Functional Evidence of Reversible Ischemic Injury Immediately After the Sympathetic Storm Associated With Experimental Brain Death

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Background: Acute brain death from increased intracranial pressure results in a transient increase in myocardial adenosine and lactate, which indicates that oxygen demand exceeds oxygen delivery during the sympathetic "storm". The aim of this study was to determine the functional significance of this period of ischemia.

Methods: Brain death was inflicted on 40 Westran pigs (36.5–68.0 kg) by inflating a 21-ml subdural balloon over 3 minutes. In 38 animals, micromanometry and sonomicrometry were used to obtain left ventricular pressure-volume loops to determine the preload recruitable stroke work (PRSW) relationship. Data files were recorded before and at 15-minute intervals after beginning balloon inflation. Plasma troponin I was measured before and 60 minutes after beginning balloon inflation in the 38 instrumented and 2 non-instrumented animals.

Results: All animals experienced the classical sympathetic storm. The slope of the PRSW relationship decreased, and the volume-axis intercept shifted to the right 15 minutes after beginning balloon inflation ($p < 0.0001$). Progressive incremental recovery (leftward shift) occurred between subsequent time points ($p \leq 0.0018$). In the instrumented animals, the mean plasma troponin I level increased from 1.4 ± 1.6 μg/liter to 2.8 ± 2.3 μg/liter ($p < 0.001$). However, troponin I was not detected before or after induction of brain death in the plasma of either non-instrumented animal ($p = 0.001$).

Conclusions: The sympathetic storm produced transient contractile dysfunction, consistent with ischemic injury. However, troponin I release reflected surgical instrumentation and not brain death. J Heart Lung Transplant 2003;22:922–928.

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Despite ongoing interest in xenotransplantation, mechanical heart assist or replacement devices and a variety of new surgical procedures, transplantation of cardiac allografts harvested from brain-dead donors remains the only potentially definitive treatment for most patients with end-stage cardiac disease.[1,2] However, the systemic events associated with brain death adversely affect the heart, and this affects graft function after transplantation.[3,4]

Acute brain death secondary to inflation of a sub-dural balloon, which is the standard experimental model, produces a surge in sympathetic activity that leads to a dramatic but transient increase in blood pressure and heart rate.[3,4] As brain death ensues, complete loss of central sympathetic outflow and cessation of pituitary hormone secretion occurs.[3,4] There is good evidence that the sympathetic stimulation, and consequent increase in circulating catecholamines, is central to the adverse effect of brain death on cardiac allografts.[5,6]

Several investigators have demonstrated a transient increase in both adenosine and lactate levels in the myocardium immediately after the sympathetic storm.[5,7] This suggests an imbalance between oxygen requirements and oxygen delivery during the sympathetic storm. The immediate effect of this imbalance on contractile function has not been examined previously in detail. The aim of the current study was to use a load-independent index of left ventricular contractility to look for functional evidence of transient ischemic contractile dysfunction to determine the practical significance of the previously observed metabolic changes.

METHODS

Our institutional animal experimentation ethics committee approved the experiments, and we conducted them in accordance with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes.

Animals and Anesthesia

Each of 40 Westran pigs (36.5–68.0 kg) received pre-medication with an intramuscular injection of ketamine (10 mg/kg), midazolam (1 mg/kg), and atropine (1.2 or 1.8 mg). We induced general anesthesia with intravenous thiopentone (50-mg boluses, to effect) and maintained anesthesia with inhaled isoflurane (1–3% inhaled gas) and intravenous fentanyl (5-μg/kg boluses). The animals were intubated and ventilated with 100% oxygen. Normal saline (0.9%) was infused intravenously at a rate of 10 ml/kg for the first hour and at 5 ml/kg thereafter. Prophylactic lignocaine (1 mg/kg) was administered before sternotomy. Arrhythmias during instrumentation were treated with internal direct current countershock (10–30 J) and additional lignocaine (1 mg/kg). We continuously monitored pulse, cardiac rhythm, arterial pressure, expired CO_2, and core temperature in all animals.

Cardiac Instrumentation and Data Acquisition

In 38 of the 40 animals, hearts were exposed with median sternotomy. A flow probe (Transonic Systems Inc., Ithaca, NY) was placed around the left anterior descending artery (LAD), close to its origin. Ultrasonic dimension transducers (2 mm in diameter, Sonometrics Corp., London, ON) were attached to the epicardium to measure the base–apex major axis and anterior–posterior minor axis dimensions of the left ventricle. We used a transmyocardial approach to place a micromanometer-tipped catheter (Millar Instruments Inc., Houston, TX) in the left ventricle. Dimension and pressure data were obtained at a sampling rate of 200 Hz and were digitized (Sonometrics Corp., London, ON).

