Transplant International

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Brain death provokes very acute alteration in myocardial morphology detected by echocardiography: preventive effect of beta-blockers

René Ferrera,[1] Guylaine Hadour,[1] Fabienne Tamion,[2] Jean-Paul Henry,[2] Paul Mulder,[2] Vincent Richard,[2] Christian Thuillez,[2] Michel Ovize[1] and Geneviève Derumeaux[1]

1 Inserm, U886, Université de Lyon, Université Lyon 1, Lyon, France
2 Inserm U644, Université de Rouen, Rouen, France

Keywords
brain death, echocardiography, heart injury, β-blockade.

Correspondence
René Ferrera PhD, INSERM – U886, Faculté de médecine Lyon Nord, Laboratoire de Physiologie, 8, Avenue Rockefeller, 69373 Lyon Cedex 08, France. Tel.: +33-4-78-77-72-42; fax: +33-4-78-77-71-75; e-mail: rene.ferrera@recherche.univ-lyon1.fr

Received: 7 July 2010
Revision requested: 7 August 2010
Accepted: 7 October 2010
Published online: 16 November 2010

doi:10.1111/j.1432-2277.2010.01184.x

Summary

Our objective was to evaluate immediate acute changes in myocardial function during the autonomic storm of brain death (BD). Wistar rats were divided into four groups (n = 8/group): controls without any treatment, β-blocker (Esmolol®, 10 mg/kg), calcium channel blocker (Diltiazem®, 10 mg/kg), or alpha-blocker (Prazosin®, 0.3 mg/kg). Treatments were administered intravenously 5 min before BD induction. Echocardiography (ATL-5000, 8 MHz) was performed to measure left ventricular (LV) dimensions and fractional shortening at baseline, during BD induction and 5 min and 15 min after BD. In controls, BD was immediately associated with an increase in wall thickness and a decrease in LV cavity dimension. This myocardial wall hypertrophy was completely prevented by β-blockers, but not with calcium- and alpha-blockers. Extensive myocardial interstitial edema was found in all groups, except in the β-blocker group. Myocardial wall hypertrophy was also prevented during a longer follow-up of 180 min after BD in β-blocker group as opposed to controls. In conclusion, BD is associated with an immediate and severe myocardial damage related to an important interstitial edema which is prevented by β-blockers.

Introduction

During brain death (BD), the prevention of cardiac graft dysfunction related to the autonomic storm and the toxicity of catecholamine remains controversial [1–3]. Moreover, the extent of myocardial structural damage and the functional recovery of donor hearts obtained from BD donors differ according to the cause and modality of BD. Indeed, BD-induced damages are correlated with the increase in catecholamine release [4] and the rate of progression towards BD. Cardiac sympathectomy and beta-blockers infusion before BD induction have been shown to prevent myocardial injury in experimental BD models [5–7]. In addition, a clinical study has also recently demonstrated the cardioprotective effect of treatment of autonomic storm including beta-blockers [8]. However, none of these papers has clearly studied morphological changes occurring during the Cushing reflex and the acute impact of beta-blockade.

Thus, the goal of this study performed in a rat model of BD induced by an acute increase in intracranial pressure was (i) to describe by echocardiography the sequential changes in myocardial morphology and function occurring during the autonomic storm, (ii) to compare the potential protective effect of a pretreatment by beta-blockers, calcium inhibitor or alpha-blockers, during this initial phase of BD.

Methods

The investigation conformed to the Guide for the Care and Use of Laboratory Animals published by the US

National Institutes of Health (NIH Publication No. 85-23, revised 1996).

Anesthesia and surgery

Male Wistar rats (450–500 g) were anesthetized with an intraperitoneal injection of sodium pentobarbital (60 mg/kg) followed by inhaled isoflurane (2%) until BD induction. After tracheotomy, rats were mechanically ventilated, at a rate of 55/min and using a volume ventilation of 1 ml/min with oxygen-enriched air. Mechanical ventilation was adjusted by arterial blood gas measurements before BD induction. Systemic blood pressure was monitored with an indwelling catheter placed in the femoral artery. A right parietal craniotomy was performed and a balloon was introduced into the subdural space.

