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Review

The role of the autonomic nervous system in cerebral blood flow regulation in stroke: A review

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ABSTRACT

Stroke is a pathophysiological condition which results in alterations in cerebral blood flow (CBF). The mechanism by which the brain maintains adequate CBF in presence of fluctuating cerebral perfusion pressure (CPP) is known as cerebral autoregulation (CA). Disturbances in CA may be influenced by a number of physiological pathways including the autonomic nervous system (ANS). The cerebrovascular system is innervated by adrenergic and cholinergic nerve fibers. The role of the ANS in regulating CBF is widely disputed owing to several factors including the complexity of the ANS and cerebrovascular interactions, limitations to measurements, variation in methods to assess the ANS in relation to CBF as well as experimental approaches that can or cannot provide insight into the sympathetic control of CBF. CA is known to be impaired in stroke however the number of studies investigating the mechanisms by which this occurs are limited. This literature review will focus on highlighting the assessment of the ANS and CBF via indices derived from the analyses of heart rate variability (HRV), and baroreflex sensitivity (BRS), and providing a summary of both clinical and animal model studies investigating the role of the ANS in influencing CA in stroke. Understanding the mechanisms by which the ANS influences CBF in stroke patients may provide the foundation for novel therapeutic approaches to improve functional outcomes in stroke patients.

1. Introduction

The brain, a metabolically active organ with limited capability for substrate storage, requires a constant supply of oxygen and nutrients to sustain resource intensive neuronal activity (Kisler et al., 2017). It is one of the most highly perfused organs in the human body (Williams and Leggett, 1989); representing ~2 % of body weight and receiving up to 15 to 20 % of resting cardiac output (Xing et al., 2017) (ref). Nevertheless, the skull, a rigid structure surrounding the brain, permits only very minimal changes in cerebrospinal fluid and/or tissue expansion. It is thus of paramount importance to have strictly regulated mechanism(s) to maintain an optimal cerebral blood flow (CBF), and thus, cerebral blood volume (Ainslie et al., 2013; Heistad et al., 1978).

The ability of the brain to maintain CBF despite changes in the cerebral perfusion pressure (CPP) is known as cerebral autoregulation (CA) (Ruesch et al., 2021). CA can be static or dynamic (dCA), static CA is the autoregulatory response to steady-state changes in arterial blood pressure (ABP) or intracranial pressure (ICP) (Lassen and Christensen, 1976) and dCA is the autoregulatory response to rapid changes in ABP (Payne, 2016). Alterations in dCA has been demonstrated in the acute and chronic phases of ischemic stroke (Intharakham et al., 2019; Nogueira et al., 2021; Salinet et al., 2013a; Salinet et al., 2013b). There is reason to suspect that the ANS may play a role in these observed changes in CBF control mechanisms as symptoms of autonomic failure, such as postural hypotension and urinary incontinence, are common in stroke (Allan, 2019; Dumoulin et al., 2007; Kong and Chuo, 2003). Also, studies have demonstrated abnormalities in a number of homeostatic autonomic functions in patients with stroke, including altered (1) heart

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rate variability (HRV) (Arnao et al., 2020; Collins et al., 2012; Kim et al., 2018), a tool commonly used for the non-invasive assessment of cardiac autonomic function where power spectral analysis of beat-to-beat intervals reveal a range of frequency components that have been ascribed to the influence of autonomic control of heart rate (HR), (2) baroreceptor sensitivity (BRS) (De Vilhena Toledo and Junqueira, 2008; Ogoh and Tarumi, 2019a; Sabino-Carvalho et al., 2020; Szili-Török et al., 2001) which describes the ability of the baroreceptors to regulate short-term BP-fluctuations by modifying HR and peripheral vascular diameter, (3) high resting HR is a common non-invasive indicator of autonomic dysfunction (AD), associated with increased risk of cardiometabolic disease and mortality (Weinstein et al., 2021; Wittstock et al., 2021) and (4) non-postural and postural changes in BP (Mankoo et al., 2020; Minhas et al., 2019; Nicolini et al., 2014; Nicolini et al., 2020). However, no literature review to date has summarized the evidence base for the role of the ANS in CBF control specifically in stroke. This is despite the co-occurrence of autonomic disturbances and CBF abnormalities (Castro et al., 2014a, 2014b), suggesting a potential link to stroke. Therefore, the aim of this narrative review is to summarize the known literature on ANS control of CBF in stroke.

