CARDIAC COMPLICATIONS IN ACUTE STROKE

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ABSTRACT

Heart and brain have many connections both in physiology and disease. Most of literature refers to brain complications of heart disease. In this review we examine the cardiac complications seen in acute stroke, which are rather frequent in clinical practice, and need attention from both neurologist and cardiologist.

Keywords: acute stroke, ECG, heart failure, myocardial ischemia

INTRODUCTION

Medical complications in ischemic or hemorrhagic acute stroke are relatively frequent, and represent the most important cause of mortality, after neurologic complications. They are described in 40-96% of correctly followed-up patients, especially in severe acute stroke and elderly (1).

Following the infectious complications, the cardiovascular ones are frequent and might be prevented (e.g. venous thromboembolism) and efficiently treated (e.g. hypertensive reaction in acute stroke). Among all cardiovascular complications, the true cardiac ones are very severe. About 19% of patients with stroke experience at least one significant cardiac event during hospitalization period (e.g. arrhythmia, repolarization changes on ECG, acute coronary syndrome, etc.) (2).The high rate of cardiovascular complications results from common risk factors shared between cerebrovascular pathology, atherosclerosis and arterial hypertension. The predictive factors for a cardiac event are: first of all, the severity of stroke; history of coronary disease (symptomatic in 20-30% of cases and asymptomatic in up to 40% of cases); history of heart failure or systolic left ventricle dysfunction; diabetes mellitus; renal failure (serum creatinine > 1.5 mg/dl) (2). Most of the patients who experience a cardiac complication already suffer from a cardiovascular disease, either known or unknown (arrhythmia, ischemic heart disease, arterial hypertension, different atherosclerotic determinations) or comorbidities.

Cardiac or cardiovascular complications have short or long term prognostic implications: worsening of the neurologic event (through subsequent hemodynamic disorders); delaying recovery and rehabilitation of the patient; increasing acute mortality because of neurologic and non-neurologic causes (2,3). The cardiac mortality rate over a three months follow-up period was 2-6%. The annual rate of myocardial infarction was 2.2%, and the mortality following a vascular non-stroke cause was 2.1% (2). Cardiac mortality accounts for 19.4% of all deaths at three months after the stroke.

The incidence and type of cardiac complications in acute stroke depend on the nature of the neurologic event: more significant in subarahnoidian (SAH) and intracerebral hemorrhage (ICH), but also in ischemic infarction (large vessels disease). The severity of stroke remains the most important factor which favours and leads to complications (4).

When dealing with cardiac complications in acute stroke, it is mandatory to establish if the cardiac changes: 1) are a direct result of stroke and its effects on the autonomic system and the subsequent neurohormonal factors; 2) are a direct result of stroke (e.g.

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atrial fibrillation, AF); 3) are coincidental circumstances. These data have prognostic and therapeutic implications. Therapeutic dilemmas rise when the cardiac complications have potential negative and hemodynamics effects on cerebral lesion (e.g. antithrombotic treatment).

The most significant cardiac complications in stroke, either hemorrhagic or ischemic, are:

1) electrocardiographic repolarization ST segment and T wave changes;

2) cardiac arrhythmias;

3) heart failure, myocardial ischemia – necrosis and "stress" cardiomyopathy;

4) neurogenic pulmonary edema.

ELECTROCARDIOGRAPHIC REPOLARIZATION CHANGES

Almost any type of electrocardiographic changes have been described in neurologic lesions, such as acute stroke (5), including different types of arrhythmias: AF, atrial flutter, ventricular tachicardia (VT), premature ventricular beats (PVC) and significant ventricular repolarization changes.

Electrocardiographic changes might immediately regress, along with neurological stabilization, but some of them are persistent and more likely to preced the neurologic event. In different clinical trials, the incidence of electrocardiographic changes was high, up to 75-92%, but a lower proportion around 15-30% seems to be more appropriate when it comes to real life (5). Electrocardiographic repolarization anomalies and significant arrhythmias were initially described in subarahnoidian hemorrhage (SAH), where they have a high incidence, but also in cases of intracerebral hemorrhage (ICH) and ischemic acute stroke. The most frequent repolarization changes are QT interval prolongation, ST segment depression, T wave and Q wave changes.

