Stroke–heart syndrome: clinical presentation and underlying mechanisms

Jan F Scheitz, Christian H Nolte, Wolfram Doehner, Vladimir Hachinski, Matthias Endres

Cardiac complications are a frequent medical problem during the first few days after an ischaemic stroke, and patients present with a broad range of symptoms including myocardial injury, cardiac dysfunction, and arrhythmia, with varying overlap between these three conditions. Evidence from clinical and neuroimaging studies and animal research suggests that these cardiac disturbances share the same underlying mechanisms. Although the exact cascade of events has yet to be elucidated, stroke-induced functional and structural alterations in the central autonomic network, with subsequent dysregulation of normal neural cardiac control, are the assumed pathophysiology. This dysregulation can promote myocardial necrosis, microvascular dysfunction, coronary demand ischaemia, and arrhythmogenesis. These stroke-associated cardiac alterations can be summarised as a distinct so-called stroke–heart syndrome. Independent cohort studies have shown a strong association between this syndrome and unfavourable short-term prognosis; however, long-term consequences, including secondary cardiac events and death, are less well described and specific therapeutic targets are scarce. An integrated view of stroke–heart syndrome will offer opportunities to expedite research and inform clinical decision making.

Introduction
Cardiac complications represent a major medical challenge during acute stroke care.1–3 Severe adverse cardiac events including acute coronary syndrome, heart failure, and cardiac arrhythmia are reported in approximately 20% of patients with ischaemic stroke in randomised controlled trials, occurring predominantly within the first 3 days after the event.4 In addition, a broad range of oligosymptomatic, early (first few days to weeks) cardiac complications can be observed with contemporary diagnostic measures.4–8 Patients with ischaemic stroke are particularly prone to cardiac injury, because of the advanced age at which strokes generally occur, prevalence of cardiac comorbidities, and vascular risk factors. Importantly, cardiac complications after ischaemic stroke are associated with a poor functional prognosis and are the second leading cause of death in the first few weeks after the event.1–4

The clinical observation that ischaemic stroke is often accompanied by electrocardiogram (ECG) alterations or by an increase of unspecific cardiac blood biomarkers was first described in the 1950s and 1960s.9–10 In the past 10 years, animal studies, clinical cohort studies, and neuroimaging studies have provided increasing evidence that the varying cardiac disturbances appearing after stroke probably share the same underlying mechanisms.9–10 Although stroke-induced alterations of physiological autonomic cardiac control seem to have a crucial role, the underlying pathological mechanisms are unclear and therapeutic targets are unknown. This insufficient evidence might be due to the fact that each cardiac complication has been individually studied in some detail, but not as a distinct and whole clinical entity.

In this Review, we outline the most recent evidence suggesting that these cardiac events can be summarised as a distinct so-called stroke–heart syndrome. Moreover, we aim to provide an overview of the clinical manifestations of stroke–heart syndrome, summarise presumed underlying mechanisms, and derive implications of the concept for research and practice. We will focus on ischaemic stroke, although similar occurrences of neurocardiogenic injury can be observed in other acute brain disorders, including subarachnoid haemorrhage, haemorrhagic stroke, traumatic brain injury, and seizures.16 The population of patients with ischaemic stroke, however, differs markedly from that of patients with other acute brain disorders, regarding age and cardiovascular comorbidities; furthermore, brain dysfunction due to ischaemic stroke entails a distinct time course and vascular distribution location. Cerebral consequences of impaired cardiac function have been reviewed elsewhere.17

Cardiac complications associated with stroke
The concept of stroke–heart syndrome (ie, cardiac manifestations induced by an ischaemic stroke) as a direct consequence of brain ischaemia implies that cardiac disturbances occur after the onset of neurological deficits. Strong evidence suggests that the frequency and severity of stroke–heart syndrome peak within the first 3 days after the event.1–3,8 Most of these stroke-associated cardiac disturbances are transient, but a subgroup of patients show poor short-term and probably long-term outcome.16,18–20 Stroke–heart syndrome must be distinguished from cardiac disturbances secondary to systemic disease, such as sepsis, anaemia, or poor oxygenation (panel). Distinguishing stroke–heart syndrome from concomitant or preceding acute coronary syndrome (ie, due to coronary plaque rupture or thrombosis) can be especially challenging, although algorithms for diagnostic pathways have been suggested.11

Studies in animals and humans have convincingly shown that stroke-related factors, such as ischaemic lesion location (especially involvement of the [right] insula) and stroke severity, correlate with the extent of subsequent cardiac injury and dysfunction.14,15,21 Although stroke-related cardiac dysfunction can occur
Panel: Proposed criteria for stroke–heart syndrome by the Center for Stroke Research Berlin

Clinical description
Evidence of acute myocardial injury, cardiac dysfunction, or cardiac arrhythmia following ischaemic stroke.

Clinical characteristics
There are a broad range of clinical presentations including repolarisation changes; cardiac arrhythmia; cardiac autonomic imbalance with blood pressure alterations; exacerbation of heart failure; takotsubo syndrome secondary to acute stroke; myocardial injury with cardiac biomarker changes; and acute myocardial infarction.

