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JACC STATE-OF-THE-ART REVIEW

Post-Stroke Cardiovascular Complications and Neurogenic Cardiac Injury

JACC State-of-the-Art Review

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ABSTRACT

Over 1.5 million deaths worldwide are caused by neurocardiogenic syndromes. Furthermore, the consequences of deleterious brain-heart interactions are not limited to fatal complications. Cardiac arrhythmias, heart failure, and nonfatal coronary syndromes are also common. The brain-heart axis is implicated in post-stroke cardiovascular complications known as the stroke-heart syndrome, sudden cardiac death, and Takotsubo syndrome, among other neurocardiogenic syndromes. Multiple pathophysiological mechanisms with the potential to be targeted with novel therapies have been identified in the last decade. In the present state-of-the-art review, we describe recent advances in the understanding of anatomical and functional aspects of the brain-heart axis, cardiovascular complications after stroke, and a comprehensive pathophysiological model of stroke-induced cardiac injury. (J Am Coll Cardiol 2020;76:2768–85) © 2020 by the American College of Cardiology Foundation.

The brain and heart interactions have been investigated for centuries and have gained special attention in the last decade. Increasing evidence supports the physiological and pathophysiological interplay of the nervous and cardiovascular systems. Over 1.5 million deaths worldwide are explained by the involvement of neurocardiogenic mechanisms, including post-stroke cardiovascular complications, sudden unexpected death in epilepsy, Takotsubo syndrome (TTS), and neurogenic sudden cardiac death (1–4). Importantly, despite the better portrayal of neurocardiogenic

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HIGHLIGHTS

- Stroke-induced cardiac injury is caused by autonomic and inflammatory mechanisms mediated by damage to the brain-heart axis.
- Some of the recently identified mechanisms could be targeted for prevention of cardiovascular complications of stroke.
- Mechanistic research and clinical trials are needed to develop specific therapies for prevention of neurocardiogenic syndromes.

syndromes, little improvements have been made in the development of specific therapies targeting the brain-heart axis for preventing cardiovascular complications and death after stroke. In the present state-of-the-art review, we describe recent advances in the understanding of anatomical and functional aspects of the brain-heart axis and post-stroke cardiovascular complications (5,6), the paradigmatic expression of neurogenic cardiovascular complications. We also provide a comprehensive and updated pathophysiological model explaining post-stroke cardiovascular events (7,8).

THE BRAIN-HEART AXIS

CENTRAL AUTONOMIC NETWORK. The heart has its own conduction system, known as the intrinsic cardiac nervous system (ICNS). However, at rest and during physical, emotional, and psychological challenge, heart rate and contractility are modified by the central autonomic network (CAN) (9). This network adjusts sympathetic and parasympathetic outflow to the heart and receives afferent impulses from the myocardium and baroreceptors (9) (**Figure 1**). At the cardiac level, the CAN's sympathetic and parasympathetic efferents comprising the extrinsic cardiac nervous system (ECNS) connect with the ICNS, conveying the autonomic regulation to the cardiac conduction system and thus the myocardium (10).

The CAN consists of interconnected areas distributed throughout the neuraxis, including the insula, ventromedial prefrontal cortex, anterior cingulate cortex, amygdala, bed nucleus of the stria terminalis, paraventricular and other nuclei of the hypothalamus, periaqueductal grey matter of the mesencephalon, Kölliker-Fuse region of the lateral pons, nucleus tractus solitarius, ventrolateral medulla, and intermediate medullary reticular zone (e.g., nucleus ambiguus) (**Figure 1**) (9).

EXTRINSIC CARDIAC NERVOUS SYSTEM. The ECNS conveys parasympathetic and sympathetic modulation of the cardiovascular system.

Cardiovagal impulses arise from the CAN through pre-ganglionic parasympathetic neurons, mainly located in the nucleus ambiguus and to the dorsal motor nucleus of the vagus (11). Cholinergic preganglionic parasympathetic fibers travel within the left and right vagus nerve, reach the cardiac ganglia, and join the cardiac plexus together with cardiac sympathetic nerves (11,12). Parasympathetic cholinergic neurons richly innervate the sinoatrial node, both atria, atrioventricular node, and the ventricular conducting system, while they only sparsely innervate the ventricular myocardium.

Sympathetic preganglionic neurons have their cell bodies mainly in the intermediolateral cell column of the thoracolumbar spinal cord. The post-ganglionic cardiac sympathetic neurons originate mainly (>90%) from the middle cervical (C3 to C6) and the cervico-thoracic or stellate ganglia (C5 to T3), and to a smaller extent from the superior ganglion (C1 to C3), the vertebral ganglion (C4 to C7), and thoracic ganglia (T2 to T6) (13). Noradrenergic post-ganglionic fibers richly innervate the left and right atria and, to lesser degree, the ventricles (10). There are significantly more post-ganglionic sympathetic—as well as parasympathetic—nerves at the base than at the apex of the ventricles (10,13), which may contribute to the pathophysiology of TTS (13,14).

THE INTRINSIC CARDIAC NERVOUS SYSTEM. The ICNS consists of more than 14,000 neurons organized in approximately 550 ganglia which contain between one and over 200 neurons (15). Although neurons are scattered throughout the heart (15), there are highly dense regions known as ganglionated plexi (15), which are modulated by the ECNS mediating sympathetic and parasympathetic activity (10,12). The aortic root ganglionated plexus connects to nerve fibers travelling along the coronary arteries (15), which mediate critical coronary artery constriction during stress (16).

HEMISPHERIC AND PERIPHERAL LATERALIZATION OF AUTONOMIC FUNCTION. Characterizing the lateralization of hemispheric (e.g., insular cortex) and peripheral regulation of cardiovascular autonomic function is complex. Some assessing hemispheric differences in sympathetic and parasympathetic

ABBREVIATIONS AND ACRONYMS

AIS = acute ischemic stroke

AFDAS = atrial fibrillation detected after stroke

AMI = acute myocardial infarction

CAD = coronary artery disease

CAN = central autonomic network

cTn = cardiac troponin

ECG = electrocardiographic

ECNS = extrinsic cardiac nervous system

HF = heart failure

ICH = intracerebral hemorrhage

ICNS = intrinsic cardiac nervous system

LV = left ventricular

SAH = subarachnoid hemorrhage

SHS = stroke-heart syndrome

SIHI = stroke-induced heart injury

TTS = Takotsubo syndrome

cardiovascular modulation have shown conflicting results, particularly in stroke patients (17–19). Regarding the peripheral regulation of cardiac autonomic function, data suggest that the right vagus nerve mainly innervates the sinoatrial node, whereas the left vagus largely innervates the atrioventricular node. Yet, evidence from animal studies or from invasive vagus stimulation do not confirm these observations (20). In summary, to date, the clinical relevance of lateralization of cardiovascular autonomic function remains uncertain (21).

CARDIOVASCULAR COMPLICATIONS AFTER STROKE: STROKE-HEART SYNDROME

In 2016, 5.5 million deaths were related to the occurrence of stroke worldwide (22). Given that one-fifth of deaths in stroke patients have a cardiovascular cause (23), it is estimated that over 1 million post-stroke cardiovascular deaths occur each year among survivors of cerebrovascular events. Still, cardiovascular death is only the tip of the iceberg, as stroke is related to increased risk of nonfatal cardiovascular complications (2). Post-stroke cardiac events have been grouped clinically under the term "stroke-heart syndrome" (SHS) (5) and are caused by several pathophysiological mechanisms known as "stroke-induced heart injury" (SIHI) (5,7,8,24) (**Figure 2**). The SHS can be classified into 5 main categories: 1) ischemic and nonischemic acute myocardial injury presenting with elevated cardiac troponin (cTn), which is usually asymptomatic; 2) post-stroke acute myocardial infarction (AMI); 3) left ventricular (LV) dysfunction, heart failure (HF), and post-stroke TTS; 4) electrocardiographic changes and cardiac arrhythmias including post-stroke atrial fibrillation (AF); and 5) post-stroke neurogenic sudden cardiac death.

