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Brain–heart instability windows: A dynamic state framework for predictive neurocardiology

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Abstract

Neurocardiovascular disorders such as atrial fibrillation–related stroke, syncope, autonomic dysfunction, and post-stroke arrhythmogenesis are commonly evaluated using static risk models that estimate long-term baseline susceptibility but do not capture short-term physiological variability across interacting brain–heart systems. Emerging longitudinal data show that rhythm burden, autonomic variability, blood pressure variability, and inflammatory tone can fluctuate over time, although whether these fluctuations converge into clinically meaningful vulnerability states remains unproven. This conceptual narrative review proposes brain–heart instability windows (BHIWs) as a hypothesis-generating framework for studying temporally bounded reductions in coupled neurocardiovascular stability. The framework organizes candidate instability across autonomic, electrical, hemodynamic, thrombo-inflammatory, and neural domains. It also introduces a brain–heart measurement stack integrating continuous digital signals, structured physiologic assessments, and structural or biological anchors. Candidate BHIWs are defined as sustained or recurrent deviations from individualized baseline patterns, especially when temporally aligned abnormalities occur across at least two physiologically coherent domains. The framework is intended to complement, not replace, established risk models by supporting empirical investigation of dynamic vulnerability, cross-domain convergence, and future decision pathways such as monitoring intensity, telemetry duration, orthostatic evaluation, and therapeutic timing. Prospective validation is required before BHIWs can inform clinical management.

Keywords: Brain–heart interaction; Neurocardiology; Autonomic dysfunction; Atrial fibrillation; Cerebrovascular autoregulation; Physiological variability; Dynamic risk modeling; Predictive neurocardiology

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1. Introduction — From episodic diagnosis to continuous forecasting

Neurocardiology has historically evolved around discrete clinical events. Stroke is diagnosed following the emergence of focal neurological deficit.[1] Atrial fibrillation (AF) is identified when captured on electrocardiography.[2,3] Syncope is evaluated after transient loss of consciousness, often through retrospective clinical reconstruction.[4] Even autonomic dysfunction is commonly characterized through snapshot testing—tilt-table responses, isolated blood pressure measurements, or short-duration rhythm monitoring.[5,6] This event-centered paradigm has produced substantial advances

in prevention and acute management, including anticoagulation strategies, rhythm control approaches, and secondary stroke prevention protocols.[7] Nevertheless, it remains predominantly reactive in structure.

Beyond conceptual reframing, the proposed instability-based perspective intersects with several domains of contemporary neurocardiology. Atrial fibrillation–related stroke, post-stroke arrhythmogenesis, orthostatic intolerance and syncope, autonomic dysfunction syndromes, and disorders of cerebral perfusion regulation all involve dynamic interactions between cardiac rhythm, vascular control, and neural regulatory networks. These interactions are empirically established at the level of individual physiological systems. However, whether they converge into discrete, temporally bounded cross-organ vulnerability states remains a testable hypothesis rather than an established clinical construct.[8-10] In aerospace and extreme physiological environments, including microgravity exposure, adaptations in autonomic tone, hemodynamic distribution, and cerebral blood flow further underscore the relevance of brain–heart coupling. These observations support the biological plausibility of the brain–heart instability window (BHIW) framework but do not by themselves validate the existence of BHIWs.[11,12]

Both the brain and the heart function as excitable, oscillatory systems whose stability is continuously modulated rather than episodically determined.[13] Cardiac rhythm varies across sleep–wake cycles, autonomic tone shifts, inflammatory states, hydration status, and emotional stress.[14,15] Cerebral perfusion and neural network dynamics fluctuate in parallel, influenced by vascular resistance, autonomic balance, and metabolic demand.[13,16] Emerging evidence indicates that several physiological variables relevant to stroke, arrhythmia, and syncope can change dynamically before, during, or around clinical events. These observations support the possibility that some neurocardiovascular events may be influenced by evolving physiological trajectories, although the specific concept of a bounded cross-organ instability window remains to be prospectively demonstrated.[9,17] From this perspective, neurocardiovascular disorders may be understood not solely as diseases of structural pathology, but as disturbances of temporal physiological regulation.

The rapid expansion of wearable sensors, implantable loop recorders, continuous electrocardiographic monitoring, cuffless blood pressure estimation technologies, and digital phenotyping platforms has expanded the scope of ambulatory physiological observation.[18-20] Longitudinal heart-rate variability (HRV) dynamics, rhythm irregularity burden, sleep-associated autonomic fluctuations, activity-linked hemodynamic responses, and multiday blood pressure variability can now be measured outside the clinic.[21,22] Wearable-based AF detection and remote rhythm monitoring have demonstrated increasing diagnostic sensitivity and feasibility in population settings.[23,24] Collectively, these developments provide the technical capacity to characterize physiological trajectories rather than isolated datapoints.

Despite this progress, interpretation of continuous signals remains fragmented. Digital metrics are often analyzed in isolation rather than within an integrated cross-organ stability framework.[25,26] Current risk prediction models for stroke, AF-related thromboembolism, and syncope continue to rely primarily on static demographic and structural variables, whereas temporal instability patterns—such as short-term variability shifts, arrhythmic clustering, and nonlinear autonomic transitions—are less systematically incorporated into clinical inference.[20,25,27-30]

These considerations support a complementary focus on instability assessment: identifying whether continuous autonomic, electrical, hemodynamic, and thrombo-inflammatory signals can define phases of heightened cross-organ vulnerability.[19,31]

Methodologically, this article is designed as a conceptual narrative review rather than a systematic review or meta-analysis. The reviewed literature was selected to synthesize evidence across neurocardiology, autonomic physiology, cardiac electrophysiology, cerebrovascular regulation, thrombo-inflammatory biology, wearable and implantable monitoring, and systems-level risk modeling. The goal is not to provide an exhaustive quantitative assessment of all studies in these areas, but to integrate established observations into a hypothesis-generating framework for dynamic neurocardiovascular vulnerability. Accordingly, the article combines narrative synthesis with conceptual model development, while distinguishing established evidence from biologically plausible inference and unvalidated research propositions.

Building on this conceptual narrative review structure, this work hypothesizes that some neurocardiovascular events may be temporally concentrated within bounded phases of reduced physiological resilience, which are termed "brain–heart instability windows" (BHIWs). This proposal should be interpreted as a conceptual and hypothesis-generating framework, not as evidence that such windows have already been clinically validated. The framework integrates three levels of inference: established evidence that autonomic, electrical, hemodynamic, inflammatory, and neural variables fluctuate over time; biologically plausible mechanisms through which these fluctuations may interact across brain–heart systems; and testable but currently unproven propositions that coordinated cross-

domain deviations may define transient states of increased vulnerability.[19] The framework presented here is intended as a conceptual scaffold to guide empirical investigation and to support the development of physiology-informed forecasting approaches in neurocardiovascular medicine.

2. The brain and heart as coupled excitable systems

The brain and the heart are often approached as distinct clinical domains; however, both may be understood as excitable biological networks governed by shared electrophysiological and regulatory principles.[32,33] Neuronal circuits and cardiac myocytes generate action potentials through tightly regulated ion-channel dynamics, translating membrane depolarization into coordinated electrical and functional output.[34,35] In both organs, excitability extends beyond individual cellular properties and emerges from network organization, connectivity, and modulatory influences.

2.1. Ion-channel–dependent excitability

At the cellular level, neuronal firing and cardiac conduction depend on voltage-gated sodium, potassium, and calcium channels that define threshold behavior, propagation velocity, refractory characteristics, and repolarization stability.[32,35,36] Alterations in ion-channel conductance, expression, or modulation can influence network synchrony in cortical circuits or modify arrhythmic susceptibility in the myocardium.[37,38] Inflammatory mediators, autonomic signaling, metabolic stress, and ischemic conditions have been shown to influence channel kinetics in both tissues[39,40], suggesting that channel-level perturbations may represent a mechanistic point of convergence in cross-organ vulnerability.

2.2. Oscillatory rhythm generation

Both organs function as oscillatory systems. Cardiac rhythm arises from sinoatrial pacemaker activity and conduction network synchronization, whereas brain function depends on multiscale oscillations distributed across cortical and subcortical circuits.[41,42] Stability in each system reflects a dynamic balance between excitation and inhibition, depolarizing and repolarizing currents, and local versus network-level synchronization.[37,41,43] Destabilization in these oscillatory systems may manifest as arrhythmia in the heart or as seizure activity, dysregulated neural oscillations, or impaired network coordination in the brain.[37,38,42] These parallels support the view that rhythm instability may be understood as a systems-level phenomenon rather than solely a tissue-specific abnormality.

2.3. Autonomic gain modulation

Cardiac rhythm and cerebral perfusion are continuously modulated by autonomic regulation. Sympathetic and parasympathetic inputs dynamically influence heart rate, conduction velocity, vascular tone, and blood pressure variability.[44,45] The central autonomic network—including cortical, subcortical, and brainstem structures—integrates emotional, metabolic, and homeostatic inputs to regulate cardiovascular output and vascular resistance.[46,47] Fluctuations in autonomic gain may transiently alter electrical stability, modify perfusion thresholds, and influence systemic vulnerability.[9,48] Heart-rate variability (HRV) provides one quantifiable index of autonomic modulation and has been associated with both cardiovascular and neurological outcomes.[49,50]

2.4. Perfusion–metabolism coupling

Cerebral function depends upon relatively stable perfusion, which is maintained through coordinated cardiac output, vascular compliance, and autoregulatory mechanisms.[51,52] Variability in cardiac output or systemic blood pressure may influence cerebral blood flow dynamics, particularly in individuals with impaired autoregulation, endothelial dysfunction, or structural vascular disease.[46,53] Under such conditions, perfusion fluctuations may interact with neural metabolic demand and inflammatory signaling to modulate neurological vulnerability.[54,55]

Conversely, acute brain injury, stroke, or neurodegenerative processes may disrupt autonomic balance and have been associated with secondary cardiac electrical disturbances, including arrhythmias and repolarization abnormalities.[10,56] These observations suggest that perturbations in one system may influence stability in the other through shared autonomic and hemodynamic pathways.

2.5. Bidirectional regulation and coupled stability

The relationship between brain and heart is therefore plausibly bidirectional. The central autonomic network exerts ongoing regulatory influence over cardiac rhythm and vascular tone[45,48], while cardiac output variability and systemic hemodynamics contribute to cerebral perfusion stability and neural metabolic homeostasis.[50,57] Electrical, autonomic, inflammatory, and hemodynamic pathways provide potential routes through which perturbations may propagate across systems.

Clinical phenomena such as AF, syncope, post-stroke arrhythmia, or progressive cognitive decline are traditionally categorized within distinct specialties. However, these conditions may, in some cases, reflect interacting instability processes within coupled excitable networks rather than entirely independent pathologies.

Recognizing the brain and heart as interdependent excitable systems provides a mechanistic foundation for the BHIW construct and for interpreting longitudinal physiological signals within a coupled network context.

3. Limitations of static risk stratification frameworks

Contemporary neurocardiovascular risk assessment relies predominantly on models derived from population-level associations. Tools such as the CHA_2DS_2-VASc score for AF-related stroke risk, structured orthostatic testing protocols for syncope evaluation, single-timepoint electrocardiography for rhythm diagnosis, and clinic-based blood pressure averages for vascular risk stratification have substantially improved clinical standardization and guideline implementation.[58,59] These frameworks have contributed meaningfully to reductions in morbidity and mortality. However, they are primarily designed to estimate long-term baseline susceptibility rather than short-term dynamic vulnerability.

3.1. Time-agnostic risk estimation

Many widely used risk models are largely time-agnostic in structure. The CHA_2DS_2-VASc score assigns weighted points based on age, hypertension, diabetes, heart failure, prior stroke, and vascular disease[60,61]—variables that typically change gradually. As a result, the model yields an estimated annualized risk that is relatively stable over time. Similarly, syncope risk stratification tools and orthostatic hypotension criteria rely on discrete measurements obtained during clinical evaluation.[59,62] Snapshot electrocardiography captures rhythm at a single moment [24,63], and blood pressure–based risk assessment frequently depends on averaged clinic readings.[58,64]

While such approaches estimate cumulative probability effectively, they are not designed to detect short-term increases in physiological vulnerability.

3.2. Limited incorporation of dynamic physiological states

Static risk models primarily incorporate structural comorbidities and demographic characteristics. Dynamic physiological states—such as shifts in autonomic tone, acute inflammatory activation, dehydration, sleep disruption, or metabolic stress—are less systematically integrated into routine risk estimation.[65,66] Yet accumulating evidence suggests that AF burden may cluster temporally, that thromboembolic risk may fluctuate in relation to arrhythmic activity, and that syncope risk may increase during transient autonomic instability.[67,68]

From this perspective, existing models effectively quantify baseline susceptibility but are less equipped to characterize evolving physiological states.

3.3. Averaging and loss of variability structure

A further methodological limitation relates to averaging. Blood pressure, HRV, and rhythm irregularity metrics are often reduced to mean values for clinical interpretation.[58,69] However, nonlinear systems research indicates that instability may emerge through alterations in variability structure, entropy, clustering, or short-term fluctuation dynamics rather than through shifts in mean levels alone.

Short-lived bursts of sympathetic activation, transient repolarization variability, or episodic perfusion reductions may carry disproportionate physiological significance, yet remain attenuated when signals are averaged across extended time intervals. Pre-event destabilization signatures have been reported in several domains: HRV pattern changes preceding arrhythmic episodes[70,71], blood pressure variability associated with cerebrovascular outcomes independent of mean pressure[69,72], and AF episodes occurring in temporally clustered patterns.[67,73] These findings suggest that vulnerability may not be uniformly distributed across time but may instead fluctuate.

3.4. Temporal vulnerability as an underrepresented dimension

Static models are designed to estimate who is at risk over months or years, not when risk may transiently increase. Consequently, therapeutic decisions are often calibrated to long-term averages rather than evolving physiological states.

The conceptual distinction between static and dynamic risk models is illustrated in Figure 1.

This limitation becomes more salient in the context of continuous monitoring technologies. Digital devices are capable of detecting variability shifts, arrhythmia clustering, and autonomic transitions in near real time. However, without a conceptual framework for integrating these dynamic signals, clinical interpretation remains anchored to static paradigms.

The central challenge may therefore be theoretical rather than technological. Neurocardiovascular risk appears to have both baseline and state-dependent components. Bridging this gap requires consideration of disorders such as stroke, arrhythmia, and syncope not solely as cumulative risk outcomes, but as potential manifestations of evolving state transitions. Defining and operationalizing temporally bounded vulnerability phases represents a possible next step in complementing probabilistic stratification with dynamic state assessment.

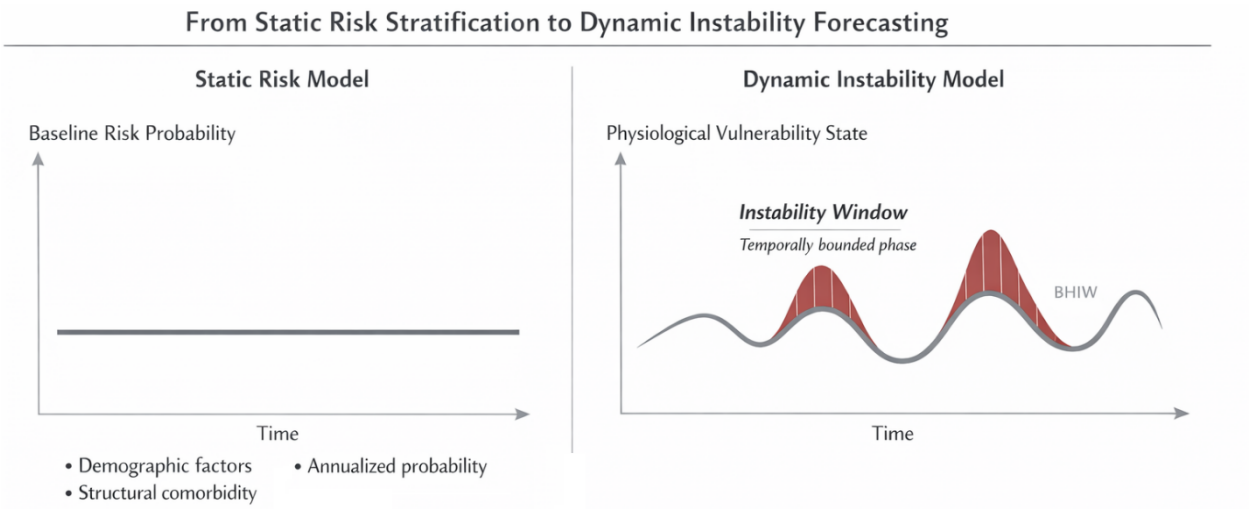


Figure 1. Static versus dynamic conceptualizations of neurocardiovascular risk. Traditional risk models estimate long-term probability based primarily on demographic characteristics and structural comorbidities and are largely time-agnostic in structure. In contrast, the brain–heart instability framework conceptualizes vulnerability as temporally dynamic, characterized by evolving physiological states across autonomic, electrical, hemodynamic, thrombo-inflammatory, and neural domains. Discrete peaks represent instability windows—temporally bounded phases of reduced cross-organ regulatory stability during which event probability may be transiently increased. Original figure created by the author for this article.

4. Defining brain–heart instability windows

Consistent with the conceptual narrative review design, this section translates the preceding evidence synthesis into a provisional framework for defining and studying BHIWs. Several components of neurocardiovascular risk—including autonomic tone, rhythm burden, blood pressure variability, inflammatory activity, and neural regulatory capacity—vary over time. Whether these fluctuations converge into discrete intervals of reduced cross-organ regulatory stability remains an open empirical question. To formalize this question, we introduce the construct of brain–heart instability windows (BHIWs).

For the purposes of this review, BHIWs are provisionally defined as candidate temporally bounded intervals of coordinated cross-organ physiological deviation that are hypothesized to reflect reduced regulatory stability and potentially increased cerebrovascular or arrhythmic vulnerability. Operationally, a candidate BHIW should include: identifiable onset and resolution; deviation from an individualized baseline or validated reference range; persistence or recurrence beyond brief artifact-level fluctuation; and either convergence across at least two physiological domains or strong deviation within one domain supported by relevant structural or biological substrate.

The conceptual architecture of this framework is illustrated in Figure 2.

Within this framework, BHIWs are conceptualized as dynamic state transitions rather than static disease markers. They are characterized by measurable perturbations in autonomic regulation, electrical rhythm dynamics, hemodynamic control, thrombo-inflammatory balance, or neural resilience. Importantly, BHIWs are not synonymous with disease presence; rather, they denote intervals during which compensatory buffering mechanisms may weaken, variability architecture may reorganize, and cross-organ coupling may become more fragile.[74,75] Throughout this review, the term "window" therefore refers to a proposed inferential construct rather than a clinically validated diagnostic entity. The novelty of the BHIW construct lies not in individual variability metrics, which are well established, but in the structured integration of cross-domain temporal convergence as a state-based vulnerability model.