Time course
Begins early after ischaemic stroke; cardiac alterations usually peak within 72 h after ischaemic stroke onset. Cardiac injury or dysfunction are either newly detected after the ischaemic stroke event, or clear evidence shows worsening of cardiac function after stroke.

Risk factors
The occurrence and severity of stroke–heart syndrome depends on premorbid cardiac disease, age, and vascular risk factors, but also on stroke-related factors, such as stroke lesion site within the central autonomic network and stroke severity.

Differential diagnoses
There must be conceptual distinction from other causes of cardiac injury or dysfunction including: systemic diseases, such as sepsis; chronic but stable heart failure; pulmonary embolism; pulmonary hypertension; acute kidney injury; chronic kidney disease; myocarditis; and recent cardiac intervention. There must be distinction from causes of coronary demand ischaemia not attributable to stroke (eg, anaemia and reduced blood oxygenation). There must be distinction from myocardial ischaemia due to coronary plaque rupture or plaque thrombosis (type 1 myocardial infarction).

See Online for appendix

Cardiac biomarkers
Elevations in cardiac biomarkers (ie, cardiac troponin and brain natriuretic peptide) are among the best-studied manifestations of stroke–heart syndrome. Cardiac troponin is the preferred biomarker to detect myocardial injury and diagnose myocardial infarction. High-sensitivity cardiac troponin assays enable detection of this biomarker in more than 90% of patients with ischaemic stroke, with approximately 30–60% of these patients showing at least one cardiac troponin value above the upper reference limit in serial measurements (ie, cardiac troponin elevation). In community-based studies of otherwise healthy individuals (adults or without prior heart failure) from the general population, cardiac troponin concentrations were found to be generally lower than in studies including patients with ischaemic stroke (appendix). Even minor elevations of this biomarker after stroke are independently associated with poor functional outcome. Importantly, in two cohort studies of 1016 and 834 patients with ischaemic stroke, approximately 5–20% showed a rise or fall pattern in cardiac troponin amount, suggesting acute and not chronic myocardial injury. Patients with such dynamic cardiac troponin concentrations following stroke have a more than three-times increased risk of in-hospital mortality (table). In 250 consecutive patients with ischaemic stroke, N-terminal pro b-type natriuretic peptide concentrations rose within 2 days after ischaemic stroke and fell subsequently. A meta-analysis of 16 studies (n=3498) showed that N-terminal pro b-type natriuretic peptide measured within 5 days after stroke is on average 255 pg/mL lower among survivors of stroke than in non-survivors.

Cardiac arrhythmia
Pathological ECG findings upon hospital admission can be observed in 70–90% of patients with ischaemic stroke if abnormalities indicating pre-existing heart disease—such as Q waves or signs of left ventricular hypertrophy—are included. The most frequently observed ECG changes early after stroke are changes in repolarisation, and include prolonged rate corrected QT (QTc) time (in 20–65% of patients), ST segment changes (in 15–25% of patients), and inverted T waves with altered amplitude and width (so-called cerebral T wave, in 2–18% of patients). Most of
these ECG alterations are transient and peak early after stroke. For instance, rate of QTc prolongation upon hospital admission was shown to decline from 45 (65%) of 69 patients to 18 (26%) patients at 48 h thereafter. Importantly, these ECG alterations identify individuals at risk for clinically relevant arrhythmia. Prolonged QTc time has been linked to occurrence of myocardial injury (measured by cardiac troponin elevation), severe cardiac arrhythmia, and sudden cardiac death after stroke.

Cardiac arrhythmias are strongly associated with an unfavourable outcome. Kallinmäki and colleagues used an automated arrhythmia detection system in a single stroke unit and identified 139 episodes of severe cardiac arrhythmias causing clinical symptoms or requiring urgent clinical evaluation in 126 (25%) of 501 patients within 72 h after stroke onset. 81 (58%) of these patients had clinically relevant episodes of atrial fibrillation, whereas ventricular or supraventricular tachycardia, sinus-node dysfunction, and second-degree or third-degree atrioventricular block were detected in the remainder. Old age and high stroke severity were independently associated with these arrhythmias. Tachyarrhythmia was observed more often than was bradyarrhythmia.

Detection of atrial fibrillation early after stroke is a diagnostic challenge: atrial fibrillation can be newly diagnosed in about 7–10% of patients during the first 3–5 days. Detection increases to 24% or more with cardiac monitoring over 6–12 months. Debate is ongoing as to whether part of these atrial fibrillation episodes are triggered by stroke–heart syndrome and are not the cause of the initial stroke. Debate is ongoing because newly detected atrial fibrillation has been linked to stroke location involving the central autonomic cardiac control, and the data are conflicting as to whether stroke recurrence is not as high when atrial fibrillation is newly detected as when atrial fibrillation is already known before the stroke. Part of atrial fibrillation episodes after stroke might be triggered by stroke–heart syndrome. Nonetheless, detection of atrial fibrillation after stroke probably reveals cardiac vulnerability (ie, pre-existing atrial cardiopathy) to develop subsequent persistent or permanent atrial fibrillation. Therefore, treatment with oral anticoagulants should not be challenged until more evidence on secondary stroke prevention in patients with newly diagnosed atrial fibrillation is available. Potential pathophysiological models of newly diagnosed atrial fibrillation have been reviewed elsewhere.