We recorded data files before inducing brain death (BD + 0) and at 15-minute intervals from the beginning of brain death induction (BD + 15, BD + 30, BD + 45, BD + 60). These files were recorded immediately before and during transient occlusion of the inferior vena cava. Mechanical ventilation was suspended during data acquisition.

We used SonoSOFT 3.1.3 Software (Sonometrics Corp., London, ON) to acquire and analyze the data files. The prolate ellipsoid model was used to calculate epicardial left ventricular volume from the dimension data ($LVV = \pi.a.b^2/6$, where LVV = left ventricular volume, a = the major axis length, and b = the minor axis diameter). We then constructed pressure-volume loops. End-diastole was determined automatically, using the left ventricular pressure trace. The pressure and volume at the end-diastolic time point were recorded. Stroke work was calculated as the area of the pressure-volume loop for each beat (end-diastole to end-diastole). The association between stroke work and end-diastolic volume, termed the preload recruitable stroke work (PRSW) relationship, was determined using linear regression analysis of data obtained during vena caval occlusion.

Induction of Brain Death

We introduced a Foley catheter into the animal's sub-dural space through a right frontoparietal burr

hole. After acquiring baseline data, we inflated the balloon with water in 3-ml increments every 30 seconds to a total of 21 ml. Fifteen minutes after beginning balloon inflation, we terminated anesthesia to allow clinical confirmation of brain death. No additional fluid or inotropic support was provided after induction of brain death.

We recorded pulse, mean arterial pressure, and coronary artery flow rates at 30-second intervals for the first 10 minutes after beginning balloon inflation and at 5-minute intervals thereafter.

Troponin I Release

We used plasma troponin I as the biochemical marker of myocardial injury. Because surgical instrumentation may be a confounder, we determined troponin I release in 38 instrumented and 2 non-instrumented animals. Samples were obtained immediately before inducing brain death (BD + 0) and at 1 hour after beginning brain-death induction (BD + 60) and assayed using the AxSYM microparticle enzyme immunoassay platform (Abbott Laboratories, Abbott Park, IL).

Statistical Analysis

We performed statistical analyses with SPSS for Macintosh 6.1.1 (SPSS Inc., Chicago, IL). Differences were considered statistically significant at $p \leq 0.05$. Hemodynamic and plasma troponin I data are reported as the mean ± the standard deviation. Hemodynamic data were compared using analysis of variance for repeated measures. We investigated significant differences in the analysis of variance for repeated measures model using the Student's *t*-test for paired samples with a Bonferroni correction for multiple comparisons. In the instrumented animals, the pre–brain death and post–brain death plasma troponin I data were compared using the Student's *t*-test for paired samples. To compare the instrumented and non-instrumented animals, we assessed the post–brain death troponin level as a dichotomous categoric variable (greater than the pre–brain death troponin I level or not detected/unchanged from the pre–brain death troponin I level), and used Fisher's exact test.

Stroke work and epicardial end-diastolic volume estimates were normalized, within individual animals, to the respective steady state values at the baseline data acquisition point. Mean regression equations for the PRSW relationship were then derived at each time point using multiple linear regression.[8] The general linear model used was:

$$Y = b_0 + \Sigma_{i=1 \text{ to } n-1} p_i \cdot P_i + b_1 \cdot X \quad (1)$$

where Y is normalized stroke work, X is normalized epicardial end-diastolic volume, b_1 is the slope of the relationship, b_0 is the stroke work (y) axis intercept, and the term $\Sigma_{i=1 \text{ to } n-1} p_i.P_i$ accounts for individual animal variability. The regression coefficients are reported as the mean ± the standard error. Two further indices were derived from the regression coefficients for the purpose of describing the normalized PRSW relationship at each time point. These were the volume (x) axis intercept ($-b_0/b_1$) and the stroke work index, (SWI; $b_0 + b_1$). Stroke work index (SWI) is the regression estimate of the mean normalized stroke work when the normalized epicardial end-diastolic volume is 1 (i.e., at the baseline steady state end-diastolic volume). It represents the interaction between changes in the slope and the volume-axis intercept of the relationship at the normal operating volume of the heart, which is the most physiologically relevant end-diastolic volume.