Under this model, events such as ischemic stroke, syncope, AF onset, malignant ventricular arrhythmia, and cognitive decompensation are proposed as possible clinical contexts in which regulatory redundancy may become transiently compromised.[76,77] This association remains hypothetical; the framework instead provides a structured approach for testing whether temporal convergence across physiological axes carries incremental predictive value.

We propose a taxonomy of BHIWs organized according to dominant physiological domain, recognizing that in

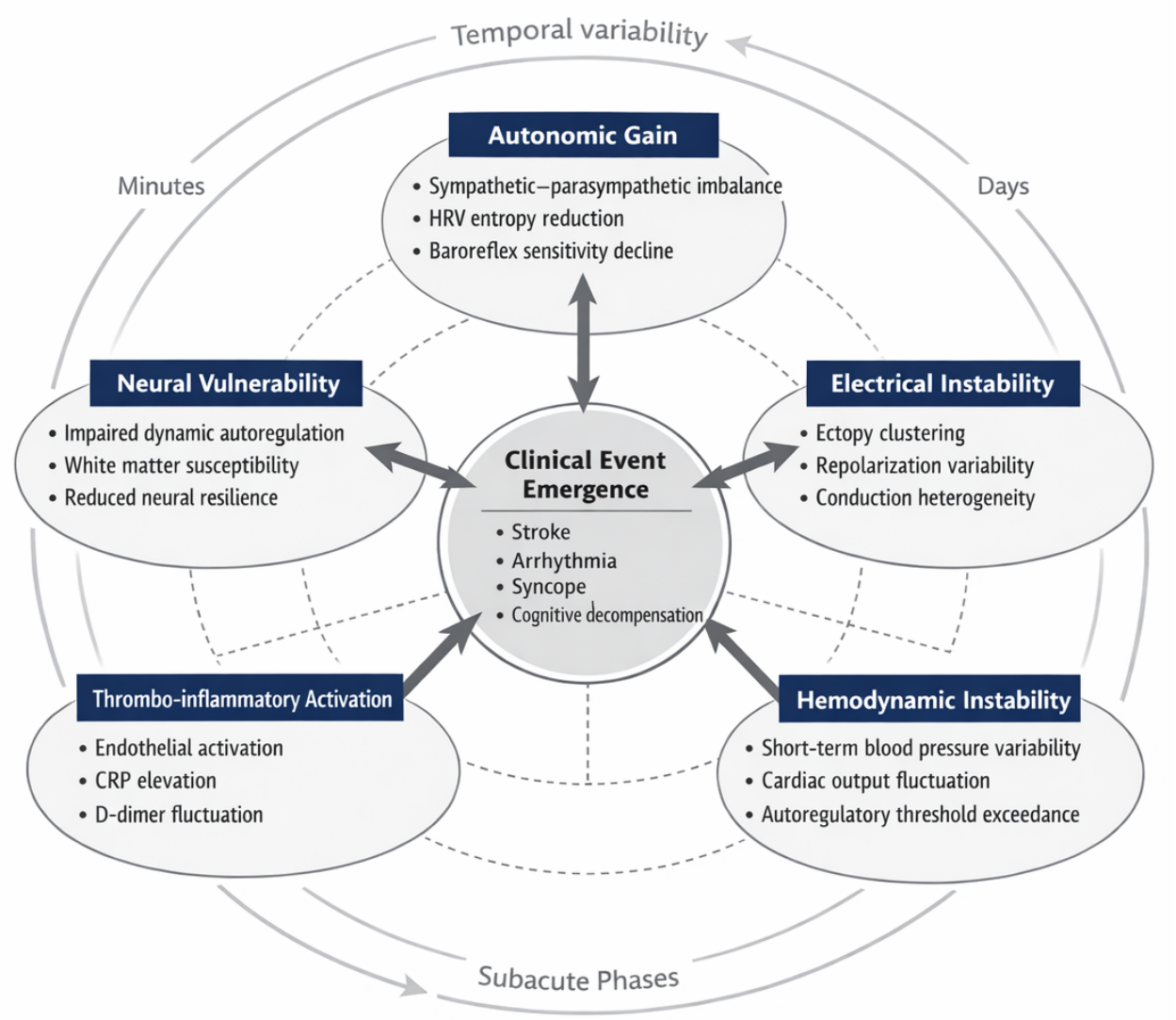


Figure 2. The brain–heart instability framework: coupled excitable systems and temporal vulnerability. The framework conceptualizes neurocardiovascular events as potentially emerging during temporally bounded reductions in cross-organ stability, a hypothesis that requires prospective validation. Five interacting physiological domains, namely autonomic gain, electrical instability, hemodynamic instability, thrombo-inflammatory activation, and neural vulnerability, are proposed to converge toward a candidate transient state of heightened vulnerability. Radial arrows represent coordinated destabilization, while dashed inter-domain links denote bidirectional interaction among regulatory axes. The outer temporal ring emphasizes that instability unfolds across minutes to subacute phases. Clinical events are hypothesized to arise preferentially during convergence of destabilizing axes rather than from isolated static risk factors. For research purposes, such convergence should be prespecified using temporal alignment, magnitude of deviation from baseline, minimum duration or recurrence criteria, and rules for handling discordant signals. Original figure created by the author for this article.

practice these domains may overlap and interact. The structured domain taxonomy is summarized in Figure 3.

To avoid conflating evidence levels, the taxonomy below distinguishes between established physiological or clinical associations and the more speculative claim that these associations define temporally bounded cross-organ instability windows. In Table 1, individual mechanisms and measurable signals are treated as evidence-supported where appropriate, whereas cross-domain convergence and window-based prediction are treated as investigational.

A structured summary of the proposed BHIW taxonomy, including candidate mechanisms, measurable signals, clinical associations, current evidence maturity, and whether each component is clinically measurable or

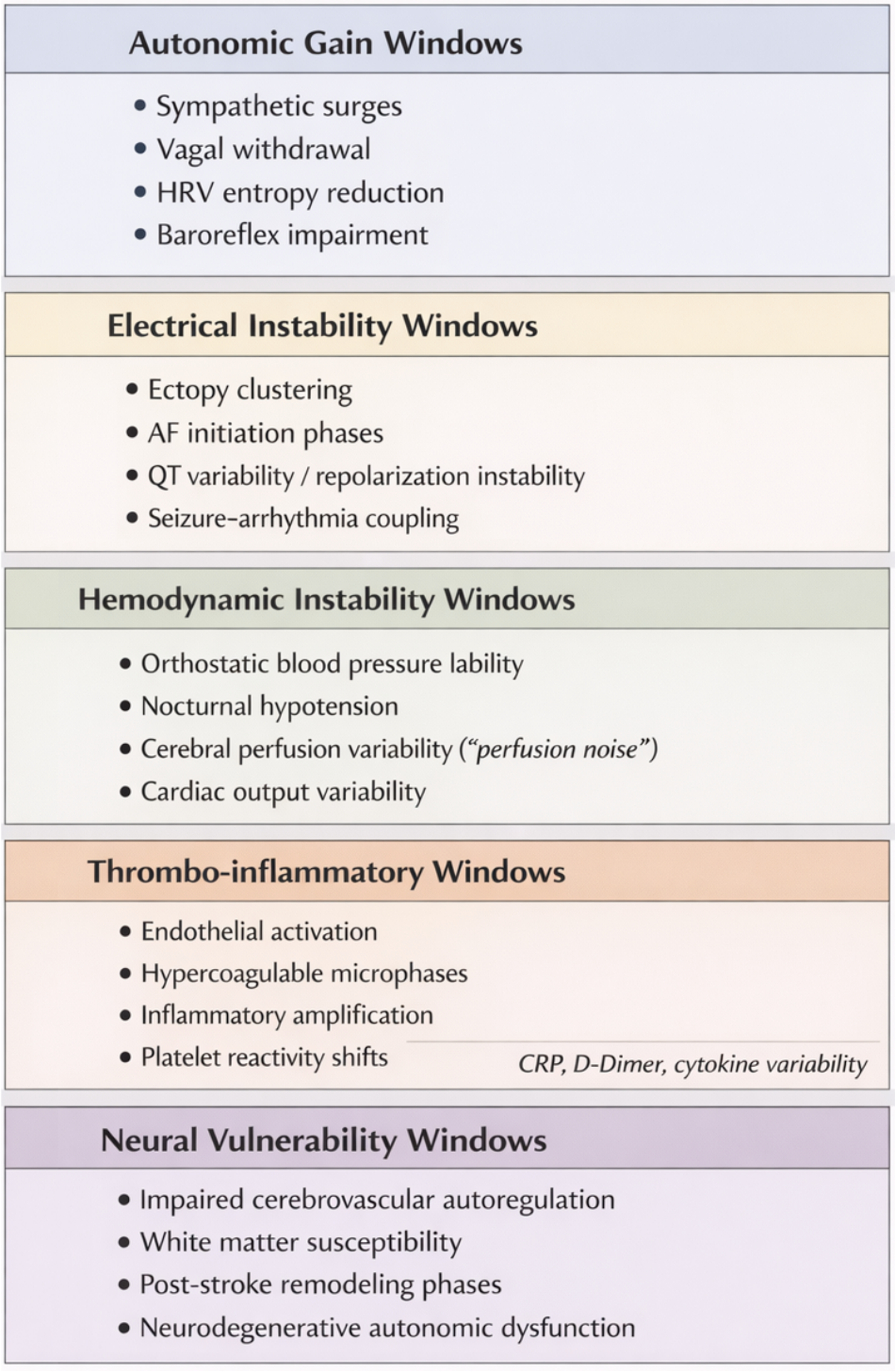


Figure 3. Taxonomy of brain–heart instability windows across physiological domains. Brain–heart instability windows (BHIWs) are categorized according to dominant physiological axis: autonomic gain, electrical instability, hemodynamic instability, thrombo-inflammatory activation, and neural vulnerability. Each domain reflects temporally bounded reductions in regulatory stability. Although presented discretely for conceptual clarity, domains frequently overlap and may converge during periods of heightened vulnerability. The taxonomy provides a structured framework for empirical investigation and cross-domain signal alignment. Original figure created by the author for this article.
Abbreviations: AF: Atrial fibrillation; CRP: C-reactive protein; HRV: Heart-rate variability.

primarily research-stage within the BHIW framework, is provided in Table 1.

For conceptual clarity, these domains may be broadly grouped into four interacting categories: regulatory (autonomic–electrical), hemodynamic, thrombo-inflammatory, and neural vulnerability axes. The more granular distinctions below are presented for mechanistic specificity rather than categorical rigidity.

4.1. Autonomic gain windows

Autonomic gain windows refer to intervals during which sympathetic–parasympathetic balance is acutely or subacutely altered, potentially amplifying downstream electrical and hemodynamic variability. Given the central role of autonomic modulation in regulating cardiac excitability, vascular tone, and cerebral perfusion, even modest shifts in autonomic gain may influence cross-organ stability.

Table 1. Brain–heart instability windows: mechanisms, signals, clinical associations, and translational status

Window type	Core mechanism	Representative measurable signals	Clinical measurability/ Research status	Illustrative clinical manifestations	Current evidence maturity
Autonomic gain window	Transient sympathetic–parasympathetic imbalance leading to reduced regulatory buffering	HRV entropy reduction; nonlinear HRV metrics; baroreflex sensitivity decline; autonomic tone shifts	Clinically measurable in part through HRV, autonomic testing, and baroreflex assessment; BHIW classification based on temporal convergence remains research-stage.	AF initiation, blood pressure lability, orthostatic intolerance	Moderate: established associations; dynamic convergence hypothesis remains investigational
Electrical instability window	Reduced excitability threshold, repolarization heterogeneity, conduction variability	Ectopy clustering density; AF episode aggregation; QT variability; beat-to-beat repolarization dispersion	Clinically measurable through ECG, ambulatory rhythm monitoring, patch monitoring, and implantable loop recorders; interpretation as a temporally bounded BHIW remains investigational.	AF onset, ventricular arrhythmia, ictal arrhythmia	Established in cardiology; cross-organ coupling hypothesis remains emerging
Hemodynamic instability window	Perfusion variability exceeding autoregulatory capacity	Short-term BP variability; orthostatic oscillatory responses; cardiac output variability spikes; nocturnal hypotension patterns	Clinically measurable through office/ambulatory BP monitoring, beat-to-beat BP testing, tilt-table testing, and orthostatic assessment; dynamic window prediction remains research-stage.	Syncope, including vasovagal syncope as a mixed autonomic–hemodynamic event; transient cerebral hypoperfusion; silent ischemic injury	Moderate: strong variability data; window construct remains investigational
Thrombo-inflammatory window	Transient endothelial activation and procoagulant amplification	CRP elevation; D-dimer fluctuation; platelet reactivity shifts; cytokine variability	Clinically measurable in part through CRP, D-dimer, coagulation indices, platelet assays, and inflammatory markers; temporally aligned thrombo-inflammatory window modeling remains investigational.	Embolic stroke, microembolism susceptibility	Emerging: biological plausibility established; temporal clustering requires validation
Neural vulnerability window	Impaired cerebrovascular autoregulation or reduced neural resilience	White matter hyperintensity burden; impaired dynamic autoregulation metrics; cognitive performance variability	Clinically measurable in part through MRI markers, dynamic autoregulation testing, cognitive assessment, and autonomic evaluation; BHIW-based temporal vulnerability classification remains research-stage.	Cognitive decline, post-stroke arrhythmogenesis, perfusion-sensitive injury	Established in neurology as substrate evidence; temporal window hypothesis remains investigational

Abbreviations: AF: Atrial fibrillation; BHIW: Brain–heart instability window; BP: Blood pressure; CRP: C-reactive protein; ECG: Electrocardiogram; HRV: Heart-rate variability; MRI: Magnetic resonance imaging.

4.1.1. Sympathetic surges

Acute sympathetic activation—precipitated by emotional stress, sleep deprivation, systemic inflammation, infection, pain, or metabolic perturbation—can increase sinus rate, shorten atrial refractory periods, enhance triggered activity, elevate blood pressure variability, and alter vascular resistance.[78,79] Such surges may transiently lower the threshold for arrhythmia initiation and influence cerebral perfusion dynamics, particularly in individuals with impaired autoregulation. Sympathetic predominance may also interact with inflammatory and coagulation pathways, suggesting potential mechanistic overlap between autonomic and thrombotic axes.

4.1.2. Vagal withdrawal

Parasympathetic withdrawal diminishes heart-rate variability and attenuates inhibitory modulation of atrioventricular conduction and atrial excitability.[80,81] Reduced vagal tone has been associated with adverse cardiovascular outcomes and increased arrhythmic susceptibility.[76,82] From a systems perspective, vagal withdrawal may reflect reduced regulatory buffering capacity. Within the BHIW construct, such shifts may signal heightened autonomic instability.

4.1.3. Baroreflex impairment

The arterial baroreflex provides rapid negative feedback control of blood pressure fluctuations. Transient or chronic reductions in baroreflex sensitivity permit exaggerated oscillations in systolic and diastolic pressure, contributing to orthostatic instability and cerebral perfusion variability.[83,84] During intervals of reduced baroreflex buffering, autonomic perturbations may translate more directly into hemodynamic variability.

4.1.4. HRV entropy reduction

Beyond conventional time-domain and frequency-domain HRV metrics, nonlinear measures—such as approximate entropy, sample entropy, detrended fluctuation analysis, and multiscale complexity indices—capture the adaptability of autonomic control systems. Reduced variability complexity has been associated with diminished physiological resilience and adverse cardiovascular outcomes.[76,82,85] Within the BHIW framework, reductions in entropy may serve as candidate digital markers of autonomic gain windows, reflecting decreased adaptability and increased susceptibility.

Sick sinus syndrome requires separate interpretation. Although sinus-node dysfunction may be associated with reduced or abnormal HRV complexity, this pattern should not be interpreted as a purely autonomic entropy signal. In sick sinus syndrome, reduced variability may reflect intrinsic sinoatrial node disease, sinus pauses, chronotropic incompetence, or bradycardia–tachycardia transitions rather than autonomic gain alone. Within the BHIW framework, sick sinus syndrome is therefore best considered primarily within electrical instability windows, while recognizing that it may secondarily influence autonomic and hemodynamic stability.

Collectively, autonomic gain windows describe intervals during which regulatory amplification mechanisms may predispose the coupled system to instability. When coinciding with electrical or hemodynamic perturbations, such intervals could plausibly amplify vulnerability.

4.2. Electrical instability windows

Electrical instability windows describe intervals characterized by transient reductions in rhythm stability within cardiac and, in certain contexts, neural excitable networks. These windows may involve altered excitability thresholds, repolarization heterogeneity, conduction variability, or synchronization disturbances.

4.2.1. Ectopy clustering

Premature atrial and ventricular contractions often demonstrate temporal clustering rather than uniform distribution.[82,86] Periods of increased ectopic density may reflect transient electrical irritability, conduction heterogeneity, or autonomic modulation shifts. In susceptible individuals, ectopy clustering has been observed to precede sustained atrial or ventricular arrhythmias[86-88], suggesting a temporally bounded phase of electrical vulnerability.

4.2.2. Atrial fibrillation initiation phases

Atrial fibrillation frequently manifests in paroxysmal bursts with identifiable pre-initiation features, including autonomic fluctuations, premature atrial activity, and localized conduction slowing.[87-89] These patterns may represent discrete electrical instability windows during which atrial substrate vulnerability is transiently heightened. Emerging data suggest that thromboembolic risk may fluctuate in relation to arrhythmic clustering and substrate activation rather than being evenly distributed across AF burden.[77]

4.2.3. Sinus node dysfunction and sick sinus syndrome

Sick sinus syndrome represents an intrinsic rhythm-generation disorder involving sinoatrial node dysfunction, sinus pauses, chronotropic incompetence, and, in some patients, alternating bradycardia–tachycardia patterns. Within the BHIW taxonomy, it is best categorized primarily as an electrical instability window because the dominant

abnormality involves impaired pacemaker function and rhythm stability. However, its clinical consequences may extend into the hemodynamic domain when pauses or bradyarrhythmia reduce cardiac output and cerebral perfusion. HRV entropy reduction in this setting should therefore be interpreted cautiously, because reduced complexity may reflect intrinsic sinus-node disease rather than autonomic dysregulation alone.

4.2.4. QT variability and repolarization instability

Dynamic fluctuations in QT interval duration and repolarization dispersion have been associated with increased arrhythmic susceptibility.[90,91] Importantly, repolarization instability may be reflected in beat-to-beat variability and temporal heterogeneity rather than solely in mean QT prolongation. Such variability may indicate reduced electrical coherence within the myocardial network.

4.2.5. Seizure–arrhythmia coupling

Electrical instability within neural networks can influence cardiac rhythm through central autonomic pathways. Seizure activity and cortical discharges have been associated with ictal bradyarrhythmias, tachyarrhythmias, and repolarization changes.[92,93] These observations support the concept that electrical perturbations in one excitable system may transiently influence stability in the other.