**Autonomic dysfunction**

Autonomic cardiac imbalance can be assessed by alterations of heart rate variability and baroreceptor reflex sensitivity. Heart rate variability is lower in patients with stroke than in healthy controls and baroreceptor reflex sensitivity is impaired during the acute phase after stroke, especially in strokes that are severe and involve the right insular cortex. Overall, evidence from clinical studies indicates an average shift towards a sympathetic predominance during the first 3 days after stroke. Reduced heart rate variability after stroke has been linked to a higher risk of short-term mortality and sudden cardiac death. Impairment of the baroreceptor reflex sensitivity has been associated with acute hypertensive crises following ischaemic stroke and might precede space-occupying anterior infarction. One hypothesis is that autonomic dysfunction after stroke is exaggerated during sleep, and that sleep disruption with impaired autonomic re-patterning results in early clinical deterioration due to arrhythmias and blood pressure fluctuations.

Until now, no routine clinical applications of heart rate variability and baroreceptor reflex sensitivity measurements have been established, which might be because of the absence of well-known clinical cutoffs and of methodological standardisation. However, both parameters could identify patients at risk of blood pressure alterations, severe cardiac arrhythmias, and sudden cardiac death.

**Cardiac dysfunction**

Impaired left ventricular function (ie, ejection fraction <55%) after acute stroke can occur in 8–12% of patients with mild-to-moderate stroke and, in 3–8%, left ventricular...
<table>
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<th>Measurement</th>
<th>Clinical findings</th>
<th>Associated risk factors*</th>
<th>Prognostic value</th>
<th>Limitations</th>
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<tr>
<td>Cardiac troponin&lt;sup&gt;4,5,14,25,52,53&lt;/sup&gt;</td>
<td>Myocardial injury, sensitive marker for acute coronary syndrome</td>
<td>Old age, (right) insular cortex lesions, stroke severity, heart failure, coronary artery disease, impaired kidney function</td>
<td>Associated with poor short-term and long-term outcomes, incident heart failure, secondary cardiovascular events</td>
<td>Causes of myocardial injury other than acute coronary syndrome are possible (eg, hypertensive crisis, tachyarrhythmias); premorbid concentration is uncertain; chronic mild elevations are present in about 85% of patients (high-sensitivity assay) without substantial change in serial measurements</td>
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<td>Brain natriuretic peptide (including N-terminal pro B-type natriuretic peptide)&lt;sup&gt;3,15&lt;/sup&gt;</td>
<td>Released in response to myocardial wall stress, monitor treatment of heart failure</td>
<td>Old age, female sex, stroke severity, atrial fibrillation</td>
<td>Associated with poor short-term outcome, cardioembolic stroke origin</td>
<td>Premorbid concentration is uncertain</td>
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<td>Corrected QT time&lt;sup&gt;3,5,10,12&lt;/sup&gt;</td>
<td>Repolarisation changes, risk for malignant arrhythmia</td>
<td>Pre-existing heart disease</td>
<td>Myocardial injury (cardiac troponin elevation); severe cardiac arrhythmia; mortality†</td>
<td>Certain drugs (eg, antidepressants) can prolong corrected QT; premorbid corrected QT time is unknown; cause of ST segment changes is unspecific (eg, co-medication, electrolyte amount)</td>
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<tr>
<td>T wave&lt;sup&gt;26,28,30&lt;/sup&gt;</td>
<td>Repolarisation changes</td>
<td>Pre-existing heart disease</td>
<td>Myocardial injury (cardiac troponin elevation); severe cardiac arrhythmia; mortality†</td>
<td>Certain drugs (eg, antidepressants) can prolong corrected QT; premorbid corrected QT time is unknown; cause of ST segment changes is unspecific (eg, co-medication, electrolyte amount)</td>
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<td>ST segment changes&lt;sup&gt;56,59&lt;/sup&gt;</td>
<td>Repolarisation changes, myocardial ischaemia</td>
<td>Pre-existing heart disease</td>
<td>Myocardial injury (cardiac troponin elevation); severe cardiac arrhythmia; mortality†</td>
<td>Certain drugs (eg, antidepressants) can prolong corrected QT; premorbid corrected QT time is unknown; cause of ST segment changes is unspecific (eg, co-medication, electrolyte amount)</td>
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<tr>
<td>Arrhythmia (including atrial fibrillation)&lt;sup&gt;34,40-42&lt;/sup&gt;</td>
<td>Disturbance of depolarisation or repolarisation</td>
<td>Clinically significant arrhythmia in about 25% of patients</td>
<td>Worsening of left ventricular function; mortality</td>
<td>High frequency with monitoring longer than 72 h</td>
</tr>
<tr>
<td>Atrial fibrillation&lt;sup&gt;34,40-43&lt;/sup&gt;</td>
<td>Disturbance of depolarisation or repolarisation</td>
<td>Old age, stroke severity</td>
<td>Worsening of left ventricular function; mortality</td>
<td>High frequency of newly detected atrial fibrillation with monitoring longer than 72 h; whether newly detected atrial fibrillation after stroke is the cause or consequence of stroke is unknown; whether the risk of stroke recurrence after newly detected atrial fibrillation is equal to the risk of stroke recurrence in patients with known atrial fibrillation is unknown</td>
</tr>
<tr>
<td>Baroreceptor reflex sensitivity&lt;sup&gt;24,48&lt;/sup&gt;</td>
<td>Response to short-term blood pressure variations</td>
<td>Stroke severity, right insular involvement</td>
<td>Hypertensive crisis; space-occupying infarction; mortality</td>
<td>Absence of established cutoff values and methodological standardisation; previous use of β blockers or antihypertensive drugs can affect results; baroreceptor reflex sensitivity measurements not applicable in clinical routine</td>
</tr>
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<td>Heart rate variability&lt;sup&gt;46,47&lt;/sup&gt;</td>
<td>Autonomic cardiac balance</td>
<td>Stroke severity, right insular involvement</td>
<td>Mortality; sudden cardiac death</td>
<td>Absence of established cutoff values and methodological standardisation; previous use of β blockers or antihypertensive drugs can affect results; heart rate variability measurements not applicable in clinical routine</td>
</tr>
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<td>Reduced left ventricular ejection fraction (&lt;55%)&lt;sup&gt;52,53&lt;/sup&gt;</td>
<td>Left ventricular dysfunction</td>
<td>Old age, high stroke severity, history of heart disease, high baseline cardiac troponin and brain natriuretic peptide</td>
<td>Poor short-term outcome, high risk of stroke</td>
<td>Premorbid cardiac function unknown</td>
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<td>Regional wall motion abnormalities&lt;sup&gt;54,55&lt;/sup&gt;</td>
<td>Left ventricular dysfunction</td>
<td>Old age, male sex, high burden of cardiovascular risk factors, heart disease (including coronary artery disease), stroke severity, inflammatory markers</td>
<td>Stroke recurrence</td>
<td>Premorbid cardiac function unknown</td>
</tr>
<tr>
<td>Secondary takotsubo syndrome&lt;sup&gt;31-33&lt;/sup&gt;</td>
<td>Left ventricular dysfunction</td>
<td>Old age, female sex, insular cortex stroke, stroke severity, inflammatory markers</td>
<td>Poor short-term outcome</td>
<td>Atypical types of takotsubo syndrome are probably underdiagnosed with echocardiography</td>
</tr>
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*Risk factors independently associated with the respective biomarker in observational and cohort studies. †Strongest evidence for prolonged corrected QT time. ‡Defined as arrhythmia causing symptoms or requiring urgent evaluation and treatment.