We compared the baseline PRSW relationship with the PRSW relationship at each of the 4 time points after brain-death induction using a multiple linear regression implementation of analysis of covariance with repeated measures.[8] The general linear model was:

$$Y = b_0 + \Sigma_{i=1 \text{ to } n-1} p_i \cdot P_i + \Sigma_{i=1\text{-}4} t_i \cdot T_i + b_1 \cdot X \quad (2)$$

where the term $\Sigma_{i=1-4} t_i.T_i$ accounts for differences between time points, and the other terms are as defined above. We made pairwise comparisons of the PRSW relationships at sequential time points in the same manner. To account for multiple comparisons, we used Bonferroni corrections.

RESULTS

Hemodynamic Changes After Brain Death Induction

All animals experienced the classic hemodynamic changes associated with the sympathetic storm produced by acute experimental brain death.[5,6,9] The changes in pulse, blood pressure, and coronary flow during the 60 minutes after beginning induction of brain death are depicted in Figure 1. The figure depicts all 3 peaked at the BD + 3.5 time point and stabilized by the BD + 15 time point. Between the BD + 15 and BD + 60 time points, the maximum difference between the mean for an individual time point and the mean for the pooled data was 2% for the pulse and 6% for both the mean arterial blood pressure and the LAD flow. Because we did not consider the magnitude of these observed differ-

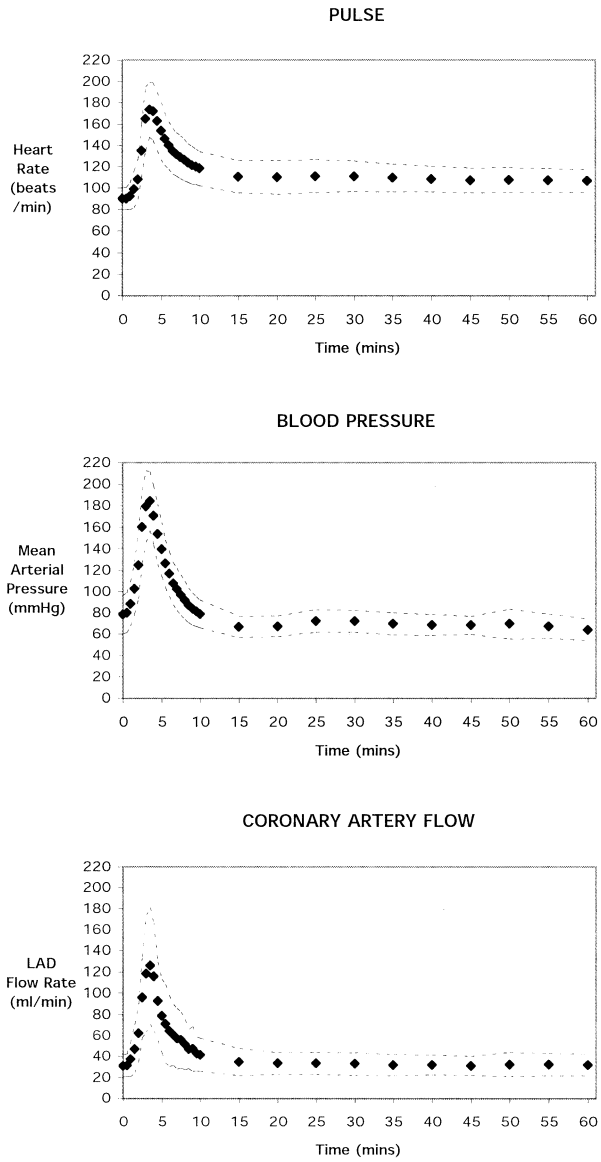

FIGURE 1 Hemodynamic changes after induction of brain death. Changes in pulse, blood pressure, and coronary artery flow rate during the 60 minutes after beginning intracranial balloon inflation are depicted. The values represent the mean ± the standard deviation of observations made at each time point for the 38 instrumented hearts. LAD, left anterior descending artery.

ences to be significance, we did not subject them to statistical comparison. Rather, we made comparisons among the BD + 0 time point data, the BD + 3.5 time point data, and the pooled data from all time points from BD + 15 to BD + 60, inclusive.

