Systematic Review

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Role of the Periaqueductal Gray in Autonomic and Electrocardiographic Alterations During Subarachnoid Hemorrhage With Intraventricular Extension: A Systematic Review

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Background: Subarachnoid hemorrhage (SAH), particularly with intraventricular extension (Fisher grade IV), is frequently accompanied by electrocardiographic (ECG) abnormalities, which are often attributed to autonomic dysfunction. The periaqueductal gray (PAG), a midbrain structure involved in autonomic and nociceptive processing, may play a pivotal role in these cardiovascular manifestations. This systematic review aims to analyze ECG alterations in patients with SAH complicated by intraventricular hemorrhage (IVH) and examine the autonomic effects of PAG stimulation in both experimental and clinical studies.

Methods: A systematic search of PubMed, Scopus, and Web of Science was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. Eligible studies included adult or neonatal patients with SAH+IVH reporting ECG or autonomic outcomes, and human or animal studies assessing autonomic effects of PAG stimulation. Data extraction focused on ECG changes, heart rate variability (HRV), blood pressure, autonomic indices, stimulation parameters, and neuroanatomical correlations.

Results: Of 59 initially identified studies, 22 met the inclusion criteria. Among these, 10 clinical studies described ECG abnormalities in Fisher IV SAH patients, including corrected QT interval (QTc) prolongation, ST-segment changes, and T-wave inversion. The remaining 12 studies, focusing on PAG stimulation, revealed its modulatory effects on HRV, heart rate, and blood pressure. Specifically, ventral PAG stimulation enhanced parasympathetic output, whereas stimulation of lateral regions was associated with sympathetic activation.

Conclusions: The review highlights a possible pathophysiological link between intraventricular blood extension in SAH and ECG abnormalities, potentially mediated by PAG involvement. Experimental data reinforce the role of the PAG in autonomic regulation. Future studies should focus on neurocardiac monitoring strategies and targeted neuromodulation in patients with hemorrhagic brain injury.

Keywords: periaqueductal gray; subarachnoid hemorrhage; intraventricular hemorrhage; autonomic nervous system; electrocardiogram; heart rate variability

Introduction

The main cardiovascular anomalies during subarachnoid hemorrhage (SAH) are arrhythmias, manifested as either tachycardia or bradycardia [1]. These alterations can involve both atrial and ventricular dynamics and are typically reflected in electrocardiographic (ECG) recordings. The most observed ECG abnormalities in SAH include corrected QT interval (QTc) prolongation, ST-segment modifications, T-wave inversion, and sometimes sinus bradycardia or tachycardia [1,2]. According to Di Pasquale *et al*. [3], up to 90% of patients with SAH exhibit cardiac rhythm alterations. The presence of blood in the subarachnoid space causes cortical brain irritation, since intraventricular blood can irritate the periventricular white matter or, as in this case, the grey matter surrounding the sylvian acqueduct (SA). This process is often accompanied by inflammation of the ventricular walls. Hydrocephalus associated with tetraventricular hemorrhage results from the compression of neural tissue adjacent to the ventricular walls [4]. Neurons in the grey matter can undergo depolarization in response to chemical or mechanical stimuli, including secondary axonal stretching [5,6]. Fisher grade IV SAH is characterized by the presence of intraventricular hemorrhage (IVH) and is associated with a high risk of vasospasm development [7–9]. Intraventricular blood can lead to hydrocephalus, which may be acute due to obstruction of cerebrospinal fluid (CSF) flow, or chronic as a result of inflammatory scarring that impairs CSF reabsorption at the arachnoid granulations [10,11]. In the acute setting, mechanical distension, blood-induced irritation, and transependymal edema may lead to centrifugal propagation of inflammation, potentially affecting the periaqueductal gray (PAG). To the best of our knowledge, this is the first systematic review in the literature to investigate a possible association between ECG abnormalities and PAG involvement during Fisher grade IV SAH [12]. Specifically, this review aims to explore electrocardiographic alterations occurring in SAH with intraventricular extension and the autonomic effects of PAG stimulation in both clinical and experimental models. While most literature focuses on global autonomic or endocrine dysfunction during SAH, this review seeks to clarify the pathophysiological link between ventricular blood accumulation and cardiac dysautonomia mediated by midbrain structures such as the PAG.

Methods

This systematic review was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, with two primary objectives: first, to investigate electrocardiographic abnormalities and autonomic dysfunction in the context of subarachnoid hemorrhage and intraventricular hemorrhage; and second, to synthesize existing evidence on the autonomic effects of periaqueductal gray stimulation, with a focus on outcomes measured via heart rate variability, heart rate, blood pressure and ECG. This review was not registered in International Prospective Register of Systematic Reviews (PROSPERO). At the time of protocol development, the scope of the study—which integrates clinical data with experimental and mechanistic evidence from animal and neurophysiological research—did not meet PROSPERO's eligibility criteria, as the database primarily accepts systematic reviews focused on clinical outcomes and strictly defined Patient, Intervention, Comparison, and Outcome (PICO) frameworks. Nonetheless, all methodological steps were conducted in accordance with PRISMA 2020 guidelines [13] to ensure transparency and reproducibility. The complete PRISMA 2020 Checklist has been prepared and is included as **Supplementary Material** to ensure full transparency and methodological rigor. A comprehensive literature search was conducted across PubMed, Scopus, and Web of Science databases, covering the period from January 2005 to December 2023, with an updated search performed in March 2025. No language restrictions were applied. To ensure full reproducibility, complete Boolean search strings, including MeSH terms, free-text keywords, logical operators, and field qualifiers, were used. The PubMed strategy combined MeSH and Title/Abstract fields and was structured as follows: (("Subarachnoid Hemorrhage"[Mesh] OR "subarachnoid hemorrhage"[Title/Abstract] OR SAH[Title/Abstract]) AND ("Intraventricular Hemorrhage"[Mesh] OR "intraventricular hemorrhage"[Title/Abstract] OR IVH[Title/Abstract]) AND ("Electrocardiography"[Mesh] OR electrocardiogram[Title/Abstract] OR ECG[Title/Abstract] OR "heart rate variability"[Title/Abstract] OR HRV[Title/Abstract])) OR (("Cerebral Hemorrhage"[Mesh] OR "intracerebral hemorrhage (ICH)"[Title/Abstract] OR ICH[Title/Abstract]) AND (autonomic[Title/Abstract] OR "autonomic nervous system"[Mesh]) AND (electrocardiogram[Title/Abstract] OR ECG[Title/Abstract])) OR (("Periaqueductal Gray"[Mesh] OR "periaqueductal grey"[Title/Abstract] OR PAG[Title/Abstract]) AND (stimulation[Title/Abstract] OR "deep brain stimulation (DBS)"[Mesh] OR DBS[Title/Abstract] OR microinjection[Title/Abstract]) AND (ECG[Title/Abstract] OR "heart rate variability"[Title/Abstract] OR HRV[Title/Abstract] OR autonomic[Title/Abstract])). The Scopus search was conducted using the TITLE-ABS-KEY fields and followed the same conceptual structure, comprising three blocks: subarachnoid and intraventricular hemorrhage with ECG/Heart Rate Variability (HRV); intracerebral hemorrhage and autonomic dysfunction and ECG; and periaqueductal gray and stimulation modalities and autonomic outcomes. Similarly, the Web of Science search used the Topic Search (TS=) operator to identify studies on SAH + IVH and ECG abnormalities, autonomic dysfunction in hemorrhagic events, and autonomic effects of

periaqueductal gray stimulation. In all databases, Boolean operators were applied exactly as presented, and no restrictions were placed on study type or species, allowing inclusion of mechanistic and preclinical studies relevant to the physiological role of the PAG. Finally, manual citation tracking of all included articles was performed to capture additional eligible studies.

Studies were included if they met the following criteria: (1) original data from human or animal models and quantitative measurement of autonomic function, such as HRV, Heart Rate (HR), Blood Pressure (BP), Muscle Sympathetic Nerve Activity (MSNA), or ECG; (2) For the PAG stimulation objective, studies were required to involve any type of direct or indirect stimulation—including DBS, N-methyl-D-aspartate (NMDA)/Acetylcholine (Ach)/Arachidonoylethanolamide (AEA) microinjection, or Transcutaneous Electrical Nerve Stimulation (TENS)—and to specify anatomical targeting of the PAG, including dorsal, ventral, lateral, or dorsolateral columns; and (3) For the SAH/IVH objective, studies needed to document ECG abnormalities or autonomic dysfunction in the setting of acute cerebral hemorrhage. Exclusion criteria for both groups included theoretical reviews without empirical data, absence of autonomic or ECG outcomes, non-central or non-PAG-related stimulation for PAG studies, and stroke or hemorrhage studies not involving SAH/IVH for the first objective.

