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Relationship Between Brain Death and Takotsubo Cardiomyopathy: A Comprehensive Neurocardiogenic Approach Focused on Donation of the Heart.

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ABSTRACT

This analysis explores the relationship between brain death and Takotsubo cardiomyopathy (TT), also known as "broken heart syndrome." Both conditions share an exaggerated response of the autonomic nervous system, generating an overload of catecholamines that affect the myocardium and can cause severe complications. The study highlights how brain death induces ventricular dysfunction, like the patterns observed in TT, and highlights the potential reversibility of these dysfunctions, with important implications for optimizing the use of donor hearts in circulatory arrest. In addition, autonomic modulation is addressed as a promising therapeutic avenue to improve prognosis and reduce adverse events. The work underscores the need for innovative approaches to clinical management and future research that facilitates the development of therapeutic strategies targeting autonomic activity and inflammation.

Keywords: Takotsubo, brain death, heart transplantation, cardiac dysfunction, ischemic heart disease, cerebral vascular event

Introduction

Takotsubo cardiomyopathy (TTC), also known as "broken heart syndrome," is a transient left ventricular disorder that resembles acute myocardial infarction (AMI) in its clinical presentation, but without significant coronary obstruction. Its initial description occurred in the seventies of the last century and its name is attributed to Sato in 1990 [1]. Originally considered rare and benign with a frequency of approximately 2% of acute coronary syndromes, an increase in mortality has now been observed with records of 5.6% [2,3]. Previously, brain-heart syndrome had been described since the mid-twentieth century with a frequency of approximately 20% of patients with cerebral vascular events and high mortality [5]. Brain death, on the other hand, triggers hemodynamic dysfunctions that also affect the heart, generating patterns of myocardial dysfunction similar to those observed in TTC. Both conditions share pathophysiological mechanisms related to overstimulation of the autonomic nervous system (ANS) and the massive release of catecholamines. This interaction, known as the brain-heart axis, highlights the brain's influence on cardiovascular function, especially in critical stressful situations [1,6]. This brief review offers an in-depth analysis of the links between both pathologies, their underlying mechanisms and their impact on clinical management and heart transplantation, especially at a time when the number of heart donors in asystole is increasing.

Research indicates a significant overlap between the neurological and cardiovascular responses in both brain death and Takotsubo syndrome (TTS). Central to these conditions is the intense release of catecholamines, leading to transient cardiac dysfunction, also described as neurogenic stunned myocardium or stress-induced cardiomyopathy. This autonomic surge and its effects on myocardial tissue illustrate a potential shared mechanism for myocardial injury during critical neurological episodes, such as brain death.

The catecholamine storm as a common mechanism

In both pathologies, the exaggerated response of the ANS results in a storm of catecholamines, which severely affects the myocardium. In brain death, increased intracranial pressure stimulates the massive release of norepinephrine and epinephrine, resulting in transient ventricular dysfunction [7,8]. In TTC, the catecholamine release is triggered by an emotional or physical stressful event, inducing characteristic apical akinesia and compensatory basal dysfunction [9]. The catecholamine increase has been described during acute neurological injuries, including subarachnoid hemorrhage (SAH), is paralleled by similar myocardial responses seen in Takotsubo cardiomyopathy. This excessive sympathetic discharge not only precipitates ventricular dysfunction and myocardial stunning but also leads to reversible left ventricular apical ballooning, which typifies TTS. The sustained adrenergic activation and systemic vasoconstriction increases myocardial oxygen demand without a commensurate rise in oxygen delivery, exacerbating myocardial ischemia.

These effects are mediated by the excessive binding of catecholamines to beta-adrenergic receptors, which generate coronary vasoconstriction, endothelial dysfunction and oxidative stress, exacerbating myocardial injury [10].

While this dysfunction is reversible, it is associated with serious complications, such as cardiogenic shock, ventricular arrhythmias, and sudden death.

Brain Changes and Autonomic Dysfunction

Functional magnetic resonance imaging (fMRI) studies have shown that patients with TTC have disruptions in brain areas critical for emotional and autonomic regulation, such as the insula, amygdala, and hippocampus [11]. These areas are involved in emotional-autonomic integration, which explains how extreme stress triggers cardiac events. This same dysfunction is observed in brain death, suggesting that both pathologies share a neurocardiogenic origin [12].

