Right ventricular function after brain death: Response to an increased afterload

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Abstract

Objective: A major cause of early postoperative morbidity and mortality after cardiac transplantation is right ventricular (RV) failure which is attributed to the inability of the donor’s RV to acutely compensate for the recipient’s elevated pulmonary vascular resistance. This study was performed to determine: (1) the acute effects of brain death on the RV function; and (2) the adaptation potential of the RV to a progressive increase in RV afterload.

Methods: In 13 anesthetized, open-chest dogs (eight with brain death vs. five control with sham operation), brain death was induced by inflation of a subdural balloon catheter. Heart rate, RV systolic and end-diastolic pressure (RVSP, RVEDP), pulmonary arterial pressure (PAP), and cardiac output (CO), and pressure-length loops (sonomicrometry) were recorded. Afterload increase was induced 2 h after brain death induction by constriction of the pulmonary artery with an increase in RVP from 25 to 50 mmHg in 5 mmHg steps.

Results: Cushing phenomenon occurred within a few minutes after brain death induction, with a significant increase of HR (229 ± 10 vs. 89 ± 6 min⁻¹, P < 0.001), CO (3.2 ± 0.2 vs. 1.7 ± 0.1 l/min, P < 0.001), PAP (30.4 ± 2.5 vs. 15.5 ± 1.3 mmHg, P < 0.01), RVSP (55 ± 5 vs. 23 ± 2 mmHg, P < 0.001) and RVEDP (7.4 ± 0.9 vs. 3.3 ± 0.6 mmHg, P < 0.001). All these values were also significantly (P < 0.01) higher than the time corresponding values of the control group. The analysis of the pressure-length loops showed a hypercontractile state. Within 15–60 min, all parameters turned to baseline and remained stable for up to 2 h. When afterload was increased progressively, RVEDP increased markedly in the brain death and slightly in the control group (9.4 ± 0.7 vs. 4.2 ± 1.1 mmHg, P < 0.01, at RVSP = 50 mmHg). On the other hand, the increase of peak positive dP/dt was significantly higher in the control group (430 ± 37 vs. 644 ± 55 mmHg/s, P < 0.01, at RVP = 50 mmHg). However, global RV pump function characterized by CO and stroke work was similar in both groups. While regional RV contractility remained unchanged in the brain death group in terms of pressure–length relationships, RV contractility significantly increased in the control group.

Conclusion: (1) Brain death per se does not result in an acute impairment of RV function. (2) While control animals adapt to an increased afterload by the homeometric, as well as the heterometric regulation, after brain death, an increase in RV preload follows elevations in RV afterload by the Frank-Starling mechanism subserving the increased stroke work required to ensure unchanged pump function. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Brain death; Right ventricle; Contractility; Regulation; Frank-Starling mechanism; Transplantation

1. Introduction

Orthotopic heart transplantation in patients with congestive heart failure and severe pulmonary arterial hypertension can result in acute perioperative right ventricular failure of the allograft and subsequent...
death. The normal donor right ventricle, when abruptly presented with the high-resistance pulmonary vasculature of the recipient’s lungs, initially dilates in an attempt to maintain pulmonary blood flow and left atrial filling [1]. If the pulmonary hypertension is severe, the right ventricle (RV) may become hypococontractile, resulting in a low cardiac output state. However, recent studies suggest that not pulmonary hypertension per se but pre-existent myocardial damage [2–4], as a result of studies suggest that not pulmonary hypertension per se resulting in a low cardiac output state. However, recent studies suggest that not pulmonary hypertension per se resulting in a low cardiac output state. However, recent the right ventricle (RV) may become hypococontractile, atrial filling [1]. If the pulmonary hypertension is severe, attempt to maintain pulmonary blood flow and left the right ventricle (RV) may become hypococontractile, atrial filling [1]. If the pulmonary hypertension is severe, attempt to maintain pulmonary blood flow and left the right ventricle (RV) may become hypococontractile, atrial filling [1]. If the pulmonary hypertension is severe, attempt to maintain pulmonary blood flow and left the right ventricle (RV) may become hypococontractile, atrial filling [1]. If the pulmonary hypertension is severe, attempt to maintain pulmonary blood flow and left the right ventricle (RV) may become hypococontractile, atrial filling [1]. If the pulmonary hypertension is severe, attempt to maintain pulmonary blood flow and left the right ventricle (RV) may become hypococontractile, atrial filling [1]. If the pulmonary hypertension is severe, attempt to maintain pulmonary blood flow and left pulmonary vascular resistance may also play a role in cardiac dysfunction.