2. Autonomic nervous system and cerebral blood flow regulation

There is general agreement that cerebral tissue metabolism, arterial blood gases, ABP and neurogenic stimuli are key determinants of CBF regulation (Willie et al., 2014a), though the role of cardiac output remains disputed (Deegan et al., 2008; Ogoh et al., 2015). The entire vasculature of the brain is widely innervated by adrenergic and cholinergic fibers of extrinsic and intrinsic origins (Brassard et al., 2017; Hamel, 2006). Thus, sympathetic nerve activity (SNA) and parasympathetic nerve activity (PNA) are probably implicated in the control of cerebral vessel diameter and cerebral blood supply [reviewed in: (Ainslie and Brassard, 2014; Brassard et al., 2017; Goadsby, 2013; Koep et al., 2021; Sandor, 1999; ter Laan et al., 2013)], although this topic has been controversial since the description of perivascular nerve fibers in cerebral vessel walls (Edvinsson, 1975; Fog, 1939a; Fog, 1939b). Owing to the varied interpretations of a wide range of studies, understanding the role of the autonomic nervous system (ANS) in controlling and/or regulating CBF can be challenging.

The question of whether SNA has a tonic influence on the regulation of CBF has been contentious. Indirect studies of the SNA, involving complete removal of the sympathetic activation by cervical ganglion excision have previously resulted in increase in the CBF (Shenkin et al., 1951; Shenkin, 1969; Jeng et al., 1999), and the effect of cerebral SNA has been suggested to be opposite to that of the peripheral SNA in relation to ICP (Guild et al., 2018). Cerebral SNA is not directly affected by the changes in the ABP, rather it is affected by changes in the blood volume hence the ICP (Schmidt et al., 2005). Pharmacological blockade of the ANS results in a change in CBF, suggesting an autonomic role in CBF control (Ogoh et al., 2008; Zhang et al., 2002). Hamner et al. showed a frequency dependent role of the SN system in regulating CBF (Hamner et al., 2010). By demonstrating increased gain between pressure and flow, and increased coherence following SN system blockade at higher frequencies (>0.05 Hz or 20 s) in healthy volunteers, however, CA function was left intact at lower frequencies. The frequency-dependent increased gain between pressure and flow may be due to the ANS influencing dCA but not the static component (Dawson et al., 2000; Hamner et al., 2010). Gelpi et al. (2022) suggests sympathetic activation may affect but not necessarily impair CA. A preserved MAP and mean CBF velocity may suggest the preservation of the static component of CA. The increased coherence is hypothesized to be due to a myogenic response in resistance vessels and/or nitric oxide dependent dilation (Hamner et al., 2010). The presence of a myogenic response during dCA to maintain CBF has also been suggested in the context of ICH patients. Whilst evidence of this myogenic response and NO mediated vasodilation induced by the ANS has been postulated, direct evidence for a cerebrovascular myogenic mechanism in response to a sympathetic blockade does not exist (Hamner et al., 2010). The unavailability of direct assessments of the cerebral SNA renders it difficult to demonstrate its role in CBF regulation and this opens the opportunity for further research in this field.

There exist several plausible explanations for the contradictory findings on the sympathetic control of the cerebral circulation (Ainslie et al., 2014). As discussed by Ainslie and Brassard (2014), some of these reasons are: redundant mechanisms within the brain (Busija and Leffler, 1987; Gross et al., 1983), heterogeneous distribution of sympathetic innervation, the influence of the experimental model utilized on the blood brain barrier permeability, species differences in cerebrovascular responsiveness to sympathetic nerve (SN) stimulation (Hamel, 2006; Wagerle et al., 1986; Wagerle et al., 1990), variation in the duration and the intensity of SN stimulation (Sercombe et al., 1979), and the influence of perfusion pressure (Aaslid et al., 2007; Schmidt et al., 2009; Tzeng et al., 2010a, 2010b). Also, sympathetic vasoconstriction may be dampened by increased metabolite release, such as during aerobic exercise (e.g. functional sympatholysis (Remensnyder et al., 1962)). Given that resting brain metabolism is higher than in skeletal muscle metabolism (Muller et al., 2002), there is likely to be a metabolic restriction on the ability of the SN system to induce cerebral vasoconstriction (Brassard et al., 2010; Gross et al., 1980).