QT interval prolongation is the most frequent ECG anomaly and correlates with acute stroke (45% of patients). It is more likely to appear in SAH as compared to ischemic stroke. One trial including 580 patients revealed a rate of cQT > 500 msec in 16% of cases, but other trials found even a higher percentage (6,7). QT interval prolongation and QT dispersion increase the risk of ventricular tachyarrhythmia (*torsade de pointes*) or sudden death, apparently not explained by the stroke (5,6).

ST segment depression is described in almost one third of patients with acute stroke (7). The ST segment changes appear mainly in the lateral precordial derivations and suggest subendocardial ischemia. They have a different significance in elderly patients or if they have known coronary artery disease, diabetes mellitus, arterial hypertension or renal disease. Asymptomatic coronary artery disease might be present in nearly 40% of patients with acute stroke (5). Repolarization anomalies often may rapidly regress without being associated with biological markers of myocardial necrosis. Troponin T values may be moderately increased in acute stroke in almost 10% of patients with normal coronary arteries (4). ST segment depression, along with other repolarization anomalies, might be the expression of a neurogenic induced cardiomyopathy ("stress" related) (7).

Hight amplitude T waves, and especially the negative ones, were described in intracerebral hemorrhage ("cerebral T waves"). They are probably induced by a neural mechanism; negative T waves quickly disappear after cerebral cellular death (7).

The presence of U waves, apart from electrolytic disturbances, was described in 12% of patients with stroke. The U waves may be either isolated or associated with other changes of ventricular repolarization. Their significance is not very clear yet.

CARDIAC ARRHYTHMIAS

Different types of **cardiac arrhythmias** are detected at the time of admission in the emergency room or during continuous monitoring in the intensive cerebrovascular care units, and are quite frequent (at least 25% of patients). A study performed on 150 patients with acute stroke (two thirds ischemic and one third hemorrhagic stroke) found that the incidence of arrhythmias was 28.7% and of new ECG changes 75% (5). Some of the arrhythmias were already present before stroke, but one third of them were directly associated with the cerebral event, through neural and ischemic factors.

The predictive factors for arrhythmias are advanced age, ECG changes at the time of hospitalization and history of arrhythmias (6).

Cardiac arrhythmias in acute stroke have a negative impact on short-term prognosis: they lead to hemodynamic instability, which has an important impact on cerebral perfusion in critical areas; they also increase the risk of recurrent thromboembolism and sudden death (especially in patients with ICH, in whom the incidence of VT is around 10%) (5).

Ventricular tachyarrhythmia and atrial fibrillation/flutter have important clinical and prognostic significance. The predictive factors for VT were previously specified. Ventricular tachycardia and fibrillation are more frequently seen in SAH and ICH as compared to ischemic stroke.

Paroxysmal atrial fibrillation in the acute phase of stroke was seen in 10-15% of patients and accounts for 32.5% of all the arrhythmias, together with VT (5). The presence of AF raises important issues regarding the etiology of stroke (cardioembolic or non-cardioembolic) and its treatment (the urgency of treatment, the opportunity of antithrombotic treatment). Advanced age, premature atrial beats prior to stroke and history of cardiovascular disease increase the probability of AF development during stroke.

The mechanism of cardiac arrhythmias and the ECG changes during stroke are probably neurogenic, through sympathetic hyperstimulation. A similar mechanism explains the stress cardiomyopathy described in stroke. Other causes associated with ECG changes in stroke should be ruled out before supporting the neurogenic mechanism: recent myocardial ischemia (ischemic heart disease), ventricular dysfunction, electrolyte and metabolic disorders.

Arrhythmias and repolarization ECG changes are more likely to be detected in SAH, but also in ischemic stroke with right insular cortex impairment (5, 8). The insula is one of the most important areas of the cortex, involved in the autonomic function control. It has different interconnections with limbic system, thalamus and other cerebral areas associated with sympathetic function. The lesions, especially of the right hemisphere, might lead to disinhibition of the insular cortex and increase of the sympathetic tone (8). In patients with cerebral ischemia or SAH, there is an increase in serum catecholamine concentration, with autonomic cardiovascular reflexes impairment (5, 6). A severe increase in catecholamine level (both circulating and cellular), as it occurs in stroke and pheochromocytoma, leads to myocardial changes in the form of myocitolysis (contraction band necrosis). This type of lesions are the underlying cause of ECG changes, arrhythmogenesis and regional ventricular dysfunction, which are all seen in stroke (8,9). The cellular and molecular mechanisms responsible for the neurocardiogenic injury, including the ECG changes, are presented in Fig. 1 (7).

