INTRODUCTION

The relationship between heart and brain in the setting of acute cerebrovascular stroke has been a subject of debate for decades ***(Koppikar et al., 2013).***

A proportion of Stroke patients may have cardiac complications: systolic dysfunction, troponin elevation, atrial fibrillation, or changes on Electrocardiography (ECG) ***(Wira et al., 2011).***

Different ECG changes are observed in cerebro-vascular stroke patients even in absence of primary cardiac disease and these ECG changes can be predictors of prognosis ***(Jaikar et al., 2014).*** This may support a central nervous system origin of these ECG abnormalities ***(Togha et al., 2013)*** and actually these changes could appear at any stage of the disease ***(Jiang et al., 2015).***

The huge majority of findings are fully reversible ***(Jespersen and Fischer, 2008).*** And in general, ECG changes are identical in ischemic and hemorrhagic cerebro-vascular accidents (CVAs), independent of the nature of accident ***(Kanrar et al., 2015; Somasundaran et al., 2015).***

Historically, it has been believed that intracranial processes may cause (ECG) disturbances ***(Surawicz, 1966; Kreus et al., 1969; Norris, 1979),*** rhythm disturbances

(Andreoli et al., 1987; Oppenhiemer **and Hachinski ., *1992)*** and altered repolarization of myocardium. These changes are more frequent consequences of hemispheric rather than of brainstem lesion ***(Hirashima et al., 2001).***

In 1947, Byer, Ashman, and Toth described a patient with intracerebral hemorrhage whose electrocardiogram (ECG) showed marked QT prolongation with large T and U waves**.** In 1954, Burch, Myers, and Abildskov reported a pattern of QT prolongation, abnormal T waves, and U waves which they considered distinctive of acute stroke**.** Sometimes ECG changes may be indistinguishable from those seen in association with an episode of severe myocardial ischemia and/or infarction ***(Cropp and Manning., 1960).***

In addition, patients often have simultaneous hypertension or coronary atherosclerosis leading to ECG abnormalities. Therefore the ECG may be misinterpreted with adverse consequences for the patient. These findings support the adjunctive role of cardiac-monitoring strategies in the acute presentation of acute ischemic stroke ***(Fure et al., 2006; Wira et al., 2011; Ebrahim et al., 2012).***

The brain–heart connection was described early in the 20^{th} century, some have implicated serum catecholamine elevations in particular with strokes

involving the insular cortex ***(Barber et al., 2007),*** and more interestingly it is most likely that it's due to ablation of inhibitory circum-insular efferents to the right insular cortex ***(Oppenheimer, 2006).***

Later, several reports have been published regarding the role of the hypothalamus in controlling cardiac rhythm, especially the function of the sinus node**.** Also morphological ECG changes of repolarization type were observed when the hypothalamus and other parts of the brain are stimulated experimentally ***(Sander and Winbeck, 2001; Barber et al., 2007).***

Repolarization disturbances and dysrhythmias occurring in acute stroke may also be due to direct neuronal effects mediated from the CNS via neurons ending on the heart ***(Caplan, 2002),*** sympathetic hyperactivity, and possibly myocardial necrosis ***(Goldstein, 1979).***

Also numerous reports have described (ECG) changes in aneurysmal subarachnoid hemorrhage (SAH) that are associated with poor outcome ***(Hersch, 1964; Cruickshank et al., 1974)*** and are often attributed to focal subendocardial damage ***(Shuster, 1960; Hunt et al., 1969; Zeppellini et al., 2001)***.

Aim of the Work

To detect the ECG changes in patients with ischemic cerebro-vascular stroke without pre-existent cardiac disease to possibly define any neurological origin of these ECG changes with correlation of these findings to site, laterality and severity.

Chapter (1):
Neuro-cardiology and relationship between Heart and Brain

The Heart and the Brain

The cardiovascular system is a closed system connecting a pump to blood vessels (i.e., arteries, capillaries, veins). The heart serves as the pump that moves blood through blood vessels thereby providing the needed oxygen and nutrients to the body and deoxygenated blood to the lungs. To achieve this goal, a normal human heart must beat regularly and continuously for one's entire life. Heartbeats originate from Auto-rhythmic cardiac cells pacing discharge from the sino-atrial (SA) node within the heart itself. In the absence of extrinsic neural or hormonal influences, the SA node pacing rate would be about 100 beats per minute ***(Gordan et al., 2015).***