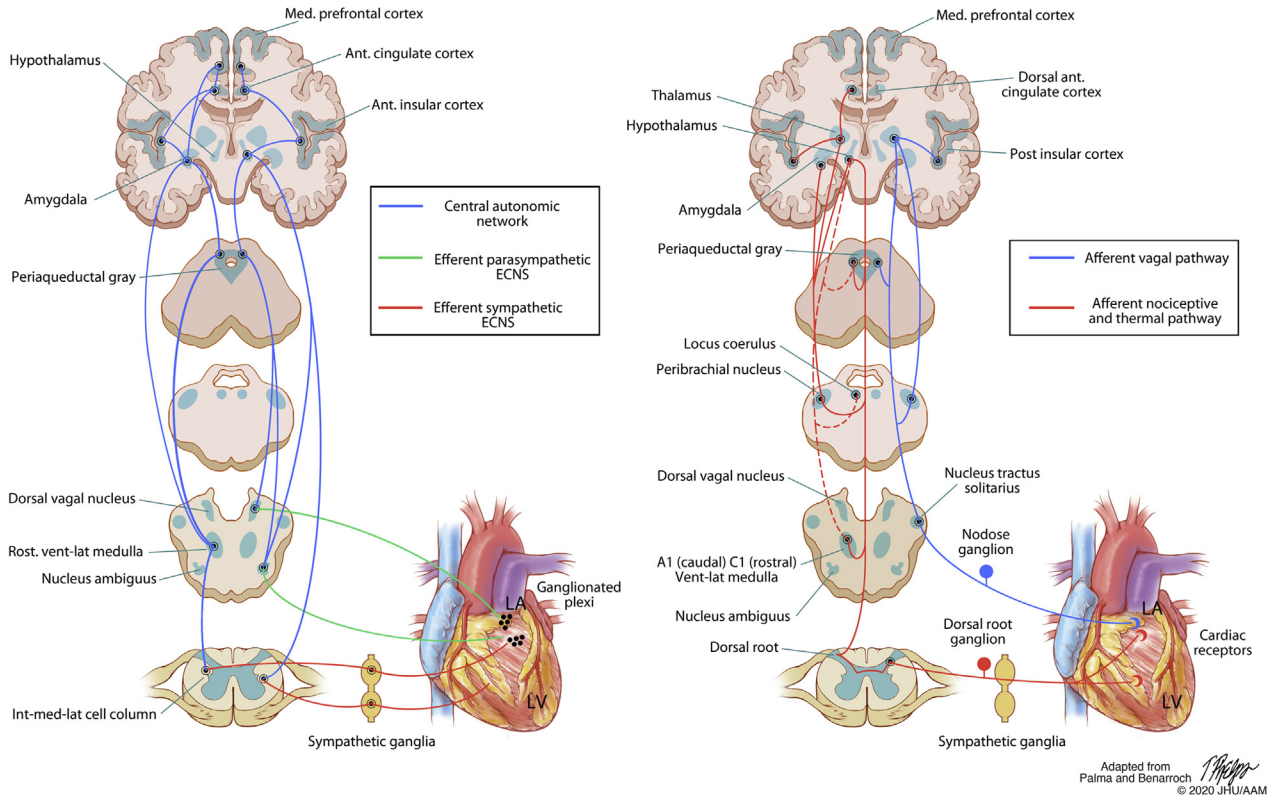
SHS: UNIQUE CLINICAL AND EPIDEMIOLOGICAL FEATURES OF POST-STROKE CARDIOVASCULAR EVENTS. First-ever acute ischemic stroke (AIS) patients without known heart disease have 25× higher risk of incident major adverse cardiovascular events than propensity-matched individuals at 30 days after stroke after adjusting for multiple covariates (2). This risk is similar for women and men (25), and is 5× higher for AIS than individuals without stroke between days 31 and 90 and is 2× higher thereafter until year 3 (2). At 1 year post-stroke, 9% of patients experience an incident cardiovascular complication, including AMI, incident HF, a new diagnosis of coronary artery disease (CAD), coronary revascularization, or cardiovascular death (2). Based on the time-varying risk of major adverse cardiovascular events after AIS, cardiovascular complications are considered as part of the SHS if they occur within 30 days of the event (2,25). Beyond this time window, cardiac events are defined as possible long-term complications, as the strength of the association with stroke is weaker (2). Although the time-varying risk of cardiac events has been only assessed for AIS, we estimate that it is similar in other types of stroke because these events are also common after acute intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH). Serious in-hospital cardiac events, including AMI, severe ventricular arrhythmias, HF, and cardiac death, have been described among 4.1% of patients with ICH (26), and are twice more frequent in SAH, being identified in up to 9% the cases (27). This underlines that patients with all types of stroke are at increased risk for cardiac events during both the shorter- and longer-term.

POST-STROKE cTn ELEVATION: ISCHEMIC AND NONISCHEMIC ACUTE MYOCARDIAL INJURY. Current guidelines recommend measuring cardiac biomarkers (preferably cTn) upon admission for AIS (28). This recommendation is strong (Class I) because the timely identification of AIS patients with cardiac disease may improve outcomes. Guidelines, however, do not specifically address the question of how to proceed if cTn is asymptomatically elevated, causing a clinical dilemma because acute coronary syndrome presentations may be atypical post-stroke, myocardial injury after stroke may occur even in the absence of obstructive CAD, and invasive coronary procedures may entail a relevant bleeding risk.

DEFINITION AND INCIDENCE OF cTn ELEVATION AFTER STROKE. Myocardial injury is defined as the elevation of cTn levels above the assay-specific 99th percentile upper reference limit (29). In the vast majority of patients with cerebrovascular events, cTn elevation occurs in the absence of typical coronary symptoms (e.g., chest pain, dyspnea) (29), unequivocal electrocardiographic (ECG) ischemic changes (e.g., ST-segment elevation) (30), or echocardiographic findings (e.g., akinetic LV wall) (31). In between asymptomatic cTn elevations and acute coronary syndromes, there are patients with cTn levels above the 99th percentile upper reference limit who do not disclose coronary symptoms but still show nonspecific ECG abnormalities or milder signs of LV dysfunction (5,32,33). Post-stroke electrocardiographic changes, LV dysfunction, and HF, with and without cTn elevation, are discussed in a later section.

Using up-to-date high-sensitivity assays, 30% to 60% of stroke patients show cTn elevation (5), in the majority of cases in the absence of coronary

