INTRODUCTION

The relationship between the heart and the brain is complex and integral in the maintenance of normal cardiovascular function. Certain pathological conditions can interfere with the normal brain-heart regulatory mechanisms and result in impaired cardiovascular function. The mechanisms through which the central and autonomic nervous systems regulate the heart and the manner in which their impairment adversely affects cardiovascular function have been reviewed. The stress-related cardiomyopathies appear similar in that they seemingly occur during times of enhanced sympathetic tone and may be precipitated in part or entirely by excessive endogenous or exogenous catecholamine stimulation of the myocardium ***(Samuels, 2007).***

The growing interest of anesthesiologists in stress-related cardiomyopathy syndrome is the result of an increasing number of cases of this syndrome, traditionally 'confined' to the critical care and cardiology literature, being reported in the anesthesiology literature and the real need to address several unanswered questions, such as the true incidence of the syndrome, the multifactorial pathogenesis, individual susceptibility, the role of perioperative medications and optimal anesthetic management ***(Hessel and London, 2010).***

Neurogenic stunned myocardium, also called neurogenic stress cardiomyopathy (NSC), is part of the stress-related cardiomyopathy syndrome that can occur after severe acute neurologic injury, such as subarachnoid hemorrhage (SAH), traumatic brain injury, ischemic or hemorrhagic stroke, central nervous system infections, epileptic seizures, or any sudden stressful event ***(Lee et al., 2006).***

The cardiac involvement is expressed either in terms of electrocardiographic (ECG) signs with QT-interval prolongation, long QT-syndrome and torsade de points, ST-segment depression, T-wave inversion and ventricular and supraventricular arrhythmias, or in the form of left ventricular (LV) wall motion abnormalities, myocardial necrosis enzyme release and increased B-type natriuretic peptide (BNP**)** ***(Nguyen and Zaroff, 2009).***

Takotsubo is a particular form of stress-related cardiomyopathy syndrome mimicking an acute coronary event and presenting with transient LV wall motion abnormalities characterized by apical and mid-ventricular akinesis compensated for by basal hyper-kinesis extending beyond a single epicardial coronary territory of distribution, markedly prolonged ST-segment and arrhythmias, ST-segment elevation, T-wave inversion, or all ***(Bybee and Prasad, 2008).***

AIM OF THE WORK

This work aims to review the pathophysiology of stress-related cardiomyopathy syndromes, discuss the role of perioperative medication and the optimal anesthetic management to improve the outcomes.

PATHOPHYSIOLOGY OF STRESS RELATED CARDIOMYOPATHY

Stress-related cardiomyopathy syndrome includes; neurogenic stress cardiomyopathy (NSC) and Takotsubo syndrome (left ventricular apical ballooning syndrome). Takotsubo syndrome was termed by Japanese for octopus traps that fishermen still use to catch octopus due to the left ventricle takes the shape of an octopus trap **(figure 1)**. There is significant overlap between them in clinical appearance, underlying pathophysiology and reversibility ***(Steptoe and Kivimaki, 2012).***

