

# Brain–Heart Interaction

## Cardiac Complications After Stroke

Zhili Chen,\* Poornima Venkat,\* Don Seyfried,\* Michael Chopp, Tao Yan, Jieli Chen

**Abstract:** Neurocardiology is an emerging specialty that addresses the interaction between the brain and the heart, that is, the effects of cardiac injury on the brain and the effects of brain injury on the heart. This review article focuses on cardiac dysfunction in the setting of stroke such as ischemic stroke, brain hemorrhage, and subarachnoid hemorrhage. The majority of post-stroke deaths are attributed to neurological damage, and cardiovascular complications are the second leading cause of post-stroke mortality. Accumulating clinical and experimental evidence suggests a causal relationship between brain damage and heart dysfunction. Thus, it is important to determine whether cardiac dysfunction is triggered by stroke, is an unrelated complication, or is the underlying cause of stroke. Stroke-induced cardiac damage may lead to fatality or potentially lifelong cardiac problems (such as heart failure), or to mild and recoverable damage such as neurogenic stress cardiomyopathy and Takotsubo cardiomyopathy. The role of location and lateralization of brain lesions after stroke in brain–heart interaction; clinical biomarkers and manifestations of cardiac complications; and underlying mechanisms of brain–heart interaction after stroke, such as the hypothalamic–pituitary–adrenal axis; catecholamine surge; sympathetic and parasympathetic regulation; microvesicles; microRNAs; gut microbiome, immunoresponse, and systemic inflammation, are discussed. (*Circ Res.* 2017;121:451–468. DOI: 10.1161/CIRCRESAHA.117.311170.)

**Key Words:** brain injury ■ brain ischemia ■ heart failure ■ inflammation ■ stroke

Cardiac injury is common in patients with cerebrovascular disease.<sup>1–3</sup> In 1947, Byer et al<sup>4</sup> first reported that cerebral vascular disease can cause myocardial damage and arrhythmia. The specialty that deals with the brain–heart connection is now referred to as neurocardiology.<sup>5</sup> Typically, stroke (ischemic stroke, brain hemorrhage, and subarachnoid hemorrhage [SAH]) induces neurovascular uncoupling and disrupts cerebral autoregulation, which then renders cerebral blood flow directly dependent on cardiac function.<sup>6</sup> Multiple interactions occur among the various forms of cardiovascular and cerebrovascular diseases. Myocardial injury, ischemia-like electrocardiographic changes, and arrhythmias are frequently encountered in acute stroke patients, even in the absence of primary heart disease, which support a central nervous system (CNS) origin of these electrocardiographic abnormalities.<sup>1–3,7</sup> Using a meta-analysis, including 25 studies with a total of 2690 patients, van der Bilt et al<sup>8</sup> found that cardiac dysfunction is associated with an increased risk of death, delayed cerebral ischemia, and poor outcome after SAH. On the basis of accumulating clinical evidence, it is likely that there exists a causal relationship between brain damage and heart dysfunction. It is important to determine whether cardiac dysfunction in patients is triggered by stroke, is an unrelated complication, or is the underlying cause of stroke. Therefore, investigating

the brain–heart interaction after stroke is highly clinically significant.

### Scope of This Review

A multitude of brain injuries such as stroke (ischemic stroke, brain hemorrhage, or SAH), traumatic brain injury (TBI), brain tumor, and various causes of intracranial hypertension can lead to cardiac dysfunction, arrhythmias, and heart failure. Brain–heart syndrome broadly refers to heart damage caused by various brain disorders. The ability to accurately diagnose the occurrence and development of brain–heart syndrome is highly valued in the clinic. This review article focuses on brain–heart interaction after stroke of CNS origin. The role of location and lateralization of brain lesions in brain–heart interaction, clinical manifestations, pathophysiology, and mechanisms of brain–heart interaction after stroke are discussed.

### Cardiac Damage and Stroke in the Light of Risk Factors and Pre-Existing Heart Disease

Cardiac complications leading to morbidity and even mortality in the days immediately after an acute stroke include heart attack, congestive heart failure, cardiac arrest, and abnormal heart rhythms like atrial fibrillation.<sup>5</sup> Converging risk factors for cerebrovascular and cardiovascular diseases,

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**Nonstandard Abbreviations and Acronyms**

<b>BBB</b>	blood–brain barrier
<b>CNS</b>	central nervous system
<b>cTnl</b>	cardiac troponin I
<b>cTnT</b>	Cardiac Troponin T
<b>HF</b>	high frequency
<b>HPA</b>	hypothalamic pituitary adrenal
<b>HRV</b>	heart rate variability
<b>hsTnT</b>	high-sensitivity troponin T
<b>IL</b>	interleukin
<b>LF</b>	low frequency
<b>MBP</b>	myelin basic protein
<b>MCP-1</b>	monocyte chemoattractant protein-1
<b>MiR</b>	MicroRNA
<b>NSC</b>	Neurogenic stress cardiomyopathy
<b>NT-proBNP</b>	N-terminal fragment of B-type natriuretic peptide
<b>SAH</b>	Subarachnoid hemorrhage
<b>TBI</b>	traumatic brain injury
<b>TLRs</b>	Toll-like receptors

such as hypertension, diabetes mellitus, high cholesterol, and age, exacerbate cardiac injury irrespective of stroke cause or subtype.<sup>9</sup> Therefore, severe heart problems are more likely caused by systemic dysfunction–induced vascular damage, inflammation, and immune responses, such as in hypertension and diabetes mellitus, rather than a direct neural causation, although brain damage may act to worsen cardiac dysfunction.<sup>10,11</sup> The Framingham study reported that stroke incidence more than doubled in the presence of coronary heart disease, more than tripled with hypertension, increased 4-fold with cardiac failure, and increased 5-fold with atrial fibrillation.<sup>9</sup> Approximately 20% of ischemic strokes are caused by cardiac disease, the major risk factor being atrial fibrillation.<sup>9</sup> In addition to being the most common tachyarrhythmia in acute stroke, atrial fibrillation is also highly associated with an increased risk of systemic thromboembolism.<sup>9,12</sup> A history of cardiovascular diseases and hypertension increases incidence of electrocardiographic abnormalities in comparison to ischemic stroke patients with no primary heart disease.<sup>13</sup> The aging population is largely affected by heart failure because of structural or functional damage to the heart affecting ventricular blood filling and ejection fraction.<sup>14</sup> In this review, to specifically elucidate the brain–heart interaction of CNS origin in the setting of stroke, we discuss the mechanisms of brain–heart interaction after stroke without pre-existing heart disease. How diabetes mellitus, hypertension, age, sex, atrial fibrillation, and pre-existing heart disease influence brain–heart interaction are beyond the scope of this review and are not discussed.

### Cardiac Damage as a Consequence of Stroke

The second leading cause of post-stroke death is cardiovascular complications.<sup>15</sup> Broadly, stroke-induced cardiac damage may lead to fatality, potentially lifelong cardiac problems (such as heart failure), or mild and recoverable damage, such

as neurogenic stress cardiomyopathy (NSC) and Takotsubo cardiomyopathy. Cardiac dysfunction manifested during the acute phase after brain injury usually resolves over the following several weeks alongside improvement of neurological function.<sup>15</sup> Stabilization of the patient in relation to the type of stroke takes precedence over treatment of the heart dysfunction. NSC is diagnosed by reduced left ventricular (LV) ejection fraction, ventricular wall motion abnormalities, and elevated serum cardiac enzymes. Although Takotsubo cardiomyopathy shares the symptoms and transient nature of NSC, it is caused by psychological stress in the absence of physical damage to the brain. The telltale sign of Takotsubo cardiomyopathy is apical ballooning, caused by a weakening of the heart's muscular cells. Still, Takotsubo cardiomyopathy and NSC may induce ventricular wall motion abnormalities in other regions of the heart.<sup>16,17</sup> Many studies focus on the impaired contraction of the ventricle, which results in low ejection fraction, but it seems that the relaxation of the ventricle is also disrupted in NSC. Clinical symptoms of cardiac dysfunction after brain hemorrhagic stroke and ischemic stroke are summarized in Table 1.

### Hemorrhagic Stroke–Induced Cardiac Damage

Experimental animal studies and clinical data indicate a gradient of NSC, where electrocardiographic abnormalities are found in 40% to 100% of SAH patients and 5% SAH patients have serious cardiac arrhythmias.<sup>18</sup> Cardiac arrhythmias are associated with an increased risk of cardiovascular comorbidity, prolonged hospital stay, and poor outcome or death after SAH.<sup>18</sup> The life-threatening ventricular arrhythmia is also associated with elevated creatine phosphokinase myocardial fraction mass and increased troponin T level in left side of intracerebral hemorrhagic stroke patients.<sup>19</sup> Eighty percent of patients exhibit ischemic-like electrocardiographic changes within 1 year after intracerebral hemorrhage or SAH.<sup>20</sup> In SAH patients, the Hunt–Hess grading score of severity shows that electrocardiographic changes are observed consistently at the lower grades, but echocardiography changes are found predominately in patients with higher grades.<sup>21</sup> It is likely that less severe electrocardiographic changes precede structural alterations, as QTc (the interval between peak contraction and repolarization) prolongation does not predict ventricular wall motion abnormalities, but more severe electrocardiographic changes like inverted T waves and elevated Troponin levels, secreted by damaged sarcomeres, can predict ventricular wall motion abnormalities.<sup>16</sup> Lee et al<sup>22</sup> found that in spontaneous and traumatic brain hemorrhage patients, 7.2% (no history of cardiac disease patients) show acute cardiac dysfunction and 43% have LV hypertrophy.<sup>22</sup> Acute cardiac dysfunction is independently associated with in-hospital death<sup>22,23</sup> and associated with a diminished 1-year functional outcome.<sup>20</sup> LV diastolic dysfunction reflects abnormalities in atrial filling by venous return, atrial contraction, and ventricular relaxation capabilities. Although LV diastolic dysfunction is a cause of cardioembolic stroke (present in 15%–25% of the population, increasing with age and hypertension<sup>24</sup>), more than half of SAH patients develop LV diastolic dysfunction, despite experiencing a stroke of noncardioembolic origin.