FIGURE 1 Central Autonomic Network and Extrinsic Cardiac Nervous System

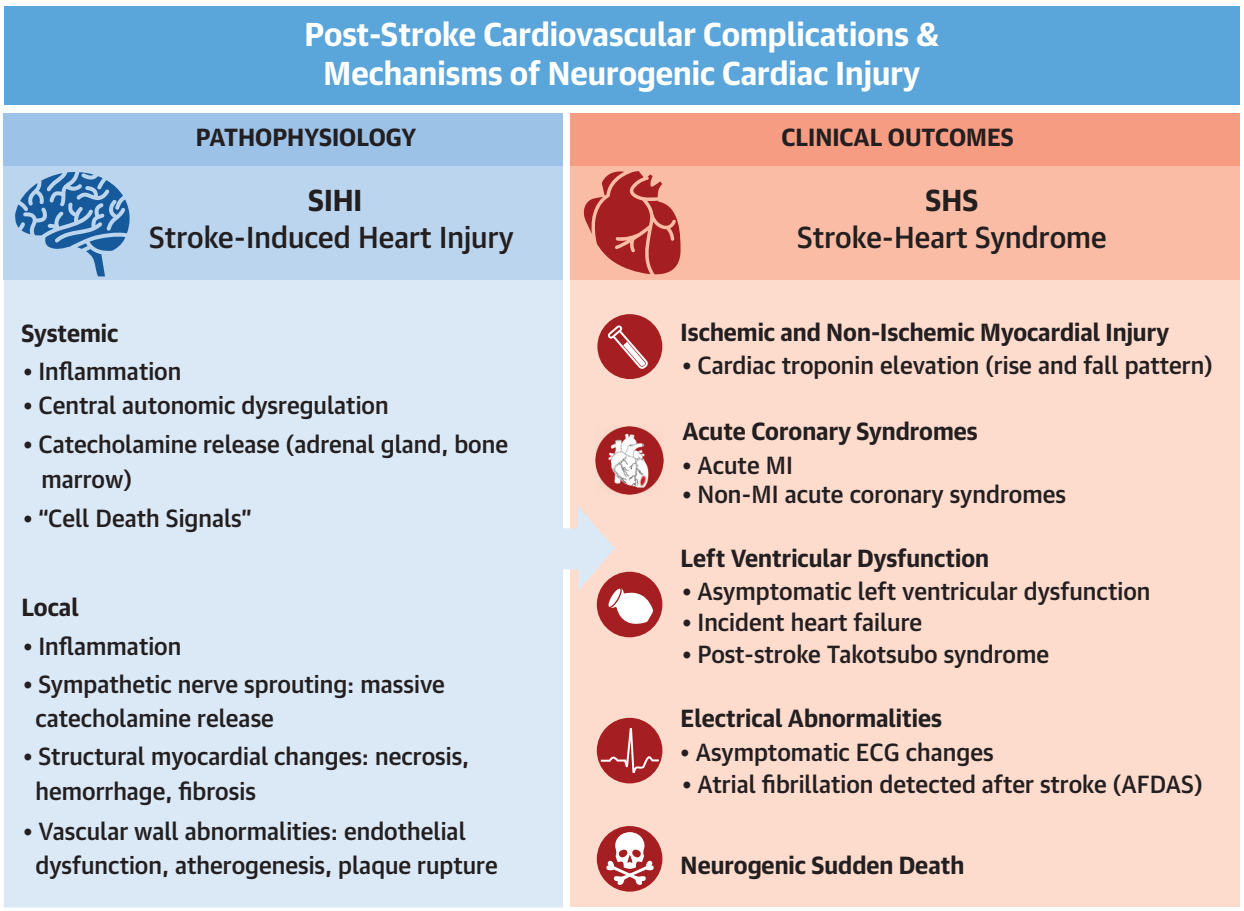


(A) Efferent system. **(B)** Afferent system. The **dotted red line** represents a parallel viscerosensory pathway arising from the catecholaminergic neurons of the A1/C1 group of the ventrolateral medulla, which send projections to the hypothalamus, periaqueductal gray, and locus ceruleus. Based, with permission, on a figure included in Palma et al. (12). ECNS = extrinsic cardiac nervous system; LA = left atrium; LV = left ventricle.

symptoms (34). cTn elevation is more commonly found in elderly patients and those with structural cardiac disease, such as HF and CAD (5,32). In addition, stroke-related factors, such as severity and, probably more important, lesion site, have been linked with myocardial injury post-stroke (5,35). Especially lesions within the right anterior insular cortex, which plays an important role within the CAN, are associated with post-stroke acute myocardial injury (35). This evidence supports stroke-induced mechanisms as promoters of cTn elevation. Although data using high-sensitivity cTn assays are scarce, elevation of cTn levels have also been reported in 20% to 40% of patients with ICH and SAH, and linked with higher clinical severity, cardiopulmonary complications, and poor outcomes (36–40). Accounting for differences in cTn assay characteristics, the frequency of myocardial injury seems to be highest in SAH, despite the fact that these patients are younger and have fewer pre-morbid cardiac comorbidities (36–40).

ACUTE VERSUS CHRONIC MYOCARDIAL INJURY. Notwithstanding the high specificity of cTn levels to identify and quantify myocardial injury, the underlying etiology includes a diverse spectrum of ischemic and nonischemic causes (41). A first crucial step is to differentiate acute from chronic myocardial injury by applying serial measurements of cTn (6,41,42). Acute myocardial injury manifests with a rising and/or falling pattern of cTn levels, whereas no such dynamic pattern is present in chronic myocardial injury due to clinically stable structural heart disease (6,41,42). Approximately 85% of stroke patients have persistently elevated cTn, representing chronic myocardial injury (5,32). Acute myocardial injury is associated with higher short-term mortality relative to chronic myocardial injury (32). Thus, the underlying cause of acute myocardial injury after stroke

FIGURE 2 Post-Stroke Cardiovascular Complications and Mechanisms of Neurogenic Cardiac Injury

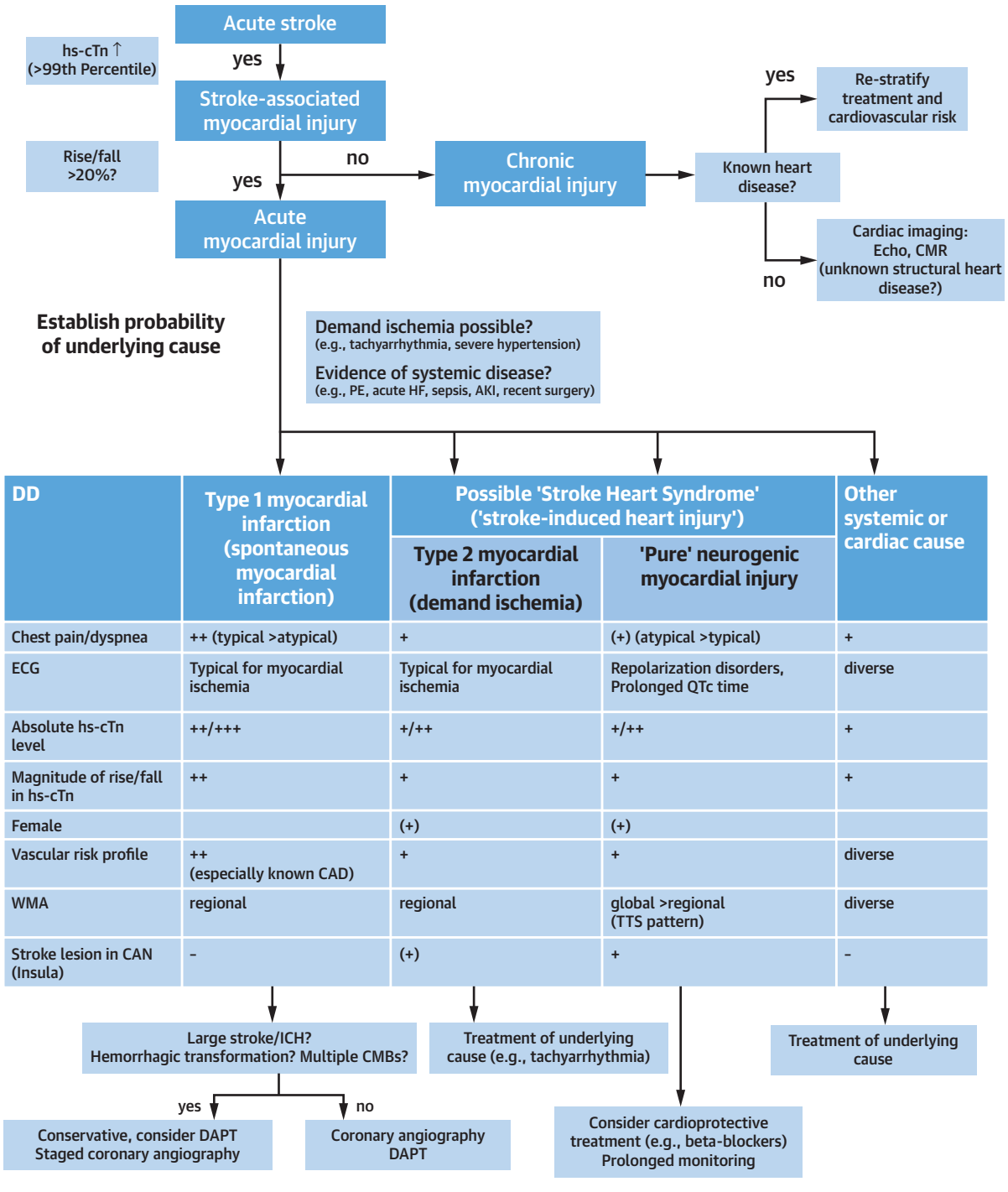


Stroke-induced heart injury (SIHI) is the concept that encompasses the series of pathophysiological processes leading to the "stroke-heart syndrome" (SHS), the clinical cardiovascular outcomes that can occur after stroke. ECG = electrocardiographic; MI = myocardial infarction.

should be determined in a timely manner to improve outcomes (Figure 3). Myocardial ischemia due to spontaneous AMI is usually the first working diagnosis, but it must be distinguished from myocardial ischemia due to oxygen supply/demand mismatch (e.g., type 2 AMI) and causes of nonischemic myocardial injury (e.g., inflammation). The higher the levels of cTn and their rise or fall, the greater the odds that the cause is an AMI (32). However, there are only limited data to provide clear cTn cut-off values for AMI in stroke patients. Importantly, coronary angiography in AIS patients with cTn levels above a guideline-defined "rule-in" cut-off for AMI revealed a coronary culprit lesion in only nearly one-fourth of patients, whereas no obstructive CAD was present in one-half of the cases (43). Acknowledging that this assumption is based on a small study, the results suggest that that nonischemic mechanisms are a possible cause of myocardial injury after stroke.