Table: Biomarkers and measurements of cardiac dysfunction within the first few days of acute ischaemic stroke.
function can be severely impaired (ie, ejection fraction of <40%). These findings are limited by the fact that the prevalence of impaired left ventricular function before stroke is not known. Old age, high stroke severity, history of heart disease, and high baseline cardiac troponin are predictors of impaired left ventricular function.

Impaired left ventricular dysfunction or left ventricular wall motion abnormalities after stroke have been associated with poor functional outcome (two-times increased risk of modified Rankin Scale score >2). Takotsubo syndrome is a particular type of left ventricular dysfunction that can be observed in acute ischaemic stroke. It is an acute heart failure syndrome with most patients showing a characteristic pattern of left ventricular dysfunction (apical ballooning) that resembles a Japanese octopus trap called takotsubo. Clinical consensus recommends coronary angiography to rule out acute coronary syndrome and show left ventricular dysfunction, especially in patients with ST segment elevation. Echocardiography should be considered to identify regional wall motion abnormalities in patients with stroke. Clinicians should be aware that besides the apical ballooning type, midventricular, basal, and focal types of takotsubo syndrome can be differentiated. The focal type of takotsubo syndrome can resemble focal wall motion abnormalities seen in acute coronary syndrome; in these cases, cardiovascular MRI can be useful to diagnose takotsubo syndrome. This syndrome predominantly affects postmenopausal women and is often preceded by stressful physical or emotional triggers. Although the left ventricular dysfunction recovers markedly over time, in an international cohort of 1750 patients with takotsubo syndrome, long-term prognosis at 10-year follow-up was similar to that of myocardial infarction. Acute neurological disorders (ie, ischaemic stroke, intracranial haemorrhage, and seizures) are also common triggers of takotsubo syndrome. The syndrome has been reported in 0–5–1.2% of patients after acute stroke and, when secondary to acute stroke, can occur without the presence of emotional or psychological stress.

Transient myocardial impairment occurs typically within the first 10 h after stroke onset, with full or partial recovery within 3 weeks. Notably, although echocardiographic and electrocardiographic signs along with elevations of cardiac troponin can clearly indicate acute contractile impairment, patients often remain asymptomatic (or might be unable to report symptoms because of neurological deficits). Still, takotsubo syndrome secondary to acute stroke has been linked to a three-times or more increase in in-hospital mortality.