2. Material and methods

2.1. Animals

A total of 13 beagle dogs, weighing 14–17 kg, were used in this experiment. All animals received humane care in compliance with the ‘Principles of Laboratory Animal Care’ formulated by the National Society for Medical Research and the ‘Guide for the Care and Use of Laboratory Animals’ prepared by the Institute of Laboratory Animal Resources and published by the National Institutes of Health (NIH Publication No. 86-23, revised 1985).

2.2. Brain death model

Experimental brain death was produced by creating intracranial hypertension. A Foley catheter was introduced into the subdural space through a parietal burr hole in the skull. A rapid injection of 15 ml of saline inflated the balloon of the catheter, which produced an acute increase in intracranial pressure. Brain death occurred within a few minutes in all animals and cerebellar herniation caused interruption of neurological pathways between the midbrain and the spinal chord.

2.3. Preparation

The dogs were anaesthetized with an intravenous bolus of pentobarbital (Nembutal-Abbott, 12 mg/kg), paralyzed with pancuronium bromide (Pancuronium-Organon 0.1 mg/kg as a bolus and then 4 µg/kg per min) and endotracheally intubated. The level of anesthesia was maintained with morphine intravenously (Dipidolor-Janssen 1 mg/kg as a bolus and then 15 µg/kg per min). After lateral thoracotomy in the 4th intercostal space, the pericardium was incised.

Cannulas were inserted to monitor pulmonary arterial pressure (PAP), right ventricular peak systolic pressure (RVSP) and its first derivative (dP/dt), right ventricular end-diastolic pressure (RVEDP), right atrial pressure (RAP) and left ventricular pressure (LVP). Blood pressures were recorded by Gould pressure transducers which were connected to an analog strip chart recorder (Astromed). Cardiac output (CO) was measured by an electromagnetic flow probe on the ascending aorta. Stroke volume (SV) was estimated from the integrated flow signals. Ultrasonic crystal transducers were implanted subendocardially parallel to the minor axis in the anterolateral wall of the right ventricle to assess segment length shortening. This pair of crystals provide a segment length along the right ventricle’s principal directions of shortening [5]. The outputs from the ultrasonic and RV pressure transducers were plotted continuously and simultaneously as an X–Y plot on a memory oscilloscope to obtain a pressure-length loop for the myocardial segment. All these data were recorded on a magnetic tape for subsequent computer analysis.

RV stroke work was calculated as

\[
SW = SV(RVSP - RVEDP)
\]

RV segmental work was calculated as

\[
W = \frac{1}{2} L (dP/dT) dT
\]
Experimental protocol

2.4. Where hormonal substances were used.

logic norms. Intravenous crystalloid solution was ad-
mixed in the patients to determine the levels of the circulating cate-
cholamines epinephrine (EPI) and norepinephrine (NOR). Arterial blood gases and serum electrolytes were measured and, if necessary, corrected to physio-
lógic segment length.

where EDL and ESL denote end-diastolic and end-sys-
tolic segment length.

Arterial blood samples were taken at regular intervals to determine the levels of the circulating cate-
cholamines epinephrine (EPI) and norepinephrine (NOR). Arterial blood gases and serum electrolytes were measured and, if necessary, corrected to physiologic norms. Intravenous crystalloid solution was admin-
istrated to maintain the fluid balance. Nopressor or hormonal substances were used.

2.4. Experimental protocol

After surgical preparation and instrumentation, steady state baseline (baseline 1) data were recorded and blood samples were taken. Then, in eight dogs, brain death was induced. The other sham-operated five dogs served as controls without brain death induction. Pressure, flow and dimension data were registered on line for 2 h, blood samples were collected at 1, 5, 60 and 120 min after brain death induction. In the control group, a sham-operation was performed and the same protocol was utilized.