Electrical instability windows therefore describe intervals during which excitability thresholds may be reduced and synchronization more fragile. When coincident with autonomic gain or hemodynamic instability windows, these phases may plausibly contribute to increased cerebrovascular or arrhythmic vulnerability. Further empirical investigation will be necessary to determine the predictive validity of these proposed temporal categories.

4.3. Hemodynamic instability windows

Hemodynamic instability windows may arise when fluctuations in systemic blood pressure, cardiac output, or vascular resistance exceed the compensatory buffering capacity of cardiovascular and cerebrovascular autoregulatory mechanisms. Because cerebral perfusion is closely linked to systemic hemodynamics, even transient perturbations may influence neurological vulnerability. Within the brain–heart instability framework, these windows describe intervals during which perfusion reliability may be reduced and flow–metabolism coupling potentially becomes less stable.

4.3.1. Orthostatic blood pressure lability

Orthostatic hypotension is a recognized contributor to syncope, falls, and cerebral hypoperfusion syndromes.[94-96] Beyond overt hypotension, subtle orthostatic lability—characterized by exaggerated beat-to-beat variability, oscillatory systolic pressure responses, or delayed baroreflex compensation—may indicate transient limitations in autonomic or vascular buffering systems.[97,98] Such dynamic lability may not meet formal diagnostic thresholds yet could produce intermittent reductions in cerebral perfusion pressure. In individuals with impaired vascular compliance, small vessel disease, or reduced autoregulatory reserve, these transient perfusion shifts may plausibly represent hemodynamic instability intervals associated with symptomatic or subclinical consequences.

Vasovagal syncope is best categorized as a mixed autonomic gain–hemodynamic instability phenomenon. Its initiating mechanism is primarily autonomic, involving reflex-mediated changes in sympathetic withdrawal, vagal activation, vasodilation, and/or bradycardia. However, its clinical expression occurs through hemodynamic collapse and transient cerebral hypoperfusion. Within the BHIW framework, vasovagal syncope may therefore be placed primarily under autonomic gain windows, with downstream expression as a hemodynamic instability window when compensatory vascular and cardiac responses fail to preserve cerebral perfusion.

4.3.2. Nocturnal hypotension

Sleep involves circadian modulation of autonomic tone and blood pressure regulation. While physiological nocturnal dipping is generally adaptive, excessive dipping or paradoxical nocturnal hypotension has been associated with ischemic stroke risk, white matter progression, and cognitive decline in certain populations.[99,100] During sleep, reduced sympathetic tone and altered vascular responsiveness may transiently narrow perfusion margins. In the presence of carotid stenosis, microvascular disease, or impaired autoregulation, nocturnal hemodynamic shifts may coincide with periods of increased cerebral susceptibility.

4.3.3. Cerebral perfusion variability ("perfusion noise")

Cerebral blood flow is ordinarily stabilized through autoregulatory mechanisms that buffer systemic pressure fluctuations within a defined range.[13,101] However, aging, hypertension, diabetes, small vessel disease, and neurodegenerative conditions can impair autoregulatory efficiency.[13,102,103] Under such circumstances, systemic hemodynamic variability may translate into amplified cerebral perfusion variability—conceptualized here as "perfusion noise." These microfluctuations have been associated with endothelial stress, oxidative signaling, and

metabolic strain[102-104] and may contribute cumulatively to microvascular injury. Importantly, such variability may remain clinically silent while potentially influencing long-term structural integrity.

4.3.4. Cardiac output variability

Transient reductions or oscillations in cardiac output—arising from arrhythmic pauses, paroxysmal atrial fibrillation, bradyarrhythmias, or tachyarrhythmias—can alter cerebral perfusion dynamics.[94,98,104] Even brief output fluctuations may interact with vulnerable cerebrovascular substrates, particularly in individuals with impaired collateral circulation or limited cerebrovascular reserve. In this context, electrical variability and hemodynamic variability may become mechanistically intertwined.

Hemodynamic instability windows therefore describe intervals during which systemic flow reliability may be reduced. When temporally aligned with autonomic or thrombo-inflammatory perturbations, these windows could plausibly contribute to increased symptomatic or subclinical risk. Further investigation will be required to define their predictive significance.

4.4. Thrombo-inflammatory windows

Beyond electrophysiologic and hemodynamic variability, cerebrovascular vulnerability is influenced by dynamic changes in endothelial function, coagulation balance, and inflammatory signaling. Thrombo-inflammatory windows refer to temporally bounded shifts in vascular biology that may transiently favor prothrombotic states.

4.4.1. Endothelial activation

The endothelium regulates vascular tone, platelet adhesion, anticoagulant balance, and inflammatory signaling. Acute stressors—including infection, oxidative injury, metabolic disturbance, and systemic inflammation—can induce endothelial activation, characterized by increased expression of adhesion molecules and procoagulant mediators.[105,106] Such activation may transiently shift the vascular milieu toward a prothrombotic profile. In the setting of AF or turbulent atrial flow, endothelial activation could plausibly lower the threshold for thrombus formation.

4.4.2. Hypercoagulable microphases

Coagulation dynamics fluctuate in response to circadian rhythms, cytokine signaling, autonomic modulation, and metabolic stress.[107,108] Variability in platelet aggregation potential, fibrinogen levels, and thrombin generation capacity may produce short-lived hypercoagulable microphases that are not captured by static laboratory measurements. When coincident with electrical or hemodynamic variability—such as arrhythmic clustering—these microphases may contribute to transient increases in embolic susceptibility.

4.4.3. Inflammatory amplification

Inflammatory signaling has bidirectional effects on cardiac electrophysiology and vascular thrombogenicity.[109,110] Cytokine surges have been associated with ion-channel modulation, altered atrial conduction properties, and changes in refractory dynamics, while simultaneously influencing platelet activation and endothelial function. These interactions suggest potential cross-domain amplification during inflammatory states.

Clinically, inflammatory amplification may also be relevant in conditions where valvular or endocardial inflammation increases embolic vulnerability. Infective endocarditis represents a prototypical example in which infection-driven endothelial injury, vegetation formation, systemic inflammation, and embolic risk intersect. Non-infective immune-mediated conditions may provide related but mechanistically distinct examples. Rheumatic fever and rheumatic valvular inflammation can promote endothelial and valvular injury, inflammatory remodeling, and thromboembolic susceptibility, while systemic lupus erythematosus may be associated with Libman–Sacks endocarditis, antiphospholipid-related thrombosis, and sterile valvular vegetations. These examples do not establish BHIWs directly, but they illustrate how inflammatory, endothelial, valvular, and coagulation pathways may converge to create temporally variable thromboembolic vulnerability.

4.4.4. Platelet reactivity shifts

Platelet responsiveness varies across circadian cycles and inflammatory conditions.[105,111] Enhanced platelet reactivity during acute stress or infection may transiently elevate embolic propensity, particularly in individuals with underlying arrhythmic substrate or endothelial dysfunction.

Thrombo-inflammatory windows thus describe intervals during which vascular and coagulation equilibrium may shift toward increased vulnerability. These shifts may be clinically silent yet could acquire significance when aligned with concurrent electrical or hemodynamic instability.

4.5. Neural vulnerability windows

The final axis of the instability taxonomy concerns intrinsic cerebral susceptibility. Neural Vulnerability Windows refer to intervals during which the brain's capacity to buffer perfusion variability, embolic burden, or autonomic perturbation may be reduced.

4.5.1. Impaired cerebrovascular autoregulation

Cerebral autoregulation maintains relatively stable blood flow across varying systemic pressures. Stroke, traumatic injury, chronic hypertension, small vessel disease, and neurodegenerative processes can impair this buffering capacity.[112,113] During such intervals, systemic blood pressure or cardiac output variability may exert greater influence on cerebral perfusion. Under these conditions, otherwise modest hemodynamic shifts may carry increased physiological significance.

4.5.2. White matter susceptibility

White matter is particularly sensitive to microvascular instability and perfusion variability. Blood pressure variability and endothelial dysfunction have been associated with progression of white matter hyperintensities and microstructural injury.[114-116] Instability windows characterized by perfusion variability or thrombo-inflammatory activation may contribute to cumulative subclinical injury over time.

4.5.3. Post-stroke remodeling phases

Following acute cerebrovascular injury, dynamic remodeling occurs across autonomic, inflammatory, and electrophysiologic domains.[17,56,117] The post-stroke period has been associated with sympathetic predominance, reduced HRV, and increased arrhythmic susceptibility. These remodeling phases may represent intervals of heightened cross-organ vulnerability.

4.5.4. Neurodegenerative autonomic dysfunction

In neurodegenerative disorders such as Parkinson's disease, Lewy body dementia, and multiple system atrophy, progressive autonomic impairment alters blood pressure regulation, cardiac variability, and baroreflex sensitivity.[118-120] These changes may reduce systemic buffering capacity and increase susceptibility to orthostatic hypotension, perfusion variability, and arrhythmia.

4.5.5. Integrative synthesis: temporal convergence of instability axes

Across autonomic, electrical, hemodynamic, thrombo-inflammatory, and neural domains, several forms of physiological variability are temporally structured rather than uniformly distributed. The BHIW framework proposes that some of these fluctuations may cluster into phases of reduced regulatory buffering and fragile cross-organ coupling. Whether such clustering provides incremental value for predicting stroke, syncope, arrhythmia, or cognitive outcomes remains to be determined through longitudinal validation.

5. The brain–heart measurement stack

Having defined the instability construct and domain taxonomy, we next describe the "brain–heart measurement stack," a multilevel architecture for mapping candidate BHIWs onto measurable physiological signals across temporal and biological scales. The stack integrates continuous digital monitoring, structured physiologic assessment, and structural–biological anchors, as illustrated in Figure 4.

The measurement stack is grounded in three premises. First, many physiological signals relevant to neurocardiovascular risk are temporally dynamic, potentially evolving over minutes, hours, or days rather than existing as static attributes. Second, no single biomarker fully captures cross-organ resilience within coupled excitable systems. Third, inferential confidence in a putative instability window increases when coordinated deviations emerge across multiple physiological layers. In this formulation, dynamic vulnerability is best approached as a multiscale phenomenon requiring layered observation rather than reliance on isolated metrics.

5.1. Continuous digital signal layer

At the highest temporal resolution, continuous digital monitoring may provide early signatures of evolving instability. Wearable sensors, implantable loop recorders, ambulatory electrocardiography, and remote physiological monitoring technologies enable longitudinal characterization of variability architecture rather than single-timepoint measurements.

Nonlinear HRV metrics represent a particularly informative domain. While conventional time- and frequency-domain measures summarize autonomic tone, nonlinear indices—such as entropy-based measures, fractal scaling exponents, and multiscale complexity analyses—capture aspects of autonomic adaptability. Reductions in variability complexity have been associated with diminished physiological resilience and adverse cardiovascular outcomes.[121,122] Within the brain–heart instability framework, such reductions may reflect early autonomic destabilization preceding overt electrical or hemodynamic perturbation.

Continuous rhythm monitoring similarly permits characterization of electrical variability beyond binary arrhythmia detection. Ectopy clustering density, AF episode aggregation, sinus pause burden, bradycardia–tachycardia patterns, chronotropic response, beat-to-beat interval dispersion, and dynamic repolarization variability may indicate transient reductions in rhythm stability.[123,124] Temporal clustering patterns may represent

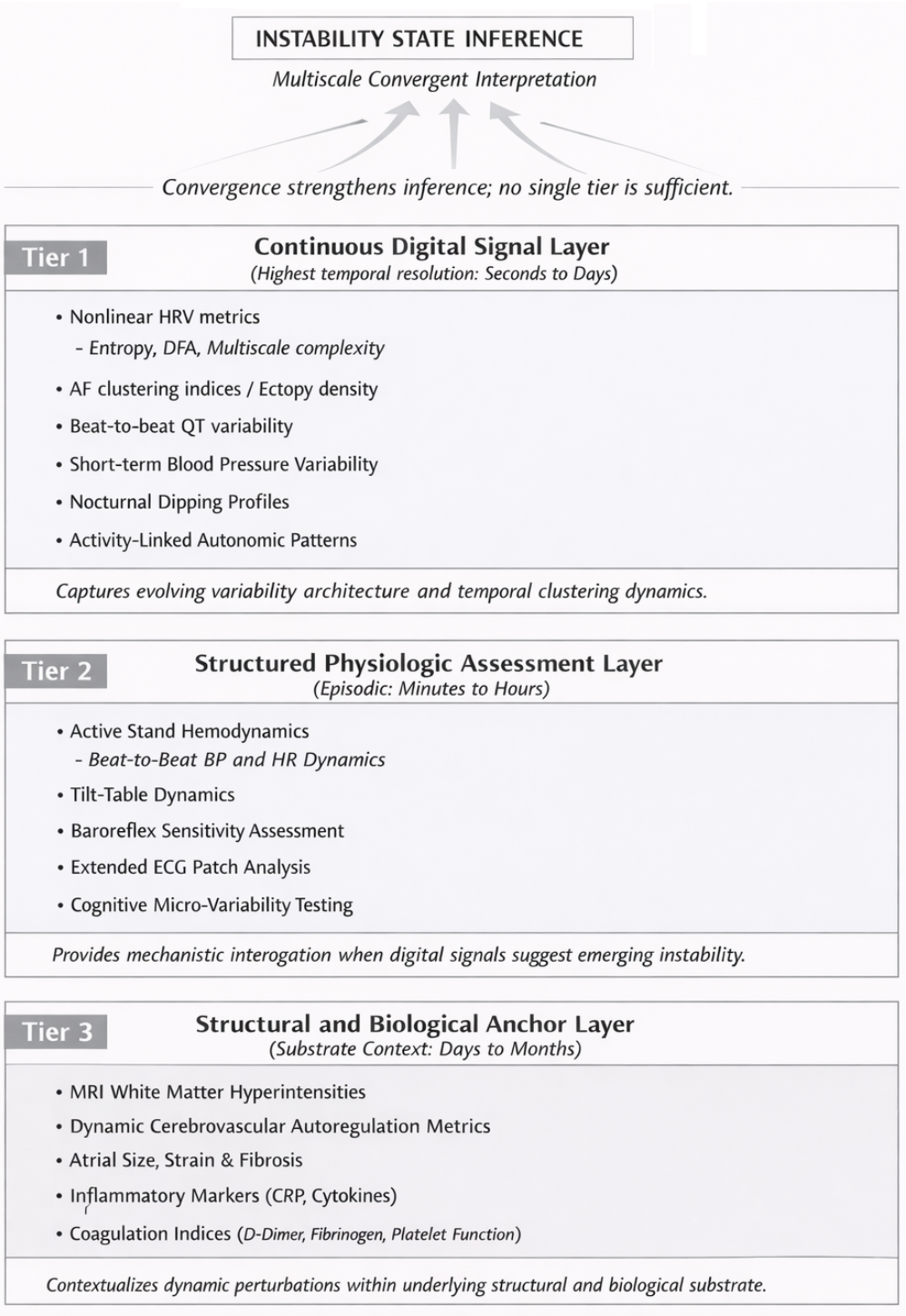


Figure 4. Multiscale measurement architecture for detecting brain–heart instability windows. The brain–heart measurement stack integrates continuous digital signals, structured physiologic assessments, and structural–biological anchors across temporal scales. Candidate instability states are inferred when coordinated deviations emerge across tiers rather than within isolated domains; this inference remains probabilistic and investigational. The framework conceptualizes dynamic neurocardiovascular vulnerability as a multiscale phenomenon requiring layered observation and cross-domain convergence. Original figure created by the author for this manuscript.

Abbreviations: AF: Atrial fibrillation; BP: Blood pressure; CRP: C-reactive protein; DFA: Detrended fluctuation analysis; ECG: Electrocardiogram; HR: Heart rate; MRI: Magnetic resonance imaging.

candidate electrical instability windows even when overall arrhythmia burden appears modest.

Circadian and sleep-associated autonomic dynamics offer an additional dimension of state assessment. Wearable-derived nocturnal HRV profiles, blood pressure dipping patterns, and autonomic transitions during sleep reflect integrated central–peripheral modulation. Deviations from expected nocturnal profiles—including exaggerated dipping or autonomic flattening—may correspond to evolving hemodynamic or electrical instability windows.[100,125]

Emerging cuffless blood pressure estimation technologies and pulse transit–based proxies allow approximation of short-term variability outside the clinic. Oscillatory variability spikes or altered variability structure may reflect hemodynamic fragility not captured by clinic-based averages.[126,127] Activity-linked autonomic response profiling further informs buffering capacity under physiological stress. Altered heart-rate responsiveness to standardized activity patterns may signal impaired autonomic reserve.[128] Collectively, the digital layer offers continuous mapping of physiological variability patterns that may precede overt clinical destabilization.

5.2. Structured physiologic assessment layer

Continuous digital signals provide temporal resolution, but structured physiologic testing offers mechanistic specificity. This intermediate layer refines interpretation of digital variability through controlled interrogation of regulatory systems.

Active stand testing with beat-to-beat hemodynamic monitoring enables quantitative assessment of baroreflex sensitivity and orthostatic compensation. Abnormal recovery slopes, exaggerated oscillatory responses, or reduced baroreflex gain may be consistent with Autonomic gain or hemodynamic instability windows.[129,130]

Tilt-table testing similarly permits controlled evaluation of autonomic–vascular responsiveness. Beyond categorical syncope diagnosis, dynamic tilt signatures—including latency to instability and recovery dynamics—may reflect underlying buffering fragility within cross-organ regulatory networks.[131,132]

Extended electrocardiogram (ECG) patch monitoring enhances detection of arrhythmia clustering and repolarization variability, potentially improving operationalization of electrical instability windows relative to single-timepoint electrocardiography.[133,134]

Brief, repeatable cognitive assessments administered digitally may detect micro-fluctuations in executive function or processing speed. Variability in performance, rather than mean score alone, may serve as a surrogate indicator of neural vulnerability windows in selected populations.[135,136]

This intermediate layer thus strengthens mechanistic interpretation when digital signals suggest evolving instability.

5.3. Structural and biological anchor layer

At a slower temporal scale but with higher substrate specificity, structural and biological markers contextualize dynamic perturbations within underlying pathophysiological frameworks.

Systemic inflammatory markers, including C-reactive protein (CRP) and cytokine profiles, provide indices of thrombo-inflammatory tone and endothelial activation.[109,137,138] Temporal elevations may align with thrombo-inflammatory windows, particularly in the presence of arrhythmic clustering or systemic stress.

Coagulation indices—including D-dimer, fibrinogen levels, platelet function assays, and thrombin generation parameters—reflect dynamic shifts in prothrombotic balance.[139] Relative elevations may correspond to transient hypercoagulable microphases that converge with electrical or hemodynamic instability.

Neuroimaging markers such as white matter hyperintensities and microstructural integrity measures provide structural evidence of cumulative perfusion variability.[116,140] Longitudinal progression may support the hypothesis of repeated hemodynamic instability windows.

Cardiac structural remodeling—including atrial enlargement, strain abnormalities, and fibrosis burden—defines the arrhythmic substrate upon which transient perturbations operate.[141,142] Such substrate characteristics may amplify the impact of dynamic instability.