**Table 1. Summary of Clinical Manifestation of Cardiac Dysfunction After Stroke in Patients**

	SAH	IS	Comments
TTC	TTC is a transient left ventricular apical ballooning syndrome	Women are more prone to TTC and risk increases with age (IS in post-menopausal stage) <sup>15</sup>	TTC is often misdiagnosed as acute coronary heart disease <sup>172</sup>
	It is typically triggered by physical or emotional stress		Patients are at risk for recurrence
	It is diagnosed by elevated cardiac enzymes, WMA, and ECG changes		
Stress-induced cardiomyopathy	Dyspnea and chest pain, ECG abnormalities such as ST-segment elevation, T-wave inversion, prolonged QT interval, and echocardiographic WMA <sup>172</sup>		Patients may also experience post-stroke depression
	TTC-like LV dysfunction and delayed cerebral ischemia have been reported <sup>172</sup>	Early ECG abnormalities (few hours to 48 h after IS onset) <sup>15</sup>	
		Infarcts in/near insular cortex <sup>15</sup>	
		Transient LV EF reduction <sup>15</sup>	
Abnormal cardiac function and ECG abnormalities	Reduced ventricular EF		High troponin levels are related to the severity of reduced EF and LVDD <sup>173</sup>
	Cardiac dysfunction increases with severity of stroke or hemorrhage		
	75% stroke patients have some ECG abnormality <sup>11</sup>		
	Cardiac arrhythmias during acute phase ( $\approx 37.5\%$ SAH patients) <sup>18</sup>	Cardiac arrhythmias ( $\approx 22\%$ IS patients) and LVDD ( $\approx 50\%$ IS patients) <sup>24</sup>	Acute IS in right cerebral hemisphere increases susceptibility and severity of arrhythmias <sup>1</sup>
	WMA (15% to 22% SAH patients) <sup>8</sup>	LVDD may or may not be symptomatic but both cases hinder functional recovery <sup>18,19</sup>	
	Hypokinetic WMA	Severe LVDD ( $\approx 10\%$ IS patients) may indicate stroke with atrial fibrillation <sup>175</sup>	
	ECG ventricular repolarization disturbances such as ST-segment elevation and T-wave inversion that mimics acute myocardial infarction <sup>174</sup>	Impaired cardiac function after acute IS may predict a 3-mo mortality <sup>176</sup>	Patients have greater ECG abnormalities and are susceptible to developing supraventricular tachycardia <sup>177</sup>
Secondary complications	Diastolic dysfunction correlated with pulmonary edema <sup>11,176</sup> Vasospasm with increased risk of delayed cerebral ischemia <sup>172</sup>	Severity of diastolic dysfunction increases composite vascular events at 1 y <sup>24</sup>	
Recovery of cardiac function	Corrected QT prolongation, bradycardia recovers immediately after aneurysmal clipping <sup>21</sup>	LVH can persist at 7 d <sup>21</sup>	LVDD persists in TTC when systolic function recovers at predischarge <sup>180</sup>
	cTnI levels return to normal by day 7 <sup>178</sup>	ST-segment elevation/depression, T-wave inversion persists at 7 d in some patients <sup>21</sup>	TTC after stroke may be reversible <sup>24</sup>
		RWMA abnormalities tend to be temporary and improves in 66% patients at follow-up <sup>179</sup>	

cTn indicates cardiac troponin; EF, ejection fraction; IS, ischemic stroke; LV, left ventricular; LVDD, left ventricular diastolic dysfunction; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; RWMA, regional wall motion abnormalities; SAH, subarachnoid hemorrhage; TTC, Takotsubo cardiomyopathy; and WMA, wall motion abnormalities.

### Ischemic Stroke–Induced Cardiac Damage

The risk of cardiac complications increases proportionally to the severity of ischemic stroke and neurological deficits.<sup>15</sup> Likewise, impaired cardiac function as a consequence of severe acute ischemic stroke is a predictor of worse functional outcome and secondary complications.<sup>25</sup> Clinically relevant secondary complications such as vasospasm, delayed cerebral ischemia, and pulmonary edema require active management. Recent evidence suggests that ischemic stroke can cause cardiac dysfunction even in the absence of risk factors and

pre-existing heart disease.<sup>26</sup> During the first 3 months after acute ischemic stroke, 19.0% of patients experience at least 1 serious cardiac adverse event; 28.5% have LV ejection fraction  $<50\%$ ; and 13% to 29% have systolic dysfunction.<sup>27,28</sup> Approximately 67% of acute ischemic stroke patients have electrocardiographic abnormalities of ischemic and arrhythmic in the first 24 hours after stroke.<sup>29</sup> Cardiac arrhythmias are common reasons for death after acute ischemic stroke.<sup>26</sup> About 88% of stroke patients who sustain damage to the insular cortex in the right cerebral hemisphere develop myocardial injury in the weeks after ischemic stroke.<sup>1</sup>

Stroke (lacunar subtype) also induces heart problems in  $\leq 70\%$  of patients, with clinical manifestations such as electrocardiographic changes, reduced LV ejection fraction, ventricular wall motion abnormalities, and increases in serum cardiac enzymes.<sup>28,30</sup> However, there is a paucity of studies investigating the mechanisms of small or lacunar stroke-induced cardiac dysfunction in both clinical and experimental research.

### Myocardial Enzymes

cTnI (cardiac troponin I) is considered a more specific and sensitive biomarker for the detection of cardiac damage and LV dysfunction than CK-MB.<sup>31</sup> CK-MB is not completely cardiac specific and may increase in skeletal muscle injury, kidney failure, intramuscular injection, strenuous exercise, and after exposure to several toxins and drugs.<sup>31</sup> CK-MB elevations are most likely of noncardiac origin in patients with large hemispheric stroke.<sup>31</sup> Increased circulating cTnI is associated with poor clinical outcome and cardiac function, such as ST-segment elevation in myocardial infarction patients,<sup>32</sup> as well as in patients with advanced myocardial hypertrophy, fibrosis, and cardiovascular death.<sup>33,34</sup>

Serum cTnI or cTnT (cardiac troponin T) levels are indicators of cardiac damage after ischemic stroke, intracerebral hemorrhage stroke, and SAH. Elevation of serum myocardial enzymes is reported in 11% to 21% of SAH patients and in 1% to 17% of ischemic stroke patients.<sup>35</sup> SAH patients have higher levels of circulating hsTnT (high-sensitivity troponin T) and NT-proBNP (N-terminal fragment of B-type natriuretic peptide).<sup>36,37</sup> Twenty-two percent of brain hemorrhage patients have TnI elevation and 59% have NT-proBNP elevation.<sup>38</sup> In acute ischemic stroke patients, 5% to 8% patients have high level of circulating cTnI and cTnT,<sup>39,40</sup> and 65% patients have increased levels of circulating NT-proBNP.<sup>40</sup> A recent study reported that patients who had acute ischemic stroke in the dorsal anterior insular cortical region of the right hemisphere had elevated relative changes of high-sensitivity cTnT levels, which can induce autonomic dysbalance, sympathetic activation, and myocardial injury.<sup>41</sup>

The level of hsTnT and NT-proBNP are strongly related with poor long-term outcome in SAH patients and are associated with increased stroke severity, mortality, and worse neurological functional outcome after ischemic stroke.<sup>36,42,43</sup> However, using multivariate regression analysis, Etgen et al<sup>44</sup> reported that neither cardiac troponins nor NT-proBNP influence morbidity and mortality if other risk factors are considered. Nigro et al<sup>42</sup> found that BNP, but not hsTnT level, predicts short- and long-term prognosis after cerebrovascular events. Among the reported independent predictors of elevated cTnI are female sex, larger body surface area, and higher heart rate.<sup>45</sup> The American Stroke Association recommends a baseline electrocardiographic and baseline troponin assessment in patients with acute stroke to identify concurrent myocardial ischemia or cardiac arrhythmias.<sup>46</sup> Myocardial enzymes and biomarkers of cardiac dysfunction after brain hemorrhage and ischemic stroke are summarized in Table 2.