Furthermore, there are two additional concerns on the role of the SNA and PNA on CBF regulation. These include the diverse assessment methods utilized to quantify CBF (i.e. non-invasive methods such as transcranial Doppler ultrasound [TCD], near-infrared spectroscopy [NIRS] and magnetic resonance imaging [MRI] vs. invasive techniques such as thermal diffusion and brain tissue oxygen monitoring), and experimental approaches which may or may not offer insight into the SN or PN control of CBF (Brassard et al., 2017).

Finally, previous human studies investigating the impact of SNA, or PNA, on the regulation of CBF have been limited, owing to the difficulty of studying the influence of the SNA or PNA on human brain vessels (Ainslie et al., 2014). It is tempting to address this issue solely with global SNA (Brassard et al., 2017) or PNA. In the anesthetized lamb, however, results suggest an inverse association between global and cerebral SNA (Cassaglia et al., 2008; Cassaglia et al., 2009). Therefore, whether changes in cerebral SNA or PNA affect CBF control remains to be clearly established in humans. However, as sympathetic control in humans is region specific, the term global SNA should be used with caution. The utilization of the brain norepinephrine spillover technique is a promising neurochemical method to address this knowledge gap (Mitchell et al., 2009).

3. Autonomic dysfunction and cerebral autoregulation

The association between AD and altered CA is disputed and has been investigated in several medical conditions. An inverse correlation between BRS and CA reported in healthy individuals (Tzeng et al., 2010a, 2010b; Nasr et al., 2014) has been shown to be absent in sub-arachnoid hemorrhage patients with vasospasm (Uryga et al., 2021). A recent study by Rosenberg et al., on simulated hemorrhage in healthy adults showed intact inverse correlation between BRS and CA suggesting compensatory tolerance to hypovolaemia (Rosenberg et al., 2022). Another recent study performed in patients with epilepsy suggested dysautonomia contributing to disruption of CA (Chen et al., 2020). In patients with familial autonomic failure, dCA was found to be impaired when compared with healthy controls (Castro et al., 2014a, 2014b). In 1991, Daffertshofer had shown patients with pandysautonomia to have compromised CA during orthostasis thus reducing CBF (Daffertshofer et al., 1991). AD is suggested to occur in transient ischemic attack (TIA). Mankoo et al. found orthostatic hypotension (OH) to be associated with a higher mortality in suspected TIA patients with a diagnosis of atrial fibrillation (AF) (Mankoo et al., 2020). Hence OH being a manifestation

of AD (Freeman et al., 2011) can also increase the thrombogenic risk during AF which itself is a risk factor for a variety of cerebrovascular diseases including stroke (Fig. 2) (Rydén et al., 2021). This provides further evidence to suggest impaired autonomic function is implicated in the pathophysiology of cerebrovascular disease (Magkas et al., 2019). The aforementioned studies suggest the existence of a strong relationship between AD and CA, however the relationship differs between the medical conditions based on their pathophysiology. There is a dearth in studies assessing direct relationship between AD and CA in stroke and this again opens up a window of opportunity to carry out research in this area.

4. The autonomic nervous system and stroke

The ANS can be anatomically described as the SNS, PNS and enteric nervous system. The central autonomic network (CAN) is a higher order organization of the SNS and PNS. Anatomically the CAN is described as gray matter structures in the brain and brainstem (Benarroch, 1993), which regulate cardiovascular function through SN and PN fibers collectively known as the extrinsic cardiac nervous system. The extrinsic cardiac nervous system links to the intrinsic cardiac nervous system which responds to afferent impulses from the myocardium and baroreceptors (Al-Qudah et al., 2015; Benarroch, 1993; Jimenez-Ruiz et al., 2021). Disturbances in the CAN, as a result of stroke, lead to ANS dysfunction, and hence cardiovascular dysregulation (Fig. 2).