MANAGING ELEVATED cTn AFTER STROKE. Currently, there are no recognized guidelines on how stroke patients with elevated cTn should be evaluated, treated, or followed-up from a cardiac perspective. Most stroke guidelines do, however, provide advice for post-stroke cardiac work-up irrespective of cTn elevation, including at least routine ECG, >24 h of rhythm monitoring, and echocardiography (28,44). These routine tests constitute the basis for the evaluation of possible causes of myocardial injury, which in turn is a prerequisite for specific treatments. Elevated cTn levels motivate repeated measurements to detect the "rise-and-fall" pattern typical for acute myocardial injury and to separate the plateau phase from chronic myocardial injury

FIGURE 3 Interpretation and Management of Elevated Troponin Levels After Stroke



DD	Type 1 myocardial infarction (spontaneous myocardial infarction)	Possible 'Stroke Heart Syndrome' ('stroke-induced heart injury')		Other systemic or cardiac cause
		Type 2 myocardial infarction (demand ischemia)	'Pure' neurogenic myocardial injury	
Chest pain/dyspnea	++ (typical >atypical)	+	(+) (atypical >typical)	+
ECG	Typical for myocardial ischemia	Typical for myocardial ischemia	Repolarization disorders, Prolonged QTc time	diverse
Absolute hs-cTn level	++/+++	+/++	+/++	+
Magnitude of rise/fall in hs-cTn	++	+	+	+
Female		(+)	(+)	
Vascular risk profile	++ (especially known CAD)	+	+	diverse
WMA	regional	regional	global >regional (TTS pattern)	diverse
Stroke lesion in CAN (Insula)	-	(+)	+	-

Elevation of cardiac troponin above the assay-specific 99th percentile indicates the presence of myocardial injury. If serial measurements reveal a rise/fall pattern >20%, acute myocardial is detected. The tabular part of the figure suggests factors to determine pretest probabilities for specific causes of acute myocardial injury. AKI = acute kidney injury; CAD = coronary artery disease; CAN = central autonomic network; CMB = cerebral microbleeds; CMR = cardiovascular magnetic resonance imaging; DAPT = dual antiplatelet therapy; HF = heart failure; hs-cTn = high-sensitivity cardiac troponin; ICH = intracranial hemorrhage; PE = pulmonary embolism; TTS = Takotsubo syndrome; WMA = wall-motion abnormalities.

(29,41). **Figure 3** provides an algorithm on how to manage cTn elevation in (ischemic) stroke. Patients with severe stroke or high bleeding risk (e.g., large brain infarct or hemorrhage, multiple cerebral microbleeds) may be suitable only for a conservative strategy. Basic care for an acute coronary syndrome is often still possible, because this is similar to basic care after AIS and includes the same kind of secondary prevention. When a more invasive strategy is possible, high bleeding risk may be reduced by using drug-eluting balloons instead of stents and short-acting platelet inhibition. Diagnostic coronary angiography during the early post-stroke phase is feasible and safe (6,43). Also, conditions provoking coronary demand ischemia should be treated accordingly. When disturbances in the hemostasis cause both myocardial injury and AIS, as in cancer-associated thrombosis (45), low molecular weight heparins could be considered in the setting of clinical trials. The well-established poor prognosis of stroke patients with elevated cTn warrants careful cardiac follow-up after the acute phase. For chronic myocardial injury, treatment should be directed toward underlying comorbidities. In the absence of cardiac comorbidities, evidence of chronic myocardial injury should prompt further cardiac evaluation and restaging of cardiovascular risk.

POST-STROKE AMI (AND ACUTE CORONARY SYNDROMES). Asymptomatic cTn elevation is common in all types of strokes. For the diagnosis of AMI in the context of an acute stroke, there must be clinical evidence of at least 1 of the following: coronary symptoms, definite incident ischemic ECG changes, new ischemic regional wall-motion abnormalities on cardiac imaging, and/or an acute coronary thrombus on coronary angiography (46). AMI and other acute coronary syndromes are common after stroke, with an estimated incidence of 1.7%/year in a recent meta-analysis including 130,000 patients from 58 studies (47). Incident AMI at 1 year can affect 2.6% to 3.0% of patients after first-ever AIS without known heart disease (2,48). In-hospital AMI after AIS independently doubles the risk of death at discharge and at 1 year (49). The risk of in-hospital AMI after ICH is approximately 0.3% (26). Among patients with ICH, in-hospital AMI is independently associated with 63% increased risk of death, 40% lower odds of home disposition, and 4× higher hospitalization costs (50). AMI has been reported in 6.6% and 11.1% of clinical and autopsy studies of patients with SAH, respectively (27,51). Acute coronary syndromes in patients with SAH are associated with 5× increased risk of death (52). However, the diagnosis of AMI in patients with acute SAH is challenging because transient neurogenic ECG changes (e.g., T-wave inversion), cTn elevation, and echocardiographic abnormalities can mimic acute myocardial ischemia (53).

An increase in oxygen demand (e.g., type 2 AMI) in the context of subclinical CAD may explain a proportion of cardiovascular events occurring early post-stroke in patients without known history of heart disease. At later stages, coronary events may occur as a consequence of accelerated atherosclerosis of the coronary arteries triggered by the stroke (54). Yet, the prevalence of severe asymptomatic CAD among patients with AIS is only 18% (55); thus, subclinical CAD is unlikely to explain the extraordinary higher risk of cardiovascular events post-stroke (2,25). Furthermore, considering that men with AIS are 8× more frequently diagnosed with subclinical CAD than women (55), the similar risk of incident post-stroke cardiovascular events in both sexes (25) makes nonischemic mechanisms probable, mainly among women.

POST-STROKE LV DYSFUNCTION, HF, AND TAKOTSUBO SYNDROME. Post-stroke cardiovascular complications are not limited to acute coronary events (2,25). Incident post-stroke LV dysfunction has been extensively described in animal studies of AIS (56), ICH (57,58), and SAH (59). Decreased LV ejection fraction and diastolic dysfunction have been reported widely in all types of strokes, but the lack of knowledge of the baseline cardiac status before stroke limits the ability to estimate its true incidence (33,58,60). LV dysfunction can occur with or without elevated cTn. However, high cTn is associated with lower LV ejection fraction, number of hypokinetic segments, and wall motion abnormalities (40). In a study of 1,209 AIS patients, 378 (31%) showed at least mildly impaired LV function (61). Of these, congestive HF was pre-diagnosed in only approximately one-third of patients (61). Among 208 patients with ICH, 15 (7.2%) presented with impaired LV function (58). In this study, LV dysfunction was associated with 8× higher risk of in-hospital mortality (58). A study assessing 40 patients with SAH found that 20 had signs of LV dysfunction (62). In 13 of these patients, LV function was restored within 7 days, suggesting that LV dysfunction occurs in a fairly large proportion (50%) of patients with SAH and that it is usually transient (65%) (62). N-terminal pro-B-type natriuretic peptide has been found to be elevated among patients with LV systolic or diastolic dysfunction at a median of 48 h after AIS, ICH, and SAH (63). Elevated N-terminal pro-B-type natriuretic peptide has been correlated with stroke severity (64) and increased risk of

cardiovascular events and death after ischemic stroke (65).