### Heart Rate Variability

Heart rate variability (HRV) serves as an assessment tool for autonomic cardiac control and is a measurement of the

variation in the heart beat interval (interval between successive R peaks in the QRS complex of ECG) reflecting the instantaneous fluctuation in heart rate. Heart rate fluctuation may result from the neurohumoral regulation of the body to adapt to different physiological conditions, or in response to certain pathological conditions. Heart rhythm oscillations may be categorized into 4 primary frequency bands: high-frequency (HF), low-frequency (LF), very-low-frequency, and ultralow-frequency. Respiration modulates vagal (parasympathetic) activity that contributes to the HF component of heart rate variability.<sup>47</sup> LF is thought to be the combined sympathetic and vagal response to arterial baroreceptors.<sup>48</sup> Although not an accurate measure, it is commonly interpreted that a low LF to HF ratio reflects greater parasympathetic activity relative to sympathetic activity, whereas a high LF to HF ratio indicates higher sympathetic activity relative to parasympathetic activity.<sup>47</sup> Dysfunction in the CNS can have downstream effects on spinal cord preganglionic autonomic nerves and result in HRV changes. Changes in HRV may represent an inadequate response of the autonomic nervous system to the stress associated with a more severe condition.<sup>49</sup> Studies have indicated a neural source of HRV changes in ischemic stroke patients.<sup>50</sup> In SAH patients, lowered LF/HF ratio is decreased in patients with pulmonary edema and indicates poor quality recovery and high mortality.<sup>51</sup> Left hemisphere lesions in ischemic stroke patients induce increased HF (parasympathetic) rhythms, whereas right hemisphere lesions increase the LF/HF ratio.<sup>52</sup> HRV decrease is associated with acute stroke severity, post-stroke depression, poor-quality recovery, and mortality.<sup>49,53</sup>

## Mechanisms of Brain–Heart Interaction After Stroke

The mechanisms of brain–heart interaction resulting in cardiac dysfunction after injury to the brain are discussed below and summarized in Figure 1.

### Hypothalamic–Pituitary–Adrenal Axis, Catecholamine Surge, and Sympathetic and Parasympathetic Regulation After Stroke

Many patients develop early-onset depression related to the degree of their functional deficits or late-onset depression.<sup>54,55</sup> Post-stroke depression including anxiety, fear, and stress is psychological and biochemical in nature and is largely dependent on the extent of neurological functional deficits.<sup>54,55</sup> Ischemic stress can cause Takotsubo cardiomyopathy.<sup>15</sup> The HPA axis is a master regulator of body hormones that integrates emotion, stress, physical activity state, and metabolism.<sup>56</sup> The HPA axis consisting of the complex interactions between the 3 endocrine glands—hypothalamus, pituitary, and adrenal glands—is an important part of the neuroendocrine system. The hypothalamic paraventricular nucleus is the main control center of the HPA and secretes corticotropin-releasing factor such as corticotrophin-releasing hormone and vasopressin that stimulate the pituitary gland to release adrenocorticotrophic hormone, especially under stressful conditions.<sup>57</sup> Adrenocorticotrophic hormone stimulates the adrenal gland to release the steroid hormone cortisol. Serum cortisol levels have been correlated with stroke severity and extent



**Table 2. Summary of Biomarkers of Cardiac Dysfunction After Stroke in Patients**

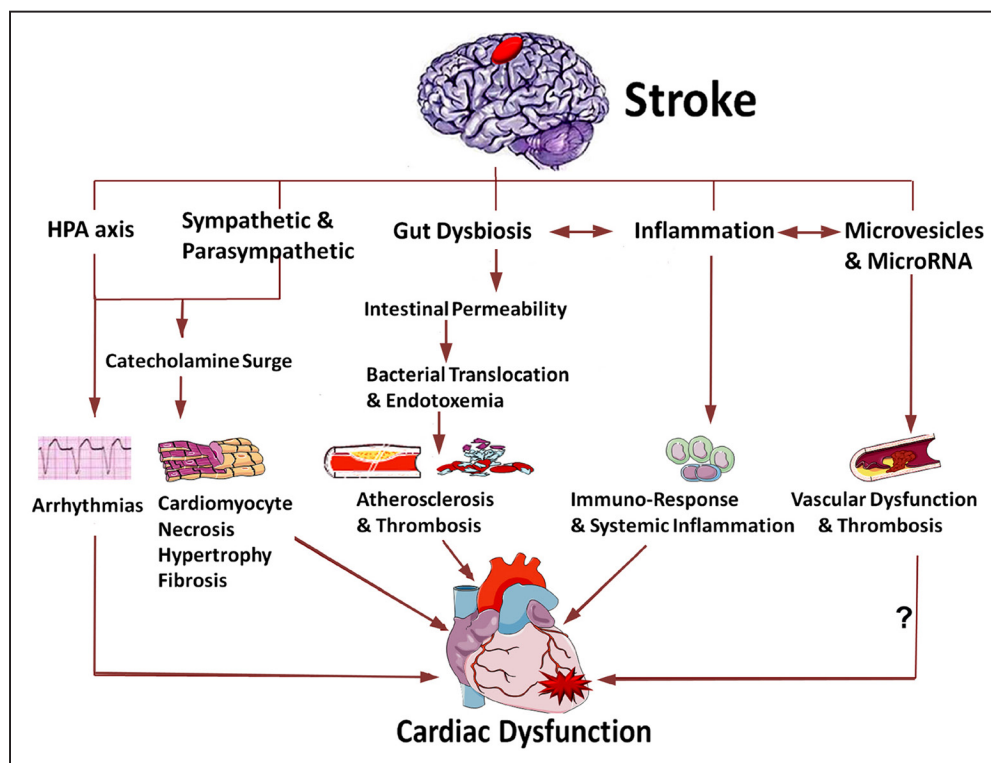
	SAH	IS	Comments
CK-MB	CK-MB level is associated with poor outcome <sup>181</sup>	CK-MB elevation after stroke may not be of cardiac origin <sup>31</sup>	CK-MB is not completely cardiac specific and may increase in skeletal muscle injury, kidney failure, intramuscular injection, strenuous exercise, and after exposure to several toxins and drugs <sup>31</sup>
		Modest and progressive increase in expression	
		Elevated for a few days	
cTn (cTnT and cTnI)	cTnI level peaks within 24–36 h after SAH <sup>37</sup>	Elevated cTns are observed in 5%–8% of IS patients <sup>39,40</sup>	cTnT is a specific and sensitive biomarker for cardiac damage
	High cTnT levels correlated with LV hypokinesia <sup>182</sup>	Circulating cTnI level is an independent predictor of stroke prognosis <sup>39</sup>	The American Stroke Association recommends a routine examination of cardiac troponin in patients with acute stroke
	Elevated cTnI levels is associated with increased risk of LVDD, in-hospital morbidity, and mortality <sup>45,178,183</sup>	Serum cTnT expression helps to evaluate myocardial injury and estimate ischemic lesion volume and is closely associated with the risk of death in patients with acute IS and severe neurological deficits at stroke onset and damage to the insular cortex <sup>41</sup>	
	May indicate delayed cerebral ischemia from vasospasm	May indicate coincidence of acute coronary syndrome or coronary artery disease <sup>43</sup>	
CRP	Elevated CRP level is an independent predictor of future stroke and transient ischemic attack <sup>184</sup>		CRP is a plasma protein that increases in response to inflammation during the acute phase of brain injury <sup>186</sup>
	Patients with an increased plasma CRP level within 72 h of stroke onset battle high mortality because of cardiovascular complications <sup>185</sup>		CRP may serve as a clinically useful risk marker for the development of unstable atherosclerotic disease, as well as a predictor of future cardiovascular morbidity and mortality <sup>186</sup>
	Stroke patients with CRP levels >1.5 mg/dL (optimum sensitivity and specificity for adverse outcome) have a worse prognosis <sup>185</sup>		
	Patients with elevated CRP levels beyond the inflammatory acute phase and at time of hospital discharge face a danger of subsequent cardiovascular complications, death, and severe neurological deficit and disability, which should be carefully factored in their follow-up treatment <sup>185</sup>		
NT-proBNP	NT-proBNP increases the risk of death and delayed cerebral ischemia <sup>40</sup>	NT-proBNP levels is increased after ischemic stroke <sup>40</sup>	NT-proBNP is the product of pro-BNP (brain natriuretic peptide precursor) being cleaved into BNP and is mainly found in myocardial cells
		Increased NT-proBNP levels is an independent risk factor for stroke <sup>40</sup>	NT-proBNP is synthesized and secreted by normal cardiac muscle cells, and levels can rapidly increase after myocardial injury or necrosis
		Increased NT-proBNP levels is associated with unfavorable functional outcome and mortality rates after stroke <sup>43</sup>	
		NT-proBNP is an indicator of ischemic stroke of cardioembolic cause	
		About 10-fold increase in NT-proBNP when TTC develops after stroke <sup>15</sup>	

CK-MB indicates creatine kinase-MB; CRP, C-reactive protein; cTn, cardiac troponin; IS, ischemic stroke; LV, left ventricular; LVDD, left ventricular diastolic dysfunction; NT-proBNP, N-terminal probrain natriuretic peptide; SAH, subarachnoid hemorrhage; and TTC, Takotsubo cardiomyopathy.

of insular damage.<sup>58</sup> Prolonged elevation of cortisol may be neurotoxic and has been associated with increased post-stroke mortality.<sup>59</sup> The paraventricular nucleus also projects directly to the rostral ventrolateral medulla, which integrates cardiac afferents, baroreceptor activity, and inputs from higher brain regions into sympathetic outflow to the heart. Stimulation of the hypothalamus activates sympathetic output and induces electrocardiographic abnormalities, arrhythmias, and myocardial necrosis.<sup>60</sup> Activation of the paraventricular nucleus of the hypothalamus in rats subjected to ischemic stroke causes arrhythmias mediated by glutamate via activation of

N-methyl-D-aspartic acid receptors.<sup>61</sup> Reduction of paraventricular nucleus activity promotes improved recovery of cardiac function after myocardial infarction.<sup>62</sup> Activation of the HPA axis after ischemic stroke causes a significant increase in catecholamines.<sup>63</sup> The catecholamine surge hypothesis is the most widely accepted mechanism of brain–heart interaction.