The baseline values for pulse, mean arterial blood pressure, and LAD flow were 90 ± 10 beats/min, 78 ± 18 mm Hg, and 31 ± 11 ml/min. At their peak, these had increased by 92%, 135%, and 309%, respectively, to 173 ± 26 beats/min, 184 ± 27 mm Hg, and 126 ± 55 ml/min (all $p < 0.001$). All 3 decreased from the peak to the post–brain death steady state levels of 109 ± 12 beats/min, 69 ± 9 mm Hg, and 33 ± 10 ml/min (all $p < 0.001$). Comparing the post–brain death steady state values to the baseline values, the pulse increased significantly (by 21%, $p < 0.001$), whereas the mean arterial pressure decreased significantly (by 12%, $p = 0.001$). The 6% increase in the LAD flow did not achieve statistical significance ($p = 0.170$).

TABLE I Preload recruitable stroke work (PRSW) relationship

Time point	Slope	y-axis intercept	x-axis intercept	SWI
BD + 0	3.34 ± 0.03	−2.32 ± 0.02	0.70	1.02
BD + 15	2.99 ± 0.04	−2.18 ± 0.03	0.73	0.81
BD + 30	3.51 ± 0.04	−2.44 ± 0.03	0.70	1.07
BD + 45	3.44 ± 0.03	−2.36 ± 0.03	0.69	1.08
BD + 60	3.38 ± 0.04	−2.30 ± 0.03	0.68	1.08

y = normalized stroke work, x = normalized epicardial end-diastolic volume. Regression coefficients (slope and y-axis intercept) were obtained from Equation 1 and are reported as the mean ± standard error. Regression estimates (x-axis intercept and SWI) are calculated from the mean regression coefficients. BD, brain death; SWI, stroke work index.

Pressure-volume Loop Analysis

Table I presents the coefficients for the mean PRSW regression equations at each time point and presents the corresponding regression estimates. Figure 2 depicts representative pressure-volume loops and the derived PRSW relationships.

In summary, the PRSW relationship at BD + 15 shifted to the right of the PRSW relationship at BD + 0 because of a decrease in slope and a rightward shift in the estimated volume-axis intercept ($p < 0.0001$). The combined effect was a 21% decrease in the SWI. At BD + 30, the rightward shift in the PRSW relationship volume-axis intercept had fully recovered, and the slope was greater than at BD + 0, resulting in a 5% increase in the SWI above baseline. This represented a significant leftward shift in the PRSW relationship between BD + 15 and BD + 30 ($p < 0.0001$) and a non-significant leftward shift in the PRSW relationship between BD + 0 and BD + 30.

At each subsequent time point, the volume-axis intercept of the PRSW relationship shifted further