To examine the adaptation potential of RV to after-
load increase, the pulmonary artery was constricted by tightening a snare around the pulmonary artery 3–4 cm distal to the RV outflow tract. An increase in RV pressure from 25 to 50 mmHg was achieved by progres-
sive constriction of the pulmonary artery. Measure-
ments were taken at all levels directly after pulmonary banding (PB) and in steady state (10, 20, 30 min after PB). After the last PB level (RVP = 50 mmHg) the snare was loosened and the dogs were then allowed to return to baseline steady state. The recorded values 2 h after brain death induction served as control (baseline 2) to this series. In the control group, the same proce-
dure was performed. Collection of arterial blood samples was performed during each step of PB.

2.5. Statistics

Data were compared over time by a paired t-test. Intergroup statistical analysis was performed with one-
way analysis of variance. All results are expressed as the mean ± S.E.M. A probability value less then 0.05 was considered significant.

3. Results

3.1. Effect of brain death on hemodynamics, right ventricular function and catecholamine release

The baseline measurements were not significantly different in the two groups (Table 1). The heart rate (HR), right and left ventricular, as well as mean pul-
monary arterial pressures and CO for both groups were within the normal range for dogs. In the control group, all parameters remained unchanged during the next 2 h until the beginning of the second protocol.

Brain death induction resulted in the well-known Cushing type reaction with hypertension and tachycar-
dia for a period of 10–20 min. HR (157 ± 12%, P <
0.001), CO (88 ± 9%, P < 0.001), RVSP (137 ± 10%, P < 0.001), peak positive dP/dt (366 ± 17, P < 0.001), RVEDP (125 ± 11%, P < 0.05), PAP (96 ± 9%, P < 0.001) and SS (39 ± 8%, P < 0.05) increased significantly and reached their maximum between 3 and 5 min. All these values were also significantly (P < 0.01) higher than the time corresponding values of the control group. Pulmonary vascular resistance showed only an increasing tendency without reaching the level of significance (28 ± 8%, n.s.). Representative pressure–length (P–L) loops (Fig. 1) are illustrated at baseline, 5 and 120 min after induction of brain death. During the hyperdynamic response, the loops and the end-systolic pressure–length relation showed a significant leftward shift indicating a hypercontractile state of the right ventricle. At 120 min, the pressure–length loops were nearly identical to baseline.

Thereafter, all recorded parameters decreased between 15 and 60 min and were close to baseline values at 60 min. Heart rate showed a slower decrease and reached baseline at 120 min after brain death induction. There was no significant difference between the groups at this time.

Baseline catecholamine levels were similar in both groups. In the control group they remained unchanged during the following 2 h. In the brain death group, 1–2 min after balloon inflation, a ~100-fold increase in the circulating catecholamine levels was noted. These high levels began to decrease after 5 min and were almost equal to baseline values after 120 min (Table 2).

3.2. The adaptation potential of the right ventricle

The values after 120 min served as baseline (baseline 2) for the second protocol. As shown in Tables 1 and 2, none of the parameters were different in the groups, and there was no difference between baseline 1 and baseline 2. RVSP was 21 ± 3 mmHg in the control group and 22 ± 2 in the brain death group (P = n.s., respectively. These pressure values were denoted as ‘RVSP = 20 mmHg’. The stepwise constriction of the pulmonary artery led to an increase of RVSP in 5 mmHg increments up to ‘RVSP = 50’ mmHg. The respective values of RVESP were 26 ± 1, 29 ± 1, 35 ± 1, 40 ± 1, 48 ± 2 and 54 ± 1 mmHg in the control group and 26 ± 1, 31 ± 1, 35 ± 1, 41 ± 1, 46 ± 1 and 51 ± 1 mmHg in the brain death group. HR, LVP, CO and PAP measured distally from the banding of the pulmonary artery, pulmonary vascular resistance and SS showed no significant changes during the progressive constriction of the pulmonary artery. Only a slight increasing tendency of HR from 87 ± 6 to 104 ± 7 beats/min in the control group could be observed.