The catecholamine surge theory has been closely linked to heart damage after physical and emotional stressors. Catecholamine surge can cause cardiac hypertrophy or myocardial ischemia.<sup>64,65</sup> The autonomic nervous system regulates the release of catecholamines from the adrenal glands. Brain



**Figure 1.** Summary of mechanisms for brain–heart interaction after stroke. Cardiac dysfunction after stroke may be caused by several mechanisms, including activation of the hypothalamic–pituitary–adrenal (HPA) axis, sympathetic and parasympathetic regulation, catecholamine surge, gut microbiome dysbiosis, immune responses, and inflammation, as well as the release of microvesicles and microRNA (? indicates that future studies are warranted).

injury can cause elevated sympathetic tone with an additional increase in catecholamine secretion.<sup>66</sup> Neurological injury causes excessive circulating catecholamines and massive catecholamine release from myocardial nerve endings.<sup>66</sup> The myocardium adjacent to the nerve is damaged.<sup>67</sup> The sympathetic nerve can directly release catecholamines and thereby induce cardiomyocyte toxicity. Long-term elevation of serum catecholamine produces cardiotoxicity<sup>68</sup> and may trigger edema in regions of hypokinesia, transient fibrosis, inflammation, and contraction band necrosis.<sup>69,70</sup> Experimental animal studies have demonstrated an increase in plasma catecholamine levels after ischemic stroke that was directly proportional to the incidence of myocardial lesions and cardiac damage.<sup>71</sup> The increased catecholamine levels is correlated with QT-interval prolongation and myocardial damage after SAH, whereas hypothalamic stimulation induces electrocardiographic changes without associated myocardial damage.<sup>72,73</sup>

Catecholamines act on the heart via  $\beta$  receptors to increase the strength and rate of contraction.<sup>74</sup> The  $\beta$  receptors couple to the stimulatory G protein and activate adenylyl cyclase and increase cytosolic cAMP. cAMP binds to the regulatory subunits of protein kinase A, which phosphorylates sarcolemmal L-type  $\text{Ca}^{2+}$  channels and sarcoplasmic phospholamban, which overloads mitochondria.<sup>75</sup> Mitochondrial  $\text{Ca}^{2+}$  overload triggers oxidative stress, and the subsequent opening of their inner membrane permeability transition pore along with osmotic swelling and loss of ATP synthesis leads to myocardial cell death.<sup>75</sup> Although pretreatment with  $\beta$ -blockers has been reported to decrease the incidence of myocardial lesion<sup>76</sup> and

$\beta$  blockers are commonly prescribed after Takotsubo cardiomyopathy, some studies have reported a lack of significant effect of  $\beta$  blockers on recurrence of Takotsubo syndrome rate.<sup>77</sup>

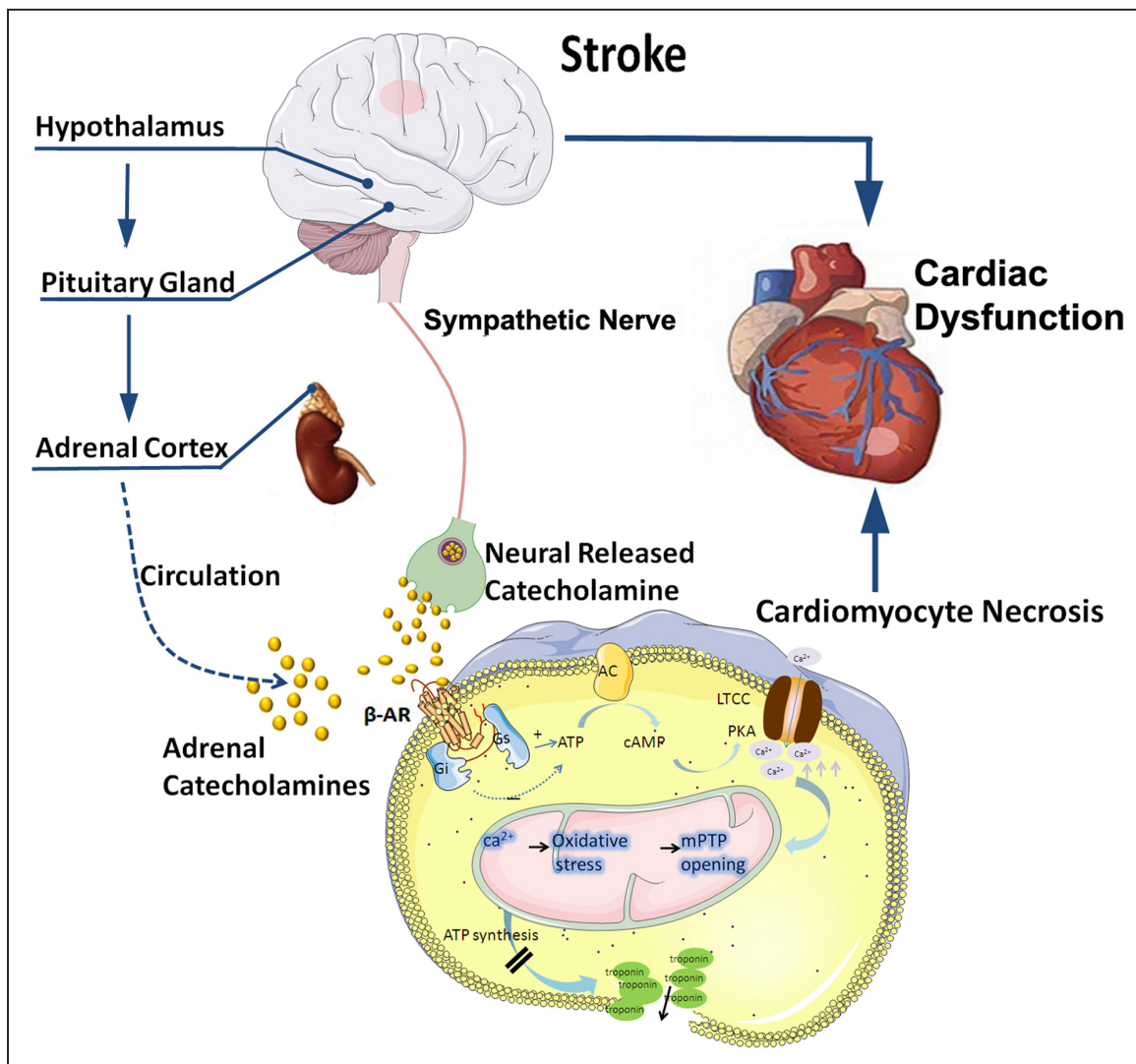
Sympathetic and parasympathetic physiology and regulation of brain–heart interaction has been described in detail elsewhere.<sup>78</sup> The forebrain plays an important role in the regulation of the autonomic nervous system in patients with hemorrhagic and ischemic stroke. Stimulating the orbital surface of the frontal lobe and the anterior cingulate gyrus affects blood pressure and heart rate.<sup>79</sup> The insular cortex is regarded as a vital part of the central autonomic network.<sup>80</sup> Ischemic lesions in the insular cortex increase the risk of cardiac complication and can cause blood pressure variations, cardiac arrhythmias, and myocytolysis.<sup>81,82</sup> The location of an ischemic lesion also affects cardiac function after stroke, and studies have reported cardiac dysfunction after ischemic damage to both left and right insular cortex.<sup>52,80,83</sup> It seems that the right hemisphere primarily controls sympathetic activity, whereas parasympathetic activity is mainly controlled by the left hemisphere.<sup>71,72</sup> Therefore, a right insular lesion decreases sympathetic tone and results in parasympathetic overactivity.<sup>80</sup> Right insular lesions are associated with higher mortality at an early stage compared with other sites.<sup>84</sup> Brain infarctions in the left hemisphere are associated with fewer incidences of arrhythmias, an increased risk of adverse cardiac outcome, increased long-term mortality, and decreased cardiac wall motion compared with stroke in other locations.<sup>85,86</sup> Elevated activity of the sympathetic nervous system observed in the acute phase of SAH induces myocardial damage and contributes to the

development of cardiac dysfunction.<sup>87</sup> Therefore, intensive heart monitoring will be particularly essential for patients with insular cortical damage. Figure 2 summarizes the role of the HPA axis, catecholamine surge, and sympathetic regulation in mediating cardiac dysfunction after stroke.