Mechanisms and pathophysiology

The evidence strongly suggests that the broad range of clinical presentations of stroke–heart syndrome probably originate from stroke-induced structural or functional alterations within the central autonomic network—a network of brain structures modulating physiological adaptation of cardiovascular function via regulation of the sympathovagal outflow to the heart. Current understanding of the neural control of cardiac function was pioneered by rigorous experiments done from 1970s to early 2000s by Clifford B Saper (USA), David Smith (UK), David Cechetto (Canada), Eduardo E Benarroch (USA), and Stephen Oppenheimer (UK).

Meta-analyses of functional MRI studies confirmed the insular cortex, prefrontal cortex, cingulate cortex, amygdala, hypothalamus, and hippocampus formation as important factors in the central autonomic network (figure 2A). Evidence suggests that sympathetic and parasympathetic cardiovascular function might be lateralised. Sympathetic activation seems to be mainly located within the prefrontal cortex, anterior cingulate cortex, left amygdala, and right anterior insular and left posterior insular cortices.

Of the brain regions aforementioned, the insular cortex is frequently affected in patients with ischaemic stroke because of its blood supply by the middle cerebral artery. The insular cortex constitutes a cortical representation of interoceptive awareness and emotional processing of the current cardiovascular state (eg, heart beat awareness). A study of 228 patients who had an MRI scan after ischaemic stroke used voxel-based lesion symptom mapping to investigate whether localisation of the ischaemic stroke precipitated myocardial injury. Although single cardiac troponin values did not show any relation to stroke lesion location, relative dynamic changes in this biomarker concentration were statistically significantly associated with right anterior insular lesions (especially the dorsal subregion, figure 2B). With this methodological approach, a similar correlation was observed in 150 patients with ischaemic stroke between lesion location and occurrence of post-stroke cardiac arrhythmias. Although several studies suggest an association between right insular stroke and several manifestations of stroke–heart syndrome (eg, myocardial injury or cardiac arrhythmia), the clinical implications of these findings are yet to be explored. The insula is strongly connected to the anterior cingulate cortex, which is involved in producing blood pressure and heart rate responses to stress. The amygdala is another important region within the central autonomic network that modulates cardiovascular response to severe emotional stimuli and has a role in processing emotions such as fear and anxiety. Activity within the amygdala on 18F-fluorodeoxyglucose PET/CT scans of 293 participants undergoing cancer screening was associated with high perceived stress, arterial inflammation, and incidence of cardiovascular events. These conditions highlight the notion that altered response to stress has important consequences on cardiovascular function.
Cardiac response to mental stress

Studies exploring the link between cardiovascular function and mental stress provide important insights into the pathophysiology of stroke–heart syndrome. As with ischaemic stroke, strong emotions, such as fear and anxiety, and unexpected happiness might lead to an overshoot activation or dysregulation within the central autonomic network.66–68 This dysregulation can even result in cardiovascular events and sudden cardiac death. A popular example of how emotionally moving events affect cardiac function is the 2·66 times increase in cardiac events in 4279 people in a metropolitan area of Germany, on match days when the German team played during the Fédération Internationale de Football Association World Cup in 2006.69 Stress-induced acute coronary syndrome during the World Cup was accompanied by higher concentrations of endothelin and pro-inflammatory markers in the blood of 58 patients with acute coronary syndrome on match days, compared with 58 matched patients who had an acute coronary syndrome event without related emotional circumstances.69

In experimental settings, mental stress can be simulated by the use of mental arithmetic or public speaking tests. Exaggerated increase in heart rate following a mental stress test has been associated with altered activation patterns within the central autonomic network.85 Moreover, increased sympathetic activation with elevated catecholamine concentrations, reduced baroreceptor reflex sensitivity, peripheral and coronary vasoconstriction, release of cardiac troponin, ischaemic ECG alterations, impaired left ventricular function, and reduced coronary blood flow can be detected following such mental stress algorithms.86,77,78 This event is called mental-stress-induced myocardial ischaemia.77 Major pathophysiological features of mental-stress-induced myocardial ischaemia are a sustained increase of systemic vascular resistance and a reduction of endothelium-dependent vasodilatation.79 Therefore, findings from some studies have suggested that coronary demand ischaemia and microvascular dysfunction play a crucial part in the occurrence of mental-stress-induced myocardial ischaemia.77 Importantly, individual susceptibility probably influences the degree of cardiovascular response to stress.76,78