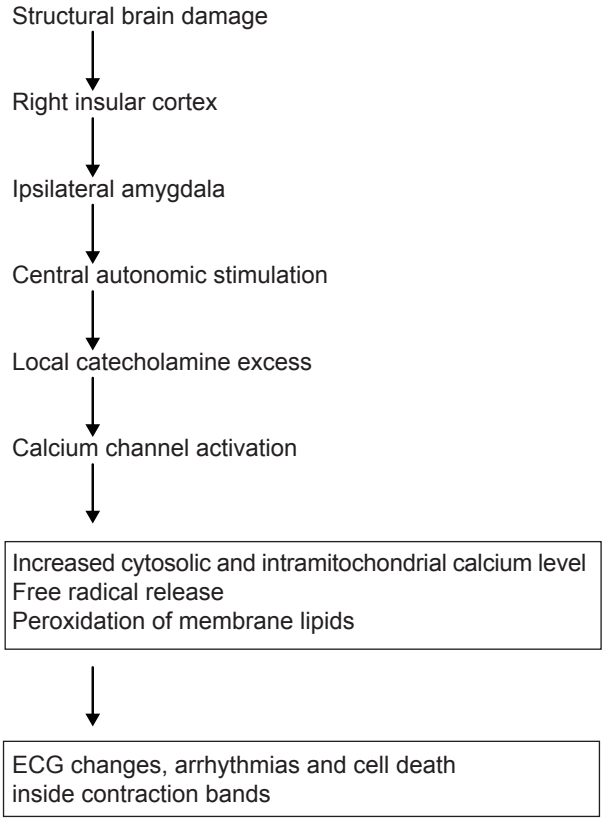

FIGURE 1. *Schematic representation of the mechanisms responsible for the neurocardiogenic injury*

A recent study shows the involvment of insular cortex in cerebral infarct and the high risk of arrhythmias and cardiac death (8). Evaluation and follow-up of 493 patients with cerebral infarction demonstrated by MRI concluded that acute cerebral infarction was independently associated with repolarization anomalies, AF, premature atrial and ventricular beats. Repolarization anomalies and AF were more frequent in the subgroup of patients with insular lesions. The right insular infarction was associated with increased global and vascular mortality, after 2 years of follow-up (8).

HEART FAILURE, MYOCARDIAL ISCHEMIA AND STRESS CARDIOMYOPATHY

Heart failure (clinical heart failure), left ventricular dysfunction and stress cardiomyopathy are three pathological conditions which can be associated with stroke. The neurologic event could either be the direct cause or the precipitant condition in all these situations.

Most frequently, heart failure or left ventricular dysfunction develop prior to stroke, and may worsen because of neurologic or non-neurologic complications onset. Heart failure may be the underlying cause of stroke, as it is the case of a cardioembolic event. Several factors may be involved in heart failure onset in acute stroke: acute myocardial infarction or ischemia, tachyarrhythmia, severe initial hypertensive reaction, fluids overload, medical complications (pulmonary infection, sepsis, etc.). Subsequently, new onset heart failure or its worsening during stroke lead to both global and cerebral hemodynamic alterations (decrease or high variations of cerebral output), which may compromise cerebral perfusion in the "penumbra" zone (cerebral infarction) and worsen stroke progression.

Myocardial ischemia and acute myocardial infarction may develop during an acute or subacute stroke. A meta-analysis of more than 30 cohort trials revealed an annual risk of 2.2% for myocardial infarction, and 2.1% for non-vascular deaths in patients with acute stroke (11). The risk for myocardial infarction varied between 2.6% in UK-TIA trial and 1.3% in VIPS trial, each of them including more than 2,000-3,000 patients. Patients suffering from acute stroke caused by large vessels disease very often have also asymptomatic coronary artery disease or peripheral artery disease, which can explain the higher risk of coronary events.