The most common clinical expression of impaired LV function is HF. In a prospective single-center study of patients with AIS without pre-existing cardiovascular comorbidities, 4.9% experienced incident HF during hospitalization (66). HF was explained by post-stroke AMI among only one-third of these patients (66). At the population level, among patients with first-ever AIS and no history of heart disease, 3.8% were newly diagnosed with incident HF at 1 year compared with 1.3% in propensity-matched individuals without stroke (hazard ratio: 3.3; 95% confidence interval: 3.1 to 3.7) (2). Acute HF has also been reported among patients with ICH. In a single-center cohort of 949 patients with acute ICH, the most frequent cardiovascular complication was acute HF, which was found in 36 (3.8%) cases (26). Interestingly, 86.1% of these patients had no previous history of HF. Similarly, evidence of congestive HF was found among 27 of 617 (4.4%) patients with SAH (27).

TTS is a distinct HF syndrome which is characterized by transient LV dysfunction with subsequent improvement usually occurring within 1 to 6 months (67,68). TTS is an intriguing example of altered brain-heart interactions resulting in acute cardiac dysfunction post-stroke. Although the pathophysiology of TTS is far from being understood, recent evidence from experimental and observational studies indicates that TTS likely originates from functional and structural impairment of the brain-heart axis (**Figure 1**) (69,70). Intense emotions and physical stress (e.g., mainly medical conditions) commonly precipitate TTS. Large register-based studies have clearly demonstrated that acute neurological disorders constitute the largest group of physical triggers with the worst clinical outcomes and slower recovery of LV function (67,69). Elderly women compose the vast majority of patients affected, which is also noted in TTS secondary to stroke (71–74). Nearly one-half of TTS patients have a prevalent neurological or psychiatric disorder, with acute triggers accounting for about one-fifth of all cases (68). Acute stroke is a frequent neurological trigger for TTS. TTS secondary to stroke occurs in 0.5% to 1% of patients with AIS, and in 15% to 25% of patients with SAH (5,72,75). A cross-sectional study from a nationally representative U.S. sample found that SAH was associated with 10-fold increased odds of TTS, whereas only modest associations were observed between AIS or ICH and TTS (76). Regardless of stroke subtypes, occurrence of TTS is a poor prognostic factor. TTS was independently associated with death after AIS in a propensity-matched registry (72). Similarly, in a meta-analysis of 25 studies including 2,690 patients with SAH, markers of cardiac damage were associated with TTS and correlated with increased risk of death (77). These data suggest that TTS secondary to stroke portends poor prognosis and therefore warrants early aggressive screening, particularly when there is evidence of cardiac dysfunction.

The terminology of cardiac dysfunction observed in the clinical setting of stroke, and especially SAH, has led to controversy. Instead of TTS, the term "neurogenic stunned myocardium" is frequently found in the published data to summarize the clinical picture of LV dysfunction and ECG changes together with elevation of cTn (67). Importantly, the term "neurogenic stunned myocardium" originated from a time when the medical community was not yet familiar with TTS, and when it was less established that there are different types of TTS (e.g., apical, midventricular, basal, and focal) (68). In fact, the concept of neurogenic stunned myocardium is in accordance with all diagnostic criteria of TTS (72). Thus, we advocate for using the term TTS secondary to neurological disorders and recommend a precise description of TTS type (49).

ELECTROCARDIOGRAPHIC CHANGES AND AF DETECTED AFTER STROKE. Electrocardiographic changes. Despite considerable inconsistencies in reporting methods, acute ECG abnormalities, including ST-segment elevation, ST-segment depression, unspecified ST-T changes, QT prolongation, T inversion, abnormal T-wave morphology, bundle branch block, and pathological Q waves, are frequent among patients with all types of stroke (78). As occurs with LV dysfunction, ECG changes are more common among patients with elevated cTn (40). It is sometimes challenging to determine which ECG changes are new post-stroke. Among 450 patients with AIS, ICH, and SAH who had at least 1 available ECG before the cerebrovascular event, 75% showed new ECG abnormalities, 28.7% constituting cardiac arrhythmias (79). Patients with SAH showed the highest incidence of cardiac arrhythmias (37.5%), followed by those with AIS (21.9%) and ICH (14.8%) (79). In the same study, the proportion of cardiac arrhythmias among patients admitted with neurological conditions not affecting the brain (e.g., peripheral neuropathies, myasthenia gravis) was only 9.8%. In unselected cohorts with and without known heart disease, ECG changes have been reported in 91% of AIS, 96% of ICH, and 76% of SAH cases (78).

After excluding patients with known heart disease, ECG changes were still present in 32% with AIS, 46% with ICH, and 75% with SAH (78).

AF detected after stroke. Patients with AIS have an elevated risk of being newly diagnosed with AF (5). Relative to propensity-matched individuals without stroke, the incident diagnosis of AF is 8× higher among AIS patients (hazard ratio: 8.2; 95% confidence interval: 7.5 to 8.9) (2). AF can be newly detected in up to one-fourth of AIS and TIA patients after applying a sequential strategy of prolonged cardiac monitoring (80–82). The yield of screening for AF after stroke strongly depends on the duration of monitoring, which highlights the importance of prolonged rhythm monitoring after stroke, especially after cryptogenic AIS (80). To define a concept for clinical practice and research, the term "atrial fibrillation detected after stroke" (AFDAS) has been coined (83). AFDAS accounts for AF cases either pre-existing or being triggered by the stroke (83). This concept of AFDAS has been recently incorporated in the 2020 European Society of Cardiology guidelines for the diagnosis and management of AF (84). Although the largest proportion of AFDAS are probably subclinical arrhythmias, which are pre-existent before the stroke and deemed to be its cause, AFDAS can be considered as a specific clinical entity, with a particular risk factor profile and possibly better outcomes compared with AF known before stroke occurrence (83,85). AFDAS possibly comprises cardiogenic (primary), neurogenic (secondary), and mixed variants (83). However, whether some AFDAS are neurogenic is a matter of debate. Clinical evidence supports post-stroke neurogenic mechanisms in patients with AFDAS (86); yet, large studies using implantable loop recorders before and after the stroke would be ideal but have not been conducted thus far. The paradigm of neurogenic AFDAS would be a low-burden paroxysmal AF occurring early after a stroke involving cerebral regions within the CAN, in a young patient without AF in previous ECG recordings and without pre-existing structural heart disease or cardiovascular comorbidities (e.g., left atrial enlargement, CAD, or HF) (83). Preclinical studies have demonstrated neurogenically induced cardiac arrhythmias post-stroke in rodents (19) and structural changes in the left atrial myocardium, which could represent the substrate for AF (24). In clinical studies, AFDAS is characteristically low burden, with over one-half of documented paroxysms lasting <30 s (87), explaining why its detection requires long-term monitoring (80) and questioning if its associated risk of recurrent stroke is as high as that of AF known before the cerebrovascular event (85). In a population-based study including 23,376 patients with AIS, AFDAS was associated with a similar risk of recurrent AIS as sinus rhythm in multivariable regression models adjusted for use of anticoagulants and the competing risk of death during follow-up. In contrast, the adjusted incidence of recurrent AIS at 1 year was 25% higher for AF known before the stroke than for sinus rhythm. The lack of difference in the risk of recurrent AIS at 1 year between AFDAS and sinus rhythm, and the lower prevalence of heart disease in AFDAS compared with AF known before stroke occurrence, suggest that the underlying pathophysiology of AFDAS may differ from that of AF known prior to the stroke. Regardless of these differences, all patients with stroke and AFDAS should receive oral anticoagulants for secondary stroke prevention (88). Additionally, AFDAS has a lower prevalence of cardiovascular comorbidities (85,89,90) and structural heart disease (91), as well as lower CHA_2DS_2-VASc score (85,89,90) compared with AF known before the stroke. AFDAS has been also reported among 2.6% to 6.0% of patients with ICH (26,92) and is independently associated with 8× higher chances of being diagnosed in strokes affecting the insular cortex (92). Furthermore, different from AIS, AFDAS is less likely to be a pre-existing subclinical arrhythmia in ICH patients because it is not a cause of cerebral hemorrhage (7). AFDAS can also be identified in 5% to 8% of patients with SAH (77). Similar to what has been reported for AIS and ICH, involvement of the right sylvian fissure, which is in tight contact with the insular cortex, has been reported more frequently among SAH patients who develop cardiac arrhythmias than those who do not (93). Together, these data support the role of neurogenic mechanisms as a trigger for AFDAS (7). To date, inflammation and autonomic dysregulation are the best documented neurogenic pathways (86). Understanding and targeting these pathophysiological pathways is essential because of the potential to prevent AFDAS from happening as well as perpetuating through AF-related atrial remodeling (86).