A total of 59 records were identified, including 53 from databases and 6 through citation tracking. After removing 9 duplicates, 50 records remained and were screened by title and abstract, resulting in the exclusion of 28 studies. Twenty-two full-text articles were assessed and included in the final synthesis, consisting of twelve on PAG stimulation and autonomic effects and ten on ECG/autonomic changes in SAH with IVH.

Two reviewers (SM and GS) independently extracted data using a standardized form tailored to each research objective. For studies on ECG abnormalities in subarachnoid and intraventricular hemorrhage, extracted variables included the study citation; etiology of hemorrhage such as aneurysmal SAH, spontaneous ICH, and IVH involvement; key ECG findings including T-wave inversion, QT prolongation, and arrhythmias; cohort size; assessment methods such as Holter ECG, continuous ECG monitoring, HRV analysis, and CT scans; evidence of autonomic dysfunction when reported; and Fisher grade and IVH status when available. For studies on PAG stimulation and autonomic function, extracted data included authors and year; number and type of subjects, whether humans or animal models; targeted PAG region such as ventral, dorsal, lateral, or dorsolateral; type of stimulation including DBS, NMDA microinjection, and TENS; HRV and ECG recording details including sampling frequency, analysis methods, and domains used; neurodiagnostic tools such as Magnetic Resonance Imaging (MRI), Diffusion Tensor Imaging (DTI), histology, and microneurography; type of autonomic involvement including sympathetic activation or vagal enhancement; and additional findings relating to behavioral effects, pain modulation, and connectivity analysis. Any disagreements in data extraction were resolved through consensus or arbitration by a third reviewer (GEU).

Given the high heterogeneity in species, study design, and outcomes, a qualitative synthesis was conducted. Results were organized based on population (human vs animal), condition or intervention (SAH/IVH vs PAG stimulation), PAG column stimulated (ventral, dorsal, lateral, dorsolateral), and primary autonomic outcomes, including HR, HRV, BP, MSNA, and ECG abnormalities. Given the heterogeneity of study designs — including clinical studies, case reports, and experimental animal models — a formal quantitative risk-of-bias assessment could not be uniformly applied. Instead, a qualitative assessment of methodological quality was performed for each study, considering sample size, clarity of methodology, presence of control conditions, and completeness of autonomic outcome reporting. The study selection process, including identification, screening, eligibility, and inclusion phases, is summarized in Fig. 1, in accordance with PRISMA 2020 guidelines.

Results

Autonomic Effects of Periaqueductal Grey Stimulation

The second objective, examining the autonomic effects of direct or indirect periaqueductal grey stimulation, encompassed 12 studies, which were divided into human trials [14–20] and experiments on animal caviae [21–25]. These encompassed experimental models in rodents and clinical studies in patients undergoing DBS for pain or Parkinson's disease, as well as one review with meta-analytic insights from neuroimaging and HRV data. A consistent theme across studies was the functional columnar organization of the PAG and its impact on autonomic output. Specifically:

- dPAG stimulation was reliably associated with increased sympathetic activity, reflected by elevated systolic blood pressure, heightened dP/dt (a measure of myocardial contractility), and increased Low frequency (LF) power in HRV spectra. In both human and animal studies, dPAG activation provoked arousal-like physiological responses, such as tachycardia and pressor effects, without significant changes in R-R intervals. These findings align with the hypothesized role of the dPAG in mediating "fight-or-flight" behavior and active coping strategies.
- In contrast, vPAG stimulation evoked parasympathetic responses, including significant hypotension, bradycardia, and increased High frequency (HF) power in HRV. In one study involving 16 patients receiving vPAG DBS for chronic pain, this parasympathetic shift

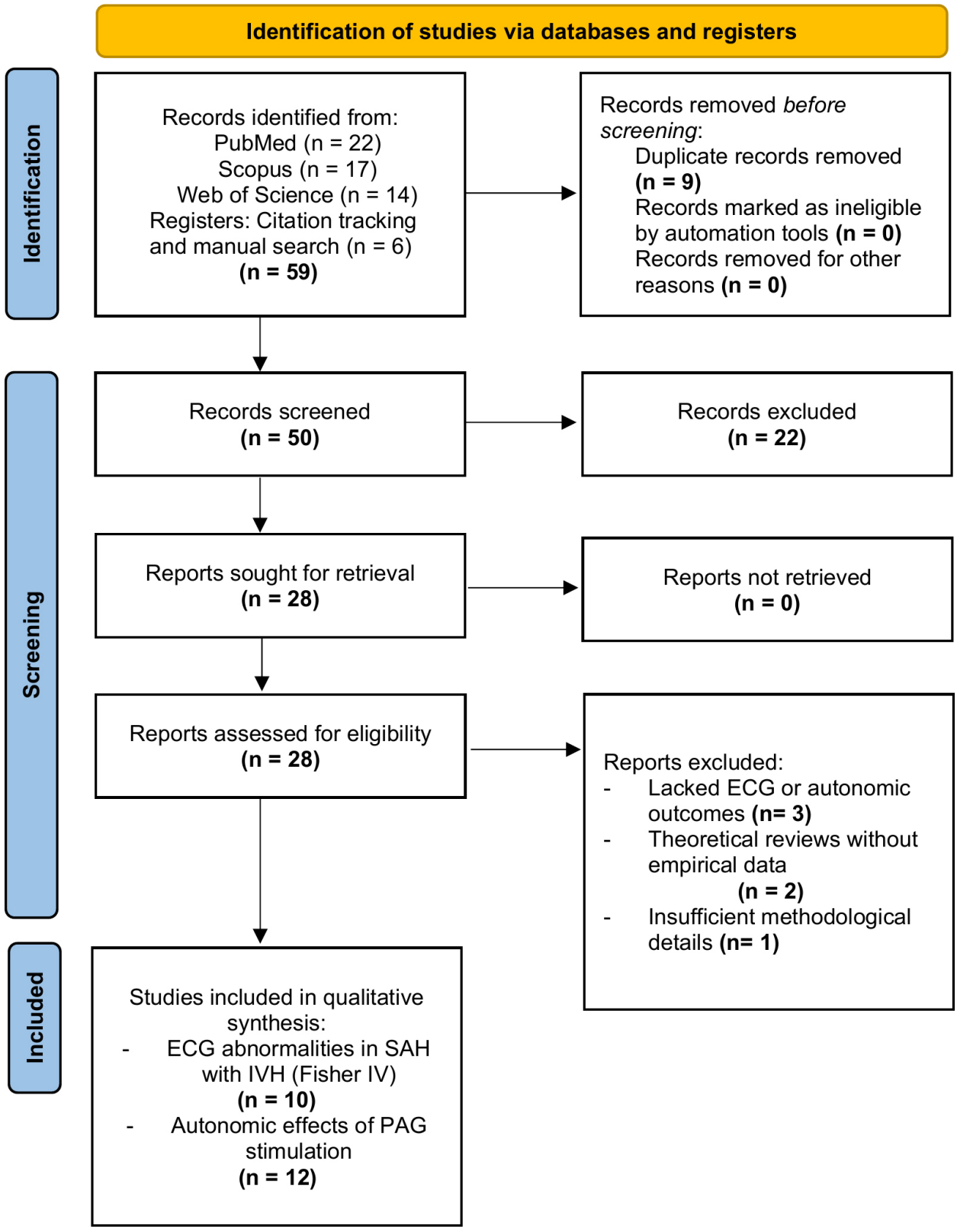

Fig. 1. PRISMA 2020 flow diagram of the study selection process. The flowchart illustrates the number of records identified, screened, excluded, and included in the systematic review. Records were retrieved from PubMed, Scopus, Web of Science, and citation tracking. A total of 22 studies were included in the final qualitative synthesis, with 10 addressing ECG/autonomic changes in SAH with intraventricular extension and 12 evaluating autonomic effects of PAG stimulation. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; ECG, electrocardiographic; SAH, Subarachnoid hemorrhage; PAG, periaqueductal gray.

was linked to both analgesic effects and enhanced vagal tone [16]. HRV changes were measured using high-resolution ECG (4000 Hz) and spectral analysis, revealing a decreased LF/HF ratio and improved pain scores on the visual analog scale. These data suggest that vPAG stimulation may be a key node in the modulation of nociception through autonomic pathways.

- Studies involving l/dlPAG showed more complex or mixed responses. In rodent models, microinjections of excitatory neurotransmitters (e.g., NMDA, acetylcholine, AEA) into these regions led to rapid increases in HR and Mean Arterial Pressure (MAP), often requiring intact connections to the Dorsomedial Hypothalamus (DMH) or Basolateral Amygdala (BLA) for full expression. Inactivation of these downstream targets blunted cardiovascular responses, suggesting the existence of functional PAG→DMH/BLA→brainstem circuits responsible for orchestrating autonomic output.

