Brain-Heart interactions during ischemic processes: Clinical and experimental evidences

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Introduction

Cerebrovascular and cardiovascular diseases, including stroke and acute myocardial infarction (AMI), have been the leading causes of death worldwide over the last 15 years according to the World Health Organization. In most cases, AMI and ischemic stroke (IS) share similar risk factors and common pathophysiological mechanisms that can be linked to atherosclerosis and atherothrombosis. Consequently, stroke and AMI patients have similar profiles and therefore may experience both diseases at a short or long term. Patients with successive stroke and AMI have a higher prevalence of vascular risk factors and an increased risk of early death compared with those who have had only one of these diseases, thus defining a high-risk group of patients [1]. In addition to these common characteristics, there are spatial, temporal and direct interactions between IS and AMI.

While cardiac disease may induce IS and is a predictor of IS (Heart-to-Brain interactions), other studies have shown that an ischemic cerebral event can lead to disturbances in heart function (Brain-to-Heart interactions). It is obvious that the brain does not function independently from the visceral organs, and there is a growing interest in the interactions between the brain and the internal organs, the heart in particular. Communication occurs either through neural (e.g., autonomic nervous system) or chemical mechanisms (e.g., endocrine system, immune system). However, our understanding of the specific communication pathways between the brain and the heart is not yet complete although they could represent a promising target for developing protective therapeutic strategies. In this narrative review, we will focus on the mechanistic influence of these brain-induced cardiovascular disturbances during ischemic processes from both a clinical and an experimental point of view.

Stroke-induced cardiovascular disorders: clinical point of view

Cardiovascular outcomes in patients after stroke

Data from a number of clinical studies have associated IS with short or long-term cardiovascular consequences [2-4] (Figure 1). It has been reported that patients with stroke present a higher risk of cardiovascular mortality and AMI (annual risk of 2.2%), leading clinicians to actively manage secondary prevention in this population [5]. A more recent meta-analysis indicates that the annual risk of AMI after stroke or transient ischemic attack (TIA) is 1.67% [6]. This annual risk appears to decrease progressively, and over time stroke recurrence becomes a more frequent cause of death than AMI [6]. In a Korean population with IS, the risk of stroke recurrence was also found to be greater than that of AMI [7]. In another study where AMI was found to affect 1.6% of IS patients, predictors of AMI included advanced age, history of coronary heart disease, chronic kidney failure, AF or conduction disorders [8]. Patients who developed AMI following IS had a 3-fold risk of intra-hospital mortality and a hospital stay that was 50% longer and more expensive than in the absence of this complication. Invasive assessment (coronary angiography) with or without treatment (angioplasty, stent) improved survival in these patients. Concerning TIA, more than half of patients had at least one cardiometabolic comorbidity (diabetes mellitus, coronary artery disease, heart failure (HF), and/or AF) and 22% had at least two comorbidities [9]. Over a 5-year follow-up period, 27% of readmissions were related to cardiometabolic complications, which accounted for 36% of deaths during this period. The 5-year mortality rate following a TIA was correlated with cardiometabolic comorbidities and with readmission rates. A meta-analysis including over 50,000 patients showed that about one-third of patients with IS and with no documented cardiovascular history had more than 50% coronary stenosis, and that 3% of IS patients were at high risk of developing an AMI within a year [10]. Prosser et al. found that, within the 3 months following an IS, 4.1% of patients died from cardiac causes and 19% of patients experienced severe cardiac events [11]. This study showed that serious cardiac events are common in the acute period after stroke and that death from a cardiac origin is the second leading cause of death after an IS. Another investigation found that three-month mortality after stroke was 18.5%; 17.8% of the deaths were from cardiologic causes [12]. During hospitalization, 6.5% of patients developed cardiovascular events including AMI and acute HF. These cardiovascular events occurred more frequently in patients with a recent

history of AMI, in those with a cardio-embolic stroke, and in those with a higher clinical severity of stroke at admission. Thus, in hospitalized IS patients, AMI and acute HF were common and were associated with an increased risk of mortality at 3 months. From one study to another, detection rates of AF are highly variable after an IS or a TIA, but a meta-analysis indicated a rate of 11.5% when monitoring was performed over 12 hours or more [13]. Extending monitoring to more than 24 hours increased the detection rate for AF, which is a frequent complication of AMI and a major cause of stroke. It is therefore crucial to detect AF, particularly considering that treatment for secondary prevention is different for patients with and without AF. Takotsubo cardiomyopathy is another type of myocardial dysfunction that has been observed after IS [14]. This complication is characterized by transient apical ventricular dysfunction and is associated with a worse short-term prognosis [15].