The increase of RVSP led to a characteristic significantly higher increase of RVEDP in the brain death group in comparison to control (Fig. 2, right panel). RVEDP was significantly higher at RVSP = 30 mmHg in the brain death group and only at RVSP = 50 mmHg in the control group in comparison to baseline. There was a significant difference between the groups at RVSP = 30–50 mmHg. RAP (7.21 ± 0.79 vs. 4.57 ± 0.71 mmHg, P < 0.05 at RVSP = 50 mmHg) showed similar changes as RVEDP. The left panel of Fig. 2 depicts the changes of peak positive dP/dt. In the control group, peak positive dP/dt increased progressively parallel to the increase of RVSP reaching the level of significance at RVSP = 30 mmHg. In contrast, the brain death group showed only a slight increase of dP/dt, which however, did not reach the level of significance even at RVSP = 50 mmHg. Fig. 3 shows global cardiac function as plot of SW vs. RVEDP. Each point represents a steady state coordinate of one RVSP level from RVSP = 20–50 mmHg. The rightward shift of the coordinates in the brain death group in comparison to control indicates lower contractility. This plot clearly

Table 2
Catecholamine concentrations after brain death

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>5 min after BD</th>
<th>60 min after BD</th>
<th>120 min after BD</th>
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<tbody>
<tr>
<td></td>
<td>Control</td>
<td>BD</td>
<td>Control</td>
<td>BD</td>
</tr>
<tr>
<td>EPI (nmol/ml)</td>
<td>0.54 ± 0.06</td>
<td>0.59 ± 0.06</td>
<td>0.52 ± 0.05</td>
<td>51.3 ± 12.4**</td>
</tr>
<tr>
<td>NOR (nmol/ml)</td>
<td>0.68 ± 0.07</td>
<td>0.57 ± 0.06</td>
<td>0.62 ± 0.06</td>
<td>78.2 ± 14.1**</td>
</tr>
</tbody>
</table>

EPI, epinephrine; NOR, norepinephrine.

Values are means ± S.E.M.

* P < 0.05; ** P < 0.001 vs. baseline; † P < 0.05; ‡ P < 0.001 brain death (BD) vs. control.
Fig. 2. Effects of increased right ventricular afterload on right ventricular peak positive dP/dt (left panel) and end-diastolic pressure (RVEDP) (right panel). All values are given as mean ± S.E.M. * \( P < 0.05 \) vs. baseline (RVSP = 20 mmHg). † \( P < 0.05 \) brain death vs. control.

Fig. 3. Effects of increased right ventricular afterload on global cardiac function. Right ventricular stroke work (SW) is plotted against end-diastolic pressure (RVEDP). Significantly higher increase of right ventricular preload follows elevations in RV afterload in the brain death (■, solid line) group in comparison to the controls (○, dotted line). Steeper increase of the SW-RVEDP relation in the control group indicates a higher contractile state than in the brain death group.

Fig. 4. Representative right ventricular pressure–segment length loops in control (left panel) and in a brain death (right panel) animals. In the brain death group, the loops were enlarged in height and width and shifted markedly to the right. In the control group, by the increase of right ventricular pressure, the width of the loops remained relatively unchanged with a slight shift to the right. L, segment length; P, right ventricular pressure.
show a characteristic difference between the groups. A steeper increase of the regional SW–EDL relationship indicates higher contractility in the control group in comparison to brain death. A linear correlation could be fitted on the steady state coordinates of the brain death group \((y = 341x + 128, r = 0.99, \text{S.D.} = 15.01; P = 0.000001)\), while in the control group the increase of the coordinates could be characterized by a second order polynomial regression \((y = 3440x^2 - 5467x + 2555, r = 0.99, \text{S.D.} = 22.25, P = 0.000001)\).

In the brain death group, a decreasing tendency of the concentration of catecholamines in plasma could be observed throughout the pulmonary banding protocol, however they did not reach the level of significance. In the control group, catecholamine concentrations showed no significant changes (data are not shown).

After the last pulmonary banding level (RVSP = 50 mmHg), the snare was loosened and the dogs were then allowed to return to baseline steady state. No differences were found between the groups and the values after 2 h of brain death induction.

