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Pathophysiological consequences of brain death

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Abstract

Hemodynamic instability after brain death is an universal clinical problem with effects on potential donor organs. Actual shortage of potential donor hearts continues to raise controversial discussion about adequate donor management with regard to graft quality. From the mid eighties numerous studies investigated the effects of brain death on the cardiocirculatory system and other organs. It could be shown that brain death induction leads to 1) an initial hyperdynamic Cushing-type reaction, followed by 2) loss of neural control and hormone depletion, 3) marked alteration of loading conditions and coronary perfusion and 4) cardiac and peripheral organ dysfunction. The causal relationship between these phenomena, however, could not be proven accurately. Studies using ex vivo evaluation of the hearts or applying load-independent indices of myocardial function suggested that brain death does not lead to an irreversible myocardial damage but only a reversible dysfunction or even more accurately a downregulation of myocardial contractility.

These results may also be of a clinical importance: based on the knowledge of the physiologic regulatory mechanisms, it is possible to conclude that hemodynamic instability in the potential organ donor should not necessarily indicate primary cardiac dysfunction. Therefore, donor hearts, especially from marginal donors, should be carefully evaluated by load-independent indices of cardiac function. Furthermore, the normalization of loading conditions in the brain dead donor may lead to an improvement of cardiac performance. In fact, an increasing number of clinical studies demonstrate that cardiac dysfunction can be reversed in potential organ donors, and the clinical outcome of transplant patients receiving hearts from primarily marginal donors is comparable to those of normal donors.

Key words: brain death, donor heart, heart transplantation

Introduction

Hemodynamic instability after brain death is an universal clinical problem with effects on potential donor organs. Actual shortage of potential donor hearts continues to raise controversial discussion about adequate donor management with regard to graft quality. The shortage of suitable donor hearts for cardiac transplantation is exacerbated by the exclu-

sion of those that exhibit contractile malfunction during the period after brain death. After cardiac transplantation, during the early post-operative period an impaired cardiac function is frequently seen. Factors like pre-existent myocardial damage, direct cardiac trauma and brain death-related damage may contribute to a reduced ischemic tolerance despite optimal cardiac preservation. Reperfusion injury and increased loading conditions

due to altered pressure-flow relationships in the pulmonary and systemic circulations may aggravate these factors.

During the last decades, the cardiocirculatory consequences of brain death on potential donor organs became extensively studied. Controversy still remains about the relative importance of neuro-humoral, metabolic or hemodynamic dysregulations and histopathomorphologic alterations and their interaction which all might have an impact on donor heart function [1-5]. On the basis of experimental and clinical data, the reduced myocardial contractility after brain death might be seen as a physiologic response to decreased pre- and afterload conditions and coronary perfusion as main determinants of myocardial pump function.

Novitzky et al. [6] postulated that the initial Cushing reaction results in direct myocardial injury and hormone depletion that leads to hemodynamic collapse. Meyers and colleagues [7] and Herijgers et al. [2] demonstrated a significant decrease in myocardial blood flow after brain death.

This significant finding would support the exclusion of potential donor hearts from hemodynamically unstable donors. Surprisingly, Wheeldon and colleagues [8] demonstrated that of the organs which initially fell outside of transplant acceptance criteria, 92% were capable of functional resuscitation. However, in their studies, no conclusion could be made as to how far decreased myocardial blood flow contributes to decreased cardiac function. As already mentioned above inadequate management masked the "true" hemodynamic properties and exercise capacity of cardiac function after brain death. In our own studies [9-11], we demonstrated that altered loading conditions are a vital component in the changes of cardiac function after brain death.

Herein is provided an overview with particular reference to physiologic changes after brain death that may lead to decreased cardiac function in the potential organ donor.

Alterations of loading conditions and coronary perfusion after brain death

Ex vivo investigations

Galinaes et al. [12] studied the phenomenon of brain death-induced hemodynamic deterioration in the rat in vivo. After 60 minutes of brain death (defined as the absence of electrical activity in the brain), a variety of indicators of cardiac contractile function fell by approximately 50% (thus cardiac index fell from 21 ± 2 to 11 ± 1 ml/min per 100 g body weight). However, once excised and perfused ex vivo, the hearts recovered a level of cardiac function that was identical to that from control animals that had not been subjected to brain death. It was also demonstrated, that when hearts were excised, stored (6 hours at 4°C), and reperfused ex vivo with blood, they also recovered a functional capability identical to that of normal hearts from animals that had not been subjected to brain death. Subsequently they could show that contractile dysfunction is reversible after brain death in the rat model in vivo.