### Blood–Brain Barrier Disruption After Stroke

The neurovascular unit is a functional unit encompassing the anatomic and metabolic interactions between the neuronal, glial, and vascular components of the brain. The blood–brain barrier (BBB) composed of endothelial cells, astrocytic end feet, pericytes, and a thick basement membrane is at the core of the neurovascular unit.<sup>88,89</sup> The BBB serves as a dynamic interface between the brain and the circulatory system, limiting the entry of potential neurotoxins and microscopic and hydrophilic molecules.<sup>88,89</sup> The BBB also protects the brain from variations in blood composition and helps maintain constant and optimal cerebral metabolism and neuronal activity.

Disruption of the neurovascular unit and BBB is a major step in the pathophysiological cascade after stroke and contributes to secondary tissue damage. Increased BBB permeability disturbs cerebral autoregulation, leads to neuronal damage, and facilitates the invasion of inflammatory factors into the injured brain.<sup>90</sup> In a vicious cycle, BBB disruption promotes entry of inflammatory factors into the ischemic brain, and inflammation increases BBB permeability. Increased BBB permeability is found in almost half the patients at 24 hours post-cardiac surgery even in the absence of stroke.<sup>91</sup> Additionally, cardiac dysfunction and cardiac surgery can lead to cerebral ischemia and stroke via hypoperfusion and cardiac embolization, respectively, and trigger systemic inflammatory responses that may either induce or aggravate BBB disruption.<sup>91</sup> BBB disruption facilitates the entry of brain-derived antigens and extracellular vesicles derived from injured brain cells to enter the blood stream and encounter peripheral immune cells, as described in detail in the following section. Therefore, there



**Figure 2.** The hypothalamic–pituitary–adrenal (HPA) axis, catecholamine surge, and sympathetic and parasympathetic regulation mediate cardiac dysfunction after stroke. Catecholamines act on  $\beta$  receptors,  $\beta$  receptors couple to the stimulatory G protein (Gs) and activate adenyl cyclase (AC), and increase cytosolic cAMP. cAMP binds to the regulatory subunits of protein kinase A (PKA), which phosphorylates sarcolemmal L-type  $\text{Ca}^{2+}$  channels (LTCC), and sarcoplasmic phospholamban, which overloads mitochondria. Mitochondrial  $\text{Ca}^{2+}$  overload triggers oxidative stress and the subsequent opening of their inner membrane permeability transition pore with ensuing osmotic swelling, and loss of ATP synthesis leads to myocardial cell death.

exists a close relationship between cardiac function and BBB integrity, but the effects are most likely indirect.

### Immunoresponse and Systemic Inflammation After Stroke

Immune system activation leading to inflammation after stroke is an important factor in stroke progression. The complex interplay of the local and systemic inflammatory responses after stroke involves many immune cell types and circulating signals and is important in understanding both infection and other secondary complications. The complex role of inflammation in stroke pathogenesis has been reviewed elsewhere.<sup>92,93</sup> In the following section, we discuss inflammatory and immune responses that may mediate brain–heart interaction after stroke, which is summarized in Figure 3.

In the acute phase of brain injury, local inflammatory responses in the brain parenchyma include microgliosis, astrogliosis, and cytokine/chemokine secretion, which occur concomitantly with endothelial cell activation.<sup>94</sup> Ischemia can lead to endothelial cell damage directly or indirectly via the release of reactive oxygen species.<sup>95</sup> Damaged endothelial cells can increase oxidative stress and rupture the BBB.<sup>95</sup> In addition, damaged endothelial cells and astrocytes at the site of inflammation can shed extracellular vesicles that rapidly cross the BBB and enter the bloodstream.<sup>96</sup> On reaching peripheral organs such as the liver, the protein and microRNA (miR) cargo of these endothelial cell and astrocyte-derived extracellular vesicles regulate acute cytokine response and mediate trafficking of peripheral immune cells to injured brain tissue.<sup>96</sup> Extracellular vesicles are emerging as intrinsic communication mediators between the brain and immune system.<sup>96</sup> The role of microvesicles and miR as mediators of brain damage induced heart dysfunction is discussed in detail later in this review.

BBB disruption facilitates the infiltration of peripheral macrophages and neutrophils into brain after stroke onset.<sup>97,98</sup> Subsequent to ischemia onset, there is an increase in extracellular ATP as a result of neuronal and glial depolarization and damaged plasma membrane of injured brain cells.<sup>93</sup> High extracellular ATP levels can activate resident microglia and stimulate inflammatory cytokine production.<sup>93</sup> Microglia and macrophages can assume a neurodegenerative M1 phenotype and increase inflammation by releasing proinflammatory cytokines. In the initial few minutes to hours after stroke onset, there is an increased production of proinflammatory cytokines (interleukins [eg, IL-6 and IL-1 $\beta$ ], tumor necrosis factor- $\alpha$ , etc), integrins, adhesion molecules (VCAM-1 [vascular cell adhesion protein], ICAM-1 [intercellular adhesion molecule], P-selectin, etc), chemokines, and their receptor molecules.<sup>93,99,100</sup> These proinflammatory molecules can further damage the BBB, initiate the recruitment of peripheral immune cells into the cerebral microcirculation and ischemic brain, and pass through the BBB into the circulation, inducing systemic inflammation.<sup>100</sup> On the contrary, the microglia and macrophages can also assume an anti-inflammatory M2 phenotype and clear cellular debris from the injured brain.<sup>93</sup>

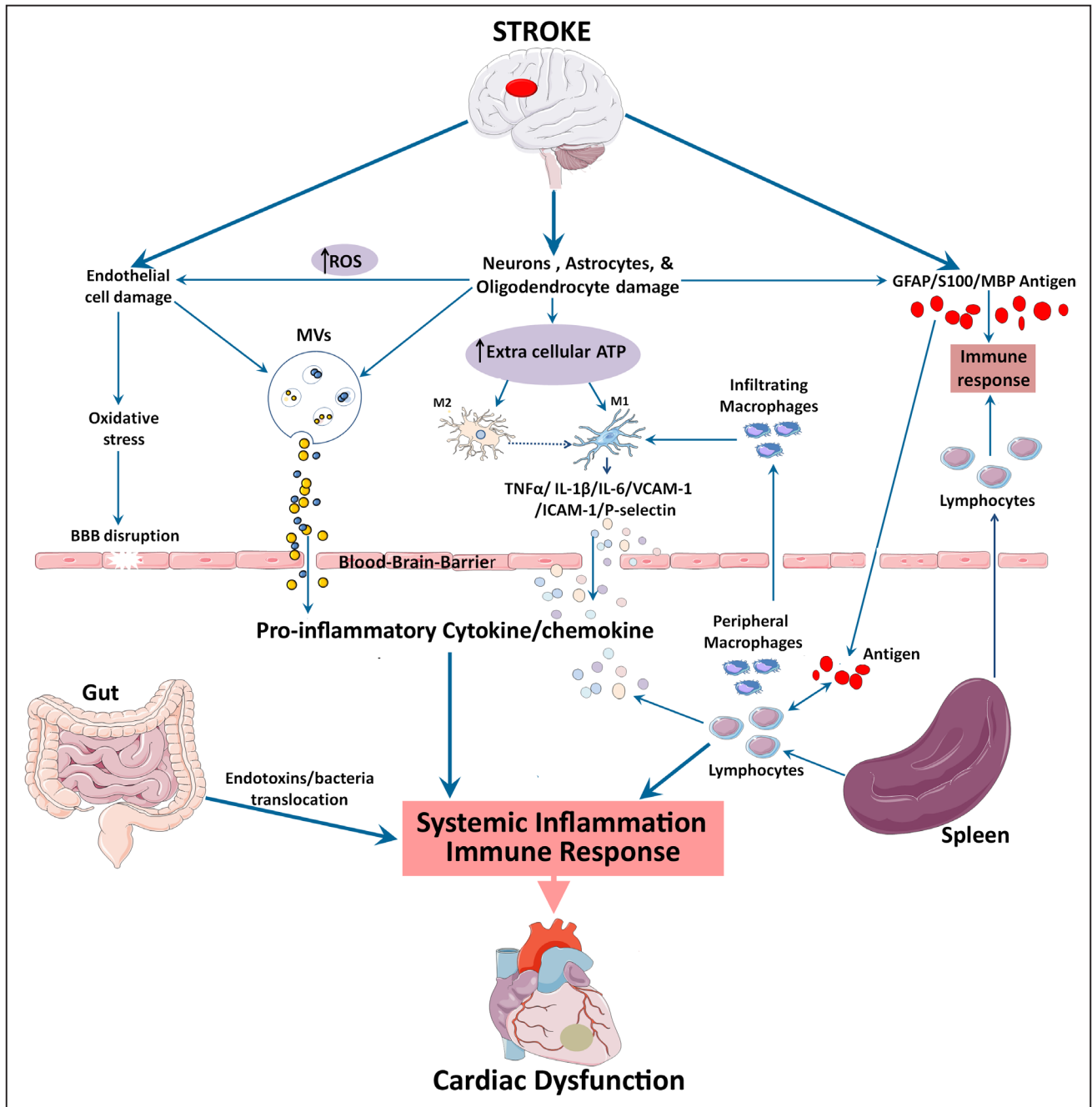
Systemic inflammatory responses are mainly driven by many cytokines, chemokines, stress hormones, and parasympathetic and sympathetic regulation.<sup>101</sup> In acute ischemic