Risk factors for stroke include dyslipidemia, diabetes, alcohol consumption, aging and cardiovascular diseases such as systemic hypertension, atrial fibrillation (AF), myocardial infarction (MI) and valvular heart disease. Importantly, these conditions also increase the risk of autonomic dysfunction (Carandina et al., 2021) (Fig. 2). ANS dysfunction can interrupt connections between the components of the CAN causing various presentations of impaired autonomic function (Fig. 2). The type of autonomic disturbance post-stroke is dependent on which anatomical structures of the CAN are affected.

Sposato et al. (2020b) proposes a stroke induced heart injury (SIHI) model to describe how disturbance of the structures within the CAN results in structural and molecular changes causing neurocardiac syndromes known as stroke heart syndromes (SHS). SHS including arrhythmias, left ventricular dysfunction and acute coronary syndrome are proposed to be due to autonomic and inflammatory mechanisms occurring post-stroke. The effect of disrupted CAN on the cardiovascular responses including systemic BP, cardiac output and aortic pressure plays a major role in determining the CA (Ogoh and Tarumi, 2019a, 2019b) (Fig. 2), and CBF in patients with stroke.

Fig. 1 depicts the relationship between stroke, autonomic dysfunction, and cardiac complications.

4.1. Heart rate variability and autonomic dysfunction in stroke

HRV is a commonly used indicator to investigate the relationship between stroke and ANS dysfunction (Al-Qudah et al., 2015; McLaren et al., 2005). Stroke has been shown to result in reduced HRV and thus ANS dysfunction (Fig. 2) when compared to controls (Hilz et al., 2011; Kuriyama et al., 2010; Robinson et al., 2003; Robinson et al., 1997; Yperzeele et al., 2015). In a study by Korpelainen et al., a group of 31 patients with middle cerebral artery (MCA) stroke showed reduced HRV in the acute phase compared to controls (Korpelainen et al., 1996). These patients had no primary cardiovascular disease, and the results were not confounded by concomitant medication use. They found that severity and size of the infarct but not the location was associated with lower HRV, and this was maintained at one- and six-months post stroke. This may infer cerebral infarction causes long-lasting dysfunction of the ANS and subsequently of CBF control due to dysfunctional SN and PN function, as reflected by the reduced HRV (Korpelainen et al., 1996).

Further studies have shown long-term outcomes post-stroke to be dependent on HRV (Colivicchi et al., 2005; McLaren et al., 2005). A cross-sectional case control study reported reduced HRV among a cohort of 76 patients aged over 75 years with stroke, compared to controls (McLaren et al., 2005). This suggests impaired autonomic function is present in the older population and may increase the risk of cardiovascular and all-cause mortality in older stroke survivors. Bodapati et al. utilized the 24-hour HRV and Cardiovascular Health Study (CHS)-score on 884 stroke-free participants and followed them over a period of 8 years (Bodapati et al., 2017). They found that two HRV parameters (coefficient of variance and power law slope) combined with CHS-score significantly improved incident stroke prediction. A 2013 large scale systematic review found lower HRV may play a role in stroke induced SN hyperactivation (Walter et al., 2013). However, lesion volume calculation is still needed to confirm these findings. More recently, Wittstock et al. have shown insular localization of ICH predicts poorer short-term