SUDDEN DEATH IN STROKE PATIENTS. According to the World Health Organization, sudden cardiac death is defined as a sudden unexpected death occurring within 1 h of symptom onset for witnessed events, or within 24 h of being observed symptom-free for unwitnessed events (94). Neurogenic sudden cardiac death has been recognized for centuries (95). However, identifying the actual cause of death in patients with sudden death is often challenging due to the scarcity of autopsy studies and availability of timely ECG recordings during the event. A diagnosis of sudden stroke-induced cardiac death can only be certified after a complete autopsy including the brain

and the heart has been performed (96). Although sudden cardiac death is part of the SHS (5), sudden neurological death, in particular due to stroke, is likely a substantial contributor to sudden deaths in stroke patients (97). Furthermore, definitions across studies (even randomized controlled trials) vary widely (23), and publications based on medical record diagnoses or epidemiological definitions tend to overestimate the role of cardiac etiologies (98). A nationwide Danish study of sudden deaths among individuals of 49 years of age or younger found that 52 (3%) of 1,968 deaths were caused by a stroke (99). Interestingly, ICH or SAH comprised 94% of stroke-related deaths. A description of pre-mortem ECG findings or cardiac pathology were not provided. A recent prospective city-wide autopsy study showed that 5.5% of World Health Organization–defined sudden cardiac deaths had a neurogenic cause, representing the second noncardiac cause after occult overdose (98). Stroke was responsible for 61% of 18 neurogenic sudden cardiac deaths and 3.1% of 335 sudden cardiac deaths (97). ICH, SAH, and AIS represented 44.4%, 11.1%, and 5.6% of neurogenic cardiac deaths and 2.4%, 0.6%, and 0.3% of overall sudden cardiac deaths, respectively. Whether these were truly cardiac or otherwise neurological deaths remains unknown. In summary, most of the existing evidence about sudden cardiac death after stroke should be regarded with caution. With regard to the potential mechanisms of sudden cardiac death after stroke, neurocardiogenic injury induced by post-stroke sympathetic overstimulation is believed to affect the myocardium and the electrical conduction system leading to death (100). Classically, the distinctive histopathological pattern of sympathetic overstimulation shows contraction band necrosis in which cardiomyocytes die in a hypercontraction state (101).

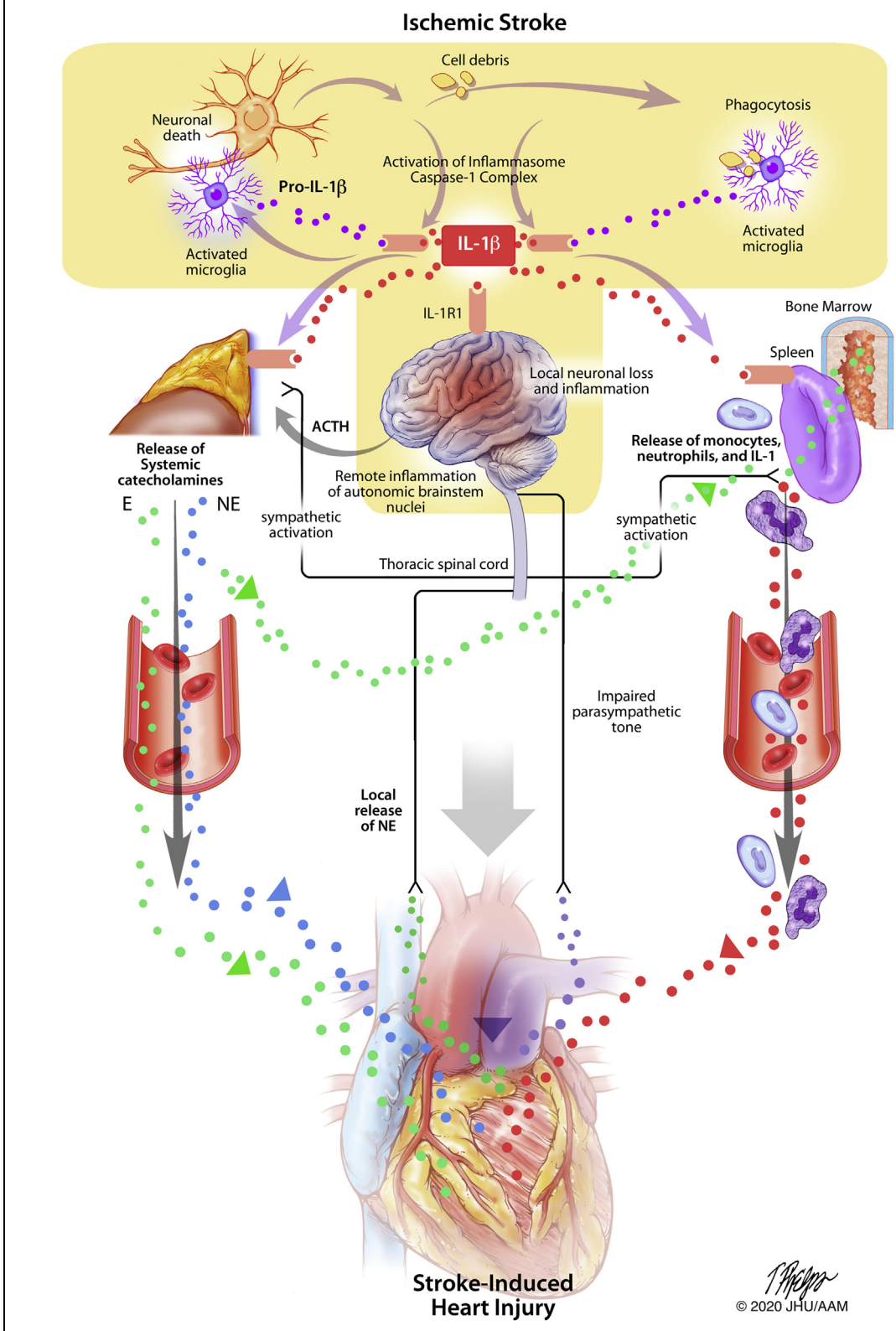
PATHOPHYSIOLOGY OF CARDIOVASCULAR COMPLICATIONS AFTER STROKE: THE CONCEPT OF SIHI

SIHI is a complex pathophysiological process leading to SHS in patients with and without underlying heart disease (8) and can be regarded as the perfect storm caused by a multiplicity of pathophysiological phenomena derived from the brain-heart interaction. The main pathways causing SIHI are autonomic dysregulation and abnormally enhanced and perpetuated inflammation.

Evidence from animal models and human studies underscore the role of autonomic dysregulation and inflammation as the pillars of SIHI. The concept of SIHI encompasses a wide spectrum of acute and chronic structural, functional, and molecular signaling myocardial changes, including contraction band necrosis, subendocardial hemorrhage, microvascular coronary endothelial dysfunction, inflammation (e.g., increased expression of HLA-DR, cytokines, neutrophils, lymphocytes, pan-leukocytes, and macrophages), oxidative stress, apoptosis, autophagy, fibrosis, altered gene expression, reduced mitochondrial activity, impaired cardiac excitation-contraction coupling, and decreased contractile function (24,102–107). Although cytokines are released acutely after stroke, the increase in their plasmatic levels is only transient, lasting a few hours to days. Despite this short-lasted systemic inflammatory response, myocardial remodeling persists for weeks or even months (24). As described in the following text, the local release of noradrenaline and the production of interleukin (IL)-1 are central in this process.