BD induction

Brain death was caused in order to induce an autonomic storm in all animals, as previously described [9]. A sudden rise in intracranial pressure was induced by an abrupt inflation of the intracranial balloon by injection of 300 μl of air. The balloon was kept inflated during the entire experiment. This method was shown to reliably stop all brain perfusion and electrical activity in the brain [9].

The model of BD induction used in this study mimics the acute trauma encountered during acute accident (frontal shock for instance) but the clinical situation are often different with a less acute process such as stroke or progressive swelling in the brain.

Protocols

Acute protocol

This protocol aimed to compare the acute effects on myocardial function and hemodynamics of three treatments that are able to prevent the hemodynamic consequences of the autonomic storm. Animals were randomly assigned to four groups: a control group without any treatment ($n = 8$), and the three groups treated by a beta-blocker (Esmolol®, Baxter, Paris, France; 10 mg/kg) (β-group) ($n = 8$), a calcium channel blocker (Diltiazem®, Teva Sante, Paris, France; 10 mg/kg) (Ca-group) ($n = 8$) and an alpha-blocker (Prazosin®, Pfizer, Paris, France; 0.3 mg/kg) (α-group) ($n = 8$) respectively. These treatments were administered by intravenous injection 5 min prior to BD induction. In order to obtain comparable hemodynamic data, the treatment doses were adjusted to obtain a 30% decrease in systolic blood pressure (SBP) from baseline values. Fifteen minutes after BD induction, the experiment was stopped and the heart was excised, weighed, and placed in Bouin fixative solution for light microscopic examination.

Chronic protocol

This protocol aimed to compare myocardial function during a longer follow-up of 180 min after BD induction in controls rats ($n = 7$) and beta-blocker (Esmolol®, 10 mg/kg) ($n = 6$).

Hemodynamics

The SBP and the heart rate (HR) were continuously monitored and were measured at baseline, 5 min prior to BD after treatment administration, during BD induction and 5 min and 15 min after BD in the acute and chronic protocols, and then every 15 min in the groups undergoing a 180-min follow-up after BD.

Echocardiography

Transthoracic Doppler echographic studies were performed in all animals before BD, during BD induction and 5 min and 15 min after BD in the acute and chronic protocols, and then every 15 min in the groups undergoing a 180-min follow-up after BD.

Transthoracic echocardiography was performed with a commercially available echocardiography system using an 8 MHz linear array transducer on a HDI 5000 (ATL System, Paris, France) as previously described [10]. M-mode measurements of wall thickness, left ventricular (LV) dimensions and subsequent LV fractional shortening were obtained from a short-axis view at the level of the papillary muscles. LV mass was calculated as follows: LV mass = $1.04\ [(\mathrm{LVd} + \mathrm{PWd} + \mathrm{IVSd})^3 - \mathrm{LVd}^3]$, where 1.04 is the specific gravity of muscle, LVd is LV end-diastolic diameter, and PWd and IVSd are end-diastolic posterior and anterior wall thicknesses.

Biologic parameters

Plasma levels of epinephrine and norepinephrine were measured 1 min after BD induction. Arterial plasma samples were immediately centrifugated (1300 *g*, at 4 °C for 10 min) and stored at −80 °C until measurement. Plasma levels of catecholamine were assessed using the Chromsystems kit for high-performance liquid chromatography analysis with electromechanical detection (Waters Company, Paris, France).

Cardiac histology

At the end of the experiment, the LV was cut perpendicular to the apex-to-base axis into three slices of equal

thickness, then dehydrated and embedded in paraffin. For each group, three to five specimens from the anterior myocardial wall were harvested for gross examination. Sections of 5 μ were cut and stained in Hemalum/Phloxine/Saffron for histologic examination. Examination was performed by two independent observers (GH and PM) to quantify the presence of myocardial interstitial edema.

Statistic analysis

We have indeed checked that data had normal distribution. ANOVA for repeated measures was used to determine significant changes within an experimental group. All variables are presented as mean ± SEM. A value of $P < 0.05$ was accepted as significant.

Results

Hemodynamics

Acute protocol

Hemodynamic parameters throughout the acute protocol are listed in Table 1. Immediately after BD, a dramatic increase in SBP and in HR occurred in the control group.