The presence of circulating troponins is a biomarker of heart tissue damage, and it has been found that 13.7% of IS patients present elevated troponins (> 50 ng/L) in the acute stage of the disease, while 50% have no angiographic signs of coronary lesions that could be at the origin of myocardial tissue necrosis [16]. A different proportion was found in the study performed by Ahn et al. They found elevated troponins (> 40 ng/L) in only 8.7% of patients after IS [17]. This increase in troponin has both cardiologic and neurological causes. Indeed, electrocardiogram abnormalities such as prolonged QT interval or Q wave duration, elevation of the ST segment, or left ventricular (LV) hypertrophy have been identified as predictors of troponin elevation. Elevation of troponin in acute brain injury is hypothesized to be a result of an imbalance between the sympathetic and parasympathetic activity leading to myocytolysis [18]. High troponin levels in these patients are thought to be related to subendocardial hemorrhage or swollen myocytes surrounding the epicardiac nerves, so-called myocytolysis. Elevated troponin has been associated with stroke severity and higher mortality, and a recent study identified elevated levels of troponin in 24.1% of IS patients [19]. Finally, some particular clinical situations may occur, such as a stress-induced cardiomyopathy following a stroke [20] or AMI during IS treatment by thrombolysis [21]. Simultaneous development of IS and AMI is uncommon but may occur under 3 specific conditions: 1/ the concomitant presence of unstable coronary and carotid plaques, 2/ IS complicating subacute AMI and 3/ the occurrence of AMI during IV thrombolysis treatment of stroke.

Of course, the heterogeneity in the results of these studies may be partly explained by differences in clinical settings, methods used for stroke ascertainment, or statistical approaches, as well as differences in the distribution of IS etiology or severity.

Stroke location and its impact on the cardiovascular system

Recent neuroscience research has started to shed light on brain-heart interactions in cognitive and emotional processes. In particular, neural responses to heartbeats, as measured with the so-called heartbeat-evoked potential (HEP), is useful for investigating cortical activity processing cardiac signals. HEP could provide a neural measure for investigating brain-viscera interactions in diverse mental processes such as stress during IS or AMI [22].

Several studies indicate that the effect on the cardiovascular system depends on the cerebral hemisphere involved in stroke; this phenomenon is called lateralization. The insular cortex is a frequent site of stroke lesions, since it is reportedly involved in about 65% of cases, with an equivalent location on the left and right cerebral hemisphere. However, when brain damage affects the right insular cortex, the consequences on cardiac function (including complex arrhythmias) are more deleterious and more frequent [23].

Conversely, another study indicates that IS patients with involvement of the left insular cortex have a higher risk of severe cardiovascular consequences [24]. Left insular stroke appeared to be an independent predictor of serious cardiac events such as cardiac death, AMI, angina or HF. The involvement of the insular cortex appears to have a greater impact on post-stroke mortality than other brain areas, particularly when lesions are located in the right insular cortex [25]. One study attempted to associate specific ischemic brain areas with increased troponin levels. Troponins were increased in 6.7% of patients, and the corresponding cerebral areas were the right insular cortex: posterior, upper and median, as well as the lower right parietal lobule [26]. Another study showed that, when a blood sample was taken some time after the initial sample taken at patient admission, and when the analysis technique was able to detect low troponin concentrations, 66% of stroke patients had an elevation of highly sensitive troponins (hs-Tn). This hs-Tn increase was associated

with brain damage on the right side, and particularly involving the insular cortex [27]. IS cardiovascular complications, such as Takotsubo syndrome, are more frequent when stroke affects the insular cortex and peripheral insular areas including the prefrontal cortex or subcortex, and in particular the right insular cortex [15].