4. Discussion

4.1. Acute effects of brain death on the right ventricular function

The present study showed that under carefully standardized conditions in anaesthetized dogs, brain death leads to a reproducible hyperdynamic response. The response of the right ventricle is similar as described previously for the left ventricle. Numerous experimental studies \([2–10]\) described that acutely elevated intracranial pressure, and subsequent brain death cause a marked increase in cardiac output and arterial pressure usually associated with tachycardia and left ventricular hypercontractility. All these responses are indicative of a generalized sympathetic nervous discharge \([11–13]\). In our study, an \(\approx 100\)-fold increase of plasma catecholamines could be observed. Great number of studies \([2,5,7,8,14]\) using experimental models of brain death also reported tremendous increases in the catecholamine levels. Many investigators found a close correlation between the hemodynamic and neuro-hormonal changes during the acute phase\([2,5,10,14]\).

In the present study, similar changes can be observed in the right ventricle as those already described for the left ventricle. Brain death leads acutely to an increase in right ventricular pump performance associated with a hypercontractile state. Elzinga et al. \([15]\) have shown in isolated ejection cat hearts, that the higher right ventricular mean pressure influences the performance of the right ventricle in a positive way. This can be due to an increased contractility or to an increased muscle fiber length in the free wall of right ventricle. The analysis of the \(P–L\) loops showed, that during the acute response after brain death, the right ventricle reaches a significantly higher contractile state causing an increase in pump function. This could be explained by the acute sympathetic activation in accordance with the higher catecholamine concentrations in plasma. Only sporadic studies \([16,17]\) describe the acute effects of catecholamines on the function of the right heart. These showed an acute increase in the contractile performance and a subsequent increase in pump function after infusion of norepinephrine or epinephrine.

The pulmonary vasculature seems to be less influenced by the Cushing reaction as the systemic vasculature. Previous studies \([2–5]\) showed a significant increase of systemic vascular resistance during the acute phase. In the present and in our previous study \([5]\), pulmonary vascular resistance showed no significant changes. The influence of brain death on the pulmonary circulation is a point of controversial discussion. Most of the authors \([2–4,9,10,18,19]\) found elevated pulmonary artery pressure after brain death-induction. A reported \([2,18]\) sequence of events of marked rise in left ventricular filling pressures to exceed—for several
seconds during the acute phase—the level of pulmonary arterial pressure leading to the generation of pulmonary edema has not been observed in the present study. Similarly to the study of Brashear et al. [9], increased pulmonary arterial pressure could be explained rather with significantly increased CO then with changes of pulmonary vascular resistance. This is in contrast to changes of the systemic circulation in which a significant increase in systemic vascular resistance could be observe after brain death [2,5,10].

There are only few data about the changes of right ventricular function and pulmonary circulation after the acute phase. In the studies of Bittner et al. [3,4,19], mean pulmonary arterial pressure remained stable up to 4 h and showed an increase after 6 h. RVEDP and pulmonary flow were also constant during the first 4 h and increased only parallel to mean pulmonary arterial pressure. However, at the same time, pulmonary vascular resistance became significantly lower in their study. In the present study, no significant changes of the pulmonary circulation were observed during the first 2 h after brain death induction which is in agreement with other studies [3,4,19]. In a previous study [5], we showed that pulmonary hemodynamics remains stable even up to 5 h. After the acute phase, right ventricular pump performance showed no significant changes during the first 2 h if it was characterized by RVSP, SW and CO. The analysis of the P–L loops and peak positive dP/dt taking account its load-dependency, suggest that not only global performance but also myocardial contractility remains unchanged in comparison to baseline. In the present study, the pulmonary banding protocol was finished at 4.5 h after brain death induction and the animals were evaluated in steady state. There were no differences between the groups and in comparison to baseline (baseline 1 and 2). These data directly contradict the findings of Bittner et al [3,4,19], where pump function was maintained at a decreased afterload and contractility. In their study, high output failure developed with an increase of cardiac output and filling pressure. However, it is not clear how far these changes 4–6 h after brain death induction are directly related to brain death or to the applied volume management. Wicomb et al. [20] tested the effects of different types of management on myocardial function after brain death in a cross-circulated heart preparation. They demonstrated that volume loading and inotropic support in the brain dead organ donor increase mean arterial pressure, but may be detrimental for myocardial function. In the study of Mertes et al. [21], volume loading led also to an impairment of cardiac function. Under these aspects, decreased right ventricular contractility in the study of Bittner et al. [3,4,19] may rather reflect the management of the donor animal than brain death itself.