In further studies [1, 9, 11], our group tried to differentiate possible pathophysiological effects after brain death. For this purpose we used a canine in-situ cross-circulation heart model, brain death was induced by inflation of a subdural balloon catheter. Preload, afterload, and coronary perfusion pressure were kept identical in all hearts throughout the experiment. Induction of brain death led to a significant hyperdynamic response in all groups. After the initial hyperdynamic phase, cardiac function returned to baseline within 15 minutes and remained stable in all groups for the observation period. These experimental observations provided further evidence that (1) both neural and humoral factors contribute to the initial hyperdynamic reaction after brain death, and only in combination do they cause a maximal hemodynamic effect. (2) If loading conditions and perfusion pressure are kept constant, no car-

diac dysfunction occurs after brain death. This indicates that poor cardiac function in the potential donor may reflect altered loading conditions and impaired coronary perfusion rather than neurohumorally mediated direct myocardial injury.

Following these experimental observations a model of load-independent analysis of cardiac function after brain death was performed [9]. Special interest was focused on a possible interactive influence of brain death and cardiac preservation on postischemic cardiac function. In spite of a brain death-associated hemodynamic deterioration in situ (expressed as low mean aortic pressure and significant decrease of maximal dP/dt), myocardial function was similar to control after explantation, if assessed *ex vivo*. Beyond, after hypothermic ischemic preservation and reperfusion, complete functional recovery of control and brain-dead hearts could be observed. Furthermore these data demonstrate that hemodynamic instability after brain death may rather reflect altered loading conditions than irreversible myocardial damage. In summary, it can be stated that there is no evidence for a brain death-related impairment of ischemic tolerance.

In an *in situ* isolated canine heart study, we could confirm the fact that if coronary perfusion pressure was decoupled from aortic pressure and elevated to pre-brain death levels, coronary blood flow and the end-systolic pressure-volume relation were also restored to baseline levels [1].

In summary cardiac dysfunction after brain death seems to be reversible, and the changes of myocardial function within the donor may rather reflect altered loading conditions and coronary perfusion than irreversible injury that is due to the initial Cushing type reaction and subsequent hormone depletion.

In vivo investigations

In the majority of cases *in vivo* experiments used predominantly load-dependent hemo-

dynamic indices for description of myocardial function after brain death. Nevertheless, brain death is well known to be linked with hemodynamic deterioration: the loss of the sympathetic vasotonus [6, 13] leads to a drop of afterload with intravascular hypovolemia and reduced preload. Without maintaining a sufficient circulatory volume, the loss of vasomotor tone, diabetes insipidus and volume shifts with consecutive hypovolemia contribute towards hemodynamic collapse after 60 min as described by Shivalkar [14]. The frequently seen onset of diabetes insipidus after brain death [6, 13] may have an additional impact on the evaluation of donor hearts in 2 conditions:

1. If cardiac function is evaluated by load-dependent parameters, altered loading conditions may mask "true" myocardial pump function [8].
2. Altered loading conditions themselves may have a distinct effect on myocardial pump function, directly or owing to the modification of coronary perfusion pressure free from direct brain death-induced alterations of cardiac function.

Experimental studies that used load-independent parameters of myocardial contractility reported divergent results [13, 15, 16, 17]. For that reason altered loading conditions themselves may have a significant effect on myocardial contractility due to the homeometric (Anrepp effect) and heterometric (Frank-Starling mechanisms) autoregulation and due to the change of coronary perfusion pressure independently from direct brain death related changes of cardiac function.

Another study [18] analyzed the ventriculo-arterial coupling by means of ventricular and arterial elastance (E_{es} and E_a) in an *in vivo* model. In this case, myocardial contractility decreased parallel to the decrease of afterload, whereas the ventriculo-arterial coupling ratio remained constant. These data demonstrated that hemodynamic instability after brain death rather reflects the altered loading conditions than primary cardiac dysfunction. This finding is congruent with the

studies of Herijgers and colleagues [19] who observed that brain death induces severe haemodynamic changes due to an important reduction in afterload.