These anchors help distinguish physiologic fluctuation from biologically meaningful destabilization and provide substrate context for interpreting dynamic signals. A structured overview of the multilevel domains, representative metrics, temporal scales, clinical measurability, and current validation maturity within the BHIW framework is provided in Table 2.

Thus, the proposed measurement stack does not require entirely new categories of clinical measurement; rather, it proposes a research-stage method for temporally aligning already measurable signals across physiological domains.

5.4. Convergence across measurement layers

The brain–heart measurement stack is best understood as a multilevel inferential framework rather than a checklist

of independent tests. For research purposes, a candidate instability window should not be inferred from a single isolated abnormality. Instead, inferential confidence increases when deviations are temporally aligned across at least two physiologically coherent domains, such as autonomic–electrical, autonomic–hemodynamic, electrical–thrombo-inflammatory, or hemodynamic–neural patterns. A single-domain deviation may be considered only when it is large, persistent or recurrent, biologically interpretable, and supported by relevant substrate information.

For example, reduction in HRV complexity at the digital layer, impaired orthostatic compensation

Table 2. Multilevel measurement domains for detection of brain–heart instability windows: clinical measurability and validation maturity

Window type	Core mechanism	Representative measurable signals	Clinical measurability / Research status	Illustrative clinical manifestations	Current evidence maturity
Autonomic gain window	Transient sympathetic–parasympathetic imbalance leading to reduced regulatory buffering	HRV entropy reduction; nonlinear HRV metrics; baroreflex sensitivity decline; autonomic tone shifts	Clinically measurable in part through HRV, autonomic testing, and baroreflex assessment; BHIW classification based on temporal convergence remains research-stage.	AF initiation, blood pressure lability, orthostatic intolerance	Moderate: established associations; dynamic convergence hypothesis remains investigational
Electrical instability window	Reduced excitability threshold, repolarization heterogeneity, conduction variability	Ectopy clustering density; AF episode aggregation; sinus pauses; chronotropic incompetence; bradycardia–tachycardia patterns; QT variability; beat-to-beat repolarization dispersion	Clinically measurable through ECG, ambulatory rhythm monitoring, patch monitoring, and implantable loop recorders; interpretation as a temporally bounded BHIW remains investigational.	AF onset, sick sinus syndrome, bradyarrhythmic syncope, ventricular arrhythmia, ictal arrhythmia	Established in cardiology; cross-organ coupling hypothesis remains emerging
Hemodynamic instability window	Perfusion variability exceeding autoregulatory capacity	Short-term BP variability; orthostatic oscillatory responses; cardiac output variability spikes; nocturnal hypotension patterns	Clinically measurable through office/ambulatory BP monitoring, beat-to-beat BP testing, tilt-table testing, and orthostatic assessment; dynamic window prediction remains research-stage.	Syncope, transient cerebral hypoperfusion, silent ischemic injury	Moderate: strong variability data; window construct remains investigational
Thrombo-inflammatory window	Transient endothelial activation and procoagulant amplification	CRP elevation; D-dimer fluctuation; platelet reactivity shifts; cytokine variability	Clinically measurable in part through CRP, D-dimer, coagulation indices, platelet assays, and inflammatory markers; temporally aligned thrombo-inflammatory window modeling remains investigational.	Embolic stroke, microembolism susceptibility	Emerging: biological plausibility established; temporal clustering requires validation
Neural vulnerability window	Impaired cerebrovascular autoregulation or reduced neural resilience	White matter hyperintensity burden; impaired dynamic autoregulation metrics; cognitive performance variability	Clinically measurable in part through MRI markers, dynamic autoregulation testing, cognitive assessment, and autonomic evaluation; BHIW-based temporal vulnerability classification remains research-stage.	Cognitive decline, post-stroke arrhythmogenesis, perfusion-sensitive injury	Established in neurology as substrate evidence; temporal window hypothesis remains investigational

Abbreviations: AF: Atrial fibrillation; BHIW: Brain–heart instability window; BP: Blood pressure; CRP: C-reactive protein; ECG: Electrocardiogram; HRV: Heart-rate variability; MRI: Magnetic resonance imaging.

during structured testing, and concurrent elevation of inflammatory markers may collectively suggest an active cross-organ destabilization phase if they occur within a prespecified temporal horizon and exceed individualized baseline variability. Conversely, if one marker deviates while other domains remain stable or move in a compensatory direction, the pattern should be classified as indeterminate rather than as a confirmed instability window.

This convergence-based approach is consistent with systems biology perspectives, wherein state transitions are characterized by multiscale perturbations rather than single linear shifts. Within neurocardiology, such integration may provide a structured pathway for interpreting continuous monitoring data within a mechanistic framework.

5.5. Implications for dynamic neurocardiovascular risk modeling

Conventional risk stratification frameworks are predominantly static, relying on demographic variables and structural comorbidities. In contrast, the brain–heart measurement stack supports a complementary approach focused on dynamic state assessment.

Instability windows cannot be reliably inferred from isolated datapoints or averaged values alone. Instead, they require multidomain measurement across temporal gradients, integrating variability architecture with structural and biological context. This layered model may permit differentiation between chronic baseline risk and transient vulnerability amplification. For example, in a patient with paroxysmal atrial fibrillation, a period characterized by reduced HRV entropy, increased arrhythmic clustering, and concurrent elevation of inflammatory or coagulation markers could be operationalized as a candidate instability interval if the abnormalities exceed the individual's baseline variability, persist or recur over a prespecified time horizon, and demonstrate temporal overlap. Such a construct can be quantitatively defined and prospectively evaluated using predefined thresholds, rather than inferred retrospectively.

Operationalization of instability in this manner could support prospective testing of specific decision pathways, including adaptive rhythm monitoring intensity, selection of patients for extended post-stroke telemetry, timing of repeat orthostatic assessment, and identification of periods when supportive hemodynamic measures may be most relevant. In AF, combined rhythm clustering, autonomic shifts, and thrombo-inflammatory markers could be evaluated as research signals for intensified surveillance or adherence reinforcement, although not for changing anticoagulation outside validated protocols. The brain–heart measurement stack therefore provides a structured basis for testing whether cross-domain temporal signals can be linked to specific future clinical use cases rather than only to abstract risk modeling.

6. Clinical use cases: illustrative applications of the instability framework

The following clinical use cases are intended as illustrative applications of the BHIW framework rather than validation of the construct. They are based partly on analogical reasoning from established neurocardiovascular observations and should therefore be interpreted as hypothesis-generating examples. Each use case distinguishes established clinical observations from biologically plausible BHIW interpretations and currently unvalidated research propositions.

6.1. Use case 1: atrial fibrillation clustering and silent stroke vulnerability

Atrial fibrillation (AF) is traditionally assessed in terms of overall burden and cumulative thromboembolic risk. Evidence from rhythm monitoring suggests that AF episodes may occur in temporally clustered patterns rather than being randomly distributed.[143,144] Within the present framework, such clustering is interpreted cautiously as a possible marker of transient electrical instability within an already susceptible atrial substrate, rather than as direct evidence of a validated BHIW.

From the perspective of the BHIW framework, AF clustering may be considered a candidate use case for studying electrical instability windows. Concurrent autonomic shifts—particularly nocturnal sympathetic predominance or vagal withdrawal—have been associated with AF initiation patterns in selected populations.[88,145] Whether these autonomic patterns temporally align with arrhythmic clustering in a way that meaningfully alters short-term embolic vulnerability remains an open research question.

Emerging observational data raise the possibility that thromboembolic risk may not be uniformly distributed across time and may vary in relation to arrhythmic activity; however, this evidence remains preliminary and should not be interpreted as sufficient to guide episode-level stroke prediction or anticoagulation decisions.[146,147] Within the BHIW framework, periods characterized by arrhythmia clustering, autonomic perturbation, and prothrombotic shifts may be treated as candidate research intervals for studying microembolism vulnerability. This interpretation remains inferential and requires prospective validation with synchronized rhythm, autonomic, coagulation, and outcome monitoring.

This use case does not imply that stroke risk can currently be predicted at the level of individual AF episodes. It also does not support changing anticoagulation strategy outside guideline-directed care. Rather, it identifies a research question: whether integrating arrhythmic clustering dynamics with autonomic and thrombo-inflammatory markers improves understanding of temporal variability in thromboembolic susceptibility.

6.2. Use case 2: syncope and orthostatic collapse

Syncope and orthostatic intolerance provide a second use case for applying the BHIW framework. Orthostatic hypotension, impaired baroreflex sensitivity, and autonomic failure have well-established roles in transient cerebral hypoperfusion.[94,148,149]

Vasovagal syncope is therefore treated in this framework as a mixed use case: primarily an autonomic gain window at the level of reflex initiation, and a hemodynamic instability window at the level of clinical expression.

Within the proposed framework, episodes of syncope may correspond to hemodynamic instability windows characterized by rapid blood pressure variability, delayed compensatory responses, or transient baroreflex insufficiency. Beat-to-beat blood pressure monitoring has demonstrated that abrupt oscillatory instability may precede symptomatic collapse in susceptible individuals.[95,150]

In certain patients, particularly those with autonomic neuropathy or neurodegenerative disease, reduced buffering capacity may allow relatively minor perturbations to trigger abrupt perfusion drops. Such cases illustrate how transient reductions in regulatory reserve could culminate in overt clinical events.

This use case illustrates the distinction between baseline susceptibility and possible short-term hemodynamic vulnerability. However, whether discrete BHIWs can be prospectively identified before syncope remains to be tested.

6.3. Use case 3: post-stroke arrhythmogenesis

Acute cerebrovascular injury is frequently accompanied by alterations in autonomic tone and cardiac electrophysiology. Increased sympathetic activation, reduced heart-rate variability, and repolarization changes have been observed in the post-stroke period.[9,56,151] In some patients, these changes are associated with increased incidence of atrial or ventricular arrhythmias.

Within the BHIW framework, the post-stroke state is best framed as a use case for studying possible coupling among neural vulnerability, autonomic gain, and electrical instability domains. Structural brain injury—particularly involving insular or brainstem regions—may disrupt central autonomic regulation, thereby altering cardiac excitability thresholds.[152,153]

Secondary cardiac electrical instability in this context does not imply that stroke uniformly causes arrhythmia. Rather, it suggests that neural injury may transiently modify autonomic balance and electrophysiologic substrate, potentially increasing arrhythmic susceptibility during defined intervals.

This use case highlights the bidirectional nature of brain–heart interactions, while emphasizing that the BHIW interpretation remains a proposed research framework rather than evidence of a validated post-stroke prediction model.

6.4. Use case 4: neurodegenerative autonomic decline

Neurodegenerative disorders such as Parkinson's disease, Lewy body dementia, and multiple system atrophy frequently involve progressive autonomic dysfunction.[118,154] Impaired baroreflex sensitivity, orthostatic hypotension, and reduced HRV are common features.

Within this population, gradual loss of autonomic gain may reduce physiological buffering capacity. Flattening of cardiac variability patterns and impaired blood pressure regulation may represent chronic shifts toward reduced regulatory reserve. Superimposed stressors—such as dehydration, infection, or medication effects—may further narrow stability margins.

In this context, the BHIW framework should be applied cautiously. Instability windows may not always be sharply bounded and may instead appear as fluctuating vulnerability phases within a progressively impaired regulatory landscape. Cardiac variability flattening and orthostatic lability may serve as candidate measurable correlates, but their ability to define actionable vulnerability states remains unvalidated.[155,156]

This use case illustrates how chronic neurodegeneration may lower baseline resilience while still permitting superimposed transient instability phases that require prospective characterization.

6.5. Translational implications of clinical use cases

These clinical use cases are not intended to establish causal proof or clinical readiness of BHIWs. Rather, they identify settings in which established dynamic brain–heart interactions may be reorganized into testable temporal hypotheses.

Across AF, syncope, post-stroke states, and neurodegenerative autonomic dysfunction, a recurring pattern emerges: structural susceptibility coexists with temporally fluctuating physiological instability. Differentiating baseline risk from transient vulnerability may enhance mechanistic understanding and guide future empirical study.

Prospective validation will be required to determine whether identifying such windows improves predictive accuracy, therapeutic timing, or clinical outcomes. If validated, these use cases could inform specific research-tested decision pathways, such as adaptive rhythm monitoring intensity in AF, extended telemetry selection after stroke, anticipatory orthostatic support in patients with recurrent hemodynamic instability, or closer surveillance during neurodegenerative autonomic decompensation. Until such validation is available, these use cases should be regarded as research applications of a temporally structured instability framework, not as grounds for changing clinical management.

7. Digital integration and computational modeling

The conceptual framework of BHIWs gains practical relevance only if dynamic physiological data can be integrated, interpreted, and modeled in a structured manner. Advances in computational analytics, signal processing, and machine learning provide tools that may support such integration. However, these technologies should be viewed as methodological enablers rather than deterministic solutions.

Continuous physiological monitoring generates high-dimensional, temporally structured data streams. Translating these signals into clinically interpretable state assessments requires approaches capable of capturing variability architecture, temporal clustering, and cross-domain interaction.

7.1. Temporal clustering analysis

Many physiological events—including arrhythmic episodes, autonomic shifts, and blood pressure fluctuations—demonstrate non-random temporal distribution.[157,158] Statistical and computational techniques for clustering detection may identify periods during which event density exceeds baseline expectation.

Time-series segmentation methods, burst detection algorithms, and state-transition modeling frameworks could potentially be applied to identify candidate instability windows within continuous monitoring data. Importantly, such approaches would aim to characterize temporal structure rather than simply count cumulative burden.

At present, most clinical metrics summarize frequency or duration. Incorporating clustering analysis may provide a complementary dimension of temporal organization, although prospective validation will be required to determine clinical utility.

7.2. Early warning score development

Early warning systems have been applied in critical care and inpatient monitoring settings to detect physiological deterioration.[159,160] Extending similar concepts to ambulatory neurocardiovascular monitoring may be feasible.

In the context of BHIWs, composite indices incorporating autonomic variability, rhythm irregularity, and hemodynamic fluctuation metrics could be explored as candidate early warning scores. Such models would not predict specific events deterministically, but could estimate the probability that a patient is entering a phase of elevated vulnerability.

Development of these scores would require careful calibration to avoid excessive false positives, as well as validation across diverse populations. Nonetheless, structured risk-state estimation may offer an intermediate step between raw signal detection and clinical decision-making.

7.3. Multimodal signal fusion

Physiological instability is inherently multidimensional. Autonomic, electrical, hemodynamic, inflammatory, and behavioral signals may interact nonlinearly. Machine learning approaches capable of multimodal signal fusion could facilitate integration across these domains.[161,162]

Multivariate time-series modeling, Bayesian inference frameworks, and neural network architectures may allow joint modeling of variability patterns rather than independent signal analysis. Such approaches could help identify coordinated deviations across tiers of the measurement stack.

However, multimodal integration introduces challenges related to signal quality, temporal alignment, interpretability, and overfitting. Transparent model design and physiological plausibility should remain central considerations.

7.4. Probabilistic forecast modeling

Rather than binary prediction (event vs. no event), probabilistic modeling approaches may be more appropriate for dynamic instability assessment. State-space models and hidden Markov frameworks, for example, can represent physiological systems as transitions between latent stability states.[163-165]

Within such models, the objective would not be to forecast exact timing of stroke or arrhythmia, but to estimate the evolving probability of being within a high-vulnerability state. Risk could therefore be conceptualized as a continuous curve rather than a static category.

Importantly, probabilistic forecasting must be distinguished from deterministic prediction. Clinical translation would require rigorous validation, calibration assessment, and evaluation of impact on outcomes.

7.5. Personalized risk trajectories

Traditional risk models provide annualized population-based probabilities. In contrast, integration of continuous physiological data may permit construction of individualized risk trajectories over shorter temporal horizons.

Personalized risk curves could reflect both baseline structural susceptibility and superimposed dynamic variability patterns. Such trajectories would remain probabilistic and adaptive rather than fixed. Their potential value would lie in illustrating temporal fluctuations in vulnerability rather than assigning static labels.

The clinical implications of personalized temporal risk modeling remain speculative. Future research will need to determine whether integrating dynamic physiological signals meaningfully improves discrimination, calibration, or therapeutic timing compared with existing standards.

7.6. Positioning digital integration within predictive neurocardiology

Digital integration and computational modeling should therefore be viewed as complementary tools for exploring temporal instability rather than replacements for established risk frameworks. Their value may lie in identifying candidate state transitions and supporting hypothesis generation regarding dynamic vulnerability.

At present, the brain–heart instability framework provides a conceptual structure within which such computational approaches could be systematically developed and evaluated. Prospective validation, external replication, and assessment of clinical impact will be essential before routine implementation can be considered. A staged translational pathway from signal acquisition to predictive validation is summarized in Figure 5.

8. Toward a standardization framework for BHIWs

For conceptual frameworks to achieve methodological traction within clinical and research communities, definitional precision and reporting consistency are essential.[166,167] Without shared terminology and structured operational criteria, candidate instability constructs risk remaining heterogeneous, thereby limiting reproducibility, cross-study comparability, and cumulative scientific advancement. Accordingly, the following considerations are proposed as an initial methodological scaffold intended to stimulate empirical refinement and multidisciplinary dialogue rather than to establish prescriptive standards. Formal consensus development will require iterative validation across diverse cohorts and study designs. Because validated BHIW thresholds do not yet exist, the criteria proposed below should be interpreted as preliminary research criteria rather than clinical diagnostic standards. Their purpose is to make the framework falsifiable, reproducible, and testable across studies.

8.1. Operational definition of an instability window

To enable reproducibility, BHIWs may be operationally defined as temporally bounded intervals characterized by coordinated deviation in one or more physiological domains relative to an individual's established baseline state, hypothesized to reflect reduced cross-organ regulatory stability. Several elements of this definition merit clarification. The term *temporally bounded* implies identifiable onset and resolution rather than persistent abnormality. The concept of *coordinated deviation* suggests that instability may be more plausibly inferred when changes demonstrate internal coherence within a physiological domain or occur concurrently across multiple domains. The emphasis on *relative to baseline* underscores the potential importance of individualized reference states rather than exclusive reliance on population-derived thresholds. Finally, describing instability as *hypothesized reduced stability* maintains a probabilistic framing and avoids presuming deterministic event occurrence. This formulation positions BHIWs as dynamic vulnerability states rather than inevitable precursors to clinical outcomes.

A preliminary operational definition may therefore classify a candidate BHIW as present when four conditions are met: (1) a temporally bounded pattern is identifiable, with onset and resolution or repeated clustering within a defined observation window; (2) at least one measured signal deviates beyond expected within-person variability or a validated clinical threshold; (3) the deviation persists or recurs beyond artifact-level fluctuation; and (4) the pattern demonstrates either convergence across at least two physiologically coherent domains or a major single-domain deviation supported by relevant substrate vulnerability. These criteria are intended for research classification and should be refined according to population, outcome, and monitoring modality.