Table 1. Changes in the hemodynamic parameters after brain death induction.

	Systolic blood pressure (mmHg)	Heart rate (beats/min)
Baseline		
Control	137 ± 8	336 ± 22
β-group	145 ± 5	372 ± 10
Ca-group	137 ± 7	367 ± 18
α-group	124 ± 7	327 ± 20
Treatment		
Control	137 ± 8	336 ± 22
β-group	100 ± 7*	243 ± 8*
Ca-group	81 ± 9*	232 ± 24*
α-group	104 ± 8*	340 ± 31
Brain death induction		
Control	232 ± 10	440 ± 24
β-group	234 ± 6	290 ± 15*
Ca-group	165 ± 9*	304 ± 8*
α-group	170 ± 10*	374 ± 7*
5 min after brain death		
Control	139 ± 16	417 ± 29
β-group	158 ± 16	317 ± 18*
Ca-group	104 ± 15	310 ± 10*
α-group	96 ± 20	420 ± 11
15 min after brain death		
Control	101 ± 26	360 ± 21
β-group	99 ± 16	297 ± 17
Ca-group	77 ± 12	327 ± 19
α-group	73 ± 11	355 ± 30

*$P < 0.05$ versus control values at the same stage.

In all the treated groups, SBP significantly decreased in relation to controls 5 min after treatment administration and prior to the induction of BD ($P < 0.05$). During BD, the increase in SBP was blunted only in the groups treated by a calcium channel blocker or an α-blocker but not after β-blockade. Following BD, SBP progressively decreased in all groups without any significant difference among the groups.

Prior to the induction of BD, HR significantly decreased in the groups treated by the β-blocker or the calcium channel blocker ($P < 0.05$) but not in the α-blocker group. During induction of BD, the increase in HR was blunted mainly after β-blockade or calcium channel blockade. Following BD, HR values remained stable in β- and Ca-groups but tended to decrease in control and α-groups.

Chronic protocol

In the control group, SBP dramatically decreased from baseline values to 64 ± 12, 49 ± 5 and 36 ± 7 mmHg (60, 120 and 180 min after BD induction respectively). At 180 min after BD, HR decreased to 258 ± 45 beats/min.

In the β-blocker group, SBP did not significantly change from baseline values at 60, 120 and 180 min after BD induction (89 ± 16, 92 ± 14 and 85 ± 12 mmHg respectively) ($P < 0.05$ vs. controls). At 180 min after BD, HR decreased to 220 ± 35 beats/min (P = NS vs. controls).

Echocardiography

Acute protocol

In controls, BD was immediately associated with an abrupt increase in wall thickness and a decrease in LV cavity dimensions (Fig. 1, Table 2). This resulted in a significant increase in LV mass from 67 ± 5 at baseline to 94 ± 7 mg immediately after BD ($P < 0.01$ vs. baseline). LV fractional shortening also increased from 48 ± 5 at baseline to 73 ± 9% after BD induction (Fig. 2). These abnormalities remained stable during the 15 min after BD.

Treated groups differed in their morphological myocardial changes after BD. Whereas in Ca- and α-groups, myocardial wall thickness significantly increased, this sudden myocardial wall hypertrophy was completely prevented by β-blockers (Fig. 1, Table 2). LV end-diastolic diameter did not significantly change in β-group but significantly decreased in α-group and at a lesser extent in Ca-group (Table 2). This resulted in a significant increase in LV mass in both the Ca- and α-groups but not in the β-group. LV fractional shortening also significantly increased in Ca- and α-groups but not after β-blockers (Fig. 2).