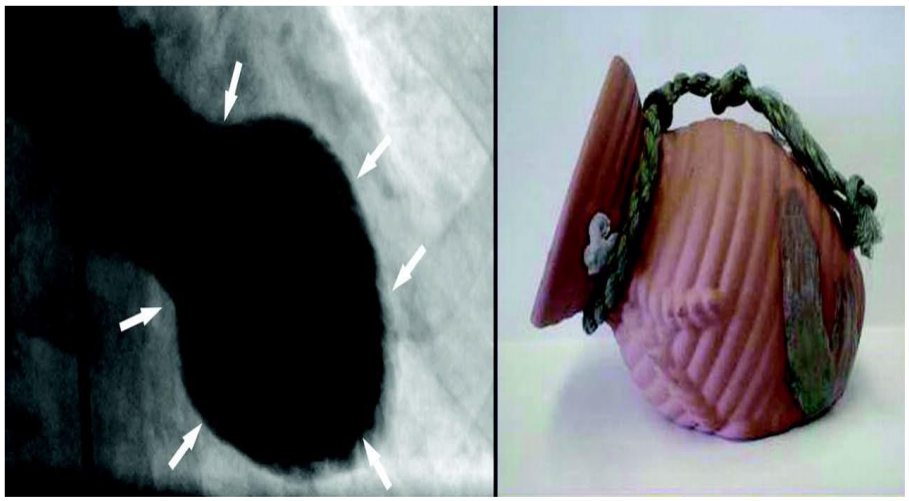

Fig. (1): Octopus shape of left ventricle
(Steptoe & Kivimaki, 2012).

Types of Takotsubo cardiomyopathy

In classic Takotsubo cardiomyopathy (TC) the left ventricular apex is non contractile, with a hyperdynamic basal part; however, several other forms have also been described including "mid ventricle Takotsubo cardiomyopathy" found in 17% of cases in which mid ventricular contractile function is impaired, but the apex and base remain hyper-dynamic. However, in the third type"basal or reverse Takotsubo cardiomyopathy" the basal ventricle is non contractile with a hyperdynamic apex. In about 30% of cases both the left and right ventricle is affected, giving the appearance of dilated cardiomyopathy **(figure 2)** ***(Haghi et al., 2006).***

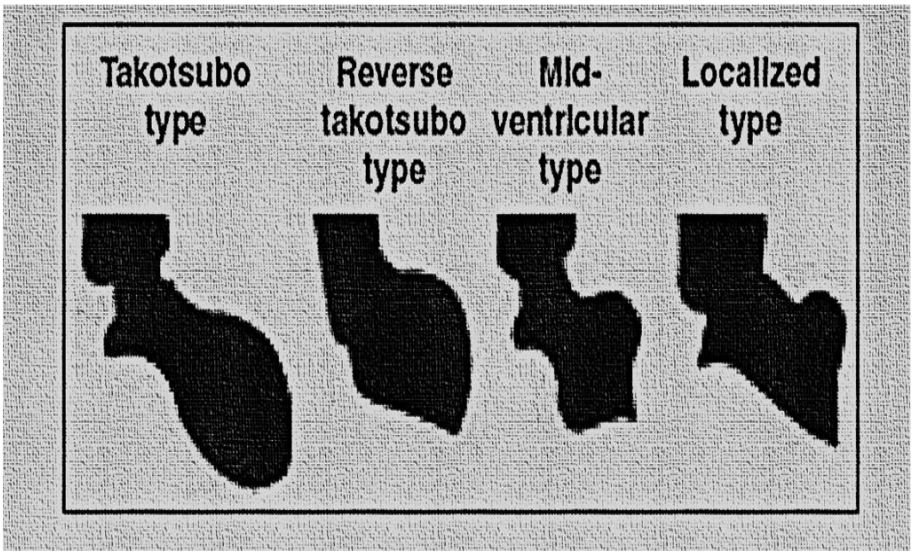

Fig. (2): Types of TC **(Haghi et al., 2006).**

The term NSC reflects the underlying pathophysiology of myocardial dysfunction related to the stress of catecholamine excess, triggered by an acute neurological injury (secondary to structural or functional brain damage). Takotsubo cardiomyopathy related to emotional or physical stress situations (primary form) and is the syndrome more frequently observed during anesthesia ***(Nojima and Kotani, 2010).***

Many theories for stress-related cardiomyopathy syndrome have been described: (i) transient multi-vessel coronary artery spasm, (ii) microvascular dysfunction, (iii) aborted myocardial infarction with spontaneous coronary thrombus lysis and (iv) the 'catecholamine hypothesis'. Observational studies and experimental models have failed to demonstrate strong validity of the first three theories, with only a few reports in recent literature, whereas the 'catecholamine hypothesis' consistent with catecholamine-mediated direct myocardial injury is widely accepted ***(Buchholz et al., 2010).***