Takotsubo syndrome is an example of how stress can result in cardiac dysfunction. Findings from a neuro-imaging study of 22 women with this syndrome and 39 healthy female controls showed that structural and functional alterations within the central autonomic network are present in patients who had a takotsubo syndrome episode.78 These findings underline that altered stress response within the central autonomic network is involved in the pathogenesis of takotsubo syndrome. In support of this hypothesis, the circulating miRNAs miR-16 and miR-26a were found to be dysregulated in a cohort of 36 patients with takotsubo syndrome, compared with 27 patients with ST-segment elevation acute myocardial infarction and 28 healthy controls.80 In mice, miR-16 regulates the expression of the serotonin transporter, and expression of miR-26a in the frontal cortex and hippocampus increases shortly after restraint stress.81,82 Additionally, excessive catecholamine release constitutes a pathophysiological hallmark of takotsubo syndrome.27,79 Catecholamine concentrations are statistically significantly higher in patients with takotsubo syndrome than in those with myocardial infarction.83 Moreover, the cellular response to catecholamines observed in cardiomyocytes derived from induced pluripotent stem cells of patients with takotsubo syndrome was higher than that found in controls.84 Notably, in a study of 222 consecutive patients with ischaemic stroke, high concentrations of catecholamines were independently associated with myocardial injury following acute ischaemic stroke.85 On a cardiomyocyte level, catecholamine overload results in disturbed calcium homoeostasis, which leads to hypercontraction of sarcomers together with increased oxidative and metabolic stress. This process can result in myocardial contraction band necrosis (typical catecholamine-mediated lesions with hypercontracted sarcomers) and impaired coronary microcirculation.86,87 In addition, the amount of endothelin in plasma is increased, which further supports the notion that endothelial dysfunction and microvascular constriction play an important part in the pathophysiology of takotsubo syndrome.27 Oestrogen is known to improve microcirculation and might explain the fact that

Figure 2: Forebrain components of the central autonomic network

(A) Overview of brain regions involved in neural control of the heart. (B) Voxel-based lesion symptom mapping analysis of 228 patients with anterior circulation stroke showing a statistically significant association of relative change in cardiac troponin levels with lesions of right anterior insular cortex (especially its dorsal portion), frontal operculum and, to a lesser spatial extent, of dorsal posterior insular cortex. Reproduced from Krause et al,14 by permission of John Wiley and Sons. *Z-values indicate statistical significance (significant if ≥3).
postmenopausal women are more susceptible to develop takotsubo syndrome.\(^8\)

**Animal stroke models**

Models of focal cerebral ischaemia in rodents (eg, middle cerebral artery occlusion) provide an opportunity to explore the mechanisms underlying stroke–heart syndrome. Several groups have shown stroke-induced cardiac dysfunction and cardiomyocyte damage in rodents undergoing middle cerebral artery occlusion, with an increase of cardiac troponin concentration and contraction band necrosis.\(^{13,42–45}\) For example, more than 60% of mice subjected to left but not right middle cerebral artery occlusion developed cardiac dysfunction, which correlated with injury to the left insula and increased concentrations of norepinephrine.\(^6\) Bleilevens and colleagues\(^7\) showed that a subgroup of rats subjected to left middle cerebral artery occlusion for 60 min developed substantial myocardial injury, which was predicted by the extent of insular involvement. Cardiac arrhythmia induced by middle cerebral artery occlusion was associated with both specific brain lesions (paraventricular nucleus) and aberration of L-type calcium channels in cardiomyocytes.\(^8\) A decrease in the amount of microRNA miR-126 might contribute to stroke–heart syndrome: miR-126 was specifically downregulated after stroke, and mice deficient in endothelial expression of miR-126 had exaggerated cardiac dysfunction after stroke.\(^{11}\) Additionally, brain damage might also lead to chronic cardiac dysfunction: mice showed worsening of left ventricular ejection fraction and an increase in left ventricular volumes during 8 weeks after right, but not left, transient middle cerebral artery occlusion, which was mediated by chronic autonomic dysfunction and ameliorated by β blockers.\(^{12}\) Overall, animal models offer us the advantage of dissecting neurocardiogenic effects directly without any cardiac comorbidity or atherothrombotic burden, and to identify causal humoral or nervous factors.

**Unifying hypothesis**

Altogether, available data provide compelling support for the concept that stroke-induced structural and functional disturbance within the central autonomic network results in an overactivated stress response involving the autonomic nervous system and the hypothalamic–pituitary–adrenal (HPA) axis (figure 3). As a consequence, excessive release of catecholamines, proinflammatory cytokines, cortisol, and other neurohumoral factors impair physiological cardiomyocyte and (micro)vascular function. This impairment promotes arrhythmogenesis and causes contraction band necrosis, microvascular dysfunction, and coronary demand ischaemia. These mechanisms can co-occur, ie, more than one can contribute to the patient’s condition. As a consequence, the broad clinical manifestations of stroke–heart syndrome, such as cardiac arrhythmia, myocardial infarction, hypertensive crisis, and takotsubo syndrome secondary to stroke might emerge.