In order to respond rapidly to the changing requirements of the body's tissues, the heart rate and contractility are regulated by the nervous system, hormones, and other factors. The intrinsic conduction system coordinates heart electrical activity. This electrical activity in the heart corresponds to electrocardiogram (ECG) wave tracings. On a normal ECG recording, the P wave reflects atrial depolarization followed by atrial

contraction. The QRS wave reflects ventricular depolarization followed by ventricular contraction and the T wave reflects ventricular repolarization ***(Gordan et al., 2015)***

Autonomic Control of the Heart

The autonomic nervous system (ANS) is the component of the peripheral nervous system that controls cardiac muscle contraction, visceral activities, and glandular functions of the body. Specifically the ANS can regulate heart rate, blood pressure, rate of respiration, body temperature, sweating, gastrointestinal motility and secretion, as well as other visceral activities that maintain homeostasis ***(Kaushansky., 2006).***

The ANS functions continuously without conscious effort. The ANS, however, is controlled by centers located in the spinal cord, brain stem, and hypothalamus. The ANS has two interacting systems: the sympathetic and parasympathetic systems. As illustrated in Figure 1 ***(Gordan et al., 2015).***

Cardiac sympathetic nervous system

The sympathetic nervous system is the component of the ANS that is responsible for controlling the human body's reaction to situations of stress or emergency (otherwise known as the "fight or flight" response),

Stimulation by the sympathetic nervous system results in the following effects on the heart

- Positive chrono-tropic effect (increase in heart rate): Stimulation by the sympathetic system nerves results in an increase of heart rate, as occurs during the "fight or flight" response.
- Positive ino-tropic effect (increase of contractility): Stimulation by the sympathetic nervous system causes an elevation in intracellular calcium (Ca2+) and thus an increase in contraction of both the atria and ventricles.

Positive dromo-tropic effect (enhancement of conduction): Stimulation by the sympathetic nervous system also enhances the conductivity of the electrical signal. For example, it increases Atrio-ventricular conduction velocity ***(Boron and Boulpaep, 2011).***

Parasympathetic nervous system

Importantly, the parasympathetic nervous system plays an antagonistic role in regulating heart function.

And in contrast to sympathetic activity, the parasympathetic nervous system has little effect on myocardial contractility. Yet it has the following effects on Heart:

- Negative chronotropic effect (decrease in heart rate): The vagus nerve directly innervates the sino-atrial node; when activated, it serves to lower the heart rate
- Negative inotropic effect (decrease in myocardial contractility): Currently, it is a matter of debate whether parasympathetic stimulation can exhibit negative inotropic effects, as the vagus nerve does not directly innervate cardiomyocytes other than that of the sino-atrial and atrio-ventricular (AV) nodes.
- Negative dromotropic effect (decrease conduction velocity): Stimulation of the parasympathetic system serves to inhibit AV node conduction velocity ***(Boron and Boulpaep, 2011).***

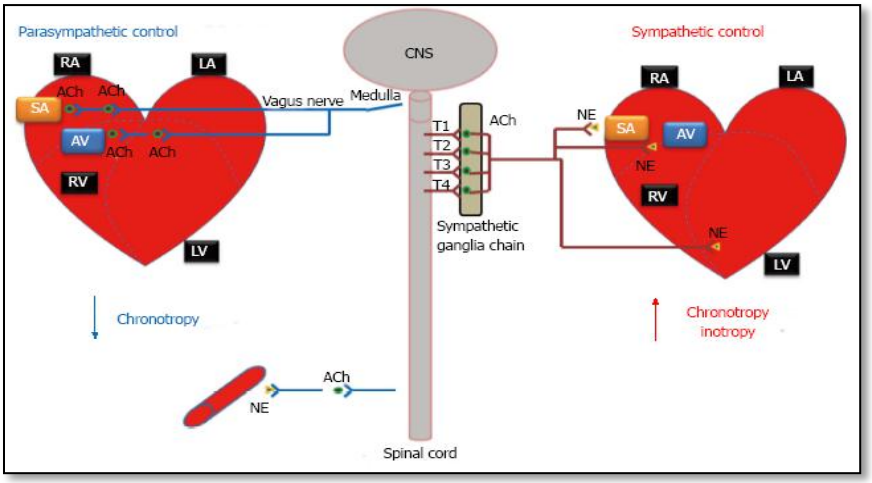

Fig. (1): Autonomic nervous system regulation of the heart function ***(Gordon et al., 2015)***