Myocardial necrosis, as a clinical manifestation of ischemia, may be absent in pacients with stroke. An acute coronary event might be suspected solely on new repolarization ECG changes, increased troponin T levels or new regional wall motion abnormalities on echocardiographic examination. Additional coronary evaluation is the only proof of an atherothrombotic coronary event. Around 20-30% of patients with ASH develop a secondary cardiomyopathy and/or regional wall motion abnormalities, rapidly reversible in the absence of an obstructive coronary disease (7). On the other hand, more than 30% of patients who suffer an acute ischemic stroke have reversible ST segment changes and an increased level of troponin; these changes are neural mediated (11). Under these circumstances, it is thereby difficult to differentiate beween non-ST elevation myocardial infarction/acute coronary syndrome (non-STEMI/ACS) and electrocardiographic and biological changes induced by the stroke, which appear in the first days after the acute cerebrovascular event and are rapidly reversible.

The concept of ***stress cardiomyopathy (CMP)*** was recently described and tends to encompass some of the pathological conditions which develop in acute intracranial events (ischemic stroke, SAH, ICH), acute medical diseases (e.g. sepsis, hyperproduction of endogenous catecholamine, as it occurs in pheochromocytoma, and possibly, emotional stress) (7). The myocardial changes resemble those characterized in sympathetic hyperstimulation or as consequence of myocardium being exposed to high concentrations of endogenous and exogenous catecholamine. Autonomic dysfunction and sympathetic hyperstimulation are responsible for cardiomyocytes and myocardium damage in acute stroke.

The most complete and best known form of stress CMP is *takotsubo CMP* or the *apical ballooning syndrome*. This condition is characterized by electrocardiographic changes similar to an acute anterior myocardial infarction, with reversible regional wall motion abnormalities at the level of ventricular apex and mid-ventricular region (*balloon-like asynergy*), all of this in the absence of coronary atherothrombotic lesions. Takotsubo CMP is more frequent in women (80%) over 60 years old, in the presence of severe emotional stress, acute medical illness or surgical intervention.

Takotsubo CMP has been initially reported in the USA, in the first days following the stroke (7). Left ventricular regional wall motion abnormalities are detected in 18% of patients with SAH (13). In acute ischemic stroke, takotsubo CMP was diagnosed in 1.2% of 569 patients hospitalized in the first 24 hours after the neurologic event. The ECG changes develop between 10 hours and 3 days after acute ischemic stroke, the cerebral infarction being located in the insular cortex or less often in the vertebrobasilar territory (14). Clinical presentation of a takotsubo CMP is similar to an ACS, with intense and prolonged precordial chest pain, suggesting myocardial ischemia; the ECG shows signs of ischemic lesion in the precordial leads, with ST segment elevation, negative T waves, prolonged QT interval, and anteroseptal Q waves in 40% of patients. The ECG changes are transient and disappear after a few days or even weeks. Evaluation of myocardial necrosis markers reveals moderate increase of troponin and CK-MB levels, rather inconsistent with the extent of the ECG changes (12,15).

Echocardiography is mandatory for the correct diagnosis of takotsubo CMP, and even coronary angiography with ventriculography might eventually be required. Echocardiography shows apical and mid-ventricular hypokinesia/akinesia/dyskinesia, along with hipokinetic basal myocardial segments. The extent of apical and mid-ventricular wall motion abnormalities ("ballooning") is not consistent with single epicardial coronary artery distribution (12). Emergency coronary angiography rules out epicardial arteries occlusion, and thus the diagnosis of coronary disease, which could have explained the magnitude of wall motion abnormalities.

In conclusion, correct diagnosis of takotsubo CMP requires three criteria to be met: a) transient left ventricle regional wall motion anomalities, with apical or mid-ventricular specific involvment; b) absence of occlusive epicardial coronary artery disease/ unstable lesions; c) ECG ischemic or necrosis changes in the anterior leads, with moderately elevated seric troponin.

Myocardial stunning is the underlying pathogenic mechanism incriminated for the "apical ballooning syndrome" (takotsubo). Three mechanisms are being discussed: 1) ischemic myocardial stunning induced by epicardial multivascular spasm; 2) myocardial stunning induced by microvascular coronary dysfunc-

tion; 3) catecholamine mediated myocardial injury (7, 9). The myocardial changes described in takotsubo are most likely the result of catecholamine excess, myocyte calcium overload and myocytolysis (contraction bands necrosis) (Fig. 1).