Potential mechanisms of stroke-induced cardiac dysfunction

In a study in which 20% of IS patients had increased troponins (> 200 ng/L) and in which almost 25% of patients had a lesion involving the left or right insular cortex, a significant increase in serum epinephrine (E) was observed [28]. The increase in troponins was correlated with several parameters including increased E levels. Patients with elevated troponins had electrocardiographic changes and were more likely to have an AMI. The increase in troponin related to E elevation strongly suggests a sympathetic nervous system activation leading to myocardial damage. IS patients with worsening NIHSS (National Institute of Health Stroke Scale) score during hospitalization, which indicates increasing severity, were found to have higher serum levels of monocyte chemoattractant protein-1 (MCP-1) and troponins than patients with improving NIHSS scores [29]. Levels of troponins, S100B and highly sensitive C-reactive protein (CRP) were increased in patients who died. S100B is a Ca^{2+}-binding protein, expressed primarily by astrocytes and involved in the regulation of a number of cellular processes such as cell proliferation. High troponin levels were associated with high levels of thrombo-inflammation markers such as MCP-1 and tissue plasminogen factor. High troponin levels at 24 hours appeared to predict a worsening NIHSS score but not mortality. Increased serum troponin, AF, electrocardiographic changes and the presence of systolic dysfunction were associated with more severe stroke and a higher intra-hospital mortality rate [30]. These data confirm the need for cardiac monitoring in patients admitted for an IS.

The use of biomarkers for disease prediction and prognosis has demonstrated promise for identifying groups at higher risk who may benefit from more intensive prevention and treatment. In this context, growth differentiation factor 15 (GDF15) is a recently discovered stress-responsive cytokine belonging to the transforming growth factor β superfamily that is involved with inflammatory and apoptotic pathways. Circulating levels of GDF15 reflect acute and chronic cellular stressors which are associated with aging and several diseases [31,

[32]. Indeed, in cardiovascular disorders, GDF15 is a highly emerging biomarker [33] with a strong predictive value for all-cause mortality. Concerning cerebrovascular disease, GDF15 could be used as a biomarker to predict stroke risk in hypertensive patients [34] as well as mortality and stroke risk in AF [35]. Circulating GDF15 is also associated with subclinical brain injury [36]. In patients with IS, GDF15 levels are elevated and associated with worse outcomes [37]. In a Chinese population, a genotypic analysis has been undertaken on GDF15 gene variant types, and those with rs1804826G/T genotype TT or GT had higher serum levels than patients with a GG genotype. Moreover, the level of GDF15 expression appeared to play a role in the development of IS [38]. It has been proposed that GDF15 could be associated with unfavorable clinical outcomes after IS, including death and major disability [37, 39, 40]. A study from our research group further suggested that the GDF15 cytokine could be a prognostic biomarker of mortality in IS patients treated with acute revascularization therapy, either by thrombolysis or mechanical thrombectomy [41].

Stroke-induced cardiovascular disorders: <u>experimental data</u>

The clinical studies presented above clearly demonstrate that stroke is deleterious for cardiovascular function in humans. This concept has been reinforced by experimental studies carried out in rodents. The objectives of such studies were to precisely assess risk factors, relevance to specific brain areas, potential mechanisms and to consider therapeutic treatment options (Figure 2).