HRV and sympathetic nerve activity were the most frequently assessed outcomes. Intraoperative studies in awake patients confirmed that stimulation of the dorsal PAG increased MSNA burst amplitude, whereas ventral PAG DBS enhanced baroreflex sensitivity and reduced MSNA frequency. These effects were accompanied by consistent changes in BP and HR, and in some cases, by modulations of emotional states such as increasing anxiety or nausea [14,26–28]. Human studies also used advanced imaging and targeting techniques (e.g., MRI + stereotactic computed tomography) to ensure precise electrode placement and assess functional outcomes.

One review integrating fMRI studies showed a strong correlation between HRV indices and PAG activation/connectivity within the Central Autonomic Network (CAN), including the insular cortex, anterior cingulate cortex and prefrontal regions [19]. These findings provide neuroimaging evidence for the PAG's central role in flexible brain-body integration, supporting the neurovisceral integration model [29,30].

Electrocardiographic Alterations and Autonomic Dysfunction in Subarachnoid and Intraventricular Hemorrhage

A total of 10 studies met the inclusion criteria for the first objective, which focused on ECG abnormalities and autonomic disturbances in patients affected by SAH and IVH [31–40]. These studies encompassed both adult and neonatal populations, with sample sizes ranging from single-case reports to observational cohorts of more than 100 individuals. Electrocardiographic changes were consistently documented across studies and comprised a wide range of abnormalities. Among the most frequently reported findings were prolongation of the QTc interval (with values extending up to 600 ms), T-wave inversions, ST-segment depression or elevation, sinus bradycardia, and transient conduction disturbances, such as Mobitz type I atrioventricular block. Osborn (J) waves were observed in a patient with SAH, suggesting severe central autonomic dysregulation and hypothermic-like shifts in cardiac repolarization [32]. These changes occurred independently of structural heart disease, supporting the well-known neurogenic etiology [41,42]. The pathophysiological interpretation of these ECG alterations varied depending on the hemorrhage location and clinical presentation. Most authors attributed them to an imbalance of the autonomic nervous system, typically characterized by a surge in sympathetic activity due to hypothalamic or brainstem irritation. In some cases, particularly those involving posterior fossa hemorrhages or IVH, a paradoxical vagal dominance was observed, leading to pronounced bradycardia and hypotension. In several studies, intraventricular involvement was associated with more pronounced ECG abnormalities, mainly repolarization changes and QT prolongation [39,43]. In Takeuchi's retrospective study on more than 30 cases with intracranial hemorrhage (ICH and/or IVH), QTc prolongation and HR deceleration were interpreted as central autonomic responses to elevated intracranial pressure and ventricular distension [39]. In the same study was highlighted that ST depression and QTc prolongation were independent of the presence of IVH or involvement of the insular region, and it was impossible to analyse the predictive factors for ST elevation, as T wave inversion is not correlated with either the volume of the haematoma or the depth to which it extends. Although quantitative assessment of autonomic dysfunction (e.g., HRV analysis) was not routinely performed, several studies inferred autonomic involvement based on clinical signs, ECG dynamics and neuroanatomical correlations. Another case described a patient with SAH-induced sympathetic storm, manifested as hypertension, tachycardia, and ECG instability—again without primary cardiac pathology [38]. In the neonatal population, an important study demonstrated that typical adult ECG patterns seen in SAH/IVH were notably absent in preterm infants with severe IVH. This finding suggests that the immaturity of the neonatal CAN, including underdeveloped connectivity between the PAG, hypothalamus, and brainstem nuclei, may explain the blunted cardiac expression of CNS injury in this population [34]. When present, intraventricular extension of the hemorrhage appeared to play a key role in determining the severity of autonomic dysfunction [39]. The proximity of the ventricular system to autonomic integration centers, such as the periaqueductal grey, dorsal vagal nucleus, and hypothalamic nuclei, was proposed as a structural basis for this relationship [44]. However, grading systems such as the Fisher scale were inconsistently reported, limiting meta-comparative interpretation across cohorts.

A comparative synthesis of the principal findings from studies addressing ECG/autonomic alterations in SAH with intraventricular hemorrhage (Objective 1) and those inves-

Table 1. Studies Investigating ECG Alterations and Autonomic Dysfunction in Subarachnoid and Intraventricular Hemorrhage.

Aspect	Objective 1: SAH + IVH	Objective 2: PAG stimulation
Study focus	ECG abnormalities in SAH with intraventricular hemorrhage	Autonomic effects of periaqueductal gray stimulation
Population/Model	Human patients with Fisher Grade IV SAH	Animal models and patients with DBS
Main outcome measures	QTc prolongation, ST-segment changes, T-wave inversion, bradycardia, tachyarrhythmias	Heart rate variability, blood pressure changes, HR modulation
Autonomic indicators	Indirect via ECG and troponin levels	Direct HRV analysis, blood pressure, MSNA
Common ECG findings	QTc prolongation, T-wave inversion, ST changes	HR variability shifts, BP modulation
Anatomical focus	Periventricular regions, including PAG	Dorsal, ventral, lateral PAG
Mechanism hypothesized	Mechanical and inflammatory stimulation of periventricular autonomic centers	Neurophysiological modulation of sympathetic/parasympathetic tone via PAG columns
Clinical relevance	Prognostic value of ECG for monitoring neurogenic cardiac risk in SAH	Therapeutic potential in autonomic dysfunction and neurogenic hypertension

Here, the main parameters analyzed and considered in the literature search are summarized and subsequently integrated once the main objectives, schematized in the two tables above, have been described. These include anatomical variables that did not comprise isolated SAH but rather SAH with intraventricular involvement and, subsequently, the neurophysiological response secondary to PAG stimulation.

SAH, Subarachnoid hemorrhage; IVH, intraventricular hemorrhage; PAG, periaqueductal gray; ECG, electrocardiographic; DBS, deep brain stimulation; QTc, corrected QT interval; HR, heart rate; HRV, heart rate variability; MSNA, Muscle Sympathetic Nerve Activity; BP, Blood Pressure.

tigating autonomic effects of PAG stimulation (Objective 2) is provided in Table 1.

Discussion

Studies Supporting the Review Thesis

Some authors, such as Chen and colleagues, analysed how subarachnoid hemorrhage may influence the physiology of extracerebral organs [45]. For instance, the involvement of the cardiovascular system, through the autonomic nervous system, is really interesting. The main thesis put forward in this review focuses on periaqueductal inflammation following subarachnoid-intraventricular hemorrhage (i.e., Fisher IV), and it is supported by studies that have been summarized in the Tables. These studies highlight an interesting pathological link between ventricular hemorrhage, in this case involving the SA, and dysautonomia or autonomic alterations leading to cardiac rhythm abnormalities detectable on ECG. The phenomenon reflects a pathophysiological cascade that begins with inflammation of the ventricular walls, progresses to PAG edema, and ultimately leads to its dysfunction. In most cases, this association is mediated by autonomic nervous system dysregulation resulting from the imbalance between sympathetic and parasympathetic output.

Periaqueductal Grey and Autonomic Functions

SAH is frequently complicated by autonomic nervous system dysfunction, which in turn is associated with poor clinical outcomes, including cerebro-cardiac syndrome and hypertensive crises [46]. The brainstem, housing a dense network of autonomic nuclei and connective tracts, is a key hub in cardiovascular and autonomic regulation [47].

In recent reviews of the literature, authors such as Kang *et al*. [20] and Mulcahy *et al*. [19] have described the involvement of the PAG in the function of the neonatal central autonomic network, to the extent that it may be implicated in autonomic dysfunction following hemorrhagic lesions.

The PAG, situated between the midbrain and diencephalon, is a crucial node in this network, receiving inputs from limbic structures such as the anterior cingulate cortex and amygdala, and projecting to the brainstem (e.g., rostral ventrolateral medulla) and spinal cord to modulate sympathetic and parasympathetic output [20,48]. The RVLM is responsible for sympathetic control, while the nucleus ambiguus and the dorsal motor nucleus of the vagus mediate parasympathetic influence.