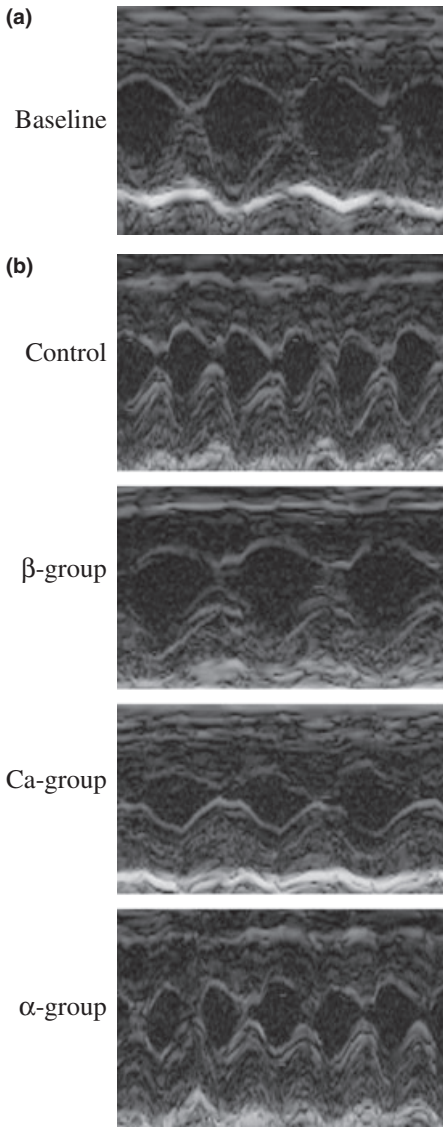

Figure 1 (a) Left ventricular M-mode tracings before brain death induction. (b) Left ventricular M-mode tracings after brain death induction in controls, β-, Ca- and α-groups. Whereas in controls, Ca- and α-groups, myocardial wall thickness significantly increased, this sudden myocardial wall hypertrophy was completely prevented in β-group.

Chronic protocol

In controls, BD was immediately associated with an abrupt increase in wall thickness and decrease in LV cavity dimensions that remained stable over the 180 min of follow-up. This resulted in a significant increase in LV mass from 53 ± 4 at baseline to 122 ± 9 mg immediately after BD ($P < 0.01$ vs. baseline) and 113 ± 4 mg at 180 min after BD ($P < 0.01$ vs. baseline; P = NS vs. 5 min after BD). LV fractional shortening also increased from 40 ± 4% at baseline to 54 ± 9% after BD induction ($P < 0.01$ vs. baseline) and then progressively decreased to baseline values at 180 min after BD.

Conversely, β-blockers prevented myocardial wall hypertrophy (58 ± 3 at baseline vs. 64 ± 4 mg immediately after BD vs. 59 ± 3 mg at 180 min after BD, P = NS vs. baseline) and demonstrated a stable LV fractional shortening over the 180 min of follow-up after BD induction (55 ± 3% at baseline vs. 61 ± 4% immediately after BD vs. 59 ± 3% at 180 min after BD, P = NS vs. baseline).

Table 2. Changes in the echocardiographic parameters after brain death induction.

	AWd (mm)	PWd (mm)	LVd (mm)
Baseline			
Control	1.7 ± 0.2	1.7 ± 0.1	6.2 ± 0.4
β-group	1.9 ± 0.1	1.8 ± 0.2	5.9 ± 0.5
Ca-group	1.9 ± 0.1	2.0 ± 0.1	5.9 ± 0.4
α-group	1.9 ± 0.2	1.9 ± 0.2	5.6 ± 0.2
Treatment			
Control	1.9 ± 0.1	1.8 ± 0.2	5.6 ± 0.5
β-group	1.9 ± 0.2	1.9 ± 0.1	6.3 ± 0.2
Ca-group	1.9 ± 0.1	1.9 ± 0.2	6.2 ± 0.4
α-group	1.9 ± 0.2	1.9 ± 0.1	5.6 ± 0.3
Brain death induction			
Control	2.9 ± 0.1*	3.3 ± 0.4*	2.8 ± 0.3*
β-group	1.9 ± 0.2†	2.0 ± 0.2†	6.0 ± 0.3†
Ca-group	2.3 ± 0.3*	2.4 ± 0.4*	5.3 ± 0.3†
α-group	2.9 ± 0.1*	2.9 ± 0.3*	3.4 ± 0.4*
5 min after brain death			
Control	3.2 ± 0.4*	3.3 ± 0.3*	3.0 ± 0.3*
β-group	2.0 ± 0.2†	1.9 ± 0.3†	5.1 ± 0.3†
Ca-group	2.6 ± 0.4*	2.7 ± 0.2*	4.7 ± 0.4*†
α-group	2.9 ± 0.5*	3.1 ± 0.2*	3.1 ± 0.3*
15 min after brain death			
Control	3.1 ± 0.3*	3.3 ± 0.2*	3.5 ± 0.4*
β-group	1.9 ± 0.2†	2.0 ± 0.3†	5.2 ± 0.3†
Ca-group	2.7 ± 0.3*	2.8 ± 0.4*	4.4 ± 0.5*†
α-group	2.7 ± 0.3*	3.1 ± 0.3*	3.2 ± 0.3*