![Figure 3: Presumed pathomechanisms underlying stroke–heart syndrome](image-url)

Ischaemic stroke results in activation or dysregulation of the central autonomic network and the hypothalamic–pituitary–adrenal (HPA) axis. Excessive release of catecholamines, proinflammatory cytokines, cortisol, and other neurohumoral factors impair physiological cardiomyocyte and (micro)vascular function. This impairment promotes arrhythmogenesis and causes contraction band necrosis, microvascular dysfunction, and coronary demand ischaemia. These mechanisms can co-occur, ie, more than one can contribute to the patient’s condition. As a consequence, the broad clinical manifestations of stroke–heart syndrome, such as cardiac arrhythmia, myocardial infarction, hypertensive crisis, and takotsubo syndrome secondary to stroke might emerge.

level, catecholamines, cortisol, and neurohumoral factors (eg, endothelin, angiotensin II, and vasopressin) lead to an increased vasoconstriction and increased systemic vascular resistance that promote coronary demand ischaemia and microcirculatory dysfunction. These processes might explain the different phenotypes of stroke–heart syndrome: coronary demand ischaemia caused by both epicardial and microvascular vasoconstriction probably promotes stroke-induced myocardial injury in some patients with stroke. Secondary to demand ischaemia, cardiac wall motion abnormalities and takotsubo syndrome-like myocardial stunning can occur. Myocardial stunning is a reversible wall motion abnormality in patients with focal ischaemia after reperfusion, but can also be induced by an acute brain injury.\(^{13,17–19}\) Both cardiac reperfusion following myocardial ischaemia and direct catecholamine toxicity can result in contraction band necrosis (also called coagulative myocyte lysis). Histopathologically, these lesions are characterised by hypercontracted sarcomeres with myofibrillar break.\(^7\) In animals, contraction band necrosis can be provoked following experimental catecholamine exposure, and can be induced by middle cerebral artery occlusion.\(^ {13,26–28}\) Therefore, contraction band necrosis could
be considered classic neurocardiogenic heart damage. Electrical instability of cardiomyocytes together with excessive adrenergic stimulation of the conductive network can lead to cardiac arrhythmia. Finally, impaired autonomic cardiac reflexes result in disturbed blood pressure regulation and hypertensive crises. Both tachyarrhythmia and hypertensive crisis can further precipitate coronary demand ischaemia leading to myocardial infarction. In other individuals, increment of parasympathetic tone following stroke can promote bradycardia and subsequent demand ischaemia.

**Stroke-induced systemic alterations**

Ischaemic stroke can induce systemic alterations that can in turn affect cardiac function and promote myocardial injury. Impaired baroreceptor reflex sensitivity and increased sympathetic activity might result in activation of the renin–angiotensin–aldosterone system, which can further sustain endothelial dysfunction, increased systemic vascular resistance, and blood pressure alterations. Furthermore, ischaemic stroke is followed by a systemic proinflammatory response that might impair cardiac function. Proinflammatory cytokines released by damaged neuronal cells have been shown to alter sympathetic output of the hypothalamic–pituitary–adrenal axis and could, thereby, further drive excessive catecholamine release. Findings from one study have suggested that ischaemic stroke could induce gut dysbiosis, which in turn can foster cardiac dysfunction. Additional research is needed to clarify the effect of these processes on the severity of stroke–heart syndrome.

**Concomitant acute coronary syndrome**

In a study of 405 consecutive patients presenting with acute cerebral infarction, patients had a high prevalence of cardiovascular risk factors and a substantial proportion had underlying (known or silent) coronary artery disease. Therefore, evidence of stroke–heart syndrome inevitably raises the suspicion of a concomitant or preceding acute coronary syndrome. Importantly, classic presentation of acute coronary syndrome can be concealed by neurological deficits such as aphasia, anosognosia, or impaired consciousness. This setting poses a clinical dilemma since diagnostic criteria that allow a reliable differentiation between stroke–heart syndrome and comorbid acute coronary syndrome have not been established. Data regarding the frequency of an underlying acute coronary syndrome are scarce. In the prospective Troponin Elevation in Acute Ischemic Stroke (TRELAS) study of 2123 consecutive patients with ischaemic stroke, 29 with an elevated cardiac troponin concentration (above a clinical cutoff to rule-in myocardial infarction in patients with typical chest pain) had a diagnostic coronary angiography to evaluate coronary vessel status. Coronary culprit lesions, suggesting acute coronary artery disease, were present in seven (24%) of 29 patients. Conversely, coronary angiography showed no coronary artery disease in 14 (48%) of 29 of patients. This finding was in contrast with the age-matched and sex-matched controls with non-ST elevation acute coronary syndrome, despite similar baseline cardiac troponin concentrations (figure 4). This particular combination of non-obstructed coronary arteries despite acute elevation in cardiac troponin has been defined as an own entity of myocardial infarction (myocardial infarction with non-obstructed coronary arteries), which is used as a working diagnosis to prompt further evaluation of its underlying causes. Echocardiography and cardiovascular MRI are useful to identify the underlying mechanisms (eg, takotsubo syndrome, coronary spasm, coronary microvascular dysfunction, and spontaneous coronary emboli). Clinicians should also be aware that a relevant proportion of patients with stroke and elevated cardiac biomarkers might have type 2 myocardial infarction. Type 2 myocardial infarction is due to coronary demand ischaemia, unlike classic type 1 myocardial infarction that is caused by coronary plaque rupture or thrombosis. Hypertensive crisis and tachyarrhythmia are important causes of type 2 myocardial infarction that have to be considered and treated.