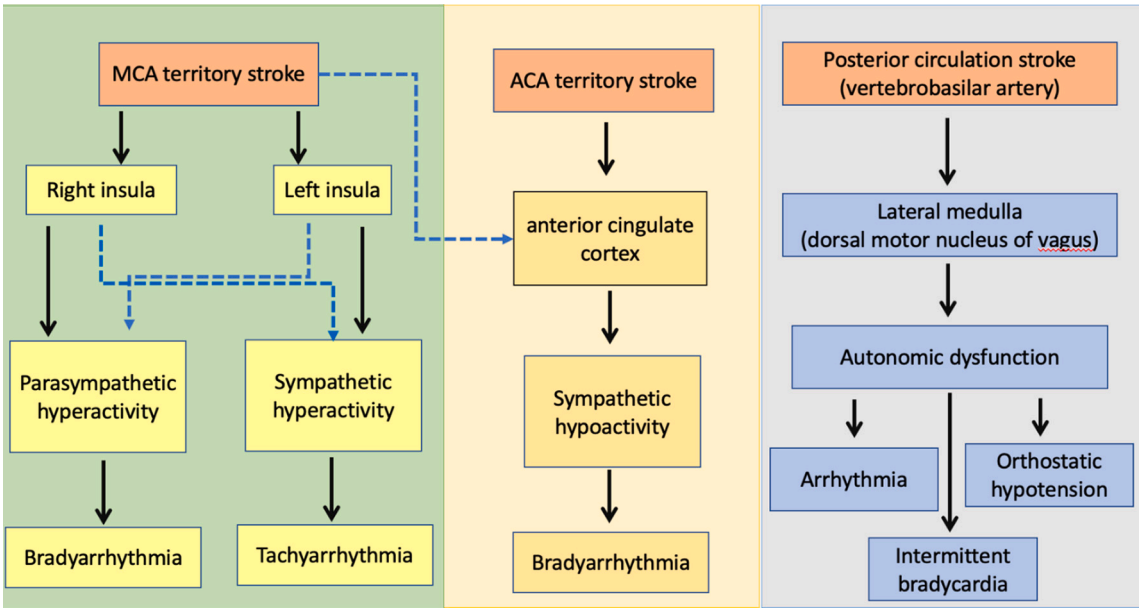

Fig. 1. Stroke induced heart injury as a result of autonomic dysfunction in key brain regions. Adapted from (Critchley et al., 2003; Mäkikallio et al., 2004; Sörös and Hachinski, 2012). MCA: middle cerebral artery. ACA: anterior cerebral artery.

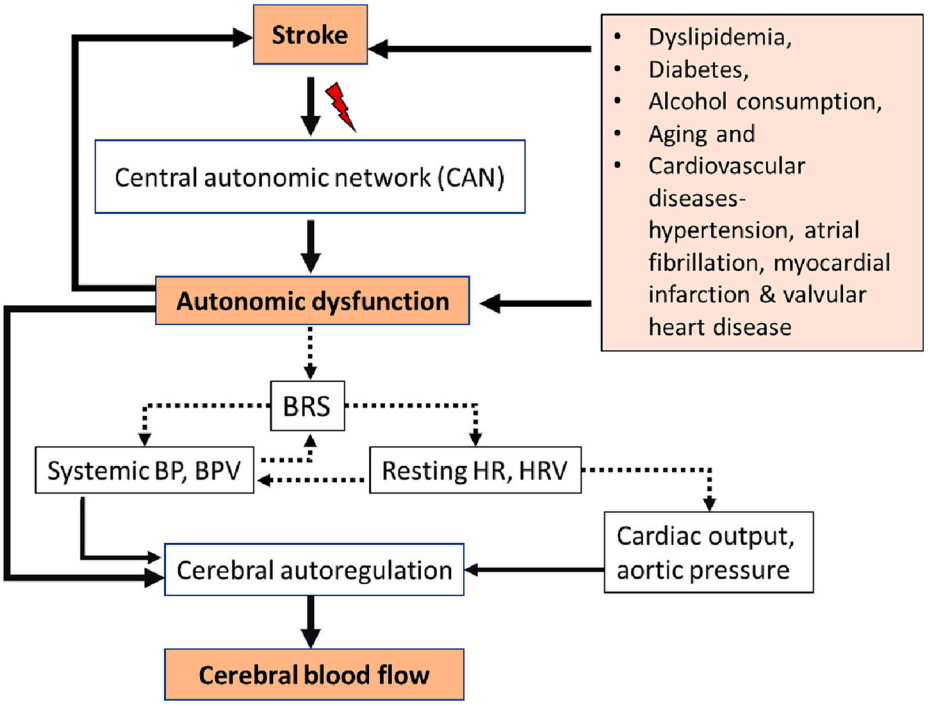

Fig. 2. Relationship between stroke, autonomic dysfunction and cerebral blood flow. Thick arrow – direct effect and broken arrow – indirect effect, BRS – baroreceptor sensitivity, BP – blood pressure, HR – heart rate, HRV – hear rate variability.

functional outcomes suggesting influence on the ANS (Wittstock et al., 2021). Further investigations to assess autonomic and cardiac function in relation to insular localized lesions is required in larger cohorts to clarify these findings.