AWd, end-diastolic anterior wall thickness; PWd, end-diastolic posterior wall thickness; LVd, end-diastolic left ventricular diameter.
*$P < 0.05$ versus baseline.
†$P < 0.05$ versus control at the same stage.

Catecholamine

In controls, plasma levels of norepinephrine (NE) and epinephrine (E) significantly increased 1 min after BD induction (from 329 ± 51 to 949 ± 261 ng/l and from 111 ± 26 to 5002 ± 1769 ng/l; both $P < 0.01$ vs. baseline values).

In treated groups, NE and E also increased following BD (β-group: 1823 ± 1031 ng/l and 3774 ± 1723 ng/l respectively; Ca-group: 2563 ± 1541 ng/l and 3745 ± 1364 ng/l respectively; α-group: 4205 ± 1847 ng/l and 3935 ± 2236 ng/l respectively; in all groups, P = NS vs. controls).

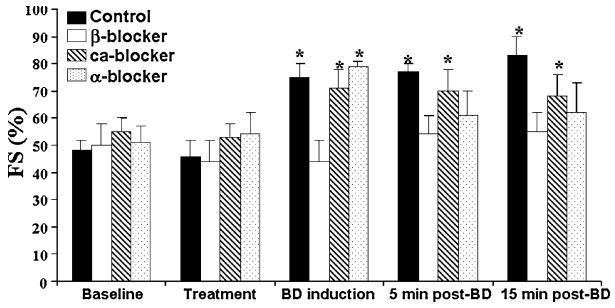

Figure 2 Left ventricular fractional shortening (FS, %) in the four groups at baseline, immediately before brain death induction and after treatment, during brain death induction and 5 min and 15 min after brain death. FS significantly increased in all groups, except in β-group (*$P < 0.05$).

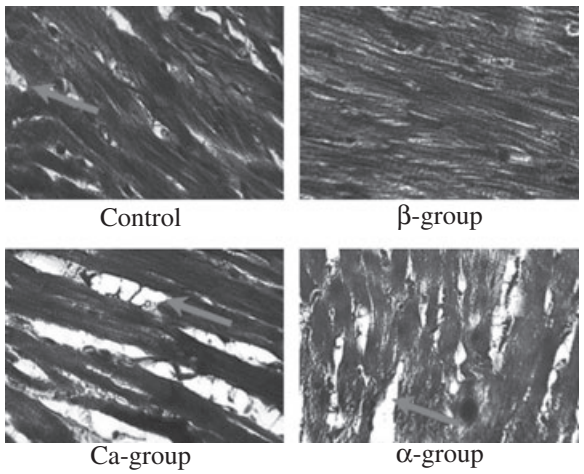

Figure 3 Extensive interstitial edema was found in explanted hearts from controls and Ca- and α-groups (arrow). In contrast, no edema was observed in β-group.

Histology

As shown in Fig. 3, extensive myocardial interstitial edema was found in explanted hearts from control rats or rats treated by the calcium channel blocker or the α-blocker. In contrast, no edema was observed in β-group.

Discussion

The main findings of this study are that: (i) BD induced immediate myocardial changes characterized by a dramatic and abrupt increase in wall thickness as assessed by echocardiography and related to myocardial interstitial edema, (ii) beta-blockers, but not calcium channel- and alpha-blockers, completely prevented these acute changes when they were administered prior to BD.