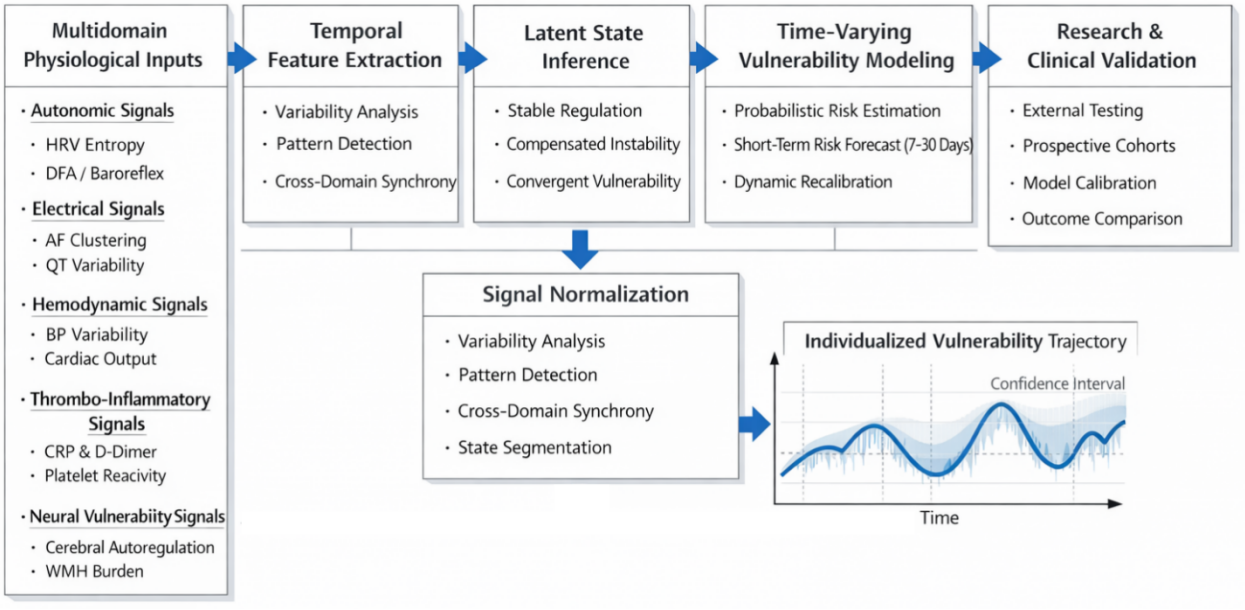


Figure 5. Translational pathway toward predictive neurocardiology. Conceptual framework illustrating progression from continuous physiological signal acquisition to state-aware probabilistic modeling and staged clinical validation. Digital metrics are organized into domain-specific instability categories, integrated across measurement tiers, and modeled using probabilistic frameworks to estimate time-varying vulnerability. Clinical translation requires retrospective enrichment analysis, prospective validation, calibration testing, and randomized implementation studies prior to integration into practice. Abbreviations: AF: Atrial fibrillation; CRP: C-reactive protein; DFA: Detrended fluctuation analysis; HRV: Heart-rate variability; WMH: White matter hyperintensity.

8.2. Preliminary research criteria for candidate BHIWs

A practical research definition of BHIWs requires prespecified criteria for duration, magnitude, convergence, and discordance. Minimum duration should be defined according to the temporal resolution of the domain being studied. For high-frequency digital signals, candidate windows may be evaluated across minutes to hours; for arrhythmic clustering or autonomic–hemodynamic patterns, hours to days may be appropriate; for inflammatory or coagulation markers, daily to subacute intervals may be more realistic. Rather than imposing a universal duration threshold, studies should prespecify domain-specific observation windows and justify them biologically.

Magnitude should similarly be defined relative to individualized baseline when longitudinal data are available. Candidate thresholds may include deviation beyond expected within-person variability, clinically validated cut points, or statistically defined abnormality such as percentile-based or standard deviation–based change from baseline. Because population thresholds may not capture individual physiological reserve, within-person change should be prioritized when feasible.

Cross-domain convergence should be defined as temporal overlap or close temporal sequencing of abnormalities across at least two physiologically coherent domains. Examples include autonomic–electrical convergence, autonomic–hemodynamic convergence, electrical–thrombo-inflammatory convergence, or hemodynamic–neural convergence. Three-domain convergence may increase inferential confidence but should not be required for all studies, because requiring too many domains may reduce sensitivity and feasibility.

Contradictory signals should be handled conservatively. If one domain suggests instability while other relevant domains remain stable, improve, or indicate adaptive compensation, the episode should be classified as indeterminate rather than as a definite BHIW. If signals diverge because of known physiological context, such as exercise, sleep-stage transition, medication timing, hydration change, or recovery from acute illness, contextual interpretation should override purely algorithmic classification. This approach preserves specificity and reduces the risk of pathologizing adaptive physiological variability.

To translate these considerations into a reproducible research structure, Table 3 summarizes preliminary

operational criteria for identifying candidate BHIWs. These criteria are intended for research classification and should not be interpreted as clinical diagnostic standards.

These preliminary criteria provide a structured starting point for empirical testing, while allowing thresholds and temporal windows to be refined according to population, monitoring modality, and target outcome.

8.3. Minimum digital metric domains

These metric domains are not intended to function as mandatory diagnostic tests. Rather, they provide candidate signal classes from which operational definitions can be constructed and tested. The specific metric combination should be prespecified according to the clinical population, monitoring duration, and outcome of interest.

Comparability across investigations may be facilitated by identifying core digital metric domains reflective of principal physiological axes. While definitive metric selection requires empirical evaluation, candidate domains could include a nonlinear HRV measure capturing autonomic complexity, an index of rhythm irregularity or temporal clustering reflecting electrical variability, a short-term blood pressure variability or hemodynamic fluctuation parameter, and a circadian modulation marker such as nocturnal dipping profile or sleep-associated autonomic transition. The intention of proposing such domains is not to constrain methodological innovation but to provide a foundational reference structure enabling baseline comparability. Additional parameters—including inflammatory indices, coagulation markers, or cognitive variability metrics—may be incorporated depending on clinical population and research objectives. The optimal combination of metrics is likely to be context-dependent and should be determined through systematic evaluation.

8.4. Reporting considerations for instability studies

Rigorous evaluation of instability constructs requires transparent and standardized reporting. Studies investigating BHIWs would benefit from explicitly defining window identification criteria, describing baseline characterization methods, specifying signal acquisition temporal resolution, and detailing threshold determination strategies. Clear articulation of whether thresholds are population-derived, individualized, or hybrid is particularly important. In addition, cross-domain integration methods, validation cohort characteristics, and statistical performance metrics—including calibration and discrimination indices—should be reported when predictive modeling is undertaken.[168,169] Transparent reporting practices consistent with established prediction model standards would facilitate replication, enable meta-analytic synthesis, and support iterative refinement of instability modeling approaches.[168,170]

8.5. Temporal classification of window duration

A central methodological consideration concerns temporal scale. Instability phenomena may manifest across heterogeneous durations, ranging from minutes in the case of acute autonomic surges, to hours during arrhythmic

Table 3. Preliminary research criteria for candidate brain–heart instability windows

Operational element	Preliminary research criterion	Interpretation
Temporal boundedness	Identifiable onset and resolution, or recurrent clustering within a prespecified observation window	Distinguishes a window from chronic abnormality
Duration	Prespecified according to domain: minutes–hours for autonomic/hemodynamic signals; hours–days for rhythm clustering; days/subacute intervals for inflammatory or coagulation markers	Avoids one universal threshold across biologically different signals
Magnitude	Deviation from individualized baseline, validated clinical threshold, or statistically defined abnormality	Distinguishes meaningful deviation from noise
Persistence/recurrence	Sustained abnormality or repeated clustering beyond artifact-level fluctuation	Reduces false-positive classification
Cross-domain convergence	At least two physiologically coherent domains deviating in temporal alignment; three-domain convergence increases confidence	Converts the framework from single-marker abnormality to systems-level inference
Single-domain exception	Major persistent deviation in one domain plus relevant substrate vulnerability	Allows clinically meaningful single-axis instability while maintaining specificity
Discordant signals	Classify as indeterminate unless explained by known physiological context or later validated by outcome association	Prevents overinterpretation of contradictory patterns
Clinical use	Research classification only until prospective validation demonstrates predictive value and clinical utility	Prevents premature clinical implementation

clustering, to days in inflammatory activation phases. Rather than imposing rigid duration thresholds, a stratified temporal classification may offer conceptual clarity. Instability intervals may be categorized as ultra-short (minutes), short (hours), intermediate (days), or extended (subacute phases), thereby aligning temporal scale with underlying physiological mechanism. Determining which durations carry clinical relevance for specific outcomes will require prospective investigation.

8.6. Threshold determination and baseline referencing

Threshold selection represents a critical methodological challenge in dynamic physiological modeling.[171,172] Fixed population-based cutoffs may inadequately capture individualized variability architecture, whereas fully personalized thresholds risk reduced generalizability and potential overfitting. A hybrid strategy may provide a balanced alternative, whereby baseline variability is established over a defined calibration period and subsequent deviations are quantified relative to personal reference distributions, potentially supplemented by population-informed constraints. Cross-domain concurrence—simultaneous deviation across autonomic, electrical, or hemodynamic axes—may strengthen inferential confidence that a meaningful instability state is present. Iterative validation across heterogeneous populations will be required to determine optimal threshold methodologies.

8.7. Rationale for methodological standardization

Standardization in this context should be understood not as rigid uniformity but as the development of a shared methodological vocabulary. By articulating provisional operational definitions, core metric domains, reporting elements, temporal categories, and threshold considerations, the brain–heart instability framework becomes more amenable to empirical testing and cross-study synthesis. These proposals are intended to encourage systematic evaluation rather than immediate clinical implementation. Prospective validation, external replication, and calibration analyses will be essential to determine predictive relevance and therapeutic implications.

Formalizing terminology and methodological considerations may facilitate structured investigation of temporal vulnerability in neurocardiovascular disorders and enhance comparability across emerging digital health research. To illustrate how the instability framework may be operationalized empirically, selected candidate research hypotheses and corresponding study designs are summarized in Table 4.

9. Potential clinical decisions if BHIWs are validated: translational implications and guardrails

The clinical value of the BHIW framework would depend on whether validated instability signals can be linked to specific decisions rather than only to general risk awareness. Potential decision points include how intensively to monitor rhythm, which patients may warrant extended telemetry after stroke, when to repeat or intensify orthostatic evaluation, whether supportive hemodynamic strategies should be timed to periods of recurrent instability, and whether dynamic signals can reinforce adherence or follow-up planning in patients already eligible for guideline-directed therapy. These possible applications remain conditional on prospective validation and should not be interpreted as current clinical recommendations.

To make these translational implications more explicit, Table 5 links candidate BHIW signal patterns to potential future clinical decision points and the validation required before implementation.

This mapping is intended to clarify the translational hypotheses generated by the framework. It does not imply that any listed decision should be implemented before prospective validation demonstrates predictive value, safety, and clinical utility.

9.1. Monitoring strategies aligned with instability states

Contemporary neurocardiovascular monitoring paradigms are predominantly episodic or burden-based. Continuous rhythm surveillance, ambulatory blood pressure monitoring, and wearable-derived autonomic metrics are increasingly utilized in both research and clinical settings. Yet interpretation of these data streams is typically retrospective and event-focused.

Within a BHIW framework, monitoring could be conceptualized as state-sensitive rather than solely event-detecting. Identification of coordinated deviations across autonomic, electrical, and hemodynamic domains might justify intensified observation during candidate instability intervals. Such adaptive monitoring strategies could potentially refine the timing of diagnostic evaluation or follow-up without altering baseline long-term management.

This approach does not imply continuous escalation of surveillance, but rather selective attention to periods characterized by physiologic convergence. Prospective studies would be necessary to determine whether such state-aware monitoring improves outcome prediction or resource allocation.

Table 4. Candidate research questions for empirical validation of brain–heart instability windows

Hypothesis	Target population	Candidate signals	Primary outcome	Proposed study design
Short-term clustering of AF episodes is associated with increased near-term embolic risk independent of annualized CHA_2DS_2-VASc score	Patients with paroxysmal AF	AF burden density; rhythm clustering indices; inflammatory markers (*e.g.*, CRP)	Ischemic stroke or systemic embolism within predefined short-term window	Prospective cohort with continuous rhythm monitoring and adjudicated thromboembolic outcomes
Reduction in nonlinear HRV complexity precedes symptomatic syncope events in autonomic dysfunction	Patients with autonomic failure or recurrent unexplained syncope	HRV entropy metrics; baroreflex sensitivity; short-term BP variability	Syncope or presyncope episodes	Longitudinal wearable-based monitoring with event-triggered analysis
Exaggerated nocturnal hypotension is associated with accelerated WMH progression	Older adults with hypertension or small vessel disease	Nocturnal dipping profiles; short-term BP variability	MRI-based WMH volume progression	Prospective imaging cohort with ambulatory BP monitoring
Convergent autonomic and hemodynamic deviations increase short-term arrhythmia initiation probability	Early-stage AF or high ectopy burden patients	HRV entropy + ectopy clustering + BP oscillation amplitude	AF initiation or sustained arrhythmia	Multimodal signal fusion study with time-to-event modeling
Combined thrombo-inflammatory activation and AF clustering predicts microembolic signal detection	Patients with AF undergoing transcranial Doppler monitoring	AF clustering indices; D-dimer; platelet reactivity	Microembolic signals or transient ischemic events	Mechanistic cohort study with synchronized monitoring

Abbreviations: AF: Atrial fibrillation; BP: Blood pressure; CRP: C-reactive protein; HRV: Heart-rate variability; MRI: Magnetic resonance imaging; WMH: White matter hyperintensity.

If validated, BHIW-informed monitoring could support adaptive surveillance strategies rather than fixed-duration monitoring alone. For example, patients with recurrent AF clustering, ectopy bursts, HRV complexity loss, or post-stroke autonomic instability might be candidates for extended patch monitoring, implantable loop recorder consideration, or closer remote rhythm surveillance in research-tested protocols. The key translational question is whether instability-guided monitoring improves clinically meaningful arrhythmia detection or outcome prediction compared with standard monitoring pathways.

9.2. Dynamic considerations in anticoagulation strategy

Anticoagulation decisions in atrial fibrillation are currently guided by validated long-term risk stratification tools such as the CHA_2DS_2-VASc score and are embedded within international guideline frameworks.[60,173] These approaches have substantially reduced stroke incidence and remain the foundation of evidence-based care.

The brain–heart instability framework does not propose replacement of established scoring systems. Rather, it raises the hypothesis that thromboembolic vulnerability may fluctuate within individuals over time, potentially influenced by arrhythmic clustering, endothelial activation, and inflammatory modulation. If future research demonstrates that such dynamic states meaningfully modify short-term embolic risk, temporally informed strategies—such as adherence reinforcement, closer monitoring during high-burden phases, or trial-based exploration of adaptive dosing paradigms—could be evaluated in controlled settings.

At present, any modification of anticoagulation intensity based on dynamic signals would require rigorous prospective evaluation. The concept should therefore be regarded as hypothesis-generating rather than practice-altering.

A more realistic near-term translational use may be adherence reinforcement or follow-up prioritization in patients who already meet guideline-directed indications for anticoagulation, rather than dynamic initiation or discontinuation of therapy. For example, if future studies show that AF clustering plus thrombo-inflammatory activation identifies periods of increased vulnerability, such information might support patient education, adherence checks, or closer monitoring within already indicated care pathways. Any change in anticoagulation initiation, interruption, dose, or intensity would require randomized evidence demonstrating net clinical benefit.

9.3. Timing of rhythm control interventions

Recent evidence suggests that earlier rhythm control

Table 5. Candidate BHIW signals and potential future clinical decision points if prospectively validated

Clinical context	Candidate BHIW signal pattern	Potential future decision point	Validation Required before use
AF surveillance	AF episode clustering, increased ectopy density, reduced HRV complexity, autonomic shift	Adaptive rhythm monitoring intensity; shorter interval follow-up; reinforcement of adherence to already indicated therapy	Prospective evidence that signal-defined intervals improve short-term event prediction or management efficiency
AF-related thromboembolic vulnerability	AF clustering plus thrombo-inflammatory or coagulation marker elevation	Research-tested timing of intensified surveillance or adherence reinforcement; not anticoagulation change outside guidelines	Demonstration of incremental predictive value beyond CHA_2DS_2-VASc and standard AF burden measures
Anticoagulation strategy	Dynamic rhythm and thrombo-inflammatory convergence in patients already under guideline-directed assessment	Future trial-based exploration of whether timing or intensity strategies improve outcomes	Randomized evidence showing benefit without excess bleeding; no current practice change
Syncope and orthostatic intolerance	Recurrent orthostatic BP lability, impaired baroreflex recovery, reduced autonomic complexity	Timing of repeat orthostatic testing; anticipatory hydration, medication review, compression, or autonomic support	Prospective validation that signal patterns predict symptomatic episodes or falls
Post-stroke arrhythmogenesis	Post-stroke autonomic shift, reduced HRV, ectopy clustering, repolarization variability	Selection for extended telemetry or prolonged ambulatory rhythm monitoring after stroke	Evidence that BHIW-guided monitoring improves arrhythmia detection or secondary prevention
Cerebral perfusion vulnerability	BP variability, nocturnal hypotension, impaired autoregulation, white matter susceptibility	Identification of patients needing closer BP-pattern review or perfusion-focused monitoring	Validation against stroke recurrence, silent infarction, cognitive decline, or imaging progression
Neurodegenerative autonomic dysfunction	Progressive HRV flattening, orthostatic lability, nocturnal BP instability	Closer surveillance during autonomic decompensation; timing of supportive interventions	Evidence that dynamic monitoring predicts falls, syncope, cognitive fluctuation, or hospitalization
General dynamic risk modeling	Cross-domain convergence across at least two coherent domains	Entry into higher-surveillance research pathway or digital early-warning protocol	Calibration, discrimination, false-positive burden, and clinical utility testing

Abbreviations: AF: Atrial fibrillation; BHIW: Brain–heart instability window; BP: Blood pressure; HRV: Heart-rate variability.

strategies in AF may influence long-term cardiovascular outcomes.[174,175] Current decision-making, however, is generally guided by symptom burden, arrhythmia duration, structural substrate assessment, and overall clinical context.

Within an instability framework, electrical instability windows—characterized by arrhythmic clustering, repolarization variability, and autonomic shifts—may represent intervals of heightened electrical vulnerability. Theoretically, aligning rhythm control interventions with such intervals could enhance procedural or pharmacologic responsiveness, or reduce recurrence risk.

Whether temporally targeted rhythm management yields measurable benefit remains uncertain. Prospective studies would be required to evaluate feasibility, safety, and comparative effectiveness relative to standard timing strategies.

9.4. Hemodynamic stabilization and autonomic modulation

Management of syncope and orthostatic intolerance commonly includes hydration optimization, medication adjustment, compression therapy, and autonomic support strategies in accordance with established guidelines.[176-178] These interventions are typically applied based on chronic diagnostic categorization rather than dynamic physiologic state detection.