Despite HRV being the most used tool to assess ANS function, the sensitivity of HRV is variable in stroke patients with only 22–57 % of patients with stroke show impaired HRV (Scherbakov et al., 2020). In addition, the Atherosclerosis Risk in Communities (ARIC) study showed lower HRV, and increased stroke incidence can be observed in a population with diabetes mellitus, but not among people without diabetes mellitus. This suggests the reduced HRV in stroke patients may be confounded by other medical conditions known to influence cardiovascular function, such as diabetes mellitus. This could be due to local baroreceptor function or central brainstem control and efferent pathways (Fyfe-Johnson et al., 2016).

The severity of stroke is commonly assessed using the National Institute of Health Stroke Scale (NIHSS) score. Stroke severity may predict the magnitude of impaired HRV and ANS dysfunction, where higher NIHSS scores inversely correlate with HRV (Kuriyama et al., 2010; McLaren et al., 2005; Nayani et al., 2016; Xiong et al., 2013). This is demonstrated in 26–77 % of studies reporting ANS dysfunction in the acute stroke setting (Jimenez-Ruiz et al., 2021; Nayani et al., 2016; Xiong et al., 2013). However, heterogeneity in stroke sub-types, stroke severity scoring systems, and sample sizes in these studies limit the interpretation of these findings. (Yperzeele et al., 2015).

Despite many studies demonstrating autonomic dysfunction, and CBF changes post-stroke, there is a paucity of studies examining these two mechanisms simultaneously. It remains unclear whether peripheral autonomic changes in HRV are a reflection of loss of autonomic control occurring in the CNS. Future studies should investigate these peripheral makers in the context of autonomic control of CBF more centrally.

4.2. Baroreceptor sensitivity and autonomic dysfunction in stroke

In addition to HRV, the baroreceptor function plays a key role in reduced ANS function post-stroke (Fig. 2). The strongest risk factor for ischemic stroke is systemic hypertension (Feigin et al., 2016). Systemic hypertension has been shown to influence ANS function through the baroreceptor reflex. Baroreceptor function is crucial in short term regulation of blood pressure, but to a lesser extent in long term regulation (Carthy, 2014). Post-stroke, a decrease in BRS is observed, resulting in increased SNA and raised blood pressure, which in turn may negatively impact CBF (Robinson et al., 2003; Yperzeele et al., 2015).

As a consequence of acute stroke, impaired central processing centers for controlling the baroreceptor reflex arc occurs, resulting in reduced BRS values which have shown to give a poorer prognosis (Mo et al., 2019; Robinson et al., 2003). Robinson et al. used power spectral analysis to measure BRS in 37 patients presenting with AIS and ICH, demonstrating significantly reduced cardiac BRS in stroke patients than controls (Robinson et al., 1997). Eames et al. used power spectral analysis to measure BRS in 56 patients presenting with AIS (Eames et al., 2002). They showed a reduction in BRS in patients with stroke (Lucini et al., 1994) than controls, but no correlation between BRS and stroke type or severity.

4.3. Stroke and cerebral autoregulation

An important mechanism which involves the ANS regulating CBF is dCA. Several studies have reported impairment of dCA during the acute phase of stroke. Schwarz et al., in 2002 showed increase in CPP and peak mean flow velocity on inducing hypertension in patients with large hemispheric stroke, the changes occurred only during a rise of 30 % from baseline and on the affected side of the brain (Schwarz et al., 2002a). It was also found that patients who underwent decompressive craniectomy had worse dCA compared to patients who received medical treatment (Schwarz et al., 2002a, 2002b). There are some studies that have shown reduced autoregulation index (ARI), a measure of dCA, in patients with AIS within 48 h of stroke (Eames et al., 2002; Saeed et al., 2013; Ma et al., 2018). In contrast, however few studies report intact ARI in AIS in the acute phase thus suggesting unaffected dCA (Reinhard et al., 2005; Lam et al., 2019).