This is the first study that: (i) monitored the sequential myocardial changes occurring immediately during the initiation of BD by echocardiography, and (ii) compared the potential protective effect of three treatments that are able to prevent the dramatic increased cardiac afterload induced by the autonomic storm. Indeed, in this specific context, no data exist both in experimental and clinical studies despite the fact that echocardiography is widely used to select the potential heart donors. However, most of the clinical studies assessing myocardial function after BD are performed in a delayed period after the occurrence of BD [11]. In addition, the choice of the drug to be administered during the autonomic storm is not clearly defined [8].

In our study, immediately after BD induction, myocardial wall thickness dramatically increased and myocardial function as assessed by LV fractional shortening was not depressed. This abrupt myocardial wall ''hypertrophy'' was concomitant with the autonomic storm, characterized by a sudden increase in SBP, HR and catecholamine levels [12]. This ''hypertrophic'' myocardial response could not be solely explained by an afterload mismatch induced by the acute increase in SBP occurring after BD. Indeed, the increase in wall thickness was similarly observed in both the calcium channel blocker- and alpha-blocker-treated groups either of which could prevent the dramatic increase in SBP immediately after BD. Moreover, wall thickness did not increase after beta-blockade despite the increase in SBP after BD. The abrupt change in LV wall thickness was also associated with a decrease in LV dimensions. One might raise the question whether this combined decrease in LV diameter was attributable to an abrupt reduction in preload giving the appearance of LV hypertrophy. We did not specifically measure the preload. However, we may speculate that LV filling was compromised by the tachycardia in the control group and was improved by slowing the HR in beta-blocker group. However, despite a similar decrease in HR in Ca group, LV wall thickness was abruptly increased. In addition, this immediate increase in myocardial wall thickness after induction of BD was associated with the occurrence of a massive interstitial edema that was observed in control, calcium channel blocker- and alpha-blocker-treated groups but not in beta-blocker-treated group. Moreover, the cardioprotective effect of beta-blockers was maintained for a longer period of 180 min after BD.

Therefore, these echocardiographic data support the hypothesis of a direct noxious effect of catecholamines: in addition to the abrupt increase in blood pressure and HR leading to increased cardiac workload, other potential mechanisms related to the autonomic storm may contribute to hemodynamic instability and alteration in myocardial function such as, imbalance between oxygen demand and consumption, loss of regulation of the peripheral vascular resistances, vasodilatation and hypovolemia. Finally,

intrinsic myocardial injury is induced by intracellular calcium overload, free radicals production and interstitial myocardial edema which tend to increase LV diastolic stiffness [13–16]. Edema has both short- and long-term adverse consequences. Indeed, Laine and Allen have demonstrated that myocardial edema induced development of myocardial interstitial fibrosis [17]. We can therefore hypothesize that myocardial edema occurring at the initiation of BD may lead to chronic edema and progressive cardiac fibrosis which may affect potential heart graft donors and post-transplant outcomes. This observation underscores the importance of limiting the formation of myocardial edema during BD and β-blockers appeared quite efficient for this purpose, as opposed to Ca- or alpha-blockers.

Among the different therapeutic strategies used to prevent the hemodynamic consequences of the catecholamine storm, only beta-blockers were able to avoid the occurrence of myocardial edema. Our results support previous observations that no myocardial damage was observed when the endogenous catecholamine release within the myocardium was prevented by a total cardiac sympathectomy before BD in baboons [5]. Recent experimental papers support also this observation but none of them has addressed the initial phase of BD, i.e. the autonomic storm [6,7].

In this study, we administrated β-blockers just before BD to prevent myocardial wall hypertrophy. In clinical situation, there is an important need for a pretreatment of BD in order to avoid the deleterious myocardial consequences of the Cushing reflex. This brings to the fore the difficulty in detecting the first signs of the autonomic storm occurring at the initiation of BD (EEG signal abolition, tachycardia and hypertension). However, in patients, BD occurrence is not always predictable. In these cases, the feasibility of a pretreatment of BD is thus difficult to apply. It should be therefore appropriate to give β-blockers, just after BD confirmation, during autonomic storm. We might expect that in the setting of acute BD, a careful follow-up of hemodynamics parameters, in order to detect precursor signs of autonomic storm, should indicate the preventive administration of short-lasting and short-acting intravenous β-blockers, such as esmolol. The outcome of our study may be to use β-blockers as soon as possible during autonomic storm of BD. Indeed, the tolerance of such a treatment has already reported in previous studies. We can hope, in these cases, to prevent subsequent damage and induce myocardial edema regression. Our study focused on a prevention strategy but did not address the important issue of potential curative effect of β-blockers administrated after BD. This unresolved issue should deserve the realization of a specific experimental study designed to evaluate curative effect of β-blockers treatment administered after BD induction.