In the 'catecholamine hypothesis' (**Figure 3)** structural brain damage and a sudden increase in intracranial pressure induce an autonomic storm with elevation in tissue and plasma catecholamine levels. Indeed, a three-fold increase in total body norepinephrine spill into the plasma is described within the first 48 h of subarachnoid

hemorrhage (SAH) and these levels can still be elevated after 1week ***(Lyon et al., 2008).***

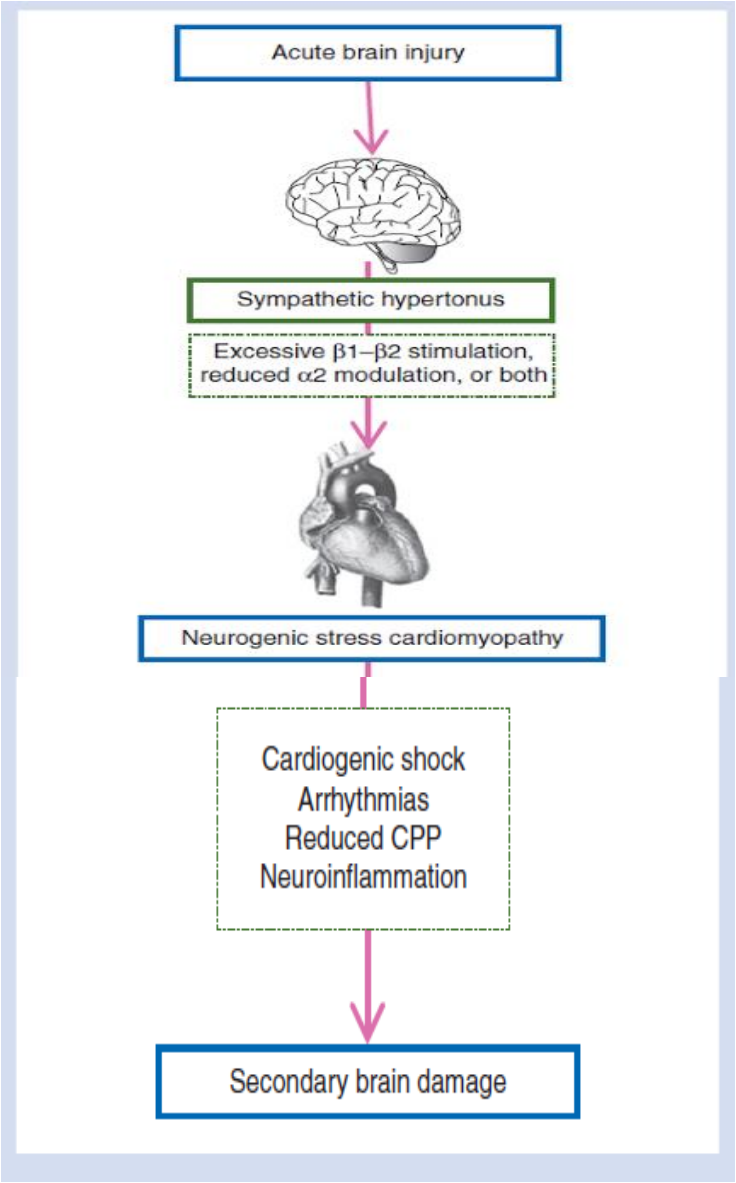

Fig. (3): Catecholamine hypothesis **(Lyon et al., 2008).**

Experimental studies show not only an immediate enhancement of activity in sympathetic nerve terminals with massive release of catecholamines into the cardiac tissue and a small leak into the systemic circulation, but also increased sensitivity to norepinephrine infusion ***(Lambert et al., 2002).***

In experimental models of brain death induced by intracranial hypertension in baboons, cardiac abnormalities were blocked by cardiac sympathectomy or denervation, but still occurred after bilateral adrenalectomy, thus supporting the endogenous release of catecholamines from myocardial sympathetic nerve terminals rather than circulating catecholamines as the mediator of neurocardiogenic injury. In an experimental model of subarachnoid hemorrhage (SAH) in dogs, plasma concentrations of norepinephrine and epinephrine increased significantly from 120 and 130 pg/ml before SAH to 1700 and 5600 pg /ml at 5 min after SAH ***(Masuda, 2002).***