Imbalance in autonomic regulation is also characterized by reduced parasympathetic tone and sympathetic hyperactivity, which increases the risk of ventricular arrhythmias and aggravates myocardial dysfunction. This alteration has important implications for treatment, as modulation of the ANS could improve clinical outcomes.

Experimental Models and New Therapeutic Perspectives

Various animal models and studies with induced pluripotent stem cells (hiPSC-CM) have allowed a better understanding of the pathogenesis of TTC and its relationship with cardiac dysfunction due to brain death. These models have identified that the differential sensitivity of adrenergic receptors in different regions of the myocardium explains typical clinical patterns, such as apical hypokinesia [6,9]. In addition, recent studies suggest that inflammation and oxidative stress play a key role in both conditions [13].

Implications for Heart Transplantation

Brain-death-induced ventricular dysfunction reflects an extreme variant of TTC, but recent studies suggest that it is reversible. The success of transplants performed with hearts that presented TTC has shown that these organs can recover completely with proper management [14]. In case of the cardiac arrest heart donor considering the taking of preventive actions in the presence of periods of hot ischemia in the harvesting process, which do not occur in the usual donor who is brain dead, but maintains his cardiac activity [14,15], the use of normothermic preservation strategies has made it possible to expand the donor pool, improving outcomes in critically ill patients with end-stage heart failure [14]. We have no experience on this issue.

However, on this basis we must emphasize that heart transplantation is a crucial procedure for patients with end-stage heart failure. Managing hearts from potential donors who have experienced brain death presents unique challenges due to transient cardiac dysfunction induced by this catecholamine release. This phenomenon, observed in both brain death and Takotsubo cardiomyopathy (TTS), is characterized by the excessive release of catecholamines that triggers transient

ventricular dysfunction, apical hypokinesia, and hemodynamic alterations [7,16,17]. The massive release of catecholamines in this context can generate an inflammatory response that contributes to greater myocardial dysfunction [18].

The brain-heart connection through the autonomic nervous system generates significant cardiac effects, including the myocardial dysfunction seen in brain-dead donors [9, 19]. This phenomenon shares common mechanisms with TTS, such as catecholamine damage that generates abnormal myocardial contraction and contraction band necrosis [20, 21]. Understanding these mechanisms is critical to maximizing the viability and functionality of transplanted organs [22].

Studies have shown that although brain death-induced cardiac dysfunction can be significant, it is potentially reversible [10]. This opens the possibility of using hearts affected by TTS as donors, provided that they are properly managed and the donor's hemodynamic conditions are stabilized [23]. Repeated evaluations of ventricular function using advanced imaging techniques can identify recovery and ensure the safety of the transplant before harvesting be made [6, 24].

Modulation of sympathetic activity and delivery of therapies to mitigate the impact of the catecholamine storm may be crucial for the stabilization of donor hearts [6,23]. Recent studies have highlighted the potential use of beta-adrenergic blockers and normothermic preservation as strategies to improve transplant viability [16, 18].

There are documented cases of successful transplants using hearts affected by TTS. The results show that, with proper management, these hearts can recover their functionality, benefiting recipient patients and expanding the pool of available donors [19,23].

Prognosis and Clinical Complications

While TTS was initially considered benign, it has been shown that it may have a significant risk of in-hospital mortality and long-term complications, such as arrhythmia and recurrence [25]. Mortality rates and serious adverse events are comparable to those of ST-elevation infarction, especially in patients with neurological comorbidities [1]. This underscores the need for long-term monitoring and more effective preventive approaches.

Conclusions

TTS and brain death share complex pathophysiological mechanisms related to catecholaminergic overload, autonomic dysfunction, and alterations in brain connectivity. Understanding these interactions is critical to improving cardiac donor diagnosis, treatment, and selection. These interactions and diagnostic methods have been extensively described before. However, in making this brief review, we emphasize the need to identify this association, especially in view of the possibility of increasing donation for heart transplantation from donors in circulatory arrest, in whom this condition can occur or in brain death donors with reversible TTS. Future research should focus on developing therapeutic strategies that modulate autonomic activity and reduce inflammation, improving clinical outcomes in both pathologies.

In Mexico, heart donation from donors in cardiac arrest is not yet legally accepted. However, takotsubo cardiomyopathy associated with brain death, based on what is reviewed here, should be taken into account and appropriately assessed and treated to increase the number of heart donors.

Conflict of interest: The authors declare that they have no conflict of interest.

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