Others demonstrated reduced coronary blood flow to be related to cardiac dysfunction after brain death [7,20-22]. How far reduced coronary blood flow induces myocardial dysfunction through means other than ischemic injury, remains to be clarified.

Although there is strong evidence for the direct effects of loading conditions on contractile function, the interrelation of coronary perfusion and contractility is more complex. Decreased coronary perfusion pressure may directly decrease contractility via the “gar-

denhose” effect. This effect could be explained by the increased intravascular pressure stretching the intramyocardial vessels and, in turn, the surrounding myocardium. In addition to the mechanical effects of coronary perfusion pressure, reduced coronary blood flow may limit oxygen supply and thereby reduce contractility. In turn, reduced oxygen demand itself, as a result of the reduced contractile state, may contribute to a further decrease of coronary blood flow.

The connections between loading conditions, coronary perfusion, and myocardial function after brain death are not fully understood. Figure 1 depicts a framework of pathophysiologic changes after brain death as well

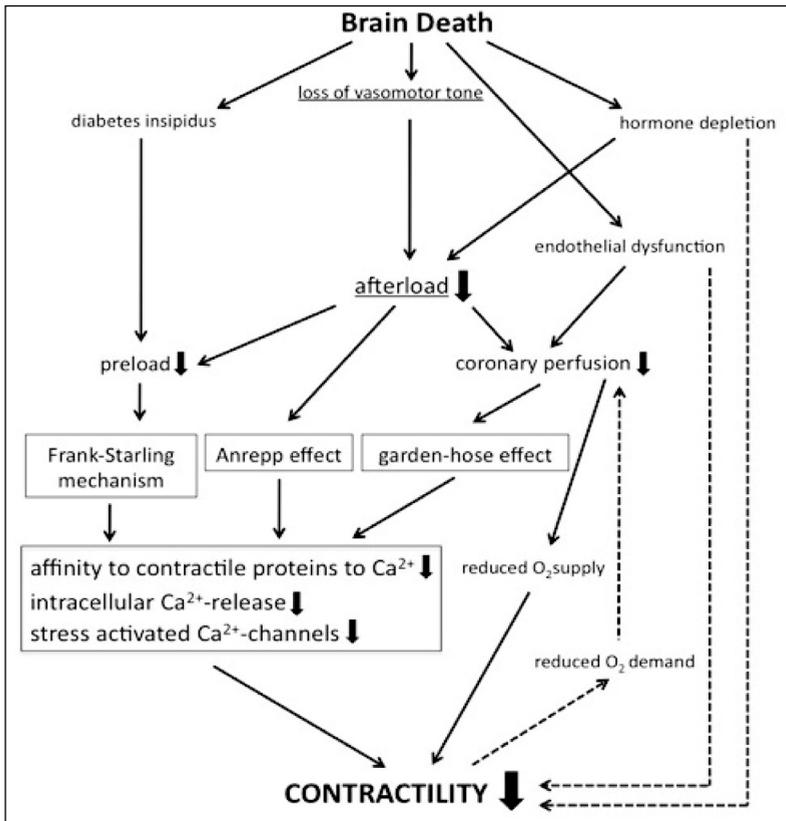


Figure 1: Pathologic changes and physiologic regulatory mechanisms in the brain dead organ donor. The central event after brain death is the loss of the sympathetic regulation of the vessels. This leads to an abrupt vasodilatation resulting in a marked decrease of aortic pressure (and thereby a significant decrease of afterload and coronary perfusion pressure) and to intravascular hypovolemia with subsequent reduction of preload. These changes result in a decrease of contractile function via the Anrepp and garden-hose effects as well as the Frank-Starling mechanism.

as determinants of cardiac function and their physiologic regulation that explain how dramatic changes of loading conditions and coronary and coronary perfusion may “downregulate” myocardial contractility in the potential organ donor [22,23].

The existence of a control system that maintains optimal stroke work over a wide range of afterload conditions by mechanisms other than neural reflexes has been demonstrated previously under different conditions [24,25], which in turn supports the hypothesis that cardiac dysfunction after brain death might be seen as a consequence of altered loading conditions. The cellular mechanisms include reduced affinity of contractile proteins to Ca^{2+} , decreased release of intracellular Ca^{2+} , and reduced activation of mechanosensitive Ca^{2+} -channels [24-26].