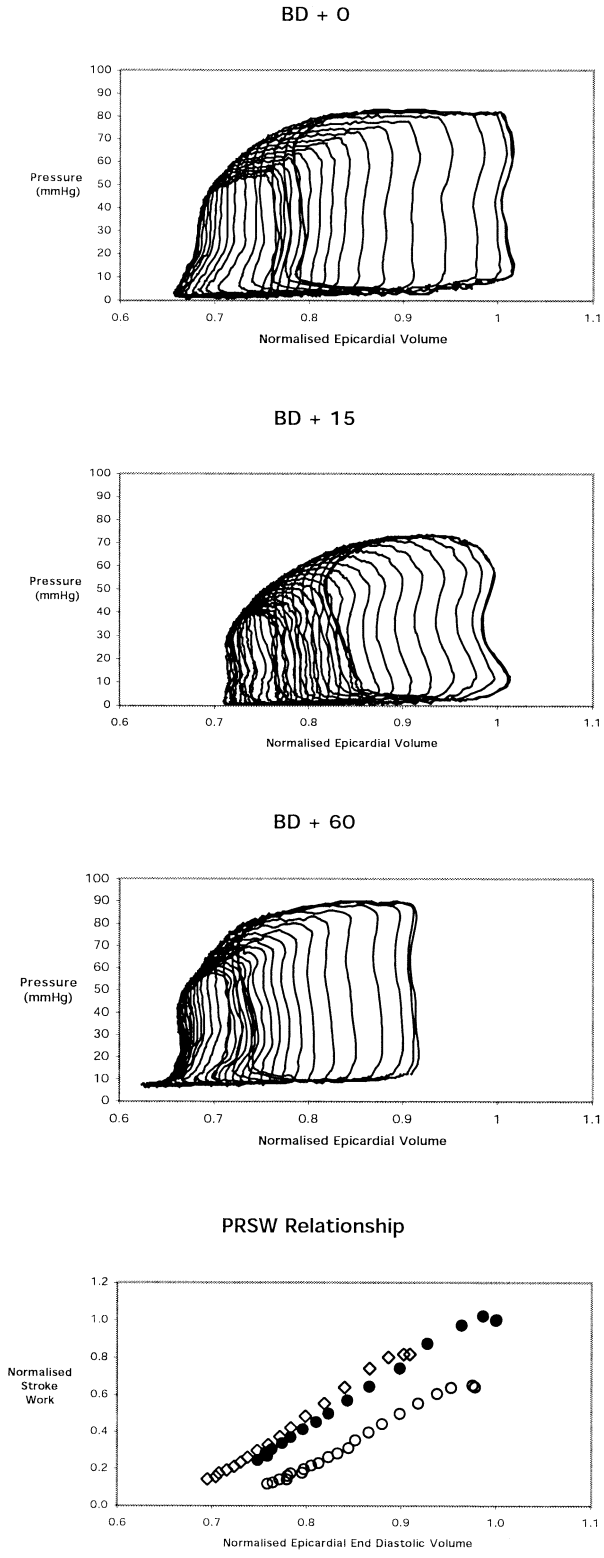

FIGURE 2 Left ventricular pressure-volume loops and the preload recruitable stroke work (PRSW) relationship. PRSW relationships for the same heart, and the pressure-volume loops from which they were derived, are depicted before (closed circles), 15 minutes (open circles), and 60 minutes (open diamonds) after beginning balloon inflation. Data obtained during transient occlusion of the inferior vena cava. Stroke work and volume are normalized to the baseline steady state stroke work and end-diastolic volume.

to the left. This was partially offset by decreases in slope, such that SWI increased by only 1% between BD + 30 and BD + 45 and did not change between BD + 45 and BD + 60. Overall, however, the successive leftward shifts in the PRSW relationship at each time point were statistically significant (BD + 30 vs BD + 45, $p < 0.0001$; BD + 45 vs BD + 60, $p = 0.0018$). The PRSW relationships at both BD + 45 and BD + 60 were significantly to the left of the PRSW relationship at BD + 0 (both $p < 0.0001$).

Troponin I Release

In the 38 instrumented animals, the mean pre–brain death plasma troponin I level was 1.4 ± 1.6 μg/liter. Post–brain death, the mean plasma troponin I level had increased significantly to 2.8 ± 2.3 μg/liter at BD + 60 ($p < 0.001$). In every instrumented animal, we detected troponin I at BD + 0 and BD + 60, and the level at BD + 60 was greater than at BD + 0. However, we could not detect troponin I in the plasma of either non-instrumented animal, before or after induction of brain death ($p = 0.001$).

DISCUSSION

Reversible Contractile Dysfunction

The PRSW relationship is a load-insensitive index of myocardial contractility.[10] Under normal physiologic conditions, the volume-axis intercept of the PRSW relationship is inherently stable.[10,11] However, ischemia causes a decrease in slope and a rightward shift in the volume-axis intercept (creep phenomenon).[12,13] Therefore, observed changes at the BD + 15 time point in the current study are highly suggestive of ischemic dysfunction. We conclude that oxygen demand during the sympathetic storm exceeded oxygen delivery. This supports results of myocardial microdialysis studies, which demonstrate acute increases in both adenosine and lactate.[5,7]

Some of the recovery in the PRSW relationship between BD + 15 and BD + 30 may be attributed to terminating anesthesia.[14] However, the sequential leftward shifts at each time point after BD + 15 supports the notion that the acute dysfunction observed at BD + 15 is reversible. The time course of functional recovery in the current study was consis-

tent with the reported time course of normalization of myocardial adenosine and lactate levels.[5,7]

The recovery in contractile function also suggests that the previously reported deterioration in contractility late after experimental induction of brain death[9] may be caused by separate processes. Indeed, Szabo et al[15] have proposed recently that the late changes merely reflect left ventricular adaptation to the altered state of the systemic circulation, through intact ventriculo-arterial coupling. They demonstrated that contractility was preserved in hearts subjected to the sympathetic storm of brain death and then cross-circulated against an intact animal's circulation for 4 hours.