Currently, no strong data are available to support diagnostic criteria for simultaneous acute coronary syndrome in patients with acute stroke, or to identify those in need of coronary interventions. Measurement of cardiac troponin can be helpful, since both absolute concentrations and relative change in are higher in acute coronary syndrome than in other conditions causing myocardial injury, but a cutoff to distinguish between myocardial injury due to stroke–heart syndrome and acute coronary syndrome has not been established. Both the ongoing PRediction of Acute Coronary Syndrome in Acute Ischemic Stroke (PRAISE, NCT03609385) and Bernese Heart and Brain Interaction in Acute Stroke studies will bring light on this issue. Until data are available, evidence of acute myocardial infarction (ie, increase or decrease by >20% of cardiac troponin in repeated measurements) should prompt non-invasive cardiac imaging (ie, echocardiography, cardiac MRI, and coronary CT). In patients with high probability of an acute coronary syndrome (typical complaints, ECG alterations, and premorbid coronary artery disease), coronary angiography should be considered on an individual case basis.

**Conclusions and future directions**

In this Review, we have described the broad clinical characteristics and underlying mechanisms of cardiac complications following acute ischaemic stroke. Clinicians should be aware that about 20% of patients with ischaemic stroke will reveal signs of an ongoing stroke–heart syndrome. The extent of pre-existing cardiac disease and underlying vascular risk factors increases an individual’s vulnerability to develop stroke–heart syndrome and moderates its severity. Stroke-specific determinants, such as stroke severity and lesion location within the central
autonomic network (especially the insular cortex), should further alert clinicians (figure I). From a pathophysiological perspective, the manifestations of stroke–heart syndrome might be regarded as the result of a stroke-induced stress-test to the heart. At least three major causes of cardiac dysfunction seem to have a role: direct myocardial catecholamine toxicity, microvascular dysfunction, and coronary demand ischaemia. Importantly, these processes are mutually dependent and can overlap in individuals.

An integrated view of post-stroke cardiac complications as a distinct stroke–heart syndrome has the potential to inform clinical decision making. Further data are needed to provide evidence-based recommendations regarding screening, diagnosis, prevention, and treatment of cardiac complications after stroke. If patients are at risk or if evidence of stroke–heart syndrome (table, panel), prolonged monitoring for cardiac arrhythmia and worsening of cardiac function, and non-invasive cardiac imaging (eg, echocardiography or cardiovascular MRI) seem warranted. To prevent occurrence of stroke–heart syndrome, electrolyte disturbances should be balanced, drugs with known QTc prolongation (such as certain antibiotics, antidepressants, and antipsychotics) should be avoided, and conditions promoting coronary demand ischaemia (such as tachyarrhythmia or hypertensive crisis) should be managed rigorously. Given the proposed pathophysiology of stroke–heart syndrome, β blockers or renin–angiotensin–aldosterone system inhibitors might be considered for cardioprotection, but no strong data to support this suggestion are available.

Several avenues for future research regarding stroke–heart syndrome include the exact pathophysiological pathways and therapeutic targets; a potential link between acute stroke–heart syndrome and incidence of long-term cardiac complications (eg, heart failure, arrhythmias, and sudden cardiac death); and predictors of the individual phenotype and prognosis. The proposed criteria of stroke–heart syndrome (panel) might be considered for the design of clinical studies and to define a suitable target population for therapeutic interventions.

The presumed mechanisms of stroke–heart syndrome identify the catecholamine storm, calcium homoeostasis in cardiomyocytes, coronary microcirculation, and coronary demand ischaemia as promising targets within clinical studies. Further key questions on the factors contributing to stroke–heart syndrome remain, including the extent of direct neurocardiogenic mechanisms versus microvascular mechanisms in individual patients, and to what degree activation the hypothalamic–pituitary–adrenal axis, direct sympathovagal imbalance, or neurohumoral mediators have a role. Methodologically, further consideration is needed for imaging the cardiac phenotype of stroke–heart syndrome with modern cardiovascular MRI or hybrid imaging techniques. Additionally, a thorough study of biomarkers (eg, circulating microRNAs) and autonomic ECG markers has the potential to identify a subgroup of patients with stroke with relevant autonomic imbalance.

Another important aspect of future research will be to determine whether stroke–heart syndrome is an acute but merely transient event, or whether cardiac disturbances persist throughout long-term follow-up. Considering ischaemic stroke as a stress test for the heart, acute cardiac alterations might be useful to detect patients at risk of future cardiovascular events. More effort is certainly needed to reassess (autonomic) cardiac function systematically throughout the long-term after the initial stroke event and monitor causes of death. Another important gap in evidence is the individual risk prediction of occurrence and severity of stroke–heart syndrome. Although lesion location within the central autonomic network, high and more dynamic cardiac troponin concentrations, and pre-morbid cardiac disease seem to be established risk factors for stroke–heart syndrome, further contributing aspects, such as sex issues, circadian rhythmicity, and epigenetic modification of stress-related genes linked to individual vulnerability to stress need to be scrutinised.
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