Factors influencing cardiovascular response to experimental cerebral ischemia

Considering that approximately 75% of stroke patients are hypertensive, this risk factor is a major target for preventing ischemic stroke [42]. Prolonged periods of hypertension can lead to changes in the cerebral vasculature [43]. Thus, experimental studies using spontaneously hypertensive rats (SHR), a widely-used model for essential hypertension, have been conducted in order to test the impact of elevated blood pressure. In one study, IS was induced in SHR and normotensive rats by right middle cerebral artery occlusion (MCAO) [44]. Six hours after MCAO, SHR rats presented a decrease in blood pressure, in renal nerve sympathetic discharge, and in plasma E which were not observed in normotensive rats who experienced the opposite effects. Therefore, there are variations in the response to cerebral ischemia that could be related to genetic differences in the autonomic nervous system. It has also been shown that arterial hypertension can be a pathogenic factor in the development of myocardial injury following stroke. In SHR, bilateral occlusion of the carotid arteries leads to an increase in heart rate (HR), in plasma enzyme activities such as lactate dehydrogenase and creatine phosphokinase, as well as arrhythmias and histological signs of necrosis and fibrosis [45]. In addition, mature rats were more sensitive to left MCAO than younger rats, and they developed higher levels of sympathetic activities and QT interval prolongations on the electrocardiogram. Therefore, the age of the rat appears to alter sympathetic regulation and contributes to an increase in mortality after IS [46]. Nevertheless, the impact of stroke on cardiac function seems to be age-independent. Indeed, in 6-8-week-old (young) or 12-month-old (age) rats, MCAO induces similar decreases in LV ejection fraction and the same elevation in HR [47]. Although the abovementioned studies showed that ischemic brain damage has cardiac consequences, hemorrhagic brain damage also likely

affects myocardial function. For instance, a stereotaxic injection of collagenase into the right striatum of rats was followed by the shortening of cardiomyocytes and a slowing of calcium flow 12 and 24 hours after hemorrhage. These events were accompanied by an increase in cardiac nitro-oxidative stress [48].

Impact of cerebral infarction location on the cardiovascular system

The phenomenon of stroke lateralization, as mentioned above, has also been observed in experimental models. Several studies have highlighted the effect of the impacted hemisphere on pathophysiology. Hachinski's team reported that a right MCAO in rats had more consequences than a left MCAO. Specifically, there was a more significant increase in arterial blood pressure, a sustained increase in sympathetic discharge of the renal nerve, an increase in circulating NE and an increase in QT interval on the electrocardiogram [49]. Similarly, 2 hours after a right MCAO, there were significantly more arrhythmias, such as ventricular fibrillation and ventricular tachycardia, associated with a prolongation in the duration of the action potential and QT intervals [50]. Bieber et al. showed that only a right MCAO had consequences on LV ejection fraction, HR, diastolic pressure, ventricular contraction and relaxation [47]. Conversely, in a study performed in mice, only left MCAO led to cardiac dysfunction with decreased LV systolic pressure, ventricular contraction and relaxation [51]. Therefore, it can be considered that cerebral ischemia has a lateral effect in both rodents and humans, but that there are differences depending on the species.

The cerebral location of stroke is also a critical point. The insular cortex is a brain area known to be involved in the regulation of the sympatho-vagal tone, which is important for determining the cardiac consequences of cerebral ischemia. A direct stimulation of the insular cortex leads to electrocardiographic changes, cardiac arrhythmias and cardiac tissue damage such as myocytolysis [52, 53]. Damage caused in the insular cortex with an excitotoxin was also found to lead to changes in mean arterial pressure and HR, but it did not cause myocardial damage [54]. When cerebral ischemic zone includes the insular cortex, arrhythmias are more frequent than when the insular cortex is not involved [50]. Studies show that the left insular cortex is involved in the integration of parasympathetic activity while the right posterior insular cortex is involved in sympathetic regulation [55, 56].

Potential mechanisms and signaling pathways involved in cerebral ischemia-induced cardiovascular disturbances

Research has explored several potential biological systems and signaling pathways in an attempt to understand the mechanisms of these deleterious brain-heart interactions [57-59]. Ischemic brain damage does appear to have a direct and long-term effect on cardiomyocytes. Indeed, it has been shown that following a MCAO or a hemorrhagic stroke in rats, there are changes in the sodium, potassium and calcium channels of cardiomyocytes isolated from the hearts of these animals. In addition, irregular activity was observed among the proteins involved in the regulation of calcium homeostasis in the hours and days following intracerebral hemorrhage. In particular, an increase was seen in the protein expression of sarco-endoplasmic reticulum Ca^{2+}-ATPase 2a (SERCA2a) and phospholamban (PLB) associated with a decrease protein expression of Na^{+}/Ca^{2+} exchanger (NCX) and voltage-dependent K^{+} channel [48]. Two hours after MCAO, gene and protein expression of a calcium channel subunit, Cav1.2, was significantly increased in the hearts of animals with arrhythmia [50]. The increased expression of Cav1.2 was also found 24 hours after MCAO and was associated with a decrease in the gene and protein expression of a sodium channel subunit (Nav1.5) and 2 potassium channel subunits (Kv4.2 and Kv4.3) [60]. These results concerning calcium homeostasis actors were confirmed in another study, 2 and 24 hours after MCAO. The expression of the ryanodine receptor was not modified by MCAO, however, those of SERCA2a and NCX were decreased as early as 2 hours post-MCAO, in contrast of those of PLB which was only increased during the acute phase following MCAO [61].