stroke, lymphocyte influx begins  $\approx$ 48 hours after stroke, and the invading T lymphocytes promote detrimental inflammatory cascades and induce delayed brain damage.<sup>97,99</sup> Although an optimal-level leukocyte infiltration is beneficial to the ischemic brain, in excess, it leads to increased intracranial pressure resulting in poor outcome or mortality.<sup>93,99,100</sup> The spleen plays a central role in mediating the peripheral immune response to ischemic stroke by increasing circulating lymphocytes and proinflammatory cytokines and chemokines such as tumor necrosis factor- $\alpha$ , MCP-1 (monocyte chemoattractant protein-1), interferon- $\gamma$ , IL-6, and IL-2, exacerbating inflammation in the acute phase after stroke.<sup>102</sup> Increased tumor necrosis factor- $\alpha$  level induces degradation of TnI, which has been associated with impaired cardiac contractility.<sup>103</sup> Splenectomy 8 weeks after chronic heart failure has been reported to significantly improve LV systolic function and reduce cardiomyocyte hypertrophy, suggesting a role of spleen in mediating cardiac function.<sup>104</sup> At a later time point, splenic atrophy and decrease in T-cell proliferation and inflammatory cytokines secretion lead to a state of immunosuppression.<sup>105</sup>

Damage-associated molecular patterns including various heat-shock proteins are released by dying brain cells after ischemic stroke.<sup>106</sup> Injured astrocytes, neurons, and oligodendrocytes release brain-derived antigens such as glial fibrillary acidic protein, S100, and MBP (myelin basic protein).<sup>107</sup> Damage-associated molecular patterns and brain-derived antigens can also pass the ruptured BBB and enter the systemic circulation. Damage-associated molecular patterns can activate TLRs (Toll-like receptors) and lead to cytokine and chemokine production.<sup>108</sup> In experimental stroke, lymphocyte response to the brain-derived antigens, such as MBP, leads to antigen-specific secretion of transforming growth factor- $\beta$ , consistent with a regulatory T cells' response.<sup>109</sup> However, in the presence of systemic inflammation, the antigen-specific autoimmune response is characterized by T-helper cells 1 and TLR activation and secretion of proinflammatory interferon- $\gamma$ , IL-2, etc.<sup>110,111</sup> TLR-4 is expressed on the cell surface of cardiomyocytes. TLR-4 activation and chronic inflammation with increased release of proinflammatory cytokines such as tumor necrosis factor- $\alpha$  IL-6, IL-1 $\beta$  have been implicated in developing heart failure and poor prognosis of heart disease.<sup>112</sup> Transforming growth factor- $\beta$  induces IL-6 increase while decreasing MCP-1 and VCAM-1 in vascular pericytes and is also instrumental in the transition from fibroblasts to myofibroblasts that may play a role in cardiac fibrosis observed in NSC.<sup>113,114</sup>

Systemic inflammatory responses are activated after spontaneous intracerebral hemorrhage, ischemic stroke, and SAH.<sup>115</sup> Systemic inflammatory responses carry an increased risk of subsequent intracranial complications such as vasospasm and normal pressure hydrocephalus, as well as systemic secondary complications.<sup>116</sup> The immune system is involved in this process in the early phases after stroke and correlates with ischemic stroke and SAH progression.<sup>116</sup> Systemic inflammatory response syndrome was found in  $\approx$ 50% of SAH patients on admission, and 85% of patients developed systemic inflammatory response syndrome within the first 4 days after admission.<sup>117</sup> Systemic inflammatory response syndrome is indicated by abnormal leukocyte counts, high respiratory and heart rate





**Figure 3.** Role of immune response and inflammation in mediating cardiac dysfunction after stroke. Local inflammatory responses in the brain, endothelial cell damage, and increased oxidative stress lead to blood–brain barrier (BBB) disruption after stroke. Release of proinflammatory cytokine and chemokines can be stimulated by damaged endothelial cells and astrocytes, activated resident microglia, and infiltrating macrophages that assume M1 phenotype, as well as the spleen. Systemic inflammatory responses are mainly driven by many cytokines, chemokines, stress hormones, as well as parasympathetic and sympathetic regulation. Gut microbiome dysbiosis after stroke can also lead to bacterial and endotoxin translocation to the blood, leading to systemic inflammation. Damage-associated molecular patterns released by dying brain cells after ischemic stroke release brain-derived antigens that can pass the ruptured BBB and enter the systemic circulation. In the presence of systemic inflammation, the antigen-specific autoimmune response leads to the secretion of proinflammatory cytokines. GFAP indicates glial fibrillary acidic protein; ICAM, intercellular adhesion molecule; IL, interleukin; MBP, myelin basic protein; MV, microvesicle; ROS, reactive oxygen species; TNF, tumor necrosis factor; and VCAM, vascular cell adhesion protein.

(>90 bpm), and abnormal body temp and can increase the risk of developing vasospasm and secondary complications.<sup>117</sup> In ischemic stroke patients, the number of CD74<sup>+</sup> cells (the MHC [major histocompatibility complex] class II invariant chain present on all class II expressing cells, including monocytes, macrophages, and dendritic cells) were significantly increased

in peripheral blood mononuclear cells compared with healthy controls.<sup>118</sup> The increased CD74-positive cells were mainly on CD4<sup>+</sup> T cells, monocytes, and dendritic cells.<sup>118</sup> In heart diseases such as myocardial infarction, elevation of circulating blood monocytes is associated with poor cardiac function and predicts poor recovery of LV systolic function at 3 months post-injury.<sup>119</sup>

There is also some evidence of cross-talk between inflammatory responses and sympathetic activation in ischemic and hemorrhagic stroke.<sup>120,121</sup> The proinflammatory cytokines released by damaged neuronal and glial cells stimulate the posterior hypothalamus to increase sympathetic output and circulating catecholamine level.<sup>122–124</sup> van der Bilt et al<sup>121</sup> found that catecholaminergic stress after brain hemorrhage coincided with influx of inflammatory cells into the heart and induced cardiac damage after SAH. Neutrophils were found embedded in the inflamed myocardium along with thrombi.<sup>121</sup> The coupling of catecholamine release with parasympathetic dysfunction regulates inflammation that induces myocardial dysfunction, thrombi formation, and cardiomyocyte cell death.<sup>121</sup> Therefore, inflammation may play an important role and as a link between brain injury and cardiac damage after ischemic stroke and SAH. The role of immune response and inflammation after stroke in mediating cardiac dysfunction is summarized in Figure 3.

Gut microbiome dysbiosis after stroke can lead to intestinal paralysis and bacterial and endotoxin translocation to blood leading to systemic inflammation,<sup>125–127</sup> as discussed in detail in the following section.

### Gut Microbiome Dysbiosis After Stroke

Our knowledge and understanding of the human microbiome and its involvement in various diseases are increasing. In particular, there is an emerging body of evidence based from experimental studies that suggests an interaction between the gut microbiome and heart as well as the gut microbiota and the CNS, referred to as gut–heart axis and brain–gut axis, respectively. The gut–blood barrier mainly regulates the absorption of nutrients and water while preventing toxins and pathogenic microorganisms from entering the blood stream. In gastrointestinal, metabolic, cardiovascular, and cerebrovascular diseases, disruption of the gut–blood barrier integrity resulting in increased intestinal permeability enables microbiota-derived molecules to enter the blood stream.<sup>125</sup>

### Brain–Gut Axis

The brain–gut axis can affect normal brain functioning and influence the pathological cascade of events in neurological diseases including stroke and TBI.<sup>128,129</sup> The brain–gut axis comprising neural and humoral pathways with signaling molecules such as cytokines, hormones, and neuropeptides can regulate immune response and lymphocyte population.<sup>129,130</sup> Alterations to the normal gut microbiota or gut dysbiosis caused by acute brain lesions can affect neuroinflammatory and immune responses in the brain and worsen neurological function.<sup>131</sup> In patients with large-artery atherosclerotic ischemic stroke or transient ischemic attack, significant gut dysbiosis is indicated by increased opportunistic bacteria and decreased beneficial bacteria.<sup>132</sup> It has also been suggested that commensal gut microbiota exert protection against ischemic damage, and their depletion or dysbiosis increases post-stroke mortality in mice and influences stroke outcome.<sup>133</sup> In addition, the extent of increase of proteobacteria in the gut of stroke patients is proportional to stroke severity.<sup>132</sup> Dietary choline and L-carnitine are transformed by gut microbiota to trimethylamine, and its oxidation yields the proatherogenic metabolite that is largely considered a disease marker.<sup>134</sup>