In the case of myocardial stunning due to sudden emotional stress, plasma catecholamine levels at presentation were 2–3 times higher than the values measured in patients with myocardial infarction and 7–34 times normal values: median epinephrine levels were 1264, 376 and 37 pg /ml, respectively; median norepinephrine levels were 2284,1100 and 169 pg /ml, respectively. These high concentrations of

catecholamines lead to calcium overload into myocardial cells, free radical production and adenosine triphosphate depletion, with resulting ECG changes, failure of myocardial contraction and possible cell death ***(Bybee and Prasad, 2008).***

In patients with extreme sympathetic discharge, a specific tissue lesion called 'myocardial contraction band necrosis' has been described, characterized by hypercontraction of sarcomeric myofibrils, eosinophilic transverse bands and interstitial mononuclear infiltration. Histological changes in NSC are characterized by myocardial disarray secondary to catecholamine overload with a significant increase in extracellular matrix protein, contraction band necrosis, mild inflammatory cell infiltration, fibrotic changes and increase in the collagen I/III ratio due to high levels of the pro-fibrotic mediators, angiotensin II and free radicals ***(Lee et al., 2006).***

The differences between the myocardial damage of ischemic disease and that of NSC are significant: with ischemic disease, cells die in a relaxed state with a polymorphonuclear cell response and necrosis in the compromised vascular territory; in NSC, cells die in a hyper-contracted state with contraction bands and early calcification and myofibrillar lesions, which are visible within minutes of onset, appearing close to cardiac nerves. Furthermore, in NSC, the regional wall

motion abnormalities extend beyond a single epicardial vascular distribution and are reversible ***(Kopelnik and Zaroff, 2006).***

A role for inflammation among the mechanisms contributing to the myocardial injury of NSC has also been proposed. While acetylcholine inhibits the release of pro-inflammatory cytokines, parasympathetic dysfunction may facilitate uncontrolled inflammation, causing myocardial damage. Furthermore, elevated levels of cytokines have been described in the cerebrospinal fluid and serum of SAH patients, contributing to neurocardiogenic damage ***(Mayo, 2011).***

The cardiovascular system responds to challenging clinical conditions through a series of well-regulated neural mechanisms involving several cardio-regulatory sympathetic pathways **(Figure 4)** that enable the cardiovascular function to adapt to different challenges. The hypothalamic-pituitary-adrenocortical and sympatho-adrenomedullary axes are the main biological systems activated during the stress response that result in neuroendocrine changes, including an increase in epinephrine and norepinephrine levels. In the last decade anetwork within the insular cortex, the anterior cingulate gyrus and the amygdala, has been found to play a pivotal role in the brain–heart axis ***(Steptoe and Kivimaki, 2012).***