4.2. Adaptation potential of the right ventricle

While the RV function after brain death during increased afterload has not been studied yet, numerous experimental and clinical investigations characterized the behavior of the normal right heart under different loading conditions.

Several investigators have previously studied the hemodynamic response to a comparable acute increase in pulmonary arterial pressure or right ventricular systolic pressure [22–28]. The results of these studies are partially controversial. In a few of these studies, a different degree of RV failure developed. Some of the differences in hemodynamic response to similar increases in RV afterload may in part be due to an unphysiologically elevated baseline sympathetic tone, as reflected by marked elevated baseline HR or blood pressure [26,27]. This might have reduced the adaptation reserve to a further increase in sympathetic tone necessary to compensate for a progressive pulmonary artery constriction [29]. Additionally, a relative hypervolemic state might also have influenced the development of RV failure [26].

In the control group of our study (animals with sham operation without brain death), similar to other experimental and clinical studies [22,23,28,30], the increase of RV afterload did not result in an impairment of the RV function, but to an increase in pump performance. The analysis of the P–L loops as well as the regional and global cardiac function curves showed a higher contractile performance and a complex adaptation process (Fig. 6). The compensatory mechanisms maintaining RV performance during increased afterload are homeometric autoregulation with augmentation of contractility and the Frank–Starling mechanism through increased myocardial stretch. The response of the sympathetic nervous system in this regulatory process can be characterized by the increasing tendency of heart rate in the control group. The increased sympathetic tone due to its positive inotropic effect may play a marked role in this kind of adaptation [23,29].

There was no evidence of any deterioration in the RV pump performance in the brain dead animals: SW increased in the similar way as in the control group and cardiac output remained stable. However, the increase in SW, which was comparable to the control group, was associated with a greater rise in RVEDP. The greater rise in RVEDP, with maintained pump performance compared to the control group, indicates the utilization of the Frank–Starling mechanism as a primary form of adaptation to increased afterload (Fig. 6). There are many possible explanations for the decreased ability of the right ventricle to adapt by inotropic mechanisms. First, brain death associated myocyte injury may play a role in the decreased contractile response. Many investigators [2,5] found histologic
damage such as focal myocytolysis or contraction bands in the left and the right ventricle of brain dead hearts. However, it was < 0.1% of the total ventricular mass [5], therefore it is very unlikely that myocardial damage is the major cause of the decreased contractile response. In a recent study [31], no correlation was found between myocardial histologic damage and cardiac function in a cat model of brain death. Furthermore, Bittner et al. [4] showed identical positive dopamine dose-contraction response relationships in normal and brain dead hearts after transplantation, indicating that brain death-injured hearts have a functional contractile reserve.

The findings of the present study may be explained by another mechanism: the loss of inotropic adaptation may be due to the denervated state of the heart. In the brain dead animal, the destruction of the central sympathetic pathways excludes the sympathetic regulation. The results of Rose et al. [23] using β-adrenergic blockade indicate that the β-adrenergic component of the sympathetic nervous system is important in the right ventricular response to afterload changes. Support for this could be found in the steeper rate of rise in the RVEDP with applied afterload during β-adrenergic blockade. The parallel increase of RVEDP with increased afterload after β-blockade was very similar to our observations in the brain death group. Abel et al. [22] showed similar changes after surgical denervation of the heart.

The changes of coronary perfusion pressure may also play a role in the impairment of contractile response to increased afterload. In contrast to pulmonary vascular resistance which remained stable after brain death, systemic vascular resistance decreases significantly resulting in lower aortic, mainly diastolic aortic pressure and therefore, coronary perfusion pressure. Even if coronary autoregulation is satisfactory to cover energy demand to maintain baseline inotropic state, it may be exhausted earlier in the brain dead animals after right ventricular afterload increase, especially at higher elevations. In a preliminary study [6], we showed that coronary perfusion is a major determinant of donor myocardial function. A decrease of left ventricular contractility after brain death could be reversed by restoring coronary perfusion pressure and flow.