In the clinical setting, Audibert *et al.* [8] reported an incidence of 63% of autonomic storm among a cohort of 152 patients with BD. In addition, they showed that the treatment by β-blockers (esmolol) was feasible and might limit the consequences of BD on hemodynamic instability and myocardial damages. This observation is supported by other reports in neurologic intensive care unit where paroxysmal sympathetic storm following traumatic brain injury, may respond to β-blocker therapy [18,19]. Furthermore, early treatment of paroxysmal sympathetic storm with β-blocker enables cerebral and hemodynamic recoveries in patients that may quickly exit the intensive care unit [20].

Beta-blockers offer many potential, but speculative advantages to limit the consequences of BD associated with autonomic storm: as recently reviewed by Audibert *et al.* [8], β-blocker treatment might: (i) preserve the β-adrenergic transduction system and therefore facilitate the effect of catecholamine infusion as a treatment of hypotension following the autonomic storm; (ii) limit the consequences of excessive sympathetic nervous system activation on gene expression profiles, cytokines and chemokines production and apoptosis.

One limitation of our study is that it focused on a standardized and reproducible model of BD associated in all cases with an acute autonomic storm. However, we know from experimental studies that the rate of progression towards BD differs accordingly to the modality of BD induction and therefore will affect the degree of organ dysfunction. This was evidenced by the experimental study by Shivalkar *et al.*, who compared two models of induction of BD by increasing the intracranial pressure suddenly or gradually by injecting saline in an epidural Foley catheter in dogs [4]. These authors demonstrated that a sudden rise in intracranial pressure inducing BD, caused irreversible myocardial injury, while a gradual rise in intracranial pressure led to lesser hemodynamic instability and myocardial damages. Likewise, in clinical situations, BD occurrence is not standardized and varies accordingly to the patient pathology (cranial shock, neurologic impairment, stroke …) leading to various hemodynamic and myocardial impairments, following the autonomic storm. In addition, there is a lack of data concerning the incidence of autonomic storm in brain-damaged patients and brain-dead organ donors and, the standardized definition of autonomic storm during BD is not yet clearly finalized. As our study aimed to assess the effect of β-blocker treatment of the autonomic storm, we have chosen a reproducible and standardized model of acute and sudden rise in intracranial pressure to induce BD in rats.

In BD patients exhibiting signs of autonomic storm, we may expect that rapid β-blocker administration may stabilize hemodynamics and prevent initial acute myocardial impairment. In other patients without sign of

catecholamine storm or showing depressed hemodynamics, the appropriate treatment can be quite different.

Indeed, Ueno *et al.* showed that the administration of catecholamine could improve hemodynamics and cardiac function [21] and this intervention is widely prevalent in clinical practice on brain dead donors [8]. In addition, a study of our group also demonstrated that cardiac function could be maintained stable during BD in pigs, despite major endocrine and catecholamine impairment [22].

In conclusion, we demonstrated that the BD-related autonomic storm is associated with dramatic changes in myocardial morphology related to an important and acute interstitial myocardial edema leading to myocardial wall hypertrophy as assessed by echocardiography. Interestingly, we showed that this initial myocardial change could be prevented by using beta-blockers and independently of the loading conditions.

Authorship

RF and GD contributed to the writing of this manuscript. GH, FT, J-PH, PM, VR, CT and MO contributed to the experimentation and the analysis of the data.