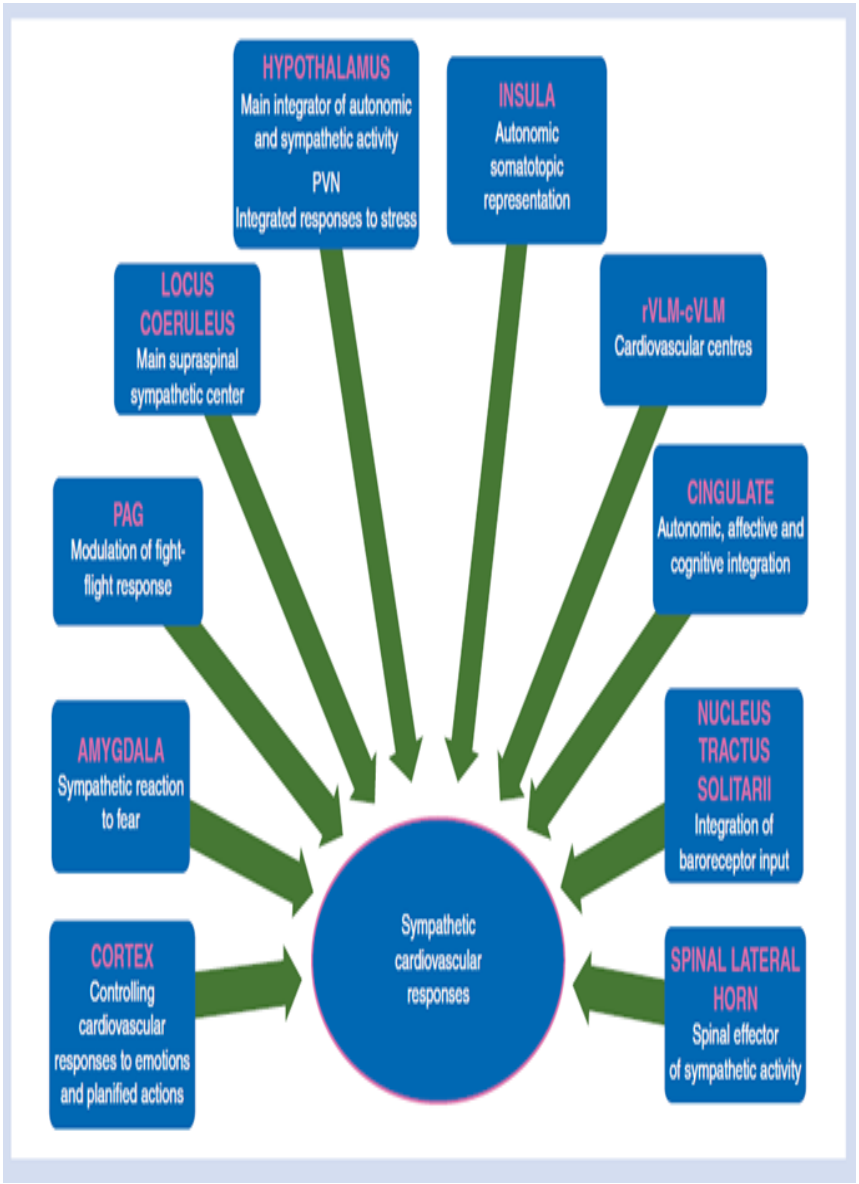

Fig. (4): Well-regulated neural mechanisms involving several cardio-regulatory sympathetic pathways **(Steptoe & Kivimaki, 2012).**

Neurocardiogenic injury and the insula

The insular cortex has a deep anatomical location **(Figure 5),** lying at the base of the Sylvian fissure and in primates it has numerous connections with the cerebral cortex, the basal ganglia and the limbic structure. Experimental and clinical studies have shown that the insular cortex plays a crucial role in the integration of autonomic function. The existence of lateralization for cardiovascular function, with sympathetic tone predominantly regulated in the right insular region and parasympathetic effects situated in the left insula, is supported by several studies ***(Nagai et al., 2010).***

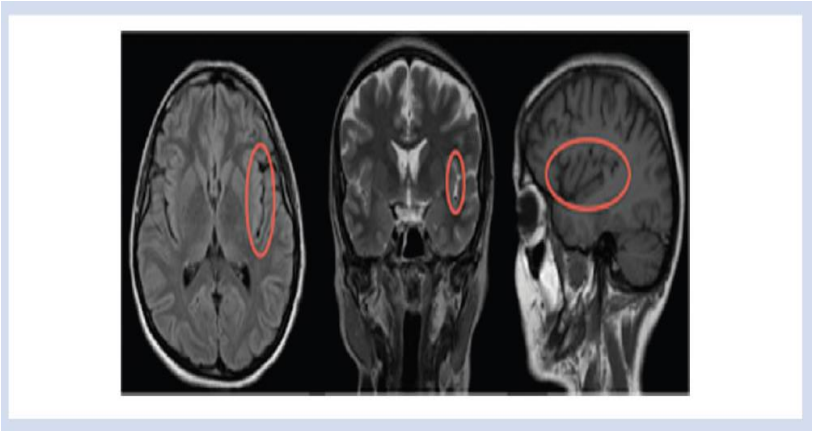

Fig. (5): Anatomical location of insular cortex **(Nagai et al., 2010).**

Electrical stimulation of the insula produces cardiovascular changes in rats, monkeys and humans, depending on the side of stimulation. Bradycardia or a depressant effect (on diastolic arterial pressure) was more