Neuro-cardiology

Due to numerous anatomic and physiological links between the brain and the heart there are a number of interactions between normal and abnormal functions of both systems (brain–heart disorders), and this interaction between heart and brain becomes increasingly important as the underlying mutual mechanisms become better understood ***(Dombrowski and Laskowitz, 2014).*** The speciality that deals with the brain-heart connection has become known as Neurocardiology ***(Van der Wall, 2011).*** Neurocardiology refers to (patho) physiological interplays of the nervous and cardiovascular systems ***(Ritz et al., 2012).***

Over the past years, there is increasing evidence about the brain heart interaction with major potential implications for treatment of cardiovascular diseases. For instance, cerebrovascular accidents (CVAs) and transient ischeamic attacks (TIAs) are frequently caused by cardiac arrhythmias such as atrial fibrillation (AF) and/or congestive heart failure, and more interestingly -In particular- atrial fibrillation may result in cognitive disorders preceding the occurrence of TIAs or CVAs ***(Van der Wall., 2012; Verheugt., 2012).*** On the other hand, cerebrovascular dysfunction may lead to electrocardiographic disorders and cardiac rhythm disturbances ***(Breet et al., 2011).***

In general Neurocardiology has many dimensions, but it may be conceptualized as divided into 3 major categories:

1- The heart's effects on the brain (eg, cardiac embolic stroke)

2- The brain's effects on the heart (eg, neurogenic heart diseases)