References

1. Herijgers P, Leunens V, Tjandra-Maga TB, Mubagwa K, Flameng W. Changes in organ perfusion after brain death in the rat and its relation to circulating catecholamine. *Transplantation* 1996; **62**: 330.
2. Todd GL, Baroldi G, Pieper GM, Clayton FC, Eliot RS. Experimental catecholamine-induced myocardial necrosis Morphology, quantification and regional distribution of acute contraction band lesions. *J Mol Cell Cardiol* 1985; **17**: 317.
3. Remondino A, Kwon SH, Communal C, *et al.* Beta-adrenergic receptor-stimulated apoptosis in cardiac myocytes is mediated by reactive oxygen species/c-jun NH2-terminal kinase-dependent activation of the mitochondria pathway. *Circ Res* 2003; **92**: 136.
4. Shivalkar B, Van Loon J, Wieland W, *et al.* Variable effects of explosive or gradual increase of intracranial pressure on myocardial structure and function. *Circulation* 1993; **87**: 230.
5. Novitzky D, Wicomb WN, Cooper DKC, Rose AG, Reichart B. Prevention of myocardial injury during brain death by a total cardiac sympathectomy in the chacma baboon. *Ann Thorac Surg* 1986; **41**: 520.
6. Ojeda-Rivero R, Hernández-Fernández A, Dominguez-Roldán JM, *et al.* Experimental treatment with β-blockers of hemodynamic and myocardial changes in organ donors. *Transplant Proc* 2002; **34**: 185.
7. Pandalai PK, McLean KM, Bulcao CF, *et al.* Acute β-blockade prevents myocardial β-adrenergic receptor desensitization and preserves early ventricular function after brain death. *J Thorac Cardiovasc Surg* 2008; **135**: 792.
8. Audibert G, Charpentier C, Seguin-Devaux C, *et al.* Improvement of donor myocardial function after treatment of autonomic storm during brain death. *Transplantation* 2006; **82**: 1031.
9. Chiari P, Piriou V, Hadour G, *et al.* Preservation of ischemia and isoflurane-induced preconditioning after brain death in the rabbit heart. *Am J Physiol* 2002; **283**: H1769.
10. Derumeaux G, Mulder P, Richard V, *et al.* Tissue Doppler imaging differentiates physiological from pathological pressure-overload left ventricular hypertrophy in rats. *Circulation* 2002; **105**: 1602.
11. Zaroff JG, Babcock WD, Shiboski SC, Solinger LL, Rosengard BR. Temporal changes in left ventricular systolic function in heart donors: results of serial echocardiography. *J Heart Lung Transplant* 2003; **22**: 383.
12. Chiari P, Hadour G, Michel P, *et al.* Biphasic response after brain death induction: prominent part of catecholamine release in this phenomenon. *J Heart Lung Transplant* 2000; **19**: 675.
13. D'Amico TA, Meyers CH, Koutlas TC, *et al.* Desensitization of myocardial β-adrenergic receptors an deterioration of left ventricular function after brain death. *J Thorac Cardiovasc Surg* 1995; **110**: 746.
14. Pogatsa G, Dubecz E, Gabor G. The role of myocardial edema in the left ventricular diastolic stiffness. *Basic Res Cardiol* 1976; **71**: 263.
15. Szabo G. Physiologic changes after brain death. *J Heart Lung Transplant* 2004; **23**: 223.
16. Ashraf MI, Schneeberger S, Brandacher G, *et al.* Control mitochondrial events associated with the development of ischemia/reperfusion-associated damage. *Transpl Int* 2009; **22**: 922.
17. Laine GA, Allen SJ. Left ventricular myocardial edema. Lymph flow, interstitial fibrosis, and cardiac function. *Circ Res* 1991; **68**: 1713.
18. Bernath O. Treatment of paroxysmal sympathetic storm with labetalol. *J Neurol Neurosurg Psychiatry* 2001; **70**: 818.
19. Do D, Sheen VL, Bromfield E. Treatment of paroxysmal sympathetic storm with labetalol. *J Neurol Neurosurg Psychiatry* 2000; **69**: 832.
20. Rabinstein AA, Benarroch EE. Treatment of paroxysmal sympathetic hyperactivity. *Curr Treat Options Neurol* 2008; **10**: 151.
21. Ueno T, Zhi-Li C, Itoh T. Unique circulatory responses to exogenous catecholamines after brain death. *Transplantation* 2000; **70**: 436.
22. Ferrera R, Ovize M, Claustrat B, Hadour G. Stable myocardial function and endocrine dysfunction during experimental brain death. *J Heart Lung Transplant* 2005; **24**: 921.