SYSTEMIC MECHANISMS OF SIHI. Post-stroke brain-bone marrow and spleen inflammatory coupling leads to systemic inflammation, which is of major relevance in the development of SIHI. Stroke results in a massive release of monocytes and neutrophils from the spleen and other organs (108) and changes in lymphopoiesis (109). A similar splenic response has been described after AMI, with rapid accumulation of monocytes in the heart (110). Therefore, it is reasonable to suspect that monocytes released by the spleen target the heart after stroke. It is not entirely understood how acute brain damage triggers the splenic monocyte release, but post-stroke impairment of the autonomic nervous system regulation of the spleen is one of the most probable mechanisms (111). The splenic nerve is indeed comprised by nearly 98% of noradrenergic sympathetic fibers (112) and all inflammatory cells, including neutrophils, lymphocytes, monocytes, and macrophages, have ß-adrenergic receptors (113). Increased sympathetic tone enhances the splenic inflammatory response, while augmented parasympathetic drive has the opposite effect. The sympathetic-dependent production of IL-1ß by splenic macrophages can be reduced by blocking ß-adrenergic receptors with carvedilol (114) or the macrophagic α-7 nicotinic receptor, similar to what occurs with cardiac macrophages (115). Catecholamine surges have been classically described after stroke. Transient elevations of adrenaline and noradrenaline after stroke are triggered by different mechanisms, including a release of adrenocorticotropic hormone (116), sympathetic stimulation of the adrenal glands (e.g., pre- and post-

FIGURE 4 Systemic Mechanisms of Stroke-Induced Heart Injury



Continued on the next page

ganglionic sympathetic nerves synapsing with chromaffin cells of the adrenal medulla) (117), and increases in plasmatic cytokines such as IL-1ß acting on the hypothalamic-pituitary adrenal axis (118).

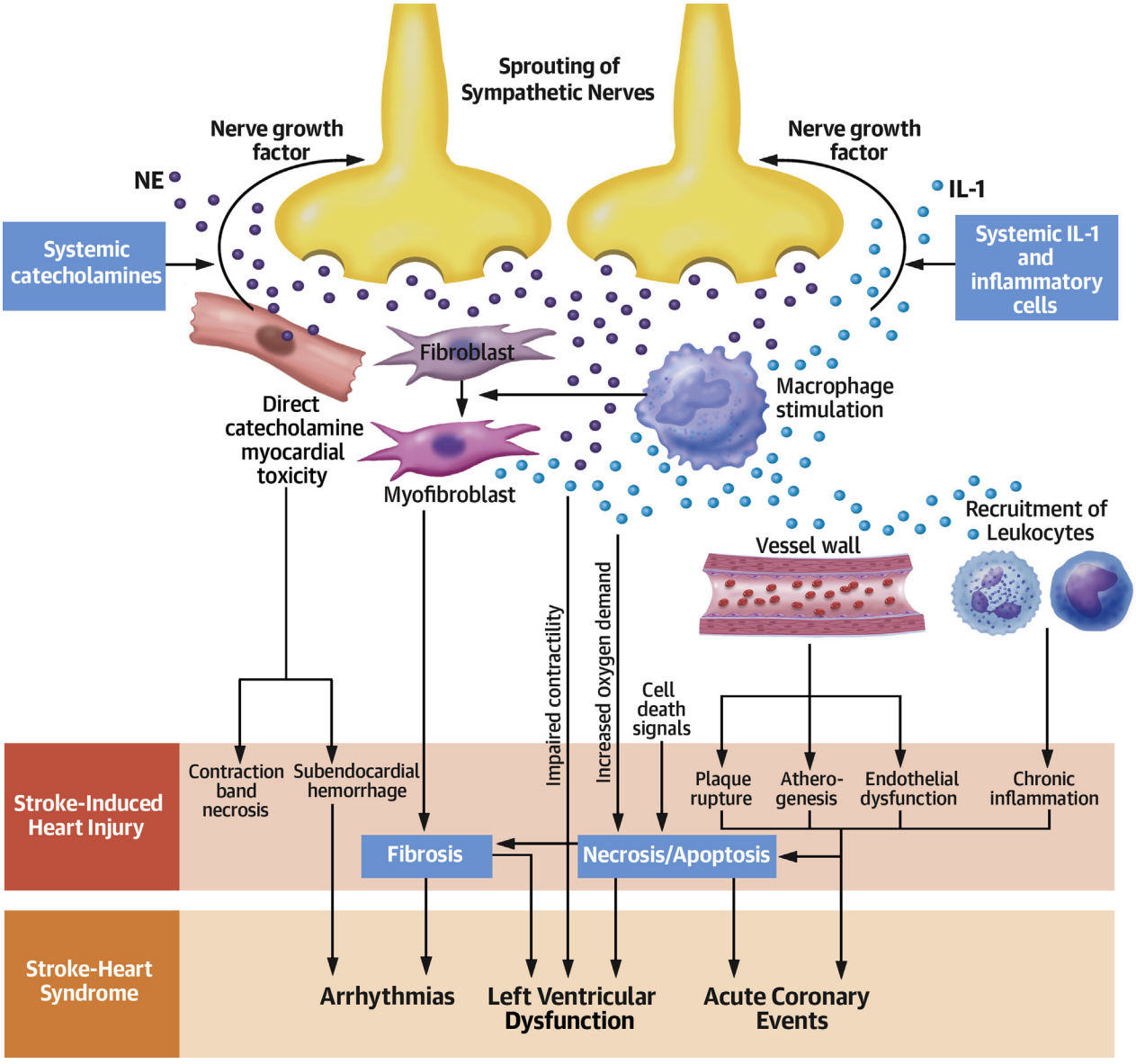
Additional systemic factors contribute to SIHI. So-called "cell death signals" have been described in in vivo and in vitro experiments in which rat cardiac myocytes undergoing ischemic-reperfusion injury were exposed to the supernatant of primary rat neurons experiencing 90-min oxygen-glucose deprivation (107). The exposure to this supernatant but not to that of nondeprived neurons resulted in decreased cell viability and mitochondrial activity (107). Impaired mitochondrial function explains non-ischemic cardiomyocyte necrosis (119). There is evidence of cardiomyocyte apoptosis and autophagy at 3 months after transient middle cerebral artery occlusion (107). How cerebral cell death signals reach the heart remains to be elucidated, but exosomes could be the carriers (120). In another rat model, AIS was associated with impaired cardiac contractility (105) confirming the results of prior experimental models showing similar findings (104,106). Decreased myocardial contractility explains the increased risk of acute HF observed after stroke (2,66). Reduced protein expression of ß1-adrenergic receptors and oxidative stress were identified as potential mechanisms of impaired inotropic function (121). The same authors found increased myocardial vulnerability to ischemia related to impaired expression of ß1-adrenergic receptors and the cardioprotective Survivor Activating Factor Enhancement signaling pathway (105).

LOCAL MECHANISMS OF SIHI. Involvement of the insular cortex and other cerebral structures in charge of the autonomic regulation of the heart leads to autonomic dysfunction after stroke (86). Neuronal death in the context of stroke results in local cerebral inflammation characterized by the activation of microglia and the production of cytokines and chemokines (**Figure 4**). Pro-interleukin-1 is activated into IL-1 by caspases, which are previously activated by the inflammasome complex in the brain. Microglia activation within the brain infarct extends to remote cerebral areas (122), possibly involving other autonomic nuclei and nerves. In rodent models of brain injury, damage to autonomic pathways results in massive release of catecholamines in the extracellular myocardium in the context of only mildly increased levels in peripheral blood (123). Not surprisingly, the most striking myocardial changes are found adjacent to intracardiac nerves after subarachnoid hemorrhage (102). In a selective insular AIS rat model, the most prominent myocardial changes were found adjacent to left atrium surrounding the pulmonary veins, the region of the atrial myocardium with the highest density of sympathetic nerve processes (24). At 30 days after stroke, endothelial dysfunction, inflammation, and fibrosis are more severe within the left atrial tissue close to ganglionated plexi compared to more distal left atrial myocardium (24). The local action of catecholamines is facilitated by the tight proximity between nerve endings and cardiomyocytes heightened by post-stroke sprouting of sympathetic processes in the myocardium, mediated by the expression of nerve growth factor resulting from the stimulation of $ß_2$-adrenergic receptors (**Central Illustration**) (13). Nerve growth factor is also released by myofibroblasts and cardiomyocytes. Noradrenaline exerts its toxicity on cardiomyocytes through altered ß-adrenergic signal transduction, causing contraction band necrosis, apoptosis, and impairment of functional contractility due to uncoupling of myocardial ß-adrenergic receptors from mechanical response (124). Noradrenaline also increases oxygen demand, stimulates coronary atherogenesis, generates endothelial dysfunction, and makes plaques prone to rupture, increasing the risk of short- and long-term acute coronary syndromes (125). In a mouse model, an HF phenotype with impairment of LV ejection fraction and LV dilatation in the context of increased peripheral sympathetic activity was induced 8 weeks after focal cerebral ischemia. The adrenergic response was deemed to be responsible for these findings given that the use of metoprolol resulted in preserved LV function by reducing extracellular cardiac remodeling and inhibiting sympathetic signaling (56). Sympathetic stimulation in turn