In the rat, a serotonergic subpopulation in the ventrolateral PAG would be responsible for producing endogenous 5-HT, while release in the rostral ventrolateral medulla would modulate the sympathoexcitatory panic response through interaction with the C1 adrenergic neurons [49]. PAG plays a critical role in cardiovascular function [50,51]. PAG is located between the diencephalon and the brainstem and has extensive connections to the spinal cord, the brainstem, the diencephalon and the cerebral cortex [52]. In humans, it has a somatotopic organization with rostro-caudal representation of the body and the face [53,54]. PAG may have a hypotensive and bradycardic action, through the nu-

cleus ambiguus and the dorsal motor nucleus of the vagus, but through the rostral ventrolateral medulla pathway, it may also contribute to increasing both the heart rate and the blood pressure [20,55]. Indeed, the dorsal motor nucleus of the vagus and the nucleus ambiguus, via the vagus nerve pathways, modulate parasympathetic activity of the heart. The nucleus ambiguus is also involved in the baroreceptor reflex. Through the rostral ventrolateral medulla, which in turn activates pre-ganglionic and post-ganglionic sympathetic neurons reaching the heart and the blood vessels, PAG contributes to increasing chronotropism and blood pressure values [56]. The role of muscarinic receptors, and therefore of the cholinergic nuclei of the lPAG, in modulating sympathetic tone has been confirmed by Ghorbani's studies using microinjections of acetylcholine and atropine, which suggested an inhibition of cardiac activity [25]. The study of the PAG-Vcn connection pathway was further investigated by Monaco through ULF-TENS trigeminal stimulation [18] HRV, a measure of autonomic balance, is frequently altered in pathological states. Ventral PAG stimulation in humans has been shown to increase HF HRV power and reduce the LF/HF ratio, indicating enhanced parasympathetic activity [16]. Moreover, PAG-mediated modulation of sympathetic tone influences myocardial contractility and peripheral resistance [16,17]. In a seminal study by Green and colleagues, six out of fifteen patients receiving ventral PAG-DBS experienced significant reductions in systolic (–14.2 $\pm$ 3.6 mmHg) and diastolic (–4.9 $\pm$ 2.9 mmHg) blood pressure [57]. Although significant changes in HRV were not consistently observed, DBS targeting the ventral and dorsal PAG nuclei was associated with notable changes in systolic blood pressure, with decreases of 14.2 mmHg and increases of 16.7 mmHg, respectively [14].

On the other hand, however, the DBS of the vPAG performed by Pereira's group produced HRV variations related to the analgesic response by the vagal parasympathetic component, with a VAS reduction [16] Further vagal analgesic responses were recorded during vlPAG DBS performed by Sverrisdóttir, with arousal patterns secondary to dlPAG stimulation [17].

Significant alterations in HR were not observed in experiments conducted by Kung *et al.* [22] on rats, where hemorrhagic lesions induced in rats associated with the use of monoaminergic neurotoxins such as dihydroxytryptamine led to increased sensitivity of baroreflexes as well as common acidosis (increased lactates) found in hemorrhagic strokes. This dual influence supports the hypothesis of PAG involvement in the autonomic cardiac loop. Indeed, the PAG projects directly to vagal preganglionic neurons—cardiovagal motor neurons—central to the baroreceptor reflex [58,59]. Using pseudorabies virus tracing, Farkas and colleagues demonstrated that sympathetic afferents to the heart involve both the lateral and ventrolateral PAG regions, interacting with premotor neurons in the hypothalamus and brainstem [60]. The experimental and clinical studies supporting these autonomic effects of PAG stimulation are summarized in Table 2 (Ref. [14–25]).

Cardiac Activity in Subarachnoid Hemorrhage

In a retrospective study conducted on 63 children and 291 adults, Yaghmoor described the electrocardiographic alterations in different types of intracranial haemorrhage, such as subdural and epidural haemorrhage, intraparenchymal haemorrhage and subarachnoid haemorrhage [61].

Cardiac abnormalities commonly reported in SAH include both rhythm and repolarization disturbances [62,63] such as T-wave inversion, QT interval prolongation, and ST-segment deviations. These changes, frequently observed also in other acute brain injuries, are potentially life-threatening and may contribute to sudden cardiac death in neurological patients [64]. In a large cohort, Frontera *et al.* [65] found that atrial flutter and fibrillation were the most frequent arrhythmias in spontaneous SAH. Weintraub and McHenry LC, Jr [66] further documented various QRS morphology changes and subendocardial hemorrhage in fatal SAH cases. Prolongations in the QTc interval have a high frequency in hemorrhagic stroke and may be considered as a statistical association with acute SAH [67], interpreted as central autonomic responses to elevated intracranial pressure [68]. Troponin elevation has also been consistently reported in SAH and ischemic stroke, even in the absence of primary cardiac disease [69,70]. Already in the past, several authors have identified a link between SAH and autonomic dysfunction (Table 3, Ref. [31–40]), manifested by cardiac activity alterations, and in many cases attempted to analyze the extent of the hemorrhage in the subarachnoid cisterns as well as the involvement of the ventricles, which in the most devastating cases are flooded [34,35,38–40,43,71,72]. Nakamura *et al.* [73] described transient ST-segment elevations in SAH patients without pre-existing cardiac pathology. Although the release of molecules, such as catecholamines, during the acute phase of SAH fuels the rise in blood pressure, there may be cases of hypotension up to shock, as described by Lee, in which this setting was characterized electrophysiologically by transient ST elevation [74]. Stimulation of the dPAG and ldPAG has been documented to increase HR, and has been performed separately by authors such as De Abreu and Dean, through injections of N-methyl-d-aspartate and anandamide, respectively [23,24]. Compared with NREM, the REM phase may be associated with changes in vascular resistance, increasing blood pressure, likely as a consequence of central autonomic modulation involving the midbrain periaqueductal gray, vestibular nuclei and other peduncular pontine nuclei [75]. Sakr and colleagues in a study of 159 patients with SAH showed that ST depression was corre-

Table 2. Summary of clinical and experimental studies on the autonomic effects of periaqueductal gray (PAG) stimulation.

Authors, year	Document type	Number of Patients/Caviae	PAG region	Type of stimulation	HRV & ECG recording	Other neurodiagnostics	Autonomic involvement	Other relevant findings	Quality assessment
Clinical Trial on Human patients: 7 studies									
Green *et al.*, 2005 [14]	Human intraoperative DBS study	15 awake patients (DBS-treated)	Ventral and Dorsal PAG	Deep Brain Stimulation (10 Hz, 120 µs, up to 3 V)	ECG lead II at 4 kHz; RR interval did not change; no HRV; BP and dP/dt recorded; SBP changes: Ventral –14.2 mmHg, Dorsal +16.7 mmHg	Post-op MRI and MRIcro for electrode localization; finger arterial pressure (Finapres); intra-arterial BP in one patient	Ventral → hypotension & reduced contractility (↓dP/dt); Dorsal → hypertension & ↑ contractility; no vagal involvement (no HR change)	Dorsal: nausea, anxiety, sweating; Ventral: reduced pulse pressure; supports PAG columnar model (ventrolateral = passive coping, dorsolateral = active coping)	Moderate risk: small sample, but precise DBS mapping and validated measures
Green *et al.*, 2010 [15]	Human intraoperative DBS autonomic study	6 male patients	Ventral and Dorsal PAG	Deep Brain Stimulation intraoperative (10–50 Hz, 3–4.5 V)	Intra-op ECG + ABP (500 Hz); RR interval stable; SBP% strongly correlated with LF power (r = 0.818); some patients had HR changes	MRI fused with Radionics for targeting; Finapres; spectral analysis of HRV and BP with MATLAB	Dorsal → ↑ sympathetic tone (↑LF); Ventral → ↓ sympathetic tone (↓LF); HF varied inconsistently	HRV power spectrum used as real-time biomarker of ANS response; different profiles for dorsal vs. ventral stimulation	Moderate–low risk: high-quality intraoperative physiology, detailed HRV
Pereira *et al.*, 2010 [16]	Human chronic DBS study	16 patients	Ventral PAG	Deep brain stimulation	ECG at 4000 Hz, downsampled; spectral HRV: ↑ HF power, ↓ LF/HF ratio (ventral); no change in dorsal DBS; HRV changes correlate with ↓ VAS pain	CT/MRI to verify electrode location; DTI and probabilistic tractography in controls	Ventral DBS → ↑ vagal tone (↑HF); dorsal DBS → no autonomic change	Analgesia linked to vagal activation; ventral PAG connected to vmPFC, ACC, amygdala	Moderate–low risk: clear HRV methodology, well-defined DBS parameters
Sverrisdóttir *et al.*, 2014 [17]	Human DBS autonomic physiology study	17 patients (10 PD, 7 pain)	dlPAG and vlPAG	DBS (ON/OFF comparison)	ECG + BP + MSNA; baroreflex slope (diastolic BP vs RR); microneurography; respiration measured	MRI/CT fusion; MNI coordinates; tilt test in PD patients; histograms of burst amplitudes	dlPAG → ↑ MSNA burst amplitude; vlPAG → ↓ MSNA frequency, ↑ BRS, ↓ BP, ↓ HR	dlPAG associated with arousal pattern (active coping); vlPAG with vagal-mediated analgesic response (passive coping)	Low risk: robust autonomic measures (MSNA, BP, baroreflex), clear design
Monaco *et al.*, 2017 [18]	Human randomized controlled physiological trial (TENS)	30 healthy women	Indirect (via trigeminal–PAG pathway)	Trigeminal ULF-TENS	2048 Hz ECG; TENS group showed ↓ LF/HF during stress ($p = 0.019$); RR and DET significant at baseline	EMG, respiration, VAS; mental arithmetic task; 8-channel polygraph	TENS enhanced vagal tone (↑HF), blunted sympathetic tone (↓LF) under stress	Effect mediated via PAG-RVM; supports neurovisceral integration theory	Low risk: randomized controlled design, well-supervised physiological measures
Mulcahy *et al.*, 2019 [19]	Human neuroimaging review/meta-analysis	Review (meta-analysis of human fMRI studies)	PAG in CAN	n/a (review article)	↓ HF-HRV linked to ↓ vagal tone; HRV used in task/rest fMRI; coupling with ACC, PFC, insula, PAG	fMRI, pulse oximetry, EEG-fMRI integration; structural lesion data	PAG involved in vagal parasympathetic regulation; HRV reflects CAN function	HRV predicts emotional regulation; Fig. 2 highlights PAG role in parasympathetic function	Moderate risk: review/meta-analysis, not primary data
Kang *et al.*, 2024 [20]	Human clinical review on autonomic dysfunction	Review (human ICH patients)	PAG in central autonomic dysfunction (ICH context)	n/a (review)	↓ HRV and baroreflex sensitivity linked to worse ICH outcomes; LF, HF, LF/HF used	DTI, HRV/BRS slope; BP variability analysis	ICH → ↑ sympathetic tone, ↓ vagal tone; intraventricular hemorrhage may injure PAG	PAG is a core node in CAN; injury leads to CV and thermal dysregulation	Moderate risk: narrative review, dependent on included sources

Table 2. Continued.