There are a few studies which have looked into dCA in the chronic phase of AIS. In 2004, Novak et al., had previously utilized a multimodal pressure-flow method and found impairment of dCA during Valsalva

maneuver in patients with minor stroke for >2 months (Novak et al., 2004). Kwan et al., utilized trans-cranial Doppler during handgrip test and found improvement in dCA after 3 months following ischemic stroke (Kwan et al., 2004). Similarly in 2014, Salinet et al., assessed CA during passive elbow movement in AIS for 3 months post-stroke and found initial deterioration of the CA followed by recovery in the later phase (Salinet et al., 2013a).

4.4. Stroke and resting heart rate

A resting HR determines cardiac output and aortic pressure which in turn determines CA (Ogoh and Tarumi, 2019a, 2019b) Fig. 2. Weinstein et al. (2021) report that a higher resting HR is associated with an increased risk of stroke (Weinstein et al., 2021). Several mechanisms have been proposed to explain this association such as stroke-induced endothelial dysfunction, particularly in patients with a high risk of cardiovascular disease (Hamner et al., 2010; Weinstein et al., 2021).

In addition to HRV and resting HR, numerous tests exist which aim to assess ANS function post-stroke, including: BRS, head-up tilt test, isometric handgrip, SN skin responses and the Valsalva maneuver (Jimenez-Ruiz et al., 2021). The autonomic reflex screen (ARS) is a candidate to standardise the assessment of autonomic function (Ives et al., 2013). ARS has been validated as a tool to assess SN and PN function in a variety of populations by allocating a standardized Composite Autonomic Severity Score (CASS), which categorised the autonomic function in a tiered points system. However, ARS is yet to be formally assessed in a population of stroke patients. The PARADISE Study attempted the use of ARS to assess pre- and post-stroke ANS function. However, this was halted due to logistical challenges and patient intolerance, particularly in relation to performing the ARS screen within 72 h of acute stroke (Jimenez-Ruiz et al., 2021; Rupprecht et al., 2020).

4.5. Stroke lateralization and autonomic dysfunction

A prospective study of 75 stroke patients subdivided into right and left hemispheric, and brainstem infarction (Chen et al., 2013), revealed significant differences between the left and right hemispheric infarction groups. This supports the hypothesized imbalance in autonomic SNA and PNA during acute stroke (Chen et al., 2013; Korpelainen et al., 1999).

Clinically, symptoms of stroke have been shown to reflect the location of the infarct. As such, stroke lateralization and localization may closely relate the autonomic cardiac dysfunction following stroke (Oppenheimer et al., 1992). Sykora et al. conducted a prospective study assessing the BRS of 45 patients presenting with acute ICH by means of TDA within 72 h of admission (Sykora et al., 2009). In addition to BRS being significantly lower in stroke patients than the controls, they found no correlation between BRS and affected hemisphere. Although, there is continued dispute on whether hemispheric lateralization differs for autonomic control (Mo et al., 2019). However, patients with left sided insular involvement have shown significantly reduced BRS than patients with right sided insular involvement (Sposato et al., 2020a). This suggests that even though the insular cortex appears to participate in processing the baroreceptor information, the left insula emerges as more dominant (Sposato et al., 2020a).

Nevertheless, multiple studies have reported conflicting results showing no lateralization and localization in HRV between right and left sided lesions. The validity of lateralization and localization of ANS dysfunction post-stroke is an area open for further investigation (Robinson et al., 1997; Walter et al., 2013). Furthermore, studies should integrate assessments of autonomic function (HRV and BRS) with CBF measurements as a potential mechanism for these findings.

5. Therapeutic implications of associations between ANS dysfunction and stroke

ANS dysfunction is associated with an increase in post-stroke mortality, yet no evidence-based treatment for ANS dysfunction is currently available. Pertaining to the autonomic dysfunction which occurs in acute stroke, it is known that BRS is reduced with an associated increase in SN drive and impaired PN function (Al-Qudah et al., 2015; Robinson et al., 2003). Consequently, end-organ damage and further cardiovascular events may follow, due to the chronic increase in SN activity. (Sykora et al., 2009).