FIGURE 4 Continued

Post-stroke neuronal death causes local inflammation by activated microglia, cytokines, and chemokines. The inflammasome complex activate caspases and these activate pro-interleukin-1 into IL-1, which is central in this process. IL-1, cytokines, and sympathetic innervation stimulate the adrenal gland, causing systemic catecholamine surges. The spleen and bone marrow release macrophages, neutrophils, and cytokines enhancing this response. Pre- and post-ganglionic autonomic nerve endings massively release catecholamines in the extracellular myocardium leading to a more severe and chronic local inflammatory response. AR = adrenergic receptor; E = epinephrine; IL = interleukin; IL-1R1 = interleukin 1 type 1 receptor; LA = left atrium; LV = left ventricle; NE = norepinephrine; ROS = radical oxygen species; SAFE = Survivor Activating Factor Enhancement.

CENTRAL ILLUSTRATION Local Mechanisms of Stroke-Induced Heart Injury



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Noradrenaline reaches the heart through the systemic circulation and sympathetic nerve endings, damages cardiomyocytes (contraction band necrosis) and the subendocardium (local hemorrhage), stimulates macrophages, and activates fibroblasts into myofibroblasts. Interleukin (IL)-1 and inflammatory cells reach the heart through the systemic circulation and further stimulates myofibroblast and macrophage activation. Inflammation induces atherogenesis, plaque rupture, and endothelial dysfunction. Cardiomyocytes, myofibroblasts, and sympathetic nerves release nerve growth factor, triggering sympathetic nerve sprouting, which further amplifies the long-term adrenergic response. Uncoupling of myocardial ß-adrenergic receptors impairs contractility and the massive release of noradrenaline increases oxygen demand. "Cell death signals" resulting from neuronal death reach enhance necrosis/apoptosis in the context of increased oxygen demand and coronary microvascular wall changes. Cardiomyocyte necrosis and the activation of myofibroblast result in enhanced fibrosis. Adapted from Tim Phelps.

leads to enhancement and perpetuation of local myocardial inflammation due to increased production of IL-1ß by macrophages. Locally released IL-1ß also plays a role in SIHI by boosting the inflammatory response (e.g., it recruits proinflammatory leukocytes) (118). Additionally, IL-1 causes dilative remodeling, anatomical substrate for HF, and arrhythmogenesis. In an insular AIS model, fibrosis

developed in the absence of evident CAD, indicating a nonischemic process (126) likely caused by sympathetic overactivation and amplified inflammation at the level of the ganglionated plexi (24). In fact, proliferation of cardiac fibroblasts and their transition to myofibroblasts occurs in the context of stimulation of $ß_2$-adrenergic receptors (13) and the local release of IL-1, other cytokines, TNF-α, and platelet-derived growth factor (127). Enhanced fibrosis in the vicinity of the pulmonary veins (24) and subendocardial involvement (102) constitute possible structural and functional substrates for the occurrence of neurogenic AFDAS (86).

SPECIFIC MECHANISMS OF TAKOTSUBO SYNDROME SECONDARY TO STROKE. The exact mechanism underlying TTS is unknown. Currently, the most favored explanation is direct catecholamine-induced myocardial toxicity and coronary microvascular spasm (14). In patients with TTS, plasma catecholamine levels have been shown to be 2 to 3 times higher than patients with AMI and 20 times higher than normal adults (128). Of note, catecholamine levels also increase within minutes following stroke onset, and peak values of creatine kinase MB and cTn after stroke correlate positively with the peak values of catecholamines (59). At the level of myocardial receptors, supra-physiological epinephrine concentrations result in switching of the receptors from Gs to a Gi-coupled state, resulting in a paradoxical negative inotropic effect (129). The role of altered cellular cardiomyocyte response to stress is supported by enhanced ß-adrenergic signaling in response to catecholamines in cardiomyocytes derived from induced pluripotent stem cells of TTS patients compared with healthy adults (130). There is also compelling evidence that individual vulnerability to TTS is increased due to brain dysfunction in the CAN, which modulates the cardiovascular response to stress (70). TTS secondary to AIS has been linked to involvement of the insular cortex (72,73), which again highlights the role of altered function within the heart-brain axis in the pathogenesis of TTS. The cascade of events resulting in SIHI may, in susceptible individuals such as elderly women, lead to the distinct clinical phenotype of TTS after stroke.

KNOWLEDGE GAPS AND FUTURE DIRECTIONS

More work is needed to guide the clinical management of stroke patients with cTn elevation. Multicenter studies should aim at refining clinical algorithms and focusing on identifying which patients require urgent coronary revascularization. Furthermore, it remains to be elucidated how much pre-morbid structural heart disease and stroke-related factors interact in the development of myocardial injury after stroke. This issue will be specifically addressed by the prospective, observational, multicenter study PRAISE (PRediction of Acute Coronary Syndrome in Acute Ischemic Stroke) (NCT03609385). In PRAISE, AIS patients with cTn elevation above cut-offs for acute coronary syndrome derived from current non-ST-segment elevation acute coronary syndrome guidelines will undergo timely diagnostic coronary angiography. The final diagnosis of acute coronary syndrome as the cause of cTn elevation will be established by a blinded endpoint committee. Elevated cTn is associated with increased risk of incident stroke in the general population and among patients with atrial fibrillation (131), suggesting a potential role in vascular risk stratification after stroke. More data about the prognostic utility of chronic myocardial injury after stroke are warranted.

Further advancement of our knowledge of TTS will help us better understand the mechanisms of neurocardiogenic syndromes in general. Registry data will have to answer the questions whether there is a distinct clinical profile of TTS secondary to neurological disorders, and whether certain treatments can improve short- and long-term outcomes after TTS. Beta-blockers and angiotensin-converting enzyme inhibitors have been suggested, but data are limited to make strong recommendations about their true clinical value. The role of these drug classes together with targeting the coronary microcirculation in TTS to improve outcomes should be tested in clinical trials. More research is needed to identify individuals at risk of developing severe complications of TTS such as arrhythmia, which is a relevant complication of TTS and has been linked to both sudden death after stroke and epilepsy.

The concept of neurogenic AFDAS challenges the classical perspective that all types of AF diagnosed in stroke patients have similar underlying pathophysiologies and outcomes. Despite this, we strongly encourage the use of oral anticoagulants for secondary stroke prevention in all patients with AFDAS, as recommended in current clinical guidelines (88,132). Advancing knowledge about this relatively novel perspective is needed. The PARADISE (Pathophysiology and Risk of Atrial Fibrillation Detected after AIS) initiative, a translational approach including population-based, clinical, and experimental studies, will provide a better understanding of neurogenic AF mechanisms after stroke (133).

Although secondary stroke prevention involves a strict control of vascular risk factors shared with cardiovascular diseases, no specific treatment exists for preventing post-stroke cardiovascular complications. More research is needed for revealing these mechanisms. We are not aware of any ongoing or planned clinical trials aiming at preventing cardiovascular complications after stroke by targeting the brain and heart connection. Well-designed experimental and clinical studies are needed to better understand SIHI mechanisms and to identify therapeutic targets beyond the treatment of atherothrombotic coronary ischemia. Targeting inflammation through the inhibition of IL-1 (134–136) and sympathetic overactivation by blocking ß-adrenergic receptors (114,137,138) are promising approaches that should be tested in a clinical trial.

CONCLUSIONS

Neurocardiogenic syndromes are becoming increasingly recognized and are currently better understood. The growing knowledge about the pathophysiology of brain-heart interactions leading to cardiovascular complications will likely result in novel therapeutic approaches in upcoming years. Collaborations among cardiologists, neurologists, pre-clinical researchers, epidemiologists, and other scientists are encouraged.

AUTHOR DISCLOSURES

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