88], 62%[2] and 61%[4], with no significant difference between membrane and bubble oxygenators. Platelet counts with CCC compare favorably with mechanical oxygenation, further supporting the physiologic nature of this technique.

There was no significant difference when comparing prebypass and post bypass leukocyte counts. The effect of CCC was variable. With mechanical cardiopulmonary bypass, leukocyte counts typically double with cardiopulmonary bypass, due to release of polymorphonuclear leukocytes and their precursors from the bone marrow.[89-91] Although leukocyte numbers increase, function is usually impaired. Leukocyte function was beyond the scope of this study.

G. Blood gases.

Blood gases did not change significantly following CCC. This is consistent with previous studies of CCC.[22, 23, 92] The lack of an increase in pCO_2 indicates that the donor is able to maintain ventilation in both patients. The lack of metabolic acidosis following CCC suggests that adequate perfusion of both patients was occurring.

H. Arteriovenous fistula.

Controlled cross circulation in the donor dog is analogous to the acute onset of an arteriovenous (AV) fistula.[9] Both result in the diversion of a portion of blood from arterial to venous circulations, bypassing the peripheral vasculature. The physiologic effects of AV fistulas have been described.[10-16, 93-95] The primary change is a decrease in systemic vascular resistance, and a subsequent increase in venous blood return. Mean arterial pressure decreases, stimulating baroreceptors, thereby causing catecholamine release.[16, 17] Heart rate increases, as does cardiac output. Myocardial performance is enhanced because of increased preload, due to the Frank-Starling law of the heart, decreased afterload from the decreased systemic vascular resistance, and increased myocardial contractility from the presence of circulating catecholamines. The degree of hemodynamic changes is proportional to the amount of blood being shunted through the fistula. Upon closure of the fistula, all hemodynamic parameters quickly return to normal, providing the duration of the fistula is short (<24 hours). Catecholamines, with their short half-lives, rapidly return to near control levels.[16]

When comparing AV fistulas to the model in the present study, it is important to realize that data points were taken before and after, but not during the "fistula." Tracings were recorded, but not tabulated and compared statistically during CCC. These data were consistent with the high output associated with AV fistulas, even though it is apparent that blood volume was shifted from the donor to the recipient dogs.

Following CCC, myocardial performance remained elevated following closure of the fistula. This was presumably due to the persistence of circulating catecholamines. Catecholamines likely remained elevated because of decreased mean arterial pressure following CCC. If blood volume had not been lost to the recipient dog, catecholamines and myocardial performance should have returned to control values.

With the presence of circulating catecholamines, heart rate should have remained elevated, while in the present study, heart rate remained at control levels. Previous studies of experimentally created AV fistulas in dogs have demonstrated unchanged heart rate in the face of elevated catecholamines and increased myocardial performance.[15] Other studies have shown that preexisting tachycardias under anesthesia can fail to accelerate under the influence of circulating catecholamines.[96, 97] Isoflurane has been shown to have a blunting effect on the baroreceptor response to hypotension.[69, 70] It is anticipated that with circulating catecholamines, SVR should have increased. Systemic vascular resistance is proportional to blood viscosity. Blood viscosity was decreased with the addition of prime solution to the combined BV of both patients. This can result in a blunting of the effect the circulating catecholamines would have on SVR.[98]

I. Mortality.

Recipient death occurred in one dog, early in the experimental protocol. This was due to premature discontinuation of CPB, prior to the point where the recipient was able to take over cardiovascular function. Donor death occurred in two dogs following CCC. These dogs had the greatest increases in SVR during CCC. They also were the only dogs to have increases in LV dP/dt max during CCC. These hemodynamic factors indicate that CCC was especially stressful in these dogs. The possibility of heartworm disease was eliminated by necropsy. For an unknown reason, these dogs had the lowest preoperative MAP's. It should be noted that this model for CCC was more stressful than typical CCC in that the duration of anesthesia was longer, because of time required for instrumentation, and because prebypass and postbypass AV fistulas were created in order to evaluate myocardial performance. The duration of anesthesia in donor dogs in this model was approximately 6 hours. Donor mortality has not been previously reported in the human and veterinary literature. The donor death was likely primarily due to the stressful nature of the experimental protocol. It should also be noted that the donor was able to support the recipient dog for the duration of CPB, with no compromise in myocardial performance.

J. Enzyme mapping.

Enzyme mapping in patients which survived the entire procedure showed no evidence of myocardial ischemia. Those which spontaneously died had areas of pallor, consistent with myocardial ischemia. Both of these dogs had repeated defibrillation. The assay for enzyme mapping requires the presence of functioning

respiratory enzymes which reduce the TTC solution to a red color. These enzymes were presumably denatured by the defibrillation, which resulted in the artifactual evidence of myocardial ischemia. In addition, since both of these deaths occurred within two hours of CPB, myocardial ischemia is likely not the reason for the abnormal results in the assay. This is because it takes at least four hours for hypoxic myocardium to show changes with the enzyme mapping technique.[72]

K. Weight ratios.

Weight ratios between donor and recipient patients were variable. There were no trends apparent when comparing weight ratios and donor or recipient mortality. It is important to note that when this technique was used clinically in people, the parent usually weighed approximately ten times the recipient. Cross circulation would clearly represent less of a burden in these cases, since a far lesser portion of the donors cardiac output would have to be shunted to the recipient.

CONCLUSIONS.

In conclusion, many of the changes seen in donor hemodynamics were likely due to a decrease in donor BV. This resulted in a decrease in CVP, VED, SV and PCWP. These in turn resulted in decreased CO, MAP and LV dP/dt max. It is speculated that the decreased BV was due to a shift from the donor to the recipient dog because of an imbalance in the roller pump mechanism. This imbalance was due to a variation in delivered flow caused by changes in inlet tubing pressure. Myocardial performance increased, as was confirmed by changes in LV dP/dt max/VED. It is speculated that this was due to increased circulating catecholamine levels, secondary to a baroreceptor response to hypotension. There was no evidence of a compromise in cardiac function immediately following CCC. Donor mortality was likely due to the stressful nature of this research protocol. Hematologic changes were primarily due to hemodilution by the prime solution.

These findings will help decrease donor mortality. It is evident meticulous care needs to be taken to eliminate, or at least account for imbalance in flow delivered by the roller pump. Blood loss should be monitored during and after CPB. In clinical cases, recipient and donor dogs will be supported with vasopressor drugs and fluid administration. This will allow lower pump speeds to be used. This will be less stressful to the donor dog, since the degree of hemodynamic changes are proportional to the volume of fluid being shunted through a "fistula."[16] In addition, lower pump speeds may result in lower volumes of blood shifted from one dog to another, because of a decreased tendency for the inlet tubing segment to collapse on the recipient side of the roller pump. Also, in clinical cases, the reservoir can be completely emptied following CCC. This will

allow the addition of transfusion of 600 ml of BV to either patient. If changes in BV are eliminated, then the physiologic effects of CCC in the donor dog should be identical to those seen with AV fistulas. Donor mortality should be minimal as has been reported in previous studies.[9, 19-22, 92]

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VITA

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After graduation, Charles completed a one year rotating internship at the Animal Medical Center in New York City. He then began a combined Master's program and surgical residency at the Virginia-Maryland Regional College of Veterinary Medicine. His thesis was directed at assessing hemodynamic changes associated with controlled cross circulation in the dog. His interests are primarily cardiovascular medicine and surgery. He is engaged to Kate Savage, a resident in Large Animal Internal Medicine, and they share three wonderful "children", Giles, Holly and Leo.

Charles A. Kuntz

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