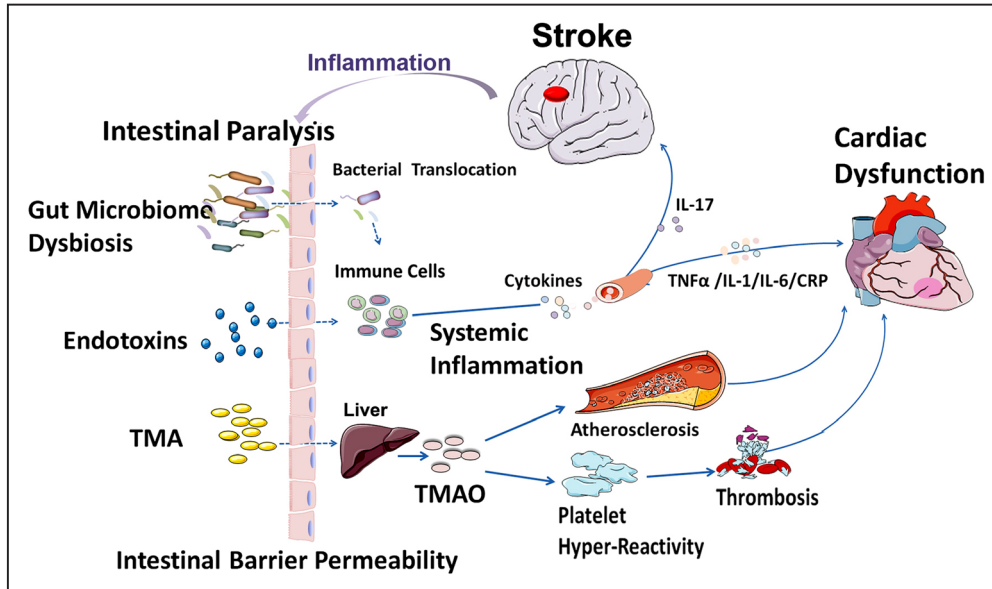
In ischemic stroke, gut dysbiosis via stress-mediated intestinal paralysis can alter T-cell homeostasis, promote migration of T cells from the intestine to the ischemic brain, and increase proinflammatory responses resulting in poor stroke outcome.<sup>130</sup> In mice subjected to transient focal cerebral ischemia, trafficking of intestinal T cells from the gut to the meninges of the brain increases neuroinflammation and the secretion of proinflammatory cytokine IL-17, which can stimulate the production of several other cytokines and chemokines and facilitate the infiltration of cytotoxic immune cells and neutrophils into the injured brain.<sup>130</sup> In mice subjected to transient focal cerebral ischemia, stroke increased gut permeability proportional to stroke severity; promoted bacterial translocation from the gut to mesenteric lymph nodes and peripheral organs such as spleen, liver, and lungs; and triggered adaptive and innate immune responses.<sup>135</sup> In ischemic stroke patients, gut dysbiosis and increased bacterial counts of *Lactobacillus ruminis* subgroup in the fecal gut microbiota was associated with elevated systemic inflammation and altered metabolism.<sup>136</sup> Bacterial metabolites have also been implicated to mediate communication between the commensal gut microbiota and the immune system, tipping the balance in favor of proinflammatory mechanism.<sup>137</sup>

### Gut–Heart Axis

Increased gut permeability can promote inflammatory responses, whereas systemic inflammation can increase gut permeability.<sup>125</sup> Bacterial and endotoxin translocation to the blood stream, increased proinflammatory cytokines, and systemic inflammation can induce or exacerbate cardiac dysfunction.<sup>126,127</sup> In an independent large clinical cohort, 3 gut microbiota-dependent metabolites including choline, trimethylamine-N-oxide, and betaine were found to be predictors of cardiovascular disease.<sup>134</sup> Gut microbes can directly contribute to platelet hyper-reactivity and increase the risk of thrombosis via trimethylamine-N-oxide generation.<sup>138</sup> Altered trimethylamine-N-oxide levels has been associated with impaired cardiac function, heart attack, and heart failure.<sup>126,138</sup> Elevated trimethylamine-N-oxide levels in the plasma of patients presenting with chest pain was found to be a predictor of short-term and long-term risk of myocardial infarction, stroke, need for revascularization, or even death.<sup>139</sup> Figure 4 summarizes the role of gut dysbiosis in mediating cardiac damage after stroke. Future studies are warranted to investigate the role of the gut microbiome in cardiac damage after stroke and investigate whether stroke-induced gut dysbiosis promotes a proinflammatory cascade, which then leads to dysfunction of other organs including the heart.

### Future Perspectives

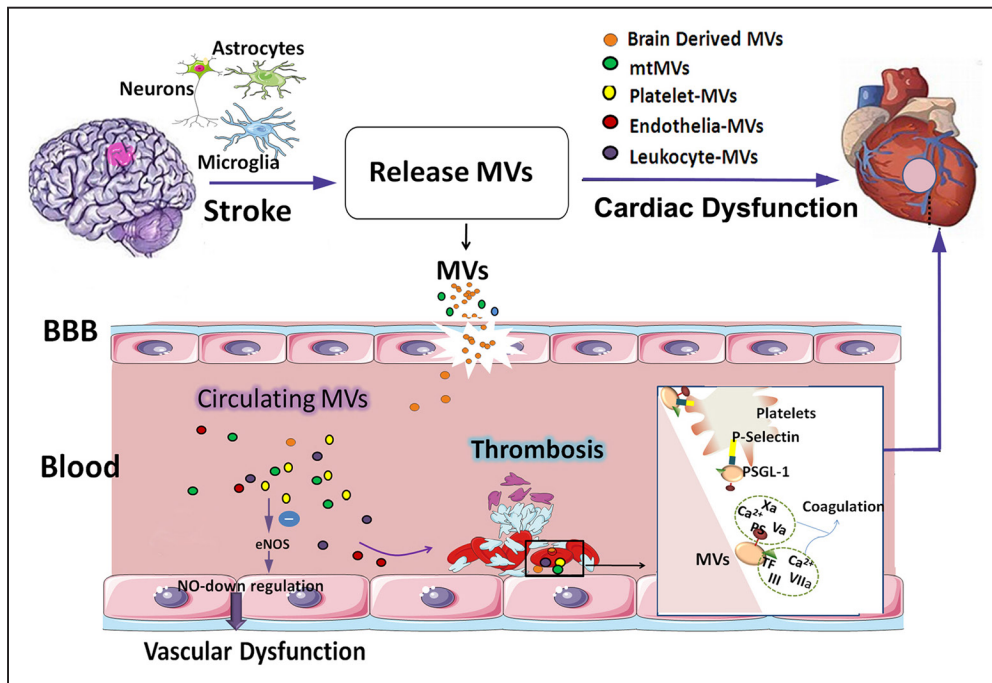
Although there exist knowledge gaps in our understanding of the mechanisms of brain–heart interaction in the setting of stroke, emerging evidence suggests that microvesicles and their cargo miR may function as mediators of interorgan and intercellular communication. Important unanswered questions relating to the role of microvesicles/miR in brain–heart interaction include How do changes in miRs in the brain affect cardiac function and vice versa? Do changes in miR expression correspond to stages of disease and recovery? Are



**Figure 4.** The brain–gut axis and gut–heart axis may mediate cardiac damage after stroke. Stroke increases intestinal barrier permeability, enabling bacterial and endotoxin translocation to bloodstream inducing inflammatory responses and proinflammatory cytokine production. Cytokine production can trigger inflammation, fibrosis, and microvascular and myocardial dysfunction. Trimethylamine-N-oxide (TMAO) is the hepatic oxidation product of the microbial metabolite trimethylamine (TMA). TMAO promotes the development of hyper-responsive platelet phenotype and enhances elevating the risk for heart failure and heart attack. CRP indicates C-reactive protein; IL, interleukin; and TNF, tumor necrosis factor.

microvesicles containing miRs transported by the circulation from the brain to heart (as well as other organs), thereby inducing damage to target tissue? Because miRs can affect

immune response, it is also possible that injured brain cells and resident and infiltrating inflammatory cells release a variety of microvesicles carrying miRs that on reaching cardiac



**Figure 5.** The role of microvesicles (MVs) released by damaged astrocytes, neurons, and microglia after stroke in mediating cardiac damage warrants future investigation. Stroke-induced elevation of circulating platelets and MVs are associated with endothelial dysfunction and coagulation leading to thrombosis. MVs induce endothelial dysfunction by decreasing NO synthesis as the result of endothelial NO synthase (eNOS) function inhibition and an increase in caveolin-1. The outer leaflet of the MVs membrane contains 2 procoagulants: phosphatidylserine and tissue factor. MVs can bind to coagulation factors and promote their activation. In addition, MVs harbor tissue factor, which can initiate extrinsic coagulation pathways and promote the assembly of clotting enzymes leading to thrombin generation. At sites of vascular injury, P-selectin exposure by activated endothelial cells or platelets leads to the rapid recruitment of MVs bearing the P-selectin glycoprotein ligand-1 (PSGL-1). The interactions between PSGL-1 and platelet P-selectin are necessary to concentrate tissue factor activity at the thrombus.

tissue have adverse effects on cardiac function? The following section explores this perspective, as summarized in Figure 5. Further studies are warranted to elucidate the role of these intercellular communication mediators in facilitating interaction between the brain and distant organs such as the heart in neurological diseases.