The involvement of nitro-oxidative stress has been reported in various studies. Fang et al. have shown that intracerebral hemorrhage leads to an early increase in 3-nitrotyrosine levels and in the expression of inducible NO synthase in the heart, suggesting a possible involvement of nitro-oxidative damage in cardiac dysfunction [48]. MCAO should also decrease the levels of superoxide dismutase (antioxidant) in the heart and increase malondialdehyde (oxidative stress marker) [62]. An increase in protein expression of NADPH oxidase 2 was observed in mouse hearts 28 days after distal MCAO [63], and there was a decrease in total anti-oxidant defenses 3 hours after MCAO in rats [64]. Our team has recently demonstrated that cerebral embolization in rats decreased protein expression of peNOS and catalase [65].

Other signaling pathways have been investigated in an attempt to explain the cardiac consequences of cerebral ischemia. The recent concept of an indirect pathological pathway of cell death originating from the brain and reaching the heart stipulates that soluble factors secreted by the ischemic brain cells may potentially be carrying cell death signals to the cardiac myocytes. In this hypothesis, “cell death signals” could be released by ischemic neurons and translated to the heart; these substances inducing deleterious toxic effects on cardiomyocytes. The signals involved were cytokines of necrosis (TNFα), apoptosis (Caspase 3, fas ligand) and autophagy (MAP1L3CA), which contributed to a decrease in the viability of cardiomyocytes [66]. It was subsequently shown that apoptosis signals (Bax/Bcl2) were increased after MCAO, either in the heart or hippocampus [64, 67]. Several studies have also reported an increase in the activation of inflammation pathways after stroke. This inflammation obviously affects the brain [68], but it can spread to other remote organs such as the heart. For example, it has been shown in mice that MCAO leads to a significant increase in the infiltration of macrophages and cardiac TGFβ expression 28 days after stroke induction [63]. We recently observed that GDF15 levels were increased in rats 2h and 24 hours after left or right cerebral embolization [65].

The sympathetic autonomic nervous system is one of the most studied factors, and it appears to play a major role in the brain-heart interactions after stroke. In 1989, Cechetto and his team showed a significant increase in plasma catecholamines: E and NE, 90 and 180 minutes after left MCAO [69]. The increase in plasma catecholamines may have different kinetics depending on age; thus, NE levels rise as early as 4 hours in elderly rats whereas it is necessary to wait 6 hours in younger rats [46]. This activation of the sympathetic autonomic nervous system seems to be initiated very quickly, with an increase in NE levels observed as early as 1 hour post-MCAO, but also to persist in the long term since this activation is still present 2 to 10 days after MCAO [49, 70]. A recent study even showed that this sympathetic activation was still present 8 weeks after surgery, with an increase not only of NE and E levels but also in cortisol levels [47]. The genetic strain of rats also seems to impact the response of the sympathetic nervous system; indeed, E levels are less increased 6 hours after MCAO in SHR rats than in Wistar rats [44]. Stimulation of a specific cerebral area such as the insular cortex also causes an increase in NE 8 hours after beginning of the experiment [52]. These high NE levels are associated with increased cardiac tissue NE levels 24 hours after left

MCAO when cardiac dysfunction is observed [51]. Catecholamines and glucocorticoids seem to increase only in cases of massive stroke (MCAO) but not in moderate stroke (coagulation of the middle cerebral artery). A link between this activation and the inflammatory context can be suggested. The increase in catecholamines induces an alteration of interferon gamma secretion by lymphocytes via the β2-adrenergic receptor, which seems to play a role in leucocyte death [4, 71].