Authors, year	Document type	Number of Patients/Caviae	PAG region	Type of stimulation	HRV & ECG recording	Other neurodiagnostics	Autonomic involvement	Other relevant findings	Quality assessment
Animal experiments on Rat caviae: 5 studies									
De Menezes *et al.*, 2009 [21]	Rat microinjection experiment	36 male Sprague–Dawley rats	l/dlPAG	NMDA microinjection (6 pmol/100 nL)	Aortic telemetry: ↑ HR by 70 bpm, ↑ MAP by 20 mmHg after NMDA into l/dlPAG	DMH/PVN inactivation (muscimol, AP5, NBQX); fluorescent beads to confirm injection sites; histology using Paxinos & Watson atlas	Responses abolished by DMH inhibition → DMH necessary for CV effects; PVN inactivation had no effect or enhanced thermal response	Bidirectional PAG–DMH communication coordinates CV and thermal stress responses; PVN non-essential in this pathway	Low risk: rigorous stereotaxic technique, histology confirmation
Kung *et al.*, 2010 [22]	Rat hemorrhage + neurochemical lesion experiment	Rats (n = 7–15 per group)	Ventrolateral PAG (vlPAG)	Hemorrhage + serotonergic lesion (5,7-DHT)	HR via femoral arterial catheter (4 kHz); no significant change in HR; renal sympathetic nerve activity (RSNA) recorded	Immunohistochemistry for Fos, serotonin; baroreflex sensitivity via sequence/spectral analysis; blood gases and lactate levels	vlPAG 5-HT neurons facilitate sympathetic recovery; lesion → faster sympatholysis, impaired recovery	↓ serotonin = ↓ RVLM and NTS terminals, ↑ baroreflex gain, ↑ acidosis/lactate during hemorrhage	Moderate risk: detailed neurochemical work but limited HR changes
De Abreu *et al.*, 2015 [23]	Rat PAG–amygdala microinjection study	46 male Wistar rats	Dorsolateral PAG (l/dlPAG)	Microinjection of NMDA	Direct MAP and HR from femoral artery; ↑HR and ↑MAP; changes attenuated by BLA inhibition	Histology with Paxinos atlas; stereotaxic injection into BLA, CEA, PAG; drug injections (AP5, CNQX, muscimol)	BLA necessary for full cardiovascular response to PAG activation; CEA had no effect	PAG → BLA → CV response; indicates specific PAG–BLA sympathetic pathway	Low risk: strong experimental controls, validated microinjection targets
Dean *et al.*, 2016 [24]	Rat endocannabinoid physiological study	34 chronic rats + 29 for enzyme/lipid assays	Dorsal PAG	Endocannabinoid modulation (AEA injection, FAAH activity)	↑ HR, ↓ HF power, ↑ LF/HF ratio; AEA microinjection → acute ↑HR by up to 44 bpm	qPCR for FAAH/MAGL/CB1R; enzyme assays; LC-MS/MS for lipidomics; RSNA	↓ FAAH activity → ↑ AEA → ↑ sympathetic outflow	AEA in PAG modulates HR via endocannabinoid signaling; HR correlates with AEA levels (R^2 = 0.597)	Moderate–low risk: robust biochemical assays, physiological correlation
Ghorbani *et al.*, 2023 [25]	Rat cholinergic modulation experiment	60 male Wistar rats	Lateral PAG (lPAG)	Microinjection of ACh, Atropine, Hexamethonium	PowerLab ECG & BP; ACh → ↓ LF, ↓ HF, ↑ HR; Atropine reversed effects	Histology, Paxinos atlas; pharmacology; HYD-induced hypotension model	Muscarinic receptors in lPAG modulate vagal/sympathetic tone; ACh → parasymp pattern	Atropine improved HYD hypotension; HRV confirms central cholinergic modulation via PAG	Low risk: precise pharmacological manipulation and HRV confirmation

This table presents human and animal studies evaluating how direct or indirect stimulation of specific PAG columns modulates autonomic function. For each study, the table reports the document type, targeted PAG region, stimulation modality (e.g., DBS, pharmacological microinjection, sensory stimulation), autonomic outcomes (HR, BP, HRV, MSNA), key methodological elements, and a qualitative assessment of study quality. The revised structure reflects the separation between clinical and preclinical evidence and incorporates standardized criteria for methodological appraisal. ↑ = increase / increased; ↓ = decrease / decreased; → = leads to / results in / is associated with.

Table 3. Summary of studies reporting ECG alterations and autonomic dysfunction in subarachnoid and intraventricular hemorrhage.

Study (Authors, year)	Document type	Etiology (e.g., Aneurysmal SAH, ICH)	Key ECG findings	Sample sizes	Assessment methods (e.g., Holter, CT, HRV analysis)	Evidence of autonomic dysfunction	Fisher grade & IVH status	Quality assessment
Mehta AC and Aziz A (1965) [31]	Case report	Aneurysmal SAH	Bradycardia (HR 50), irregular rhythm (sinus arrest, nodal escape), prolonged QTc (0.60 s), large upright T waves. Authors attribute changes to SAH, possibly raised ICP and vagal stimulation.	1 (Case Report)	Case report methodology: ECG, LP (bloody CSF), Clinical exam, Labs, Necropsy (confirmed cerebellar angioma, SAH, blood in ventricles & around Circle of Willis).	Marked vagal predominance with sinus bradycardia around 50 bpm and episodes of sinus arrest with junctional escape. QTc is reported close to 0.60 s. The authors attribute both bradyarrhythmia and QTc prolongation to raised intracranial pressure with strong vagal stimulation, rather than primary cardiac disease.	Necropsy confirmed SAH + IVH ("blood in the ventricular system"). Fisher grade not used.	High risk: single case, limited generalizability
Anderson GJ, *et al*. (1973) [32]	Case report	Ruptured vascular malformation (ICH with IVH and SAH)	Mobitz Type I AV block (responsive to atropine), subsequent sinus bradycardia (rate 50), marked ST elevation (>5 mm in V2–V4), prolonged QTc (0.58 s), J waves (Osborn waves - patient was hypothermic).	1 (Case Report)	12-lead ECG, Rhythm strip, Cerebral Angiogram, Lumbar Puncture (bloody CSF), Necropsy, Clinical Exam, Lab tests (K+ 2.8), Temp monitoring (hypothermia noted)	Autonomic imbalance with a strong vagal component supported by Mobitz type I atrioventricular block that resolved after atropine and persistent sinus bradycardia around 50 bpm. QTc is around 0.58 s and J waves are present in the context of hypothermia. The authors interpret these conduction and repolarization changes as consequences of central autonomic disturbance related to intracranial bleeding	IVH confirmed by necropsy. Fisher Grade not applicable/not used.	High risk: case report, partial methodological detail
Uemura S *et al*. (1981) [33]	Case report	SAH (from AVM rupture, associated with congenital heart disease)	"Mild cardiac failure" noted on ECG (abstract mentions ECG findings)	1 (Case Report)	CT scan, CAG (angiogram), Electrocardiogram, Clinical exam (from abstract)	Intracranial hypertension and acute heart failure are described, consistent with central autonomic disturbance, but no formal quantitative autonomic indices such as QTc values or heart rate variability measures are reported. Evidence of dysautonomia remains qualitative.	CT scan showed intraventricular hemorrhage (from abstract). Fisher grade not applicable/mentioned.	High risk: case report, limited autonomic quantification
Colavita RD and Ment LR (1986) [34]	Prospective neonatal observational study	IVH in preterm infants (<1250 g); Contrasted with adult SAH literature	No characteristic ECG changes of adult SAH (no significant QTc changes, ST/T abnormalities) were found in infants with IVH. QRS axis differed between groups but normal for age. Continuous monitoring useful for detecting bradycardia with apnea.	41 preterm infants (19 with IVH)	Continuous ECG, Serial 12-lead ECGs, Cranial Echoencephalography (for IVH diagnosis/grading), Clinical assessment (apnea).	In the neonatal cohort, continuous ECG monitoring documents frequent episodes of apnea related bradycardia in infants with intraventricular hemorrhage, while systematic QTc prolongation or ischemic ST T changes typical of adult neurogenic heart disease is not observed. Autonomic involvement is therefore suggested by recurrent bradycardic events rather than quantified repolarization indices, and no heart rate variability analysis is provided.	IVH presence and grade (Papile I–IV) determined by Echo. 19/41 had IVH (GMH, Grade II, III, IV). Fisher Grade not applicable.	Moderate risk: small sample, neonatal cohort, continuous ECG but no HRV

Table 3. Continued.