3- Neurocardiac syndromes (eg, Friedreich disease) ***(Samuels, 2007).***

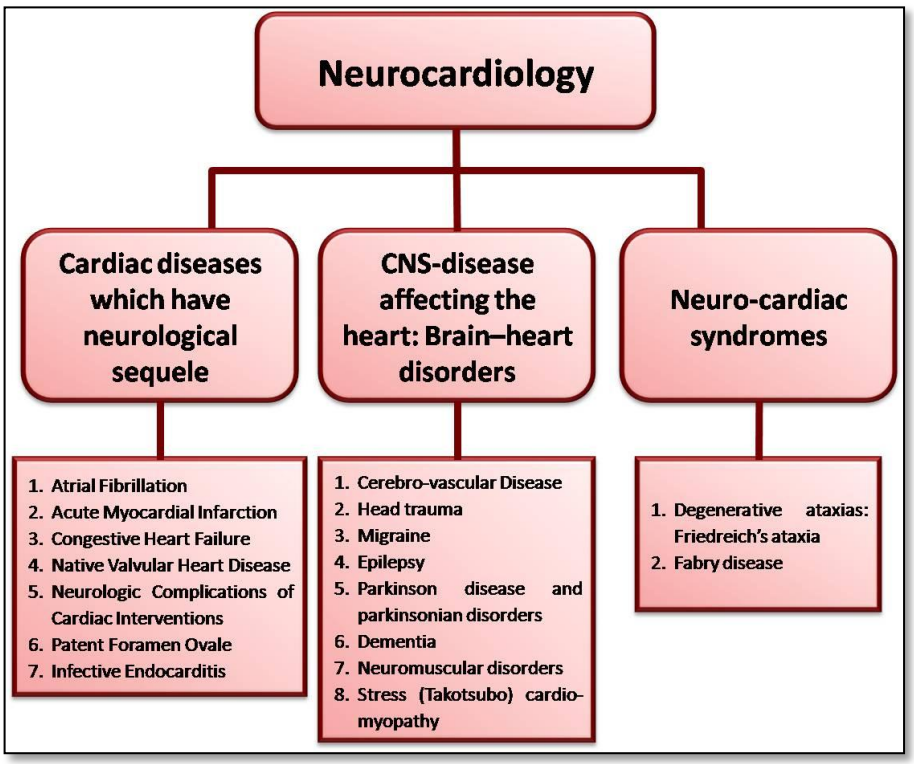

Fig. (2): Neurocardiology Dimensions

Section I

Neurological complications of cardiac disease

Cardiac diseases can be complicated by stroke, cognitive impairment, and brain infections. Those cardiac conditions including –atrial fibrillation (AF), cardiomyopathies, valvular heart disease and inter-atrial septal anomalies- account for 20%-30% of all ischemic strokes ***(Cervera et al., 2007; Furie et al., 2011).*** The mechanism of cardiogenic stroke is often embolic, but hypo-perfusion may also occur, particularly in those with cerebral steno-occlusive disease. Causes of cardio-embolic strokes are cardiac arrhythmias, particularly atrial fibrillation, valve disorders such as rheumatic and prosthetic valves, bacterial endocarditis, mitral valve prolapse and mitral annulus calcification, also it may occur due to cardiac wall and chamber abnormalities -cardio-myopathies, hypokinetic and akinetic ventricular regions after myocardial infarction, and patent foramen ovale **(Leary and Caplan, 2008).** Also, cognitive decline can be associated with congestive heart failure (CHF) and coronary artery bypass graft procedures. Whereas meningitis and brain abscesses are possible complications of infective endocarditis (IE) ***(Cervera et al., 2007; Furie et al., 2011).***

Cardiac diseases that are associated with neurological sequele

1- Atrial Fibrillation

Non valvular AF is the most common cause of cardiogenic stroke, accounting for 50% of cardiogenic emboli and 10% of ischemic strokes ***(Cervera et al., 2007).*** It affects about 1% of the general population and is the most common cardiac arrhythmia in the elderly, having a prevalence of nearly 10% in those older than 80 years ***(Furie et al., 2011).*** Also AF is associated with a 4 to 5 fold increased risk of stroke across all age groups and those who also had a prior stroke or transient ischemic attack (TIA) have an additional 2.5 fold increase in stroke risk ***(Cervera et al., 2011).***

Both persistent and paroxysmal AF increase the risk of first and recurrent embolic stroke and AF explains up to about a quarter of cryptogenic strokes in some series, the embolic stroke is explained by the stasis of blood in atria due to inefficient atrial contraction ***(Hart et al., 2000).*** Cardiac monitoring to detect paroxysmal AF in stroke patients is cost effective across a wide range of factors ***(Tayal et al., 2008; Kamel et al., 2010)***, and beside the risk of cerebral embolism, AF also represents a risk factor for hippocampal atrophy and for cognitive dysfunction probably due low cardiac output that occurs secondarily to

loss of atrioventricular synchrony, specially in old aged people in whom the regulatory compensatory mechanisms are impaired ***(Van der Wall and Van Gilst, 2013).***

2- Acute Myocardial Infarction & Left Ventricular Thrombus

There is a short and long term increased risk of stroke following myocardial infarction (MI). Although the exact cause of MI-associated stroke is often unclear, embolization from left ventricular thrombus is a possible mechanism ***(Hess et al., 1993; Goldstein and El Husseini, 2011).*** Left ventricular thrombus complicating acute myocardial infarction (AMI) results from turbulent blood flow and stasis related to an akinetic left ventricular wall segment or aneurysm, it's predictors were low ejection fraction and severe mitral regurgitation ***(Osherov et al., 2009).***

The incidence of stroke in the acute phase following MI is approximately 1%. Risk factors include large MI, anterior wall involvement, prior stroke, and increasing age ***(Goldstein and El Husseini, 2011).*** However, the risk of stroke was 0.7% at 30 days in patients with AMI without persistent ST-segment elevation ***(Goldstein and El Husseini, 2011).*** On the other hand, the long-term risk over the following 3 months after MI is about 6%, and strokes are mainly ischemic and risk factors include advancing age,

diabetes mellitus, previous history of stroke, history of hypertension, and smoking ***(Herlitz et al., 2005).***

3- Congestive Heart Failure

Congestive heart failure (CHF) can lead to cerebral embolism and hypoperfusion-related ischemia, causing both stroke and cognitive impairments ***(Pullicino et al., 2009; Klijn and Kappelle, 2010).*** The risks and mechanisms of cognitive decline with CHF are less well understood than the risk for stroke ***(Ackerman, 2001; Pullicino and Hart, 2001; Caplan, 2006),*** but severe CHF can be associated with impaired alertness, behavioral changes and cognitive impairment similar to metabolic encephalopathy ***(Almeida and Flicker, 2001; Caplan, 2006).*** Also, CHF is second after AF as a cause of cardiogenic stroke as it is accounting for 9% of strokes also due to stagnation of blood and embolus formation in the weak myocardium. Moreover, CHF and AF coexist in about 2% of stroke patients ***(Pullicino and Homma, 2010).***

In community studies, CHF is associated with more than a 2-fold increased stroke risk, and some studies suggest that the risk may increase with decreasing ejection fraction ***(Katz et al., 1993; Pullicino et al., 2000; Witt et al., 2006; Pullicino and Homma, 2010).***