Neuro-humoral changes in the brain dead organ donor

Beside changes of loading conditions, major changes of the neuro-humoral system are observed after brain death. The induction of brain death leads to sympathetic response followed by a significant depletion of certain circulating hormones [23].

Though there is a brief initial period of excessive parasympathetic activity, evidenced by a marked bradycardia only in certain cases, most of the effects of this autonomic stimulation are brought about by the sympathetic nervous system; the terms ‘sympathetic’ or ‘catecholamine’ storm have also been used to describe these events. The hemodynamic changes observed reflect the body’s attempts to compensate for the intracranial changes taking place during Cushing type reaction. The classical and well described Cushing type reaction (“emergency reaction”) to elevated intracranial pressure with initial bradycardia and rise in systemic arterial blood pressure involves complex and multifactorial neuro-humoral and metabolic mechanisms; the relative extent and interrelation of which are still not completely understood.

Although the initial Cushing-type reaction may also contribute to decreased cardiac function by direct myocardial injury, the central event after brain death is the loss of the neural regulation in general and particular, the loss of the sympathetic regulation of the vessels. This leads to an abrupt vasodilatation that results in a marked decrease of aortic pressure and thereby to a significant decrease of afterload and coronary perfusion pressure, and also to intravascular hypovolemia with subsequent reduction of preload [22]. These observations made us hypothesize that the haemodynamic collapse is caused by the withdrawal of the sympathetic tone, thereby lowering the cardiac inotropic status, and causing generalized vasodilatation, with the heart unable to substantially increase cardiac output, since chronotropic and inotropic responses are abolished.

As mentioned above, the depletion of different hormones like triiodothyronine (T3), thyroxine (T4), cortisol, insulin, adrenocorticotrophic hormone (ACTH), and antidiuretic hormone (ADH), may also contribute to decreased cardiac function after brain death. The exact mechanisms could not be elucidated, and it remains a question whether decreased cardiac function and hormone levels after brain death represent an epiphenomenon or a true causal relationship. It was speculated that hormone depletion results in an inhibition of mitochondrial function, leading to reduced aerobic metabolic oxidative processes, affecting the body as a whole. Major organ energy stores are therefore diminished, leading to deterioration of function. T3 alone leads to reactivation of the mitochondria, stimulating aerobic metabolism. Hormonal therapy to brain-dead potential organ donors has been shown to lead to metabolic and haemodynamic stability, resulting in no wastage of organs, and in improved function after transplantation [23].

Others demonstrated that there was a major change in metabolic oxidative processes following brain death. The rates of glucose, pyruvate, and palmitate utilisation were markedly reduced, and there was an accumu-

lation of lactate and free fatty acids in the plasma. Pyruvate and palmitate can only be oxidised in the mitochondria; the reduction in their metabolism indicated mitochondrial inhibition. These findings indicated an inhibition of aerobic metabolic rate, almost certainly from an inhibition of mitochondrial function, affecting the body as a whole.

The above mentioned interrelations are strongly influenced by the onset of diabetes insipidus [6, 13]. The onset of diabetes insipidus coincides with considerable fluid losses by excessive urinary output and transcapillary fluid shifts. The importance of sufficient volume substitution – including electrolyte and acid-base balancing – in order to maintain adequate perfusion to all potential donor organs has been stressed by several authors.

Conclusion

Putting together the data, we believe that the physiologic regulatory mechanisms give a plausible explanation for decreased cardiac function in the brain dead organ donor, without the necessity of irreversible tissue damage or “true” dysfunction. Under these aspects, the complex of reduced load, coronary perfusion, and contractility may represent a new steady state at a mechanoenergetic optimum in an organism that lacks neural control.

Nevertheless, it should be mentioned that this new steady state is less stable. Small changes such as further decreases in loading conditions or coronary perfusion pressure may trigger multiple vicious cycles that lead to hemodynamic collapse in the donor. For example, if the left ventricle’s ability to generate pressure becomes markedly limited, the low coronary perfusion pressure reduces the contractility. This tends to further lower coronary perfusion pressure in the face of increasing end-systolic volume and decreasing ventricular pressure. Once this vicious cycle is triggered, the ventricle can hardly recover by its own ability.

Therefore a major challenge remains the optimization of the donor management to restore physiological loading conditions and thereby improving myocardial function. Furthermore, critical evaluation of myocardial function is mandatory in order to include so called “marginal” organs in cardiac transplantation.

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