Study (Authors, year)	Document type	Etiology (e.g., Aneurysmal SAH, ICH)	Key ECG findings	Sample sizes	Assessment methods (e.g., Holter, CT, HRV analysis)	Evidence of autonomic dysfunction	Fisher grade & IVH status	Quality assessment
Arruda WO and de Lacerda Júnior FS (1992) [35]	Prospective cohort study	Mixed CVH study (55 ICH, 15 SAH - mostly aneurysmal)	Most common: Prolonged QTc (ICH 67%, SAH 53%). Others frequent: Sinus tach, Ischemic ST-T changes, LVH, Neurogenic T waves, U waves. Only 7% of ICH group had normal ECG.	70 (55 ICH, 15 SAH)	Prospective, ECG (<48 h), CT, Angio (most), Clinical/Labs (metabolic exclusions applied).	Prospective series with very frequent repolarization abnormalities not explained by metabolic disturbance. QTc prolongation occurs in about 67 percent of patients with intracerebral hemorrhage and about 53 percent of those with subarachnoid hemorrhage, while only about 7 percent of the intracerebral hemorrhage group has a completely normal ECG. The authors interpret this pattern of QTc prolongation and neurogenic T waves as strong evidence of autonomic influence on ventricular repolarization.	Fisher Grade not used (H&H used). IVH present in 21/70 patients (across both groups), but presence not correlated with specific ECG changes.	Moderate–low risk: prospective design, adequate sample, good ECG methodology
Ostábal MI *et al.* (1997) [36]	Prospective clinical observational study	Spontaneous SAH	Arrhythmias (Identified as a prognostic factor alongside IVH)	100	Clinical scales (Glasgow, Apache II, Hunt-Hess), Clinical data analysis (incl. IVH, arrhythmias).	Arrhythmias are one of the main prognostic factors studied together with intraventricular hemorrhage in one hundred patients with spontaneous subarachnoid hemorrhage. Although the abstract does not give exact percentages for each rhythm disturbance, the explicit focus on arrhythmias as a prognostic marker in this setting supports a clinically relevant degree of autonomic dysfunction.	Abstract identifies intraventricular hemorrhage as a prognostic factor studied alongside arrhythmias. Fisher grade is not mentioned.	Moderate risk: prospective design, but limited ECG details in abstract
Junttila E *et al.* (2013) [37]	Prospective ICU cohort study	SAH and ICH requiring ICU care	Repolarization abnormalities (including prolonged QTc, ischemic-like changes, and morphological alterations) are frequently observed in patients with SAH, IVH, and ICH. Ischemic-like ECG changes are associated with poorer 1-year outcomes, as assessed by the Glasgow Outcome Scale (GOS).	108 (66 SAH/IVHa, 42 ICH/IVHo)	Prospective observational study, Serial ECGs (days 0–5), TTE, Labs (incl. cTnI), Clinical data (GCS, APACHE II), Sedation/Vasoactive drugs, Outcome (1-yr GOS). Multivariate regression.	Serial ECG recordings in intensive care patients show very frequent repolarization abnormalities, including prolonged QTc and ischemic-like changes, with ischemic-like changes associated with a worse functional outcome at one year. The authors discuss sympathetic overactivity as the main mechanism and report that these ECG changes remain independently associated with poor outcome after multivariable adjustment, consistent with a strong neurogenic component.	Hemorrhage type (SAH/IVHa vs ICH/IVHo) used as grouping variable. IVH presence/grade not explicitly detailed but implied in groupings. Fisher grade not used.	Low risk: large sample, serial ECGs, multivariate analysis

Table 3. Continued.

Study (Authors, year)	Document type	Etiology (e.g., Aneurysmal SAH, ICH)	Key ECG findings	Sample sizes	Assessment methods (e.g., Holter, CT, HRV analysis)	Evidence of autonomic dysfunction	Fisher grade & IVH status	Quality assessment
Liu Y *et al*., (2013) [38]	Case report	Aneurysmal SAH	Case report detailing prolonged Paroxysmal Sympathetic Storming (PSS) post-SAH. PSS involves tachycardia, HTN, tachypnea, hyperthermia, posturing, diaphoresis. ECG not primary focus but PSS reflects extreme autonomic dysregulation.	1 (Case Report)	Case report methodology: Clinical course, Imaging (CT, Angio), Vital sign trends, Treatments...	Paroxysmal Sympathetic Storm is defined as a state of severe autonomic instability with repeated episodes of tachycardia, hypertension, tachypnea, hyperthermia and profuse sweating. In this case, prolonged storms with markedly elevated heart rate and blood pressure occur in the setting of subarachnoid hemorrhage with intraventricular extension. The authors explicitly frame the syndrome as a manifestation of extreme central autonomic dysfunction.	CT showed SAH with IVH. Fisher grade not mentioned.	High risk: case report describing PSS, no systematic ECG methodology
Takeuchi S *et al*. (2015) [39]	Retrospective cohort study	Non-traumatic, non-neoplastic ICH	ST depression (24%), LVH (20%), QTc prolongation (19%), T wave inversion (19%). QTc prolongation associated with IVH.	118 (retrospective)	ECG (<24 h), CT scans, Clinical data review, Logistic regression.	Retrospective series of one hundred eighteen patients with intracerebral hemorrhage, where QTc prolongation is present in nineteen percent of cases and ST depression, left ventricular hypertrophy and T wave inversion each occur in about one fifth of patients. Intraventricular hemorrhage is present in thirty-two patients and emerges as an independent predictor of QTc prolongation in logistic regression models, supporting a quantitative link between ventricular involvement and autonomic modulation of repolarization.	Presence of IVH (in 32/118 patients, 27%) was an independent predictive factor for QTc prolongation. Fisher grade not applicable (ICH study).	Moderate–low risk: robust retrospective design, logistic regression used
Cima K *et al*., (2017) [40]	Case report	Aneurysmal SAH (L distal ICA T-bifurcation, ruptured)	ST elevation (V2–V6, I, aVL), prominent Q waves (V1–V3). Mimicked STEMI.	1 (Case Report)	ECG, Echo (anterior hypokinesia, ↓EF), Cardiac markers (↑TnT, CK), CT head, Angio, Coiling, Autopsy (normal heart/coronaries).	Case report of aneurysmal subarachnoid hemorrhage with extensive intraventricular blood that presents as an apparent anterior ST elevation myocardial infarction. Echocardiography shows a reduced ejection fraction with regional wall motion abnormalities, and cardiac biomarkers are elevated despite normal coronary arteries at autopsy. The authors interpret this dissociation between severe but reversible myocardial injury and normal coronaries as neurogenic myocardial stunning, driven by intense catecholamine release from central autonomic activation.	Fisher Grade not mentioned. CT confirmed major SAH with extensive IVH ("bloody filling of nearly the complete ventricle system").	High risk: case report, limited generalizability

This table compiles clinical evidence describing electrocardiographic abnormalities and autonomic disturbances in patients with subarachnoid hemorrhage (SAH), intraventricular hemorrhage (IVH), or intracerebral hemorrhage (ICH). It includes each study's document type, key ECG alterations, assessment methods, autonomic involvement, and ventricular extension when available. A qualitative methodological appraisal is also provided to reflect study quality and design robustness. ↑ = increase / increased; ↓ = decrease / decreased.

lated with a worse outcome [76]. Patients with SAH appear to have an increased risk of ventricular dysrhythmias [77]. Among the multiple causes of acquired long QT intervals are electrolyte imbalance, AIDS, autonomic neuropathy and subarachnoid hemorrhage [78]. During hemorrhagic stroke, damaged cells can stimulate a cascade of immune and inflammatory responses, resulting in secondary injury and oedema [79]. Thus, altered regulation by central neural structures may result in structural or cardiac rhythm abnormalities, mediated through the autonomic nervous system [80]. A reduction in heart rate variability and baroreflex sensitivity after a stroke has been associated with a higher risk of myocardial ischaemia, myocardial infarction, arrhythmias and sudden cardiac death, which is also known as cerebrocardiac syndrome [20,55,81].