At least, it should be stressed, that independently from the possible mechanisms leading to a decreased ability of inotropic adaptation in the brain dead animal, the functional reserve of the right ventricle still remains sufficient to compensate for increased RV afterload by the Frank–Starling mechanism. Sibbald et al. [30] showed that under clinical conditions, the right ventricular pump function could be dissociated from RV contractile function. In patients with depressed right ventricular contractility (right ventricular contraction) or and severe pulmonary arterial hypertension, they achieved the maintenance of the right ventricular pump function by augmentation of right ventricular preload, thereby utilizing the Frank–Starling mechanism. However, extremely large right ventricular volumes and RVEDP can be associated with impaired right ventricular function due to right ventricular ischemia and septal bulging between the two ventricles [25,27,30]. Peak RVEDP > 10 mmHg have been described as a critical value in dogs in response to pressure overload [24,26]. In our study, no RVEDP higher than this value was occurred.

4.3. Limitations of the study

In the present study, no load-dependent indexes of contractility, such as the slope of the end-systolic pressure-volume/dimension relationship or preload recruitable stroke work were used, since a ‘Starling’ analysis in terms of rapid preload reduction (vena caval occlusion) was not performed for each state of the protocols. However, during the first 2 h after brain death pre- and afterload conditions remained stable, except the transient changes during the Cushing-type reaction and therefore, as indicated by peak positive dP/dt, the contractile state was probably similar in both groups after 120 min and there were no differences in contractility between baseline 1 and baseline 2. Dur-
ing right ventricular afterload elevation, preload and afterload vary, which may also have an effect on peak positive \( \frac{dP}{dt} \) independently from inotropic changes. At identical afterloads for each PB level, peak positive \( \frac{dP}{dt} \) showed a significant increase in the control group, while it remained unchanged in the brain death group. Even if we do not know exactly which amount of peak positive \( \frac{dP}{dt} \) change can be attributed to direct inotropic change and which one to afterload increase, the higher increase in the control group in comparison to brain death reflects higher contractile responses, since afterloads were equal for both groups. Taking into account its load sensitivity, an increase of peak positive \( \frac{dP}{dt} \) indicates a significant increase of contractility in the control group and probably, unchanged peak positive \( \frac{dP}{dt} \) reflect unchanged contractility in the brain death group.

The qualitative analysis of the steady state \( P-L \) loops [32] also indicates that afterload elevation leads to an adaptation primary by increased contractility in the control group and primary by the Frank–Starling mechanism in brain death animals. A mathematical assumption may also suggest indirectly that the right ventricular contractile performance remained unchanged in the brain death group. The \( P-L \) relationship as well as SW–end-diastolic length relationship were described as a linear relation and a slope of these relationships as a relatively load-independent index for right ventricular contractile performance [17,32–34]. A good correlation with linear regression by the segmental SW–end-diastolic length coordinates was observed in the brain death group. If the segmental SW–end-diastolic length relationship is assumed to be linear, than the steady state segmental SW–end-diastolic length coordinates of the brain death group may represent similar contractile states. On the other hand, the second order polynomial increase of the segmental SW–end-diastolic length relationship in the control group reflects an increase of right ventricular contractility (Fig. 5).

A further limitation of the present study may be the relatively short period of brain death. However, as discussed above, different management modalities may have a major influence on cardiac performance in the donor during longer observation periods. As we focused on direct brain death related changes of right ventricular performance, we chose a relatively short period of brain death to keep the influence of donor management at the minimum. Furthermore, major hemodynamic changes occur within the first 2 h after brain death in most of the studies [2–5], therefore longer observation periods would have little influence on the results of this study.

4.4. Concluding comments

In the present study, hyperdynamic reaction of the right ventricle and the pulmonary circulation occurred after brain death induction, similarly as previously described in left ventricular studies. After the acute phase, brain death itself acutely does not result in an impairment of baseline right ventricular pump performance and contractility. However, the ability of brain dead hearts to compensate for acute elevations in right ventricular afterload by positive inotropy is impaired in comparison to normal control hearts. In this experimental setting, right ventricular pump function and myocardial contractile performance dissociate in the brain dead animal: progressive increase in right ventricular afterload leads to the increase of RV work by the heterotopic regulation (increase of preload), while myocardial contractility do not increase. These findings may also have some relevance for clinical transplantation. First, even if baseline right ventricular function seem satisfactory in the donor, the adaptation to an acute elevation of afterload by inotropic mechanisms may be impaired. Second, under certain circumstances, the augmentation of preload may be useful for maintaining right ventricular pump performance by the Frank–Starling mechanism at increased afterloads. Further studies are necessary to clear the exact mechanisms leading to decreased inotropic adaptation (brain death related damage or denervated state of the heart) and to investigate the effects of additional injury by ischemia/reperfusion and transplantation procedure.