Sympathetic hyperstimulation and catecholamine excess in the myocardium are frequently described in pheochromocytoma, sometimes in SAH and cerebral ischemia with hypothalamic involvement. In experimental models of stroke, middle cerebral artery occlusion is responsible for ipsilateral insular cortex disorders, sympathetic stimulation and elevated catecholamine level in the myocytes, and finally, myocardial injury (contraction bands necrosis) (7).

In stress CMP, including stroke related CMP, the myofibrillar degenerative changes are mainly subendocardial. This process explains ventricular repolarization changes and arrhythmias (damage of the conduction system). This type of lesions, together with catecholamine induced arrhythmias susceptibility, account for the risk of sudden cardiac death seen in SAH or acute ischemic stroke (9). Around 10% of patients with acute ischemic stroke also present with elevated troponin level, explained by a nonischemic neurogenic mechanism. This particular mechanism is triggered by specific catecholamine induced myocytic lesion type (myocytolysis) (9,15).

The entire pathogenic concept of stress CMP, including major neurologic events, has encouraged therapeutic attempts aiming to break the pathogenic chain, which starts off with the "sympathetic storm" and continues with elevated catecholamine plasma levels, myocyte and contraction bands calcium channels opening, free radicals and enzymes release, and all the way to the final lesion, contraction bands necrosis. For that matter, ongoing research focuses on GABA agonists, betablockers, calcium channels blockers, free radicals scavangers and anti-oxidants.

NEUROGENIC PULMONARY EDEMA

Neurogenic pulmonary edema is a specific and relatively rare form of acute pulmonary edema, which appears in acute severe strokes (especially those with SAH or large cerebral infarction), after cerebral trauma or epilepsy episode. It has to be differentiated from cardiogenic pulmonary edema, described in severe ischemic stroke (especially SAH or large cerebral infarction). Differential diagnosis is required and targetts cardiogenic pulmonary edema triggered by arrhythmias, acute coronary syndrome, severe arterial hypertension, which may very well develop in patients with acute stroke and known cardiovascular pathology.

Neurogenic pulmonary edema mechanisms are not entirely known. The pulmonary edema is usually interstitial, and only sometimes alveolar, with fluid rich in proteins and red blood cells. The pulmonary capillary pressure is usually normal and this rules out a cardiogenic factor. Experimental data and clinical observations suggest a sympathetic mechanism, triggered by the increase of intracranial pressure or by hypothalamic lesions. Therefore, redistribution of pulmonary blood flow and increased capillary permeability follow, associated with sudden increase of left ventricular afterload. The alveolar wall injury, endothelial mechanic disruption and the increased capillary permeability are joined pathophysiological disturbances (16).

The pulmonary edema has a sudden onset, short time after the neurologic event (17). Typical signs of a pulmonary edema are apparent on clinical and X-ray examinations. The cardiovascular examination, the electrocardiography and eventually the emergency echocardiography, rule out common causes of a cardiogenic pulmonary edema. Usually, the diagnosis is based upon rulling out specific characteristics of acute respiratory distress and cardiogenic pulmonary edema.

Neurogenic pulmonary edema may be rapidly regressive once there is a specific and efficient treatment addressed for the neurologic event (intracerebral hematoma evacuation, severe reactive arterial hypertension, etc.) (17). Besides specific neurologic treatment, i.v. loop diuretics, osmotic diuretics, dobutamine or mechanic ventilation with positive end expiratory pressure may be of choice.

Cardiac complications in acute stroke, with variable degrees of severity, not very well known and still underdiagnosed, depict only one aspect of cardiovascular complications of cerebral vascular events. Deep vein thrombosis, often asymptomatic, high, intermediate or low risk pulmonary thromboembolism, reactive arterial hypertension, often severe starting from the onset of stroke, complete the spectrum of cardiovascular complications in acute stroke. Each and everyone of these complications may be succesfully prevented and treated. The essential issue in stroke is either prevention of these complications or their treatment, using specific methods in cerebrovascular diagnostic and treatment centers, facilitated by neurology and cardiology team work. Apropriate surveillance and cardiovascular monitoring of patients during acute period of stroke allow for urgent and specific treatment choices to be addressed to cardiovascular and other medical complications, their severity very often being actually underestimated.

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