Pathophysiological Mechanisms Linking SAH+IVH, PAG and ECG

Electrocardiographic abnormalities observed during SAH primarily include QTc prolongation, ST-segment elevation or depression and T-wave inversion [1]. These repolarization changes may be secondary to increased sympathetic drive or, in specific contexts, to parasympathetic hyperactivity driven by central mechanisms. For instance, T-wave alternans and QT prolongation have been attributed to thoracic sympathetic chain stimulation, often observed during hypertensive peaks or in the context of severe autonomic dysregulation [2,82]. In hypotensive states, transient ECG alterations may arise due to vagal activation, potentially originating from the ventrolateral nuclei of the PAG [83,84]. It has long been known in the neurophysiological literature that stimulation of the PAG can determine a variety of autonomic responses [15–25]. Stimulation of these nuclei can induce hypotension and bradycardia [55,60,85,86]. Indeed, chemical activation of the lateral PAG leads to sympathetic arousal, producing hypertension and tachycardia [60,87]. This duality underscores the bidirectional nature of PAG-mediated autonomic modulation. Some investigations on migraine have further supported the role of the vagus nerve in this dynamic balance [88–90]. Tan *et al*. [91] demonstrated that transcutaneous auricular vagus nerve stimulation in SAH patients not only enhanced neuroplasticity and anti-inflammatory responses but also resulted in increased heart rate, which paradoxically served as a positive prognostic indicator. The autonomic and cardiovascular manifestations of SAH are not solely due to catecholamine surge [92–94]; they also reflect the release of endogenous opioids and stress hormones with known prognostic significance [93–95]. In this context, DBS of the ventrolateral PAG emerges as a promising therapeutic strategy to counteract neurogenic hypertension—a common, often refractory complication of SAH—by rebalancing sympathetic overactivity irrespective of the initial trigger [96–99]. The sympathetic activation seen in the acute phase of increased intracranial pressure (i.e., Cushing's reflex) could serve as a compensatory response to baroreceptor-mediated vagal bradycardia, followed by reactive tachycardia and ST-segment depression with T-wave peaking, as documented in cases of SAH rebleeding [98,100,101]. This autonomic cascade likely represents a central nervous system response aimed at preserving cerebral perfusion through cardiac compensation [102,103]. The increase in endocranial pressure, by stimulating the baroreceptors, may activate vagal pathways which subsequently require compensation through an orthosympathetic response [104,105]. Moreover, the extension of hemorrhagic lesions into the third or fourth ventricle may directly impact autonomic function due to disruption of periventricular structures such as the hypothalamus and PAG, both of which are densely involved in cardiovascular control [106]. Intraventricular blood may obstruct CSF circulation, elevate local intracranial pressure and compromise cerebral perfusion in adjacent tissues [9,107]. The inflammatory response during SAH is amplified by hemoglobin breakdown products (i.e., iron cation), which promote reactive oxygen species (ROS) synthesis through Fenton and Haber-Weiss reactions, leading to oxidative neuronal damage [108,109]. Such damage exacerbates PAG excitability by lowering its neuronal activation threshold, potentially altering systemic visceral control [110,111]. Inflammation may spread by continuity into the ventricular wall and by contiguity into adjacent tissues, generating transependymal edema and affecting structures beyond the SA, including the PAG [111]. This process further facilitates neuronal depolarization and hyperresponsiveness [112,113]. Neurons may also be activated by mechanical stimuli, such as ventricular wall stretching, as previously demonstrated in animal models [6,114]. As blood enters the ventricular system, including the SA, this results in both edema and ventricular distension, particularly if hydrocephalus develops [10,11]. In acute hydrocephalus due to SAH, emergency procedures like external ventricular drainage become necessary [115]. Ventricular dilatation increases transmural pressure gradients and CSF oozing, which exacerbate periventricular inflammation and neuronal dysfunction [116–118]. Phlogistic stimuli lead to major activation of neurons due to a lowering of excitation threshold [118]. This scenario provides a plausible pathway for direct mechanical and chemical activation of PAG, leading to autonomic dysregulation and changes in ECG parameters, such as QT prolongation and T-wave inversion [61]. Supporting this, it was demonstrated that PAG neurons modulate cardiac function via projections to autonomic centers, making them susceptible to disruption under inflammatory and mechanical stress [60,119,120]. The data compiled in both tables comprise the limited but focused set of studies describing patients with ECG abnormalities during SAH with coexisting intraventricular hemorrhage, thus implicating PAG and periventricular structures in the observed autonomic effects. According to the revised Fisher grading system, any IVH, even in the ab-

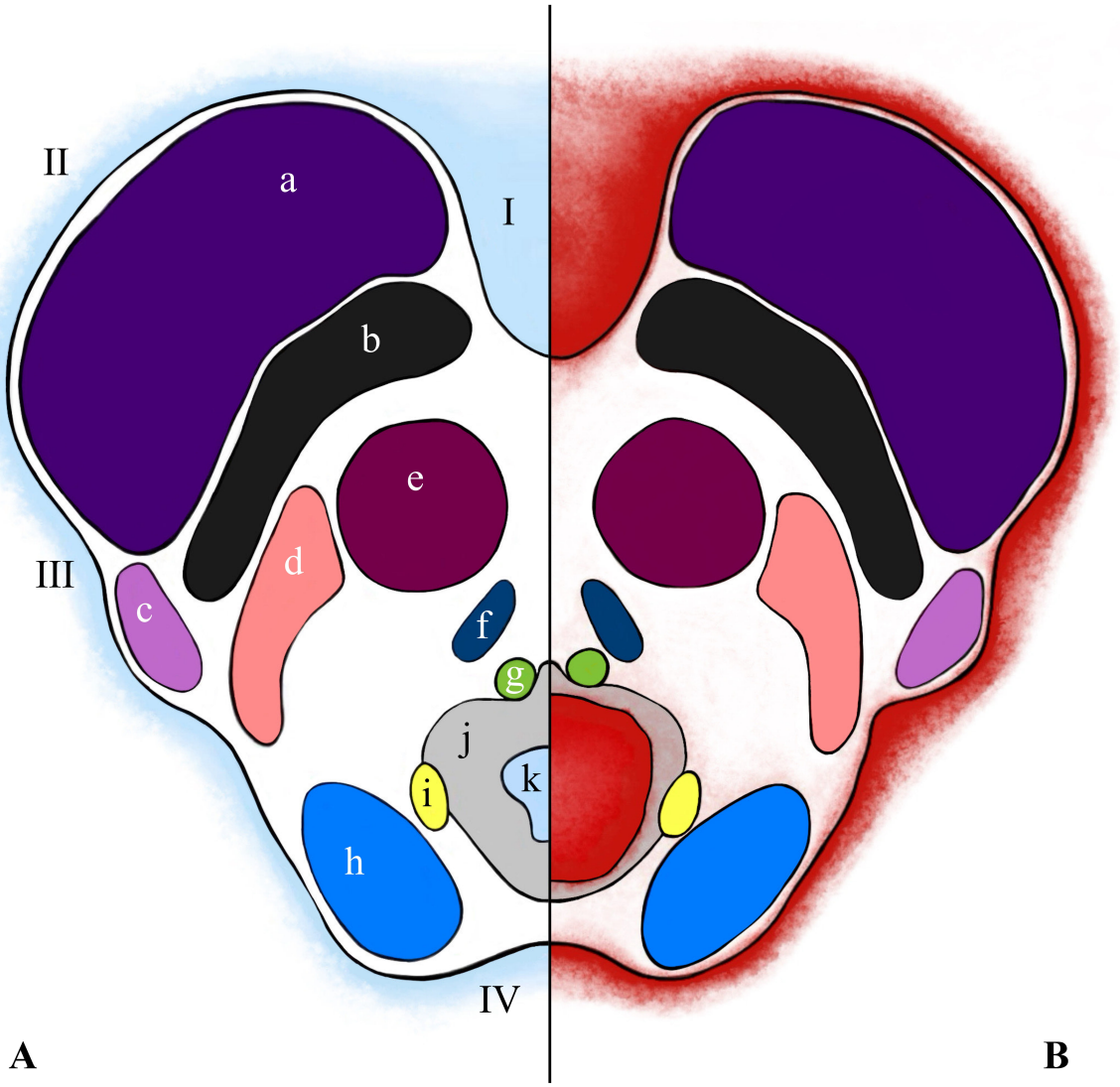

Fig. 2. Hand-drawn graphic representation of the brainstem section using Artstudio Pro for iOS (https://apps.apple.com/it/app/artstudio-pro-draw-paint/id1244142051). Comparative Midbrain Neuroanatomy in Normal and Pathological Conditions. (A) Axial section illustrating normal neuroanatomy at the level of the Sylvius aqueduct and periaqueductal gray (PAG), including surrounding brainstem structures such as the superior colliculi. For simplification purposes, the mesencephalic course of the oculomotor nerve and the oculomotor nucleus—normally located between the Edinger–Westphal nucleus (adjacent to the PAG) and the medial longitudinal fasciculus—are not depicted. The ventricular system appears of normal size, and the mesencephalic (interpeduncular) cistern is free of blood, containing clear CSF. (B) Axial section showing pathological findings with evident subarachnoid hemorrhage involving the mesencephalic cistern and ventricular system. Sylvius Aqueduct is dilated and filled with blood, accompanied by signs of inflammation in the adjacent PAG. Transependymal edema is visible around the aqueduct, resulting from increased intraventricular pressure and wall permeability, leading to periventricular infiltration and PAG involvement. **Legends:** a, cerebral midbrain pedicles; b, substantia nigra; c, medial geniculate nucleus; d, medial lemniscus; e, red nucleus; f, medial longitudinal fasciculus; g, Edinger-Westphal nucleus; h, superior colliculi; i, trigeminal nerve mesencephalic nucleus; j, periaqueductal gray; k, Silvio's Aqueduct. I, mesencephalic interpeduncular cistern; II, crural cistern; III, ambient cistern; IV, quadrigeminal cistern.