Important differences exist between the sympathetic storm induced by experimental models such as that of the current study and that observed in clinical practice. The hemodynamic changes are greater but resolve more quickly with rapid intracranial balloon inflation.[16] In the clinical setting, the potential for oxygen demand to exceed oxygen delivery still exists, and the protracted time course may, in fact, lead to a greater net deficit. This is particularly so if inotropic infusions are used to produce systemic hypertension in an effort to maintain cerebral perfusion pressure before the diagnosis of brain death or if they are used to maintain normal systemic blood pressure after the diagnosis of brain death. Thus the time to recovery may be longer in the clinical setting.

Implications for Donor Management

The current study demonstrates that the sympathetic storm does cause functionally significant myocardial ischemia. It is yet to be determined whether this period of ischemia or the subsequent exposure to high circulating levels of catecholamines contributes to the cellular events associated with brain death that are known to adversely affect graft outcome. These include triggering of apoptotic pathways[17,18] and immune activation.[17,19] Differentiating between these 2 possible causes would aid in developing interventional pharmacologic strategies to ameliorate the affects of brain death before explant.

Implications for Myocardial Preservation Strategies

The inherent logistics of cadaveric organ donation subject the donor heart to a period of extracorporeal hypothermic ischemic preservation. Conventional storage solutions provide only limited protection against ischemia–reperfusion injury and consequent early graft dysfunction. One-year mortality increases with each hour of ischemic preservation. The observations of the current study have important implications for 2 new myocardial preservation strategies currently undergoing experimental evaluation: sodium–hydrogen exchanger (NHE) inhibition[20] and pharmacologic pre-conditioning.[21]

Activation of the type I sodium–hydrogen exchanger (NHE1) on the myocyte sarcolemmal membrane is a critical step in the sequence of events that leads to calcium accumulation during ischemia and reperfusion. As NHE expression is increased by intracellular acidosis,[22] the transient ischemia associated with the sympathetic storm may result in increased NHE expression in the lead-up to the critical period of prolonged ischemia. This would increase the potential benefit of NHE inhibition by agents such as cariporide and eniporide.

Conversely, the period of transient ischemia may provide a degree of beneficial ischemic pre-conditioning for the heart. However, this would minimize the potential benefit to be gained from the use of pharmacologic pre-conditioning agents, such as the adenosine triphosphate–sensitive potassium-channel openers diazoxide and pinacidil. Indeed, experimental evidence from Farhat et al[6] suggest that acute brain death and simulation of acute brain death with bolus norepinephrine injection abolish the benefits of ischemic pre-conditioning and pharmacologic pre-conditioning.

Implications for Interpreting Troponin I Levels in Potential Donors

We attribute the plasma troponin I level at BD + 0 in the instrumented animals to the surgical trauma associated with cardiac instrumentation. We initially attributed the rapid increase in plasma troponin I between BD + 0 and BD + 60 to a combination of myocardial injury caused by the sympathetic storm and to ongoing release from the surgically traumatized myocardium. Chiari et al[23] support this interpretation; they used similar instrumentation to that of the current study in 2 groups of pigs, 1 of which they subsequently rendered brain dead by inflating a sub-dural balloon. In both of their groups, troponin I levels increased after instrumentation and continued to increase during the 3-hours they were observed. However, the increase was greater in the group subjected to acute brain death.

The absence of detectable troponin I in the plasma of either non-instrumented animal casts doubt on the above interpretation. An alternative explanation for the observations in the current study and the study by Chiari et al[23] is that the dramatic hemodynamic changes accompanying brain death alter the time course of troponin I release from

injured myocardium rather than inflict myocardial injury that results in troponin I release.

This has important implications for assessing potential organ donors because several clinical studies have reported that donor troponin levels predict cardiac dysfunction in both the donor before explant[24–26] and in the recipient after transplantation.[24] Variations in the time course of troponin release and the effect of this variability on absolute values adds an extra degree of complexity to the interpretation of troponin levels in potential donors. Rejection of potential donor hearts on the basis of increased troponin alone cannot be justified. Low-dose dobutamine stress echocardiography may be useful for obtaining corroborative evidence of significant myocardial injury.[26]

CONCLUSIONS

This study, in a porcine model of acute brain death secondary to increased intracranial pressure, demonstrates clearly that the sympathetic storm causes transient contractile dysfunction. The observed simultaneous rightward shift in the volume-axis intercept and the decrease in the slope of the PRSW relationship immediately after the sympathetic storm were consistent with underlying ischemic injury. The reversible nature of this contractile dysfunction and the absence of troponin I release from non-instrumented hearts suggests that it is unlikely that this period of ischemia would lead to cell necrosis.

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