In a study performed by our team, where cerebral embolization was induced through the injection of microspheres into the internal carotid artery, IS had an impact on heart function [65]. Our findings were corroborated by the results of previous studies. IS led to changes in LV ejection fraction *in vivo* throughout the 7-day follow-up period and to changes in the LV developed pressure *ex vivo* suggesting an "impregnation" effect on cardiac tissue as early as 2 hours and still visible 24 hours after embolization. Interestingly, the heart was also more vulnerable to ischemia-reperfusion damage *ex vivo* after an IS. The signaling pathways involved in these phenomena were: 1/ the sympathetic autonomic nervous system, with a decreased protein expression of β1-adrenergic receptors in the heart in conjunction with a significant increase in E and NE levels, 2/ nitro-oxidative stress, with changes in gene and protein expression of different oxidant and anti-oxidant enzymes, 3/ inflammation, with an increase in GDF15, and 4/ a decrease in protein expression of the SAFE cardioprotective pathway.

Following MCAO, the expression of cardiac collagen, traditionally involved in remodeling, is not increased or is even decreased, suggesting an atrophic rather than a hypertrophic signaling process. The expression of proteins known to regulate the atrophy of skeletal and cardiac muscles has been studied in order to explore the hypothesis of cardiac muscle "melting" [72]. The results showed that the expression of atrogin-1 and murf-1 proteins (muscle ring finger protein) was increased in the heart after MCAO. The expression of these proteins and cardiac atrophy are closely related to autonomic innervation. In fact, NE was significantly increased in cardiac tissue, but the activity of the enzyme controlling its synthesis was not (tyrosine-hydroxylase).

Limitations

Although an extensive literature research was conducted to document this narrative review, we did not perform a systematic review. We deliberately decided to focus on clinical and experimental data that we considered as the most relevant to address the question, and cannot exclude that some works have been missed.

Future directions

Presently, cardiac complications of IS are not sufficiently considered in clinical practice with regard to the decision-making process for implementing secondary prevention. A better understanding of mechanisms involved in brain-heart interactions is necessary to identify potential targets for innovative therapeutic strategies aiming at protecting heart in patients with IS. A translational approach is relevant for such an achievement, and further animal studies will need to consider the variability of clinical situation including the impact of age, sex, predisposing vascular risk factors, prior-to-stroke heart lesions, and acute IS revascularization therapies on post-stroke heart dysfunction.

Conclusion

Cerebral ischemia has a short and long-term deleterious impact on cardiac function that is mediated through different pathways that interact closely with each other. Processes involved in the brain-heart interaction are promising targets for future secondary prevention therapies aiming to reducing the burden of cardiac damages after IS.

Figure Legends:

Figure 1: Clinical consequences of stroke on the cardiovascular system

Ischemic stroke (IS), in particular involving the right insular cortex, is responsible for sympathovagal disturbances and triggers inflammatory processes including the release of cytokines such as MCP-1, CRP and GDF15. The cardiac impact of IS is evidenced by elevated troponins, cardiac arrhythmia, impaired cardiovascular function and increased sensitivity to myocardial infarction. Consequently, IS is characterized by a higher risk of cardiovascular events and an increased risk of mortality, acute myocardial infarction (AMI) and heart failure (HF).

Figure 2: Cardiovascular consequences of experimental cerebral ischemia

The cardiac effects of experimental cerebral ischemia in rodents, in particular these involving the insular cortex, are subject to a lateralization process that depends on species. Genetic background, such as spontaneous hypertension in rats (SHR), is also important. Cerebral ischemia induces sympathetic activation and the release of other stress hormones such as cortisol, but also “death signal” proteins and inflammatory cytokines such as GDF15. The cardiovascular consequences include an increase in blood pressure, electrocardiographic disturbances, arrhythmia, impaired left ventricular function, nitro-oxidative stress, muscle atrophy and increased vulnerability to myocardial ischemia-reperfusion injury. In cardiomyocytes, changes in ionic currents and channels are observed, inducing alterations in cardiac homeostasis and a decrease in the expression of SAFE cardioprotective proteins.

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