sence of subarachnoid blood, constitutes Grade IV SAH [9,10]. This represents the highest risk tier for hydrocephalus and vasospasm, both of which are critical contributors to autonomic instability and ECG abnormalities [121,122]. Extensive IVH may also result in delayed hydrocephalus, especially if arachnoid granulation resorption is impaired [123]. Even in early stages, when overt intracranial hypertension has not yet developed, PAG neurons may be activated by trans-ependymal fluid shifts, local inflammation, or mechanical irritation, as seen in the inflammatory involvement of periaqueductal grey matter [124]. As shown in Fig. 2, the presence of blood in the subarach-

noid space and ventricular system leads to transependymal edema, inflammatory extension beyond the ventricular walls, and progressive ventricular dilation. This anatomical progression can result in compression of periventricular grey matter structures such as the PAG, with subsequent alterations in autonomic output [116,117]. In this context, phlogistic stimuli further lower the excitability threshold of neurons, increasing the susceptibility of PAG neurons to aberrant firing. Moreover, mechanical stretching secondary to ventricular expansion—particularly involving the fourth ventricle—may contribute to sustained depolarization of PAG neurons, leading to autonomic disturbances [118]. This process provides a mechanistic link between ventricular blood load and systemic cardiovascular responses. Consistent with this view, ECG changes associated with hydrocephalus have also been reported in chronic stages [103]. Shukla documented T-wave inversion that reversed following ventricular-peritoneal shunt placement, emphasizing the role of ventricular pressure in modulating autonomic tone [125]. Similarly, in a cohort of 160 patients, Qaqa *et al.* [126] found QTc prolongation in patients with midline shift and hydrocephalus following intraparenchymal hemorrhage; these patients also exhibited an increased incidence of sinus tachycardia. ST-segment deviations (elevation or depression) are well-documented during intracranial hypertension [103]. Angiographic studies by Stober and Kunze [127] linked QTc prolongation, T-wave changes, and left stellate ganglion dysfunction, providing further evidence for lateralized autonomic effects. The insular cortex—particularly the right anterior region—has also been implicated in triggering sympathetic activation during cerebrovascular events, including SAH [128–130]. Hirashima's findings further emphasized that right-sided sylvian hemorrhage was more likely to produce ECG disturbances [131]. Interestingly, the anterior insular cortex contains von Economo neurons, which have direct projections to the PAG [132–134]. These projections may help substantiate the role of the PAG in integrating pain processing and autonomic control. Although pain-related ECG variations are known, further electrophysiological studies are needed to elucidate whether intracranial pain circuits may amplify PAG-driven cardiac effects [64,135–137]. The PAG involvement in the autonomic and nociceptive response has been further confirmed by evidence of its engagement in vagal pathways and endocannabinoid circuits [138,139]. While older literature held that only the dura mater was innervated by nociceptors, more recent studies have identified mechanosensitive afferents in the pia mater and subarachnoid vessels. These are activated by mechanical stretching and project via trigeminal V1 fibers [140,141]. According to Mehnert *et al.* [142], trigeminal afferents form a somatotopic map within the PAG (V1–V3), supporting the presence of integrated nociceptive and autonomic processing. These interactions, along with cortico-subcortical loops, suggest that the PAG may be modulated not only by mechanical stress and inflammation, but also by sensory and emotional stimuli, and this is an important finding that could open new avenues for neurophysiological investigation [143]. Although several studies have separately addressed the autonomic role of the PAG and the cardiac alterations observed during SAH, targeted investigations focusing on high-grade Fisher SAH, particularly with involvement of all four ventricles, remain lacking. This review aims to bridge that gap by proposing a direct pathophysiological link between intraventricular blood extension, periaqueductal gray dysfunction, and dysautonomia, with measurable effects on cardiac physiology.

Clinical Implications and Future Perspectives

Investigating the role of the PAG may be useful in monitoring the possible evolution of IVH and intracranial pressure [144]. In fact, given the influence of PAG dysfunction on cardiac contractility and conduction activity, future studies may benefit from using ECG recordings and their derived parameters during SAH as an indirect parameter of ventricular distension, such as periventricular inflammation. Blood-related irritation and inflammation surrounding the IV ventricle could represent a more specific parameter to study changes in endocranial pressure and adjacent compression caused by extensive oedema, particularly given the close anatomical proximity to the brainstem and its vital nuclei. From a medical statistical perspective that accounts for the coexistence of several factors, the presence of variables and the medical outcome, it could also be useful to stratify patients according to the severity of subarachnoid hemorrhage, whether associated with the presence of hematoma inside the ventricles, and thus to incorporate Fisher's scale when determining the intensity of monitoring and anticipating potential abnormalities in cardiac activity [9,92,94]. Recognizing that specific ECG changes may be associated with an important compression of critical structures in the posterior cranial fossa can help clinicians determine the timing of management, including when to anticipate a neuroimaging study and when to consider surgical intervention.

Conclusions

Electrocardiographic changes during SAH have so far been attributed to autonomic responses via diencephalic areas stimulation involved in the fine balance between sympathetic and parasympathetic activity. PAG is a neuroanatomical region not only connected to the pain response but also involved in the autonomic reactivity after specific stimuli. The role of the PAG in inducing alterations of cardiac rhythm during SAH has so far not been considered. In view of the proximity of the PAG to the SA walls and since SAHs with intraventricular involvement may cause contiguous extension of inflammatory process, the function of the PAG deserves to be further investigated with targeted studies. Furthermore, considering that the cortical-

subcortical areas of the brain in newborns are still maturing, the study of cardiac rhythm alterations during cerebral hemorrhage in this population could be useful not only in discerning the differences between pediatric and adult pathophysiology, but also in gaining a better understanding of the development of connectomics within a still-developing neural network, as well as adaptive neuroplasticity. This systematic review opens new avenues for translational research and clinical monitoring strategies integrating autonomic biomarkers in the management of high-grade SAH.

Abbreviations

SAH, subarachnoid hemorrhage; IVH, intraventricular hemorrhage; ICH, intracerebral hemorrhage; ECG, electrocardiographic; CSF, cerebrospinal fluid; CNS, central nervous system; PAG, periaqueductal gray; dPAG, dorsal periaqueductal gray; vPAg, ventral periaqueductal gray; lPAG, lateral periaqueductal gray; dlPAG, dorso-lateral periaqueductal gray; HR, heart rate; HRV, heart rate variability; MSNA, muscle sympathetic nerve activity; BP, blood pressure; SA, sylvian acqueduct; DBS, deep brain stimulation; NMDA, N-methyl-D-aspartate; ACh, acetylcholine; AEA, Arachidonoylethanolamide; TENS, transcutaneous electrical nerve stimulation; MRI, magnetic resonance imaging; DTI, diffusion tensor imaging; CAN, Central Autonomic Network; HF, high frequency; LF, low frequency; DMH, dorsomedial hypothalamus; RVLM, rostral ventrolateral medulla; BLA, Basolateral Amygdala; V1, ophthalmic division of trigeminal nerve; V2, maxillary division of trigeminal nerve; V3, mandibular division of trigeminal nerve; REM, rapid eye movement phase; NREM, non rapid eye movement phase.

Availability of Data and Materials

All data analyzed in this study are derived from published articles included in the systematic review. No new datasets were generated or analyzed during the current study. The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

SM, BDO, and GS designed the research study. SM and BDO developed the study methodology. SM, GS, EG, NLP, FG, LS, IAG, ST, GV, EC, CC, CRV, and AMDM performed the literature search and study selection. SM, EG, NLP, FG, LS, EC, CC, CRV, and AMDM curated the data. SM, BDO, GF, GEU, and GS performed the formal analysis and interpretation of the data. SM and GS drafted the manuscript. BDO, EG, NLP, FG, LS, IAG, ST, GV, EC, CC, CRV, AMDM, GF, GEU, and GS revised the manuscript critically for important intellectual content. GS supervised the study and was responsible for project administration. GS and SM validated the final content. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.24976/Discov.Med.202638205.51.

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