frequent with stimulation of the left insular cortex, whereas tachycardia or a pressor effect was elicited if the right insula was stimulated. Furthermore, the anterior part of the insular cortex subserves emotional functions, whereas the posterior part subserves ascending visceral symptoms ***(Laowattana et al., 2006).***

In clinical studies, insular cortex damage has been associated with ECG changes, arrhythmias, impaired cardiac wall motion and with a poor outcome. In patients with acute ischemic stroke, ischemia of the right insular cortex was associated with higher arterial pressure and norepinephrine levels and there was a relationship between right insular cortex lesions, ECG abnormalities and increased risk of mortality at 3 months. Other studies also showed that left insular cortex injury can be associated with cardiac dysfunction and myocardial wall motion impairment ***(Cho et al., 2010).***

The mechanism of NSC after acute brain injury may be related to disinhibition of the right insular cortex and a resulting augmentation of sympathetic tone. A shift in cardiac autonomic balance towards sympathetic predominance and subsequent decreased cardiac wall motion and alterations in cardiac rhythm may be the cause of increased cardiac morbidity in patients with left insular stroke, compared with other sites of injury ***(Christensen et al., 2005).***

The fact that the insular cortex is located in the region of the middle cerebral arteries may explain its frequent involvement in cerebrovascular accidents. Thus, evaluation of insular involvement with focused neuroimaging techniques could help stratify the relative risk of adverse outcomes when assessing a patient with acute brain injury, suggesting close cardiac monitoring ***(Nagai et al., 2010).***

Cardiac innervation abnormalities

Cardiac innervation abnormalities are described in several pathologies, including cardiac amyloidosis, dilated cardiomyopathy, Parkinson's disease and Lewy body dementia. In patients with acute brain injury, different patterns of global or regional LV wall motion abnormalities have been described, which do not match typical coronary artery distribution ***(Glaudemans et al., 2009).***

In some patients, LV kinetic abnormalities involve the apical region, as in Takotsubo syndrome. A possible explanation for this is related to the fact that the apex is structurally more vulnerable to catecholamine-mediated toxicity than the basal regions, because of a larger proportion of β2- than β1-adrenergic receptors and greater β2-adrenergic receptor induced sensitivity in the apex than in basal cardiomyocytes. Other authors have described a pattern of 'apex sparing' in > 50% of cases of NSC after SAH; this

pattern is characterized by contraction abnormalities in the basal and mid-ventricular portions of the LV wall, with no involvement of the apex ***(Paur et al., 2012).***

Polymorphisms of adrenergic receptors

Cardiac responsiveness to catecholamines is affected by genetic polymorphisms of the adrenoceptors, which are diffusely present in the general population and may be the basis of inter-individual differences in the response to therapeutic b1 agonists and antagonists in cardiovascular and other diseases. There is a correlation between specific β- and α-adrenoceptor polymorphisms and an increased release and sensitivity to catecholamines in patients with SAH and related cardiac involvement ***(Zaroff et al., 2006).***

Single adrenoceptor polymorphisms were associated with a three- to five-fold increase in the risk of cardiac dysfunction, whereas patients with combinations of two of these polymorphisms had a 10- to 15-fold increased risk of cardiac injury after SAH ***(Kumar et al., 2010).***

Cardiac tissue has two subtypes of ß-adrenoreceptor: ß1 and ß2. The ß1-adrenoreceptor stimulates only the G-αs protein. However, the ß2-adrenoreceptor can activate two G proteins, G-αs and G-αi (part of the Gs and Gi heterotrimers, respectively), which differentially regulate adenylate cyclase. The latter generates cyclic adenosine