In the context of hemodynamic or autonomic gain windows, targeted supportive strategies might theoretically be aligned with detected instability phases. For example, recurrent orthostatic BP lability, delayed heart-rate recovery, impaired baroreflex gain, or reduced HRV complexity could eventually inform the timing of repeat orthostatic assessment, medication review, hydration reinforcement, compression therapy, or other

autonomic support strategies. Such approaches would require careful validation to determine whether signal-guided intervention reduces syncope, falls, or cerebral hypoperfusion without increasing overtreatment or false-positive responses.

9.5. Personalized intervention windows

A broader implication of the BHIW framework is the potential transition from static risk categorization to individualized vulnerability profiling. Rather than conceptualizing risk exclusively as an annualized probability derived from demographic and structural variables, neurocardiovascular vulnerability may be understood as an evolving state influenced by both substrate and superimposed dynamic perturbations.

Personalized intervention windows would therefore represent intervals during which preventive or stabilizing strategies might yield greater marginal benefit. These could include reinforcement of anticoagulation adherence in patients already eligible for therapy, intensified rhythm surveillance after AF clustering or post-stroke autonomic instability, temporary hemodynamic support during recurrent orthostatic vulnerability, medication review during autonomic decompensation, or modulation of reversible triggers such as dehydration, infection, sleep disruption, or acute inflammatory stress. Importantly, such personalization would require robust validation to ensure that dynamic state identification improves discrimination and calibration beyond existing guideline-directed care.

9.6. Translational context and clinical guardrails

The translational value of the brain–heart instability framework lies not in immediate clinical directives but in reframing how temporal vulnerability is conceptualized and investigated. It provides a structure for prospective research exploring whether dynamic physiological states contribute incremental prognostic information and whether temporally aligned interventions can enhance precision without increasing harm.

Until supported by outcome-driven evidence, BHIWs should be regarded as a research construct intended to inform future predictive neurocardiovascular strategies rather than alter current standards of care. No changes to current guideline-directed management should be inferred from this framework outside of prospective trial validation.

10. Methodological, biological, and ethical limitations

The BHIW framework is proposed as a structured conceptual model intended to guide investigation of dynamic neurocardiovascular vulnerability. As with any state-based construct derived from continuous physiological monitoring, important methodological, biological, and ethical considerations must be explicitly addressed. Careful boundary definition is necessary to prevent overinterpretation and to ensure that translational applications remain evidence-informed.

10.1. Signal noise and false positive risk

Continuous digital monitoring increases temporal resolution but also increases detection of statistical deviation. Biological systems exhibit intrinsic variability across autonomic, electrical, and hemodynamic domains.[179,180] As monitoring density increases, the likelihood of identifying short-lived fluctuations also increases, though these may not have independent clinical significance.[181,182]

Importantly, the presence of a candidate instability pattern does not imply inevitability of adverse outcome. Most transient arrhythmic episodes, blood pressure oscillations, or autonomic shifts are compensated by endogenous regulatory mechanisms and do not culminate in stroke, syncope, or sustained arrhythmia.[183,184] Dynamic fluctuation alone should therefore not be equated with pathological destabilization.

Expanded anomaly detection also carries recognized system-level risks. High alert frequency may contribute to clinician alert fatigue, diminishing the signal-to-noise ratio in digital monitoring environments.[185,186] False-positive instability classifications may prompt unnecessary diagnostic testing, prolonged surveillance, or procedural referral without established benefit.[182] In some contexts, cascades of evaluation may follow marginal digital findings, increasing cost and patient burden while yielding limited incremental prognostic value.[182,187,188]

Particular caution is warranted in domains involving anticoagulation and rhythm intervention. Contemporary anticoagulation strategies are grounded in validated long-term risk stratification models and guideline-directed management.[60,184] At present, there is no prospective evidence supporting modification of anticoagulation intensity or rhythm control strategy based solely on short-term variability metrics. Premature therapeutic escalation based on unvalidated instability signals could expose patients to avoidable hemorrhagic or procedural risk.

Accordingly, the BHIW framework must not be interpreted as justification for intervention without prospective validation demonstrating incremental predictive value and favorable harm–benefit balance. Detection of physiologic deviation and initiation of treatment must remain clearly separated until outcome-based evidence supports integration.

10.2. Reverse causality and epiphenomenal risk

A second limitation concerns the causal interpretation of candidate instability signals. Observed variability shifts may function as upstream contributors to adverse events, intermediate amplifiers within broader pathophysiologic processes, or downstream reflections of evolving injury.[182,189] Distinguishing among these possibilities is essential for mechanistic clarity.

Autonomic perturbations, for example, may precede arrhythmia initiation in selected contexts.[70,87] However, autonomic shifts may also represent reactive responses to ischemia, inflammation, metabolic stress, or neurohumoral activation.[145,180,190] Similarly, reductions in HRV or changes in repolarization dynamics have been associated with adverse cardiovascular outcomes [180,191], yet these alterations may reflect generalized physiological strain rather than specific causal drivers.

Inflammatory and endothelial markers illustrate a similar ambiguity. Elevation of inflammatory mediators has been associated with AF and thromboembolic risk.[192,193] However, inflammatory activation may arise secondary to subclinical tissue injury rather than preceding it. Without longitudinal temporal sequencing and mechanistic evaluation, directionality cannot be assumed.

Failure to consider reverse causality risks mechanistic overextension. If instability signals function primarily as correlates rather than causal mediators, interventions targeting the signal may not modify outcome. Prospective cohort studies, mediation analyses, and controlled interventional trials will be required to clarify whether identified instability metrics independently contribute to event probability.[189,194]

Until such evidence is available, causal interpretation should remain cautious and hypothesis-driven.

10.3. Physiological variability versus pathology

A central conceptual challenge lies in distinguishing pathological instability from adaptive physiological variability. Biological systems are inherently dynamic. Variability across autonomic, hemodynamic, and electrophysiologic domains often reflects regulatory flexibility and preserved resilience.[195,196] Conversely, excessive rigidity or loss of signal complexity has been associated with impaired physiological reserve.[197,198]

At the same time, exaggerated variability or oscillatory amplification beyond autoregulatory capacity may contribute to dysfunction.[199,200] Both reduced variability and excessive variability have been associated with adverse outcomes, depending on context and substrate.[180,201] This bidirectional relationship complicates interpretation of dynamic signals.

For example, reductions in HRV entropy may indicate diminished autonomic adaptability. However, transient simplification of variability structure may accompany coordinated physiological states such as sleep-stage transitions or recovery phases.[202,203] Similarly, short-term blood pressure variability has been associated with cerebrovascular risk independent of mean pressure [204], yet physiologic oscillations during exertion or circadian modulation represent adaptive regulation.[100,205]

Variability restructuring—defined as reorganization of temporal patterning without clear evidence of regulatory failure—may occur during conditioning, circadian entrainment, or recovery from acute illness.[206-208] Not all deviations from prior baselines signify loss of buffering capacity. Without individualized baseline referencing and cross-domain convergence criteria, there is risk of pathologizing normal physiological fluctuation. Discordant patterns, in which one domain appears abnormal while other physiologically related domains remain stable or compensatory, should therefore be treated as indeterminate until longitudinal outcome association or mechanistic context clarifies their significance.

Therefore, not all variability shifts constitute instability. Operational definitions of BHIWs must incorporate contextual interpretation, longitudinal validation, and outcome correlation to preserve specificity and prevent overmedicalization of adaptive biological dynamics.

11. Testable hypotheses and research propositions

The BHIW framework is intended to support empirical evaluation of temporally varying neurocardiovascular vulnerability. To facilitate structured investigation, several falsifiable research propositions may be articulated. These propositions are presented not as claims, but as examples of hypotheses that can be examined in prospective observational cohorts and, where appropriate, in controlled implementation studies.

First, in patients with atrial fibrillation undergoing longitudinal monitoring, temporally bounded convergence of autonomic deviation (*e.g.*, reduction in HRV complexity), electrical instability (*e.g.*, increased repolarization variability or arrhythmia clustering), and thrombo-inflammatory activation may be associated with increased short-term ischemic stroke or systemic embolism risk compared with periods characterized by similar AF burden but without cross-domain convergence, within prespecified short-term horizons (*e.g.*, 7–30 days).[209,210] This proposition allows direct testing of whether dynamic

cross-layer coordination confers incremental vulnerability beyond arrhythmia burden alone.

Second, in individuals with paroxysmal AF or frequent ectopy, combined reductions in autonomic complexity and increases in beat-to-beat repolarization dispersion may precede arrhythmic clustering episodes more frequently than during physiologically stable intervals, within defined pre-event windows (*e.g.*, 6–24 hours).[123,211] Such analyses would permit evaluation of whether identifiable autonomic–electrical precursor signatures exist prior to rhythm destabilization.

Third, multilevel instability metrics derived from the brain–heart measurement stack may demonstrate incremental predictive value beyond established static risk models, such as CHA_2DS_2-VASc, for short-term cerebrovascular or arrhythmic outcomes. This hypothesis can be evaluated using discrimination, calibration, and reclassification indices over prespecified time horizons (*e.g.*, 30–90 days).[212-214] Demonstration of incremental value would be necessary before considering integration into clinical risk assessment paradigms.

Fourth, in populations characterized by impaired cerebrovascular autoregulatory reserve—such as individuals with small vessel disease or neurodegenerative autonomic dysfunction—short-term increases in beat-to-beat blood pressure variability may correlate with greater within-person fluctuations in cognitive performance, particularly during intervals identified as hemodynamic instability phases.[215-217] This proposition allows examination of whether dynamic hemodynamic variability carries measurable neural correlates within vulnerable substrates.

Finally, in prospective studies, monitoring strategies that selectively intensify assessment during validated instability states may increase diagnostic yield or event detection efficiency without disproportionate increases in downstream testing compared with fixed-interval monitoring approaches.[218,219] Such evaluation would clarify whether state-aware monitoring improves efficiency without amplifying overdiagnosis.

Collectively, these propositions illustrate how the BHIW framework can be operationalized in empirically testable form. Their validity remains to be established through carefully designed prospective studies.

12. Toward empirical validation of the instability framework

The brain–heart instability window framework is proposed as an investigational construct and requires staged empirical evaluation prior to consideration of clinical integration. A structured validation pathway is necessary to determine whether dynamic instability modeling provides incremental value beyond established neurocardiovascular risk assessment paradigms.

An initial phase of investigation may involve retrospective analyses of existing continuous monitoring datasets. These analyses could evaluate whether predefined instability metrics derived from autonomic variability, electrical clustering patterns, hemodynamic fluctuation indices, or thrombo-inflammatory markers demonstrate temporal enrichment prior to documented clinical events. Time series segmentation, clustering approaches, and state transition modeling may be applied to assess whether candidate instability intervals occur more frequently before events than during baseline periods.[70,87,220] Such studies would establish signal level plausibility but would not determine clinical utility.

Subsequently, prospective observational cohorts would be required to assess whether prespecified instability criteria demonstrate independent short-term predictive value when evaluated alongside established risk models. These investigations should incorporate discrimination and calibration metrics consistent with accepted standards for clinical prediction model evaluation, as well as clearly defined temporal horizons and comparison with standard of care stratification approaches.[168] Particular attention should be given to false positive rates, signal persistence across repeated measurements, and reproducibility across populations with differing substrate characteristics.

If incremental predictive value is demonstrated, randomized implementation studies may then evaluate whether state-aware monitoring strategies improve diagnostic efficiency or clinical outcomes without increasing downstream testing burden or patient harm. For example, adaptive monitoring intensity during validated instability intervals could be compared with fixed-interval surveillance strategies. Any exploration of temporally aligned therapeutic modification would require careful safety oversight and continued adherence to guideline-directed management until benefit is established through prospective trials.[17,221,222]

This staged progression from retrospective signal evaluation to prospective predictive validation and ultimately to randomized implementation testing provides a coherent methodological pathway for determining whether dynamic instability modeling meaningfully advances neurocardiovascular risk assessment. Until such validation is achieved, the BHIW framework should remain investigational.

13. Future directions — Toward predictive neurocardiology

The BHIW framework invites a broader reorientation of neurocardiovascular research from static risk estimation toward dynamic state characterization. While current evidence does not support instability-based clinical decision-making, emerging technological and conceptual advances may influence how temporal vulnerability is investigated in the coming decade.

Continuous wearable monitoring platforms are evolving in signal fidelity, battery longevity, and multimodal integration capacity. As these technologies mature, research efforts may increasingly focus on identifying reproducible physiological state transitions rather than isolated arrhythmic or hemodynamic events. The emphasis may shift from cumulative burden metrics toward temporal organization of variability patterns within and across autonomic, electrical, and vascular domains.

The development of individualized computational representations of cross-organ physiology, sometimes conceptualized as digital twins, represents another potential direction. In neurocardiology, such models could integrate electrophysiologic dynamics, autonomic modulation, perfusion variability, and structural substrate characteristics into unified state representations. Whether these approaches ultimately improve risk estimation or therapeutic timing remains uncertain, but they offer a structured framework for simulating dynamic interactions within coupled excitable systems.

Future investigations may also explore whether identifying validated instability states can inform adaptive monitoring strategies. Rather than replacing established guideline-directed management, state-aware approaches might complement static risk models by refining temporal resolution. The objective would not be deterministic event prediction, but probabilistic recognition of evolving vulnerability phases.

The instability framework may hold particular relevance in environments characterized by physiologic stress or altered regulatory dynamics. Aerospace medicine, high-altitude exposure, and prolonged immobilization provide controlled contexts in which autonomic tone, fluid distribution, and cerebral perfusion undergo measurable adaptation. Studying cross-organ instability dynamics under such conditions may yield insights into fundamental principles of regulatory resilience and system fragility.

Ultimately, predictive neurocardiology should be understood not as forecasting precise event timing, but as improving characterization of fluctuating vulnerability within interconnected neural and cardiovascular systems. Progress toward this objective will require interdisciplinary collaboration across neurology, cardiology, computational science, biomedical engineering, and aerospace physiology. The brain–heart instability framework offers a conceptual structure for organizing such inquiry, while leaving empirical validation and clinical translation to future investigation.

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References

1. Prabhakaran S, Gonzalez NR, Zachrison KS, *et al*. 2026 Guideline for the Early Management of Patients With Acute Ischemic Stroke: A Guideline From the American Heart Association/American Stroke Association. *Stroke*. 2026.

   doi: 10.1161/STR.0000000000000513

2. Tzeis S, Gerstenfeld EP, Kalman J, *et al*. 2024 European Heart Rhythm Association/Heart Rhythm Society/Asia Pacific Heart Rhythm Society/Latin American Heart Rhythm Society expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Europace*. 2024;26(4) doi:10.1093/europace/euae043

3. Van Gelder IC, Rienstra M, Bunting KV, *et al*. 2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2024;45(36):3314-3414.

   doi: 10.1093/eurheartj/ehae176

4. Sutton R, Ricci F, Fedorowski A. Risk stratification of syncope: Current syncope guidelines and beyond. *Auton Neurosci*. 2022;238:102929.

doi: 10.1016/j.autneu.2021.102929

5. Cheshire WP, Freeman R, Gibbons CH, *et al*. Electrodiagnostic assessment of the autonomic nervous system: A consensus statement endorsed by the American Autonomic Society, American Academy of Neurology, and the International Federation of Clinical Neurophysiology. *Clin Neurophysiol*. 2021;132(2):666-682.

   doi: 10.1016/j.clinph.2020.11.024

6. Thijs RD, Brignole M, Falup-Pecurariu C, *et al*. Recommendations for tilt table testing and other provocative cardiovascular autonomic tests in conditions that may cause transient loss of consciousness : Consensus statement of the European Federation of Autonomic Societies (EFAS) endorsed by the American Autonomic Society (AAS) and the European Academy of Neurology (EAN). *Clin Auton Res*. 2021;31(3):369-384.

   doi: 10.1007/s10286-020-00738-6

7. Kleindorfer DO, Towfighi A, Chaturvedi S, *et al*. 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association. *Stroke*. 2021;52(7):e364-e467.

   doi: 10.1161/STR.0000000000000375

8. Elsheikh S, Hill A, Irving G, Lip GYH, Abdul-Rahim AH. Atrial fibrillation and stroke: State-of-the-art and future directions. *Curr Probl Cardiol*. 2024;49(1 Pt C):102181.

   doi: 10.1016/j.cpcardiol.2023.102181

9. Scheitz JF, Sposato LA, Schulz-Menger J, Nolte CH, Backs J, Endres M. Stroke-Heart Syndrome: Recent Advances and Challenges. *J Am Heart Assoc*. 2022;11(17):e026528.

   doi: 10.1161/JAHA.122.026528

10. Wang L, Ma L, Ren C, *et al*. Stroke-heart syndrome: current progress and future outlook. *J Neurol*. 2024;271(8):4813-4825.

    doi: 10.1007/s00415-024-12480-4

11. Alzaabi AA, Alzaabi FM, Siddiqui RW, Siddiqui TW, Sami MM. Review of microgravity's impact on cardiovascular and nervous systems in space exploration. *NPJ Microgravity*. 2025;11(1):77.

    doi: 10.1038/s41526-025-00534-4

12. Goswami N, Blaber AP, Valenti G, *et al*. Gravity, microgravity, and artificial gravity: physiological effects, implementation, and applications. *Physiol Rev*. 2026;106(2):750-839.

    doi: 10.1152/physrev.00055.2024

13. Claassen J, Thijssen DHJ, Panerai RB, Faraci FM. Regulation of cerebral blood flow in humans: physiology and clinical implications of autoregulation. *Physiol Rev*. 2021;101(4):1487-1559.

    doi: 10.1152/physrev.00022.2020

14. Mehra R, Chung MK, Olshansky B, *et al*. Sleep-Disordered Breathing and Cardiac Arrhythmias in Adults: Mechanistic Insights and Clinical Implications: A Scientific Statement From the American Heart Association. *Circulation*. 2022;146(9):e119-e136.

    doi: 10.1161/CIR.0000000000001082

15. Wong CX, Modrow MF, Sigona K, *et al*. Preceding Night Sleep Quality and Atrial Fibrillation Episodes in the I-STOP-AFIB Randomized Trial. *JACC Clin Electrophysiol*. 2024;10(1):56-64.

    doi: 10.1016/j.jacep.2023.09.009

16. Lakatos LB, Shin DC, Muller M, Osterreich M, Marmarelis V, Bolognese M. Impaired dynamic cerebral autoregulation measured in the middle cerebral artery in patients with vertebrobasilar ischemia is associated with autonomic failure. *J Stroke Cerebrovasc Dis*. 2024;33(1):107454.

    doi: 10.1016/j.jstrokecerebrovasdis.2023.107454

17. Abadjiev DS, Toschi-Dias E, Salinet AS, *et al*. Daily rhythm of dynamic cerebral autoregulation in patients after stroke. *J Cereb Blood Flow Metab*. 2023;43(6):989-998.

    doi: 10.1177/0271678X231153750

18. Cricco R, Segreti A, Ferro A, *et al*. Advancements in Sensor Technology for Monitoring and Management of Chronic Coronary Syndrome. *Sensors (Basel)*. 2025;25(15) doi:10.3390/s25154585