### Microvesicles

Microvesicles are lipid bilayer-covered cell fragments that range in diameter from 100 nm to 1  $\mu$ m and are released into the extracellular environment by several cell types typically during cell activation or cell death via necrosis or apoptosis. Microvesicles are produced by the outward budding and fission of plasma membrane. In addition to intercellular communication via cell contact, microvesicles constitute an important mode of communication by serving as vehicles for intercellular transfer of membrane and cytosolic proteins, lipids, and RNA either locally or over long distances.<sup>140</sup> Because microvesicles retain the signature membrane protein composition of the parent cell, they can be classified by flow cytometry into different cellular microvesicles, such as endothelial microvesicles, leukocyte microvesicles, and platelet microvesicles or brain-derived microvesicles. Microvesicle shedding can also be triggered by pathological activation of inflammatory processes and activation of coagulation or complement systems or even by shear stress in the circulation. Microvesicles have a bilayered phospholipid structure exposing coagulant-active phosphatidylserine and expressing various membrane receptors, and they serve as cell-to-cell shuttles for bioactive molecules such as lipids, growth factors, miR, and mitochondria.<sup>140</sup> Microvesicles have been implicated in endothelial dysfunction, inflammation, and thrombosis.<sup>141</sup> In addition, microvesicles may also be targeted as a therapeutic delivery tool by either inhibiting their release from diseased cells or manipulating their cargo to enable shuttling of secretory molecules such as cytokines, chemokines, and growth factors.<sup>142</sup>

### Circulating Microvesicles

Many circulating microvesicles in the blood derive from cells that are in contact with the bloodstream such as platelets and endothelial cells. Circulating microvesicle level is elevated in patients with ischemic stroke, intracerebral hemorrhage stroke, and SAH and is associated with poor clinical outcome.<sup>143,144</sup> A major source of microvesicles in stroke patients is vascular endothelial cells.<sup>145</sup> Blood-derived microvesicles stimulate release of endothelial cell cytokine IL-6.<sup>145</sup> Correlation between IL-6 expression and incidence of vasospasm has been demonstrated previously.<sup>146</sup> Therefore, in peripheral blood vessels, including cardiac vasculature, IL-6 can induce vascular spasm and lead to coronary syndrome. In addition, endothelial cells secrete microvesicles that can inhibit endothelial NO synthase.<sup>147</sup> Anti-endothelial NO synthase activity leads to a decline in NO production, causing endothelial dysfunction and impaired vascular relaxation.<sup>148,149</sup> Endothelial microvesicle was significantly increased in SAH patients, and the increased endothelial cell microvesicle is related with symptomatic cerebral vasospasm<sup>143</sup> and predicts infarction post-SAH.<sup>150</sup> Microvesicles may play an important

role for secondary complications in patients with ischemic and hemorrhagic stroke.<sup>151</sup>

Previous studies have demonstrated that platelet microvesicles have 50- to 100-fold higher specific procoagulant activity than activated platelets<sup>152</sup> and are hence associated with thrombosis. Platelets play an important role in maintaining hemostasis such as thrombosis and immune response. Platelets are activated by inflammation, infection, or injury, and after their activation, microvesicles are released from platelets. In intracerebral hemorrhage, cerebrospinal fluid and plasma procoagulant MV levels are significantly increased and are related with stroke pathogenesis.<sup>144</sup> Platelet microvesicles may also serve as a link between vascular coagulation and inflammation in cardiovascular disease.<sup>153</sup> Altered platelet activity because of microvesicles derived from platelets and injured brain can lead to thromboembolic events and associated cardiac complications after brain injury such as stroke or TBI.<sup>153</sup> Circulating microvesicles derived from brain, endothelial cells, and blood cells may promote procoagulant activity and thrombin generation.<sup>153</sup> However, microvesicles can contribute to the onset and progression of some neurodegenerative and neuroinflammatory diseases, as well as to the development and regeneration of the nervous system. Activated platelets shed microvesicles, which contain a variety of growth factors augmenting endogenous neural progenitor and stem cells angiogenesis and neurogenesis, which may be used for therapy for ischemic stroke.<sup>154</sup>

### Neural Source of Microvesicles

Neurons, astrocytes, microglia, and neural stem cells release microvesicles under normal and pathological conditions. Neural microvesicles can contribute to the onset and progression of some neurodegenerative and neuroinflammatory diseases and to the development and regeneration of the nervous system after stroke.<sup>155</sup> Microglial microvesicles and astrocyte microvesicles store and release the inflammatory cytokine IL-1 $\beta$ .<sup>156,157</sup> In addition, microvesicles contribute to IL-1 $\beta$  release from glial cells.<sup>157</sup> In the acute phase of injury after TBI in mice, circulating platelet numbers did not change; however, platelet contribution to clot formation and the number of total circulating microvesicles decreased significantly.<sup>158</sup> When these TBI mice were treated with microvesicles derived from the brain tissue of sham mice, platelet contribution to clot formation normalized.<sup>158</sup> This indicates that brain tissue-secreted microvesicles generated after TBI are likely to mediate post-traumatic hypercoagulable state after TBI.<sup>158</sup> Tian et al found that microvesicles were produced from injured hippocampal cells, transmigrated through the disrupted endothelial barrier in a platelet-dependent manner, and activated platelets and thereby induce coagulopathy in TBI model.<sup>158</sup> Zhao et al<sup>159</sup> found that brain-derived mitochondrial microparticles significantly increased in the circulation after TBI. The mitochondrial microparticles synergized with platelets to facilitate vascular leakage by disrupting the endothelial barrier. The disrupted endothelial barrier allowed the release of mitochondrial microparticles into the systemic circulation to promote coagulation and enhanced fibrinolysis, vascular fibrin deposition, and thrombosis.<sup>159</sup> The underlying mechanisms and role played by microvesicles in mediating cardiac complications



after cerebral injury are emerging and warrant further study. Increased coagulation and thrombosis may induce heart damage after brain injury.

### MicroRNA

MiRs are short sequences of noncoding RNA (ca. 22 nucleotides), which regulate gene expression both transcriptionally and post-transcriptionally.<sup>160</sup> MiRs can regulate several genes, pathways, and biological networks, either acting alone or in concert with other miRs. MiRs regulate many biological processes regulating tissue repair, including angiogenesis, inflammation, and hypoxia–response.<sup>160</sup> About 50 circulating miRs are believed to be associated with cardiovascular diseases including miR-1, miR-16, miR-27b, miR-30d, miR-126, miR-133, miR-143, miR-145, miR-208, and the let-7 family.<sup>161</sup> Several miRs with key cardiac and vascular function have been reported to be affected after stroke including the following: miR-23, miR-24, miR-29, miR-30, miR-103, and miR-222 were upregulated, whereas miR-126 was downregulated.<sup>162</sup> Microvesicles also contain abundant miRs.

Endothelial cell–specific miR-126 has a key role in maintaining vascular integrity and regulating angiogenesis.<sup>163</sup> Circulating miR-126 level is significantly decreased in patients with ischemic stroke until at least 24 weeks.<sup>164</sup> Endothelial cell dysfunction is a principal step in atherosclerosis. MiR-126 deficiency has been highly associated with heart failure, atrial fibrillation, and coronary artery disease and may be associated with stroke-induced severe cardiac complications.<sup>163,165</sup> Coronary artery disease or ischemic heart disease includes stable and unstable angina, myocardial infarction, and sudden cardiac death. In myocardial infarction, circulating miR-1 increases and miR-126 decreases in proportion with cTnI plasma concentration levels.<sup>166</sup> Vascular miR-126 has been demonstrated to be consumed or taken up by the heart from the bloodstream according to a transcoronary gradient.<sup>167</sup> It has been demonstrated that ischemic stroke decreases serum and heart miR-126 expression, as well as induces post-stroke cardiac dysfunction.<sup>168</sup> Conditional specific endothelial cell miR-126 knockout mice exhibited enhanced cardiac dysfunction and increased cardiomyocyte hypertrophy, fibrosis, and inflammatory factor expression after ischemic stroke compared with miR-126 knockout control stroke mice.<sup>168</sup> The study demonstrated that decreased miR-126 may play a role in brain–heart interaction after ischemic stroke.<sup>168</sup>

In addition, circulating miR-145 also significantly increases within 24 hours of cerebral ischemia, and circulating miR-145 level is positively correlated with elevated serum inflammatory factor IL-6.<sup>169</sup> MiR-145 modulates endothelial cell function in angiogenesis and vessel stabilization.<sup>170</sup> Circulating miR-145 changes has also been reported in patients with coronary artery disease and acute myocardial infarction.<sup>171</sup> Therefore, other miRs may also regulate brain–heart interaction.

### Conclusions

In summary, brain–heart syndrome is commonly encountered in the clinic and affects the prognosis, morbidity, and mortality of patients. The secondary brain damage caused by cardiac dysfunction and impaired systemic and brain homeostasis is

a serious problem that requires attention. Although there is a necessity for specific interventions for the prevention and treatment of post-stroke cardiac complications, there is a dearth of data to guide the management of these complications. Investigation of clinical indicators to diagnose the adverse brain–heart disease at early stage will enable improved clinical management and reduce mortality. Research of novel therapies for the protection of heart after stroke warrants investigation with the potential to be applied to a large proportion of stroke patients over a wide time window.

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### Disclosures

None.

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