Mäkikallio et al. (2004) suggest the use of myocardial modulating medications such as alpha and beta receptor blockers to reduce the incidence of neurogenic heart disease post-stroke. In particular, the use of carvedilol, due to its anti-inflammatory properties, may help reduce the inflammatory consequences of stroke induced ANS dysfunction (Scanzano and Cosentino, 2015). Through the use of beta blockers, such as carvedilol, BRS can be improved to alter the response to an increased parasympathetic (PS) drive by suppressing the SNA (Mortara et al., 2000).

Laowattana and Oppenheimer (2007) conducted a prospective study on 111 stroke patients and reported that the use of beta-blockers was the '*sole independent predictor of less severe stroke on presentation*' and may provide cerebro protection. However, the use of beta blockers in acute stroke has been shown to be a contentious area, with the BEST trial, which evaluated 302 acute stroke patients, reporting an increased mortality (Barer et al., 1988). Although this study found more early deaths among patients receiving beta blocker therapy after their stroke, a further 60 patients with established beta blocker treatment at stroke onset had better outcomes, suggesting a possible protective factor to stroke outcome. Furthermore, another study suggested neuroprotective properties were associated with beta-blocker therapy, reducing the risk of early death, demonstrated by a significantly lower thirty-day case fatality of (6.8 % with beta-blockers vs 19 % without) (Dziedzic et al., 2007).

Numerous studies have proposed several other drugs to enhance BRS: ketanserin, clonidine, moxonidine and mecobalamin have all been purported to improve BRS through central and peripheral mechanisms (Liu et al., 2007; Ma et al., 2007; Turcani, 2008). However, the efficacy and safety of such medications are yet to be tested in a clinical setting (Robinson et al., 2003).

In conclusion, the explanation as to the pathophysiological cause for the apparent autonomic impairment remains unclear. The possibility of modulation of HRV or baroreflex to improve prognostic outcome in patients is still yet to be fully understood and further research is necessary to understand these mechanisms and implications for management of acute stroke.

6. Limitations of HRV

There are some important limitations to using HRV as a marker of autonomic function that should be appreciated. For example, HRV is dependent on resting HR (Monfredi et al., 2014) and could be unreliable when assessing PNS in healthy subjects (1996; Cepeda et al., 2018). However, until other measures become widespread for example, HR recovery after exercise (Gourine and Ackland, 2019), then care must be taken when interpreting HRV data. Additionally, in a population of stroke patients with AF the use of HRV as a marker of autonomic function would not be possible, excluding a significant proportion of patients from these studies.

7. Summary of autonomic function in a stroke population

Current research suggests stroke pathophysiology involves impaired autonomic function as indicated most frequently by a reduced HRV. However, the validity of HRV as a measure of autonomic function in a

stroke population is uncertain. The most common limiting factor for interpretation of ANS function in a stroke population is the heterogeneity between studies investigating ANS function in stroke. The ARS and CASS are potential measures of autonomic function that could be used to standardise assessments between centers and overcome some of these limitations. Further investigation is required to assess the validity of combining HRV and beat-to-beat BPV to assess ANS function in stroke patients as suggested by Tang et al. (2020). Other models have been proposed to standardise the assessment of ANS function in a stroke population, including the Composite Autonomic Symptom Score (COMPASS) which is used to assess the severity of autonomic symptoms (Tian et al., 2019).

8. Conclusion

In conclusion, autonomic dysfunction is common in stroke. ANS dysfunction alone is a risk factor for as well as a result of stroke. The markers of autonomic dysfunction (HRV, BRS) are reduced in stroke. The ANS is also responsible for regulating CBF up to a certain extent, hence a stroke causing ANS dysfunction can result in CBF dysregulation.

However, a key area for future research remains the harmonization of autonomic assessment between centers. The development of standard autonomic assessments such as ARS and CASS need exploring in stroke, and may address some of the heterogeneity identified by this review. Finally, this review identified a paucity of studies specifically investigating the role of the ANS in control of CBF in stroke, and research in this area should be prioritized to facilitate the identification of novel biomarkers and therapeutic targets.

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Conflict of interest

None to declare.

Data availability

No data was used for the research described in the article.

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