19. Hughes A, Shandhi MMH, Master H, Dunn J, Brittain E. Wearable Devices in Cardiovascular Medicine. *Circ Res*. 2023;132(5):652-670.

    doi: 10.1161/CIRCRESAHA.122.322389

20. Lodewyk K, Wiebe M, Dennett L, Larsson J, Greenshaw A, Hayward J. Wearables research for continuous monitoring of patient outcomes: A scoping review. *PLOS Digit Health*. 2025;4(5):e0000860.

    doi: 10.1371/journal.pdig.0000860

21. Baigutanova A, Park S, Constantinides M, Lee SW, Quercia D, Cha M. A continuous real-world dataset comprising wearable-based heart rate variability alongside sleep diaries. *Sci Data*. 2025;12(1):1474.

    doi: 10.1038/s41597-025-05801-3

22. Hernandez R, Schneider S, de Vries HJ, *et al*. Resting Heart Rate Variability Measured by Consumer Wearables and Its Associations with Diverse Health Domains in Five Longitudinal Studies. *Sensors (Basel)*. 2025;25(23) doi:10.3390/s25237147

23. Lubitz SA, Faranesh AZ, Selvaggi C, *et al*. Detection of Atrial Fibrillation in a Large Population Using Wearable Devices: The Fitbit Heart Study. *Circulation*. 2022;146(19):1415-1424.

    doi: 10.1161/CIRCULATIONAHA.122.060291

24. van Steijn NJ, Blommestijn IS, Blok S, *et al*. Enhanced

Detection and Prompt Diagnosis of Atrial Fibrillation Using Apple Watch: A Randomized Controlled Trial. *J Am Coll Cardiol*. 2026.

doi: 10.1016/j.jacc.2025.11.032

25. Qi W, Zhu X, Wang B, *et al*. Alzheimer's disease digital biomarkers multidimensional landscape and AI model scoping review. *NPJ Digit Med*. 2025;8(1):366.

doi: 10.1038/s41746-025-01640-z

26. Sun YM, Wang ZY, Liang YY, Hao CW, Shi CH. Digital biomarkers for precision diagnosis and monitoring in Parkinson's disease. *NPJ Digit Med*. 2024;7(1):218.

doi: 10.1038/s41746-024-01217-2

27. Ince C, Gulen M, Acehan S, *et al*. Comparison of syncope risk scores in predicting the prognosis of patients presenting to the emergency department with syncope. *Ir J Med Sci*. 2023;192(6):2727-2734.

doi: 10.1007/s11845-023-03395-6

28. Teppo K, Lip GYH, Airaksinen KEJ, *et al*. Comparing CHA(2)DS(2)-VA and CHA(2)DS(2)-VASc scores for stroke risk stratification in patients with atrial fibrillation: a temporal trends analysis from the retrospective Finnish AntiCoagulation in Atrial Fibrillation (FinACAF) cohort. *Lancet Reg Health Eur*. 2024;43:100967.

doi: 10.1016/j.lanepe.2024.100967

29. Askarinejad A, Bucci T, Tartaglia E, Rossi M, Lip GYH, Haghjoo M. Stroke and Bleeding Risks in Atrial Fibrillation Are Not Static but Dynamic: A Dynamic Assessment of CHA(2)DS(2)-VASc and HAS-BLED Scores in the Iranian Registry of Atrial Fibrillation (IRAF). *J Cardiovasc Electrophysiol*. 2026;37(1):110-118.

doi: 10.1111/jce.70190

30. Rimok J, Larkin-Kaiser KA. From lab to life: Wearables, real-world data, and the future of autonomic research. *Auton Neurosci*. 26 2025;264:103377.

doi: 10.1016/j.autneu.2025.103377

31. Jena N, Singh P, Chandramohan D, *et al*. Wearable Technology in Cardiology: Advancements, Applications, and Future Prospects. *Rev Cardiovasc Med*. 2025;26(6):39025.

doi: 10.31083/RCM39025

32. Trayanova NA, Lyon A, Shade J, Heijman J. Computational modeling of cardiac electrophysiology and arrhythmogenesis: toward clinical translation. *Physiol Rev*. 2024;104(3):1265-1333.

doi: 10.1152/physrev.00017.2023

33. Wang Q, Li J. Optoelectronic Interfaces for Nongenetic Modulation of Excitable Tissues. *Small Methods*. 2026;10(3):e01371.

doi: 10.1002/smtd.202501371

34. Jenkins PM, Bender KJ. Axon initial segment structure and function in health and disease. *Physiol Rev*. 2025;105(2):765-801.

doi: 10.1152/physrev.00030.2024

35. Varro A, Tomek J, Nagy N, *et al*. Cardiac transmembrane ion channels and action potentials: cellular physiology and arrhythmogenic behavior. *Physiol Rev*. 2021;101(3):1083-1176.

doi: 10.1152/physrev.00024.2019

36. Reisqs JB, Qu YS, Boutjdir M. Ion channel trafficking implications in heart failure. *Front Cardiovasc Med*. 2024;11:1351496.

doi: 10.3389/fcvm.2024.1351496

37. Duma GM, Cuozzo S, Danieli A, *et al*. Dynamic excitation/inhibition balance preceding seizure onset and its link to functional and structural brain architecture. *BMC Med*. 2025;23(1):604.

doi: 10.1186/s12916-025-04447-7

38. Lei M, Salvage SC, Jackson AP, Huang CL. Cardiac arrhythmogenesis: roles of ion channels and their functional modification. *Front Physiol*. 2024;15:1342761.

doi: 10.3389/fphys.2024.1342761

39. Obeagu EI. Inflammatory cytokines and cardiac arrhythmias: from pathogenesis to potential therapies. *Ann Med Surg (Lond)*. 2025;87(9):5607-5613.

doi: 10.1097/MS9.0000000000003499

40. Zipp F, Bittner S, Schafer DP. Cytokines as emerging regulators of central nervous system synapses. *Immunity*. 2023;56(5):914-925.

doi: 10.1016/j.immuni.2023.04.011

41. Bychkov R, Juhaszova M, Tsutsui K, *et al*. Synchronized Cardiac Impulses Emerge From Heterogeneous Local Calcium Signals Within and Among Cells of Pacemaker Tissue. *JACC Clin Electrophysiol*. 2020;6(8):907-931.

doi: 10.1016/j.jacep.2020.06.022

42. Myrov V, Siebenhuhner F, Juvonen JJ, Arnulfo G, Palva S, Palva JM. Rhythmicity of neuronal oscillations delineates their cortical and spectral architecture. *Commun Biol*. 2024;7(1):405.

doi: 10.1038/s42003-024-06083-y

43. Herzog N, Cesnaite E, Steinfath P, *et al*. Balancing excitation and inhibition: The role of neural network dynamics in working memory gating. *Imaging Neurosci (Camb)*. 2024;2doi:10.1162/imag_a_00380

44. Ooi JH, Lim R, Seng H, *et al*. Non-invasive parameters of autonomic function using beat-to-beat cardiovascular variations and arterial stiffness in hypertensive individuals: a systematic review. *Biomed Eng Online*. 2024;23(1):23.

doi: 10.1186/s12938-024-01202-6

45. Ziegler KA, Engelhardt S, Carnevale D, *et al*. Neural Mechanisms in Cardiovascular Health and Disease. *Circ Res*. 2025;136(11):1233-1261.

doi: 10.1161/CIRCRESAHA.125.325580

46. Lohman T, Sible I, Kapoor A, *et al*. Blood Pressure Variability, Central Autonomic Network Dysfunction, and Cerebral Small-Vessel Disease in APOE4 Carriers. *J Am Heart Assoc*. 2024;13(9):e034116.

doi: 10.1161/JAHA.123.034116

47. Valenza G, Cio FD, Toschi N, Barbieri R. Sympathetic and parasympathetic central autonomic networks. *Imaging Neurosci (Camb)*. 2024;2doi:10.1162/imag_a_00094

48. Candia-Rivera D, Catrambone V, Thayer JF, Gentili C, Valenza G. Cardiac sympathetic-vagal activity initiates a functional brain-body response to emotional arousal. *Proc Natl Acad Sci U S A*. 2022;119(21):e2119599119.

doi: 10.1073/pnas.2119599119

49. Jandackova VK, Scholes S, Britton A, Steptoe A. Midlife heart rate variability and cognitive decline: A large longitudinal cohort study. *Int J Clin Health Psychol*. 2024;24(4):100518.

doi: 10.1016/j.ijchp.2024.100518

50. Testai FD, Gorelick PB, Chuang PY, *et al*. Cardiac Contributions to Brain Health: A Scientific Statement From the American Heart Association. *Stroke*. 2024;55(12):e425-e438.

doi: 10.1161/STR.0000000000000476

51. Olakorede I, Bogli SY, Czosnyka M, Smielewski P. Identifying the state of cerebrovascular autoregulation using the pressure reactivity index versus the mean flow index: Why metric matters. *J Cereb Blood Flow Metab*. 2026:271678X251406516.

doi: 10.1177/0271678X251406516

52. Vu EL, Brown CHt, Brady KM, Hogue CW. Monitoring of cerebral blood flow autoregulation: physiologic basis, measurement, and clinical implications. *Br J Anaesth*. 2024;132(6):1260-1273.

doi: 10.1016/j.bja.2024.01.043

53. Ungvari A, Kallai A, Stankovics L, *et al*. Age-Related Alterations of Cerebral Autoregulation. *Life (Basel)*. 2025;15(11)doi:10.3390/life15111669

54. Larios A, Sullere S, Gu C. Cerebral blood flow and energy demand: imaging insights into neurovascular function. *Neurophotonics*. 2025;12(Suppl 2):S22810.

doi: 10.1117/1.NPh.12.S2.S22810

55. Zhong J, Li G, Lv Z, *et al*. Neuromodulation of Cerebral Blood Flow: A Physiological Mechanism and Methodological Review of Neurovascular Coupling. *Bioengineering (Basel)*. 2025;12(5)doi:10.3390/bioengineering12050442

56. Barkhudaryan A, Doehner W, Jauert N. Autonomic dysfunction after stroke: an overview of recent clinical evidence and perspectives on therapeutic management. *Clin Auton Res*. 2025;35(4):553-563.

doi: 10.1007/s10286-025-01120-0

57. Rasti SD, Sugiarto AAR, Nuryandi APA, *et al*. Revitalizing brain perfusion: Unveiling advancements through rhythm control strategies in atrial fibrillation-A systematic review. *J Arrhythm*. 2024;40(3):411-422.

doi: 10.1002/joa3.13056

58. Staplin N, de la Sierra A, Ruilope LM, *et al*. Relationship between clinic and ambulatory blood pressure and mortality: an observational cohort study in 59 124 patients. *Lancet*. 17 2023;401(10393):2041-2050.

doi: 10.1016/S0140-6736(23)00733-X

59. Wakai A, Sinert R, Zehtabchi S, *et al*. Risk-stratification tools for emergency department patients with syncope: A systematic review and meta-analysis of direct evidence for SAEM GRACE. *Acad Emerg Med*. 2025;32(1):72-86.

doi: 10.1111/acem.15041

60. Joglar JA, Chung MK, Armbruster AL, *et al*. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2024;149(1):e1-e156.

doi: 10.1161/CIR.0000000000001193

61. Lam SHM, Romiti GF, Corica B, *et al*. Stroke risk stratifications according to CHA2DS2-VASc vs. CHA2DS2-VA in patients with atrial fibrillation: insights from the GLORIA-AF registry. *Eur Heart J Cardiovasc Pharmacother*. 2025;11(5):433-440.

doi: 10.1093/ehjcvp/pvaf031

62. Juraschek SP, Cortez MM, Flack JM, *et al*. Orthostatic Hypotension in Adults With Hypertension: A Scientific Statement From the American Heart Association. *Hypertension*. 2024;81(3):e16-e30.

doi: 10.1161/HYP.0000000000000236

63. Santala OE, Lipponen JA, Jantti H, *et al*. Novel Technologies in the Detection of Atrial Fibrillation: Review of Literature and Comparison of Different Novel Technologies for Screening of Atrial Fibrillation. *Cardiol Rev*. 2024;32(5):440-447.

doi: 10.1097/CRD.0000000000000526

64. Chapman N, Jayasinghe S, Moore MN, *et al*. Absolute cardiovascular risk assessment using 'real world' clinic blood pressures compared to standardized unobserved and ambulatory methods: an observational study. *Hypertens Res*.

2024;47(10):2855-2863.

doi: 10.1038/s41440-024-01841-1

65. Deshmukh A, Covassin N, Dauvilliers Y, Somers VK. Sleep Disruption and Atrial Fibrillation: Evidence, Mechanisms and Clinical Implications. *Circ Res*. 2025;137(5):788-808.

doi: 10.1161/CIRCRESAHA.125.325612

66. Omur SE, Zorlu C, Yilmaz M. Comparison of the Relationship Between Inflammatory Markers and Atrial Fibrillation Burden. *Anatol J Cardiol*. 2023;27(8):486-493.

doi: 10.14744/AnatolJCardiol.2023.2927

67. Ahluwalia N, Koehler J, Sarkar S, *et al*. Temporal Association Between Atrial Fibrillation Burden in Cardiac Implantable Electronic Devices and the Risk of Heart Failure Hospitalization. *Circ Arrhythm Electrophysiol*. 2024;17(8):e012842.

doi: 10.1161/CIRCEP.124.012842

68. Siegler JE, Brorson JR. Device-Detected Atrial Fibrillation and the Impact of Prior Stroke in Stroke Prevention. *J Am Heart Assoc*. 2024;13(17):e037124.

doi: 10.1161/JAHA.124.037124

69. Saputra PBT, Lamara AD, Saputra ME, *et al*. Long-term systolic blood pressure variability independent of mean blood pressure is associated with mortality and cardiovascular events: A systematic review and meta-analysis. *Curr Probl Cardiol*. 2024;49(2):102343.

doi: 10.1016/j.cpcardiol.2023.102343

70. Gregoire JM, Gilon C, Marelli F, *et al*. Short-term atrial fibrillation onset prediction using machine learning. *Eur Heart J Digit Health*. 2025;6(6):1159-1168.

doi: 10.1093/ehjdh/ztaf104

71. Zhang L, Li B, Wu L. Heart rate variability in patients with atrial fibrillation of sinus rhythm or atrial fibrillation: chaos or merit? *Ann Med*. 2025;57(1):2478474.

doi: 10.1080/07853890.2025.2478474

72. Narita K, Hoshide S, Kario K. Comparison of Ambulatory and Home Blood Pressure Variability for Cardiovascular Prognosis and Biomarkers. *Hypertension*. 2023;80(12):2547-2555.

doi: 10.1161/HYPERTENSIONAHA.123.20897

73. Ghanbari H, Whibley D, Lehmann HI, *et al*. Episodes of Atrial Fibrillation and Symptoms: A Temporal Analysis. *Cardiovasc Digit Health J*. 2023;4(5):143-148.

doi: 10.1016/j.cvdhj.2023.06.004

74. Fan X, Cao J, Li M, *et al*. Stroke Related Brain-Heart Crosstalk: Pathophysiology, Clinical Implications, and Underlying Mechanisms. *Adv Sci (Weinh)*. 2024;11(14):e2307698.

doi: 10.1002/advs.202307698

75. Yu T. Neurocardiac Crosstalk: Sympathetic Remodeling and Arrhythmogenesis After Myocardial Infarction. *Curr Issues Mol Biol*. Dec 12 2025;47(12)doi:10.3390/cimb47121037

76. Hernesniemi JA, Pukkila T, Molkkari M, *et al*. Prediction of Sudden Cardiac Death With Ultra-Short-Term Heart Rate Fluctuations. *JACC Clin Electrophysiol*. 2024;10(9):2010-2020.

doi: 10.1016/j.jacep.2024.04.018

77. Peigh G, Koehler J, Majumder S, *et al*. Associations Between Changes in Maximum Daily Atrial Fibrillation Duration, Ischemic Stroke, and Mortality. *JACC Clin Electrophysiol*. 2024;10(11):2394-2406.

doi: 10.1016/j.jacep.2024.06.020

78. Shah AS, Vaccarino V, Moazzami K, *et al*. Autonomic reactivity to mental stress is associated with cardiovascular mortality. *Eur Heart J Open*. 2024;4(6):oeae086.

doi: 10.1093/ehjopen/oeae086

79. Yazdanpanah MH, Naeem F, Doma M, *et al*. Associations Between Objective Sleep Characteristics From Wearable Physiologic Monitors and Incident Atrial Fibrillation. *JACC Adv*. 2026;5(2):102539.

doi: 10.1016/j.jacadv.2025.102539

80. Huang M, Shah AJ, Lampert R, *et al*. Heart Rate Variability, Deceleration Capacity of Heart Rate, and Death: A Veteran Twins Study. *J Am Heart Assoc*. 2024;13(7):e032740.

doi: 10.1161/JAHA.123.032740

81. Ren Y, Zhang H, Tian Y. Prediction of the impact of anxiety on atrial fibrillation recurrence after radiofrequency catheter ablation based on heart rate variability. *Front Surg*. 2025;12:1653123.

doi: 10.3389/fsurg.2025.1653123

82. Orini M, van Duijvenboden S, Young WJ, *et al*. Long-term association of ultra-short heart rate variability with cardiovascular events. *Sci Rep*. 2023;13(1):18966.

doi: 10.1038/s41598-023-45988-2

83. Ishii K, Izaki T, Asahara R, Komine H. Carotid sinus baroafferent signals contribute to cerebral blood flow regulation during acute hypotension in young males: A randomized crossover study. *Physiol Rep*. 2024;12(3):e15937.

doi: 10.14814/phy2.15937

84. Yeh SJ, Lung CW, Jan YK, Lee LL, Wang YC, Liau BY. The relationship between cardiovagal baroreflex and cerebral autoregulation in postural orthostatic tachycardia disorder using advanced cross-correlation function. *Sci Rep*. 2024;14(1):25158.

doi: 10.1038/s41598-024-77065-7

85. Knight SP, Ward M, Newman L, *et al*. Cardiovascular Signal Entropy Predicts All-Cause Mortality: Evidence from The

Irish Longitudinal Study on Ageing (TILDA). *Entropy (Basel)*. 2022;24(5)doi:10.3390/e24050676

86. Marill KA, Lopez S, Hark D, Spahr J, Kapadia N, Liu SW. Increased ventricular ectopy precedes Torsades de Pointes in patients with prolonged QT. *J Electrocardiol*. 2023;80:17-23.

doi: 10.1016/j.jelectrocard.2023.04.003

87. Gavidia M, Zhu H, Montanari AN, *et al*. Early warning of atrial fibrillation using deep learning. *Patterns (N Y)*. 2024;5(6):100970.

doi: 10.1016/j.patter.2024.100970

88. Gregoire JM, Gilon C, Marelli F, Godart P, Bersini H, Carlier S. Autonomic Nervous System Activity before Atrial Fibrillation Onset as Assessed by Heart Rate Variability. *Rev Cardiovasc Med*. 2025;26(1):25364.