References

The early mortality rate for adult patients undergoing cardiac transplantation has remained unchanged between 9% and 10% for the last 5 years and 30–35% of these deaths occur through cardiac failure not related to infection or rejection. This heart failure may be related to the myocardial changes that occur after brain
death in the organ donor, inasmuch as brain death is known to be associated with donor organ dysfunction, cardiovascular deterioration, and metabolic and hormonal changes. A common clinical observation is that the brain dead organ donor requires substantial inotropes to stabilize cardiopulmonary function. Improvements in the management of the brain dead organ donor, graft preservation, and refinements in surgical transplantation techniques have allowed the utilization of hearts from previously ‘unacceptable donors’. A significant graft failure rate and marked morbidity and mortality following cardiac transplantation are caused by right ventricular failure, as a result of either a rise in pulmonary vascular resistance in the recipient or a loss of contractility in the donor heart. Since Novitzky’s introductory studies on donor brain death and cardiopulmonary function in 1984, multiple clinical and experimental investigations documented the deleterious impact of brain death on cardiac function with emphasis on left ventricular myocardium. However, the mechanisms by which brain death impacts on cardiac function, are not fully defined. Does the mechanical impact of severely increased afterload during the Cushing reflex and its associated sympathetic discharge cause ventricular distention associated with sarcomere elongation and myofibrils derangement? Alternatively, is the functional deterioration caused by cytokine release or other unknown cardiac depressant factors? Recently there has been a renewed interest in the investigation of the brain dead organ donor with focus on right ventricular function. Szabó et al. showed that baseline right ventricular function remained unchanged 2–4 h after the induction of experimental brain death, however the adaptation of the right ventricular myocardium to acutely elevated pulmonary vascular resistance was significantly diminished compared to control animals. These findings may have importance for clinical donor management. Similar results were described previously when brain dead donor hearts were acutely exposed to an increase of right ventricular afterload established by snaring the pulmonary artery and determining right ventricular power and pulmonary vascular impedance changes assessed by Fourier analysis [1]. In the past, the majority of investigations focused on the left ventricular functional changes associated with brain death. This is in part due to well described methods of assessment of left ventricular performance. Studies of right ventricular contractility and function are scarce.

Compared to the relative simplicity of left ventricular function assessment, right ventricular contractility measurements are very challenging and tedious and only a few methods are valid and reliable. For the same reason, it is noteworthy to say, that the findings of Szabó et al. can only be very carefully interpreted. Right ventricular contractility is very difficult to assess due to its difficult geometry, position changes of the interventricular septum, the impact on right ventricular dimensions by changes in left ventricular volume, and the poor correlation between regional segment changes and right ventricular volume. This is in particular the case when sonomicrometry with subendocardially placed crystals is used. They can shift during experiments leading to altered data analysis, and they require frequent epicardial echocardiographic evaluation to assess their position. The most reliable and validated method of analysis of the right ventricular myocardial contractile state and function and cavitary volume is the application of preload-independent recruitable stroke work relationship (PRSW) in combination with the ellipsoidal shell subtraction method. The relationship between stroke work and either end-diastolic segment length/dimension or chamber volume is a highly linear index of intrinsic myocardial contractility. Diastolic function and compliance and viscoelastic properties of the diastolic right ventricle can be measured during diastasis using the same experimental setting and stress–strain relationships [2]. A more valuable assessment of these brain dead donor hearts, however, could be obtained if the authors would go one step further and would evaluate cardiac function following graft preservation, cardiopulmonary bypass and cardiac transplantation. Our studies have shown impaired right ventricular function following brain death and transplantation into recipients with increased pulmonary vascular resistance and chronically induced pulmonary hypertension.

References