doi: 10.31083/RCM25364

89. Ye Z, Ramdat Misier NL, van Schie MS, *et al*. Identification of Critical Slowing of Conduction Using Unipolar Atrial Voltage and Fractionation Mapping. *JACC Clin Electrophysiol*. 2024;10(9):1971-1981.

doi: 10.1016/j.jacep.2024.04.036

90. Ninomiya Y, Enokizono K, Kawasoe S, *et al*. QT prolongation and excessive variability predicts new-onset atrial fibrillation in the health screening data of Japanese adults. *PLoS One*. 2025;20(10):e0333169.

doi: 10.1371/journal.pone.0333169

91. Smoczynska A, Loen V, Sprenkeler DJ, *et al*. Short-Term Variability of the QT Interval Can be Used for the Prediction of Imminent Ventricular Arrhythmias in Patients With Primary Prophylactic Implantable Cardioverter Defibrillators. *J Am Heart Assoc*. 2020;9(23):e018133.

doi: 10.1161/JAHA.120.018133

92. Mori S, Hori A, Turker I, *et al*. Abnormal Cardiac Repolarization After Seizure Episodes in Structural Brain Diseases: Cardiac Manifestation of Electrical Remodeling in the Brain? *J Am Heart Assoc*. 2021;10(9):e019778.

doi: 10.1161/JAHA.120.019778

93. Shlobin NA, Thijs RD, Benditt DG, Zeppenfeld K, Sander JW. Sudden death in epilepsy: the overlap between cardiac and neurological factors. *Brain Commun*. 2024;6(5):fcae309.

doi: 10.1093/braincomms/fcae309

94. Baker JR, Beach PA, Ranada SI, *et al*. Cerebral Blood Flow Dynamics in Neurogenic Orthostatic Hypotension: A Systematic Review and Meta-Analysis. *Hypertension*. 2025;82(1):106-117.

doi: 10.1161/HYPERTENSIONAHA.124.23188

95. Benditt DG, Fedorowski A, Sutton R, van Dijk JG. Pathophysiology of syncope: current concepts and their development. *Physiol Rev*. 2025;105(1):209-266.

doi: 10.1152/physrev.00007.2024

96. Wiersinga JH, Wolters FJ, Peters MJ, Rhodius-Meester HF, Trappenburg MC, Muller M. Orthostatic hypotension and cerebral small vessel disease: A systematic review. *J Cereb Blood Flow Metab*. 2025;45(1):13-31.

doi: 10.1177/0271678X241283226

97. Attiq A, Afzal S, Ahmad W, Kandeel M. Hegemony of inflammation in atherosclerosis and coronary artery disease. *Eur J Pharmacol*. 2024;966:176338.

doi: 10.1016/j.ejphar.2024.176338

98. Cheng H, Dai J, Li G, *et al*. Quantitative analysis of systemic perfusion and cerebral blood flow in the modeling of aging and orthostatic hypotension. *Front Physiol*. 2024;15:1353768.

doi: 10.3389/fphys.2024.1353768

99. Boettger P, Sedighi J, Buerke M, Braun T, Juenemann M, Omar OA. Circadian Blood Pressure Phenotyping Identifies Subtype-Specific Risk and Outcomes in Acute Ischemic Stroke: A Prospective Study. *Transl Stroke Res*. 2025;17(1):5.

doi: 10.1007/s12975-025-01400-x

100. Parati G, Pengo MF, Avolio A, *et al*. Nocturnal blood pressure: pathophysiology, measurement and clinical implications. Position paper of the European Society of Hypertension. *J Hypertens*. 2025;43(8):1296-1318.

doi: 10.1097/HJH.0000000000004053

101. Claassen JA, Meel-van den Abeelen AS, Simpson DM, Panerai RB, international Cerebral Autoregulation Research N. Transfer function analysis of dynamic cerebral autoregulation: A white paper from the International Cerebral Autoregulation Research Network. *J Cereb Blood Flow Metab*. 2016;36(4):665-80.

doi: 10.1177/0271678X15626425

102. Gottesman RF, Egle M, Groechel RC, Mughal A. Blood pressure and the brain: the conundrum of hypertension and dementia. *Cardiovasc Res*. 2025;120(18):2360-2372.

doi: 10.1093/cvr/cvaf010

103. Zhao B, Jia W, Yuan Y, *et al*. Impact of blood pressure variability and cerebral small vessel disease: A systematic review and meta-analysis. *Heliyon*. 2024;10(12):e33264.

doi: 10.1016/j.heliyon.2024.e33264

104. Webb AJS, Klerman EB, Mandeville ET. Circadian and Diurnal Regulation of Cerebral Blood Flow. *Circ Res*. 2024;134(6):695-710.

doi: 10.1161/CIRCRESAHA.123.323049

105. Mack A, Vanden Hoek T, Du X. Thromboinflammation and the Role of Platelets. *Arterioscler Thromb Vasc Biol*. 2024;44(6):1175-1180.

doi: 10.1161/ATVBAHA.124.320149

106. Zhou K, Chen Y, Pang J, Zhang J, Lu J. The endothelial-immunothrombotic storm in viral sepsis: lessons from COVID-19. *Front Immunol*. 2025;16:1681764.

doi: 10.3389/fimmu.2025.1681764

107. Geng YJ, Smolensky MH, Sum-Ping O, Hermida R, Castriotta RJ. Circadian rhythms of risk factors and management in atherosclerotic and hypertensive vascular disease: Modern chronobiological perspectives of an ancient disease. *Chronobiol Int*. 2023;40(1):33-62.

doi: 10.1080/07420528.2022.2080557

108. McHill AW, Melanson EL, Wright KP, Jr., Depner CM. Circadian misalignment disrupts biomarkers of cardiovascular disease risk and promotes a hypercoagulable state. *Eur J Neurosci*. 2024;60(7):5450-5466.

doi: 10.1111/ejn.16468

109. Mensah GA, Arnold N, Prabhu SD, Ridker PM, Welty FK. Inflammation and Cardiovascular Disease: 2025 ACC Scientific Statement: A Report of the American College of Cardiology. *J Am Coll Cardiol*. 2025.

doi: 10.1016/j.jacc.2025.08.047

110. Stoll L, Ha EE, Lo JC. Metabolic and Inflammatory Mechanisms Driving Atrial Fibrillation. *Annu Rev Pharmacol Toxicol*. 2026;66(1):519-539.

doi: 10.1146/annurev-pharmtox-062124-025403

111. Shi J, Tong R, Zhou M, *et al*. Circadian nuclear receptor Rev-erbalpha is expressed by platelets and potentiates platelet activation and thrombus formation. *Eur Heart J*. 2022;43(24):2317-2334.

doi: 10.1093/eurheartj/ehac109

112. Beishon L, Vasilopoulos T, Salinet ASM, *et al*. Individual Patient Data Meta-Analysis of Dynamic Cerebral Autoregulation and Functional Outcome After Ischemic Stroke. *Stroke*. 2024;55(5):1235-1244.

doi: 10.1161/STROKEAHA.123.045700

113. Whitaker AA, Aaron SE, Chertoff M, *et al*. Lower dynamic cerebral autoregulation following acute bout of low-volume high-intensity interval exercise in chronic stroke compared to healthy adults. *J Appl Physiol (1985)*. 2024;136(4):707-720.

doi: 10.1152/japplphysiol.00635.2023

114. Hilkens NA, de Leeuw FE, Klijn CJ, Richard E. Blood pressure variability and white matter hyperintensities after ischemic stroke. *Cereb Circ Cogn Behav*. 2024;6:100205.

doi: 10.1016/j.cccb.2024.100205

115. Janssen E, van Dalen JW, Cai M, *et al*. Visit-to-visit blood pressure variability and progression of white matter hyperintensities over 14 years. *Blood Press*. 2024;33(1):2314498.

doi: 10.1080/08037051.2024.2314498

116. Starmans NL, Wolters FJ, Leeuwis AE, *et al*. Twenty-four hour blood pressure variability and the prevalence and the progression of cerebral white matter hyperintensities. *J Cereb Blood Flow Metab*. 2023;43(5):801-811.

doi: 10.1177/0271678X221149937

117. Lago S, de Beukelaar TT, Casetta I, Arcara G, Mantini D. Heart Rate Variability and Autonomic Dysfunction After Stroke: Prognostic Markers for Recovery. *Biomedicines*. 2025;13(7)doi:10.3390/biomedicines13071659

118. Lenka A, Beach P. Approach to Cardiovascular Autonomic Dysfunction in Patients with Synucleinopathies. *Mov Disord Clin Pract*. 2025;12(12):2092-2105.

doi: 10.1002/mdc3.70268

119. Woo T, Kim J, Kim KT, *et al*. Blood Pressure Variability as a Diagnostic Marker for alpha-Synucleinopathy in Patients With Orthostasis. *J Am Heart Assoc*. 2025;14(20):e043276.

doi: 10.1161/JAHA.125.043276

120. Kim KT, Lee JH, Hong JP, *et al*. Blood Pressure Variability and Ocular Vestibular-Evoked Myogenic Potentials Are Independently Associated With Orthostatic Hypotension. *J Clin Neurol*. 2024;20(6):571-579.

doi: 10.3988/jcn.2024.0092

121. Fang SC, Wu YL, Tsai PS. Heart Rate Variability and Risk of All-Cause Death and Cardiovascular Events in Patients With Cardiovascular Disease: A Meta-Analysis of Cohort Studies. *Biol Res Nurs*. 2020;22(1):45-56.

doi: 10.1177/1099800419877442

122. Tang SY, Lin C, Ma HP, *et al*. Implication of heart rhythm complexity in predicting long-term outcomes in pulmonary hypertension. *J Formos Med Assoc*. 2025;124(9):852-857.

doi: 10.1016/j.jfma.2024.10.027

123. Amoni M, Ingelaere S, Moeyersons J, *et al*. Regional beat-to-beat variability of repolarization increases during ischemia and predicts imminent arrhythmias in a pig model of myocardial infarction. *Am J Physiol Heart Circ Physiol*. 2023;325(1):H54-H65.

doi: 10.1152/ajpheart.00732.2022

124. Loen V, Smoczynska A, Aranda Hernandez A, *et al*. Automatic measurement of short-term variability of repolarization to indicate ventricular arrhythmias in a porcine model of cardiac ischaemia. *Europace*. 2023;25(11) doi:10.1093/europace/euad341

125. Xu Y, Barnes VA, Harris RA, *et al*. Sleep Variability, Sleep Irregularity, and Nighttime Blood Pressure Dipping. *Hypertension*. 2023;80(12):2621-2626.

doi: 10.1161/HYPERTENSIONAHA.123.21497

126. Ganti V, Carek AM, Jung H, *et al*. Enabling Wearable Pulse

Transit Time-Based Blood Pressure Estimation for Medically Underserved Areas and Health Equity: Comprehensive Evaluation Study. *JMIR Mhealth Uhealth*. 2021;9(8):e27466.

doi: 10.2196/27466

127. Mukkamala R, Shroff SG, Landry C, Kyriakoulis KG, Avolio AP, Stergiou GS. The Microsoft Research Aurora Project: Important Findings on Cuffless Blood Pressure Measurement. *Hypertension*. 2023;80(3):534-540.

doi: 10.1161/HYPERTENSIONAHA.122.20410

128. Stehlik J, Schmalfuss C, Bozkurt B, *et al*. Continuous Wearable Monitoring Analytics Predict Heart Failure Hospitalization: The LINK-HF Multicenter Study. *Circ Heart Fail*. 2020;13(3):e006513.

doi: 10.1161/CIRCHEARTFAILURE.119.006513

129. M AS, O'Connor JD, Boyle R, *et al*. Slower speed of blood pressure recovery after standing is associated with accelerated brain aging: Evidence from The Irish Longitudinal Study on Ageing (TILDA). *Cereb Circ Cogn Behav*. 2024;6:100212.

doi: 10.1016/j.cccb.2024.100212

130. Lamotte G, Coon EA, Suarez MD, *et al*. Standardized Autonomic Testing in Patients With Probable Radiation-Induced Afferent Baroreflex Failure. *Hypertension*. 2022;79(1):50-56.

doi: 10.1161/HYPERTENSIONAHA.121.17805

131. Udyavar A, Shenthar J, Naik AM, *et al*. A contemporary review of the head-up tilt test: Utility and limitations. *Indian Heart J*. 2025;77(3):243-251.

doi: 10.1016/j.ihj.2025.03.014

132. van Dijk JG, Ghariq M, Kerkhof FI, *et al*. Novel Methods for Quantification of Vasodepression and Cardioinhibition During Tilt-Induced Vasovagal Syncope. *Circ Res*. 2020;127(5):e126-e138.

doi: 10.1161/CIRCRESAHA.120.316662

133. Kwun JS, Lee JH, Park BE, *et al*. Diagnostic Value of a Wearable Continuous Electrocardiogram Monitoring Device (AT-Patch) for New-Onset Atrial Fibrillation in High-Risk Patients: Prospective Cohort Study. *J Med Internet Res*. 2023;25:e45760.

doi: 10.2196/45760

134. Rakai E, Etminani F, Younan N, *et al*. Systematic, randomized atrial fibrillation screening using detailed phenotyping with a risk prediction model combined with patch electrocardiogram in a Swedish population aged 65 years or older: the CONSIDERING-AF trial. *Europace*. 2025;27(9)doi:10.1093/europace/euaf190

135. Campbell LM, Weinstein AM, Henneghan A, *et al*. Exploring the relationship between mean performance and within-person variability on smartphone-based cognitive testing in adults across the lifespan. *NPP Digit Psychiatry Neurosci*. 2025;3(1):15.

doi: 10.1038/s44277-025-00036-x

136. De Anda-Duran I, Sunderaraman P, Searls E, *et al*. Comparing Cognitive Tests and Smartphone-Based Assessment in 2 US Community-Based Cohorts. *J Am Heart Assoc*. 2024;13(2):e032733.

doi: 10.1161/JAHA.123.032733

137. Lopez-Galvez R, Rivera-Caravaca JM, Mandaglio-Collados D, *et al*. Endothelial activation, cell-cell interactions, and inflammatory pathways in postoperative atrial fibrillation following cardiac surgery. *Biomed J*. 2025;48(4):100821.

doi: 10.1016/j.bj.2024.100821

138. Seidel M, Bogdahn D, Seibert FS, *et al*. Rhythm control in persistent atrial fibrillation improves endothelial function without uniform anti-inflammatory effects: A 9-month prospective cohort study. *Int J Cardiol Heart Vasc*. 2026;63:101879.

doi: 10.1016/j.ijcha.2026.101879

139. Teissandier D, Moustafa F, Denaives A, *et al*. Thrombin generation in real life bleeding patients on oral anticoagulants reversed (or not) with (activated) prothrombin complex concentrate. *Thromb Res*. 2023;223:184-193.

doi: 10.1016/j.thromres.2023.01.022

140. Sible IJ, Nation DA. Blood Pressure Variability and Cerebral Perfusion Decline: A Post Hoc Analysis of the SPRINT MIND Trial. *J Am Heart Assoc*. 2023;12(12):e029797.

doi: 10.1161/JAHA.123.029797

141. Chahine Y, Chamoun N, Kassar A, Bockus L, Macheret F, Akoum N. Atrial fibrillation substrate and impaired left atrial function: a cardiac MRI study. *Europace*. 2024;26(11) doi:10.1093/europace/euae258

142. Karakasis P, Theofilis P, Vlachakis PK, *et al*. Atrial Fibrosis in Atrial Fibrillation: Mechanistic Insights, Diagnostic Challenges, and Emerging Therapeutic Targets. *Int J Mol Sci*. 2024;26(1)doi:10.3390/ijms26010209

143. Henriksson M, Martin-Yebra A, Butkuviene M, *et al*. Modeling and Estimation of Temporal Episode Patterns in Paroxysmal Atrial Fibrillation. *IEEE Trans Biomed Eng*. 2021;68(1):319-329.

doi: 10.1109/TBME.2020.2995563

144. Saiz-Vivo J, Corino VDA, Martin-Yebra A, Mainardi LT, Hatala R, Sornmo L. Atrial fibrillation episode patterns as predictor of clinical outcome of catheter ablation. *Med Biol Eng Comput*. 2023;61(2):317-327.

doi: 10.1007/s11517-022-02713-x

145. Vandenberk B, Haemers P, Morillo C. The autonomic nervous system in atrial fibrillation-pathophysiology and non-invasive assessment. *Front Cardiovasc Med*. 2023;10:1327387.

doi: 10.3389/fcvm.2023.1327387

146. Becher N, Metzner A, Toennis T, Kirchhof P, Schnabel RB. Atrial fibrillation burden: a new outcome predictor and therapeutic target. *Eur Heart J*. 2024;45(31):2824-2838.

doi: 10.1093/eurheartj/ehae373

147. Singer DE, Ziegler PD, Koehler JL, Sarkar S, Passman RS. Temporal Association Between Episodes of Atrial Fibrillation and Risk of Ischemic Stroke. *JAMA Cardiol*. 2021;6(12):1364-1369.

doi: 10.1001/jamacardio.2021.3702

148. Khan MS, Miller AJ, Ejaz A, *et al*. Cerebral Blood Flow in Orthostatic Intolerance. *J Am Heart Assoc*. 2025;14(3):e036752.

doi: 10.1161/JAHA.124.036752

149. Vidal-Petiot E, Pathak A, Azulay JP, Pavy-Le Traon A, Hanon O. Orthostatic hypotension: Review and expert position statement. *Rev Neurol (Paris)*. 2024;180(1-2):53-64.

doi: 10.1016/j.neurol.2023.11.001

150. Wang L, van Poelgeest EP, Klop M, Claassen J, Hoekstra AG, van der Velde N. Beat-to-Beat Blood Pressure Monitoring and Orthostatic Hypotension-Related Falls in Two Cohorts of Older Adults. *Geriatrics (Basel)*. 2025;10(4)doi:10.3390/geriatrics10040102

151. Mitrica M, Lorusso L, Badea AA, *et al*. The Hidden Heart: Exploring Cardiac Damage Post-Stroke: A Narrative Review. *Medicina (Kaunas)*. 2024;60(10)doi:10.3390/medicina60101699

152. Marins FR, Limborco-Filho M, D'Abreu BF, *et al*. Autonomic and cardiovascular consequences resulting from experimental hemorrhagic stroke in the left or right intermediate insular cortex in rats. *Auton Neurosci*. 2020;227:102695.

doi: 10.1016/j.autneu.2020.102695

153. Tian X, Wang J, Wang X, *et al*. Topography of the insular cortex in heart rate control: high-precision mapping reveals critical role of the middle short gyrus. *Front Neurosci*. 2025;19:1665378.

doi: 10.3389/fnins.2025.1665378

154. Rissardo JP, Gadelmawla AF, Khalil I, Abdulgadir A, Bhatti KS, Fornari Caprara AL. Epidemiology of autonomic dysfunction in Parkinson's disease (Review). *Med Int (Lond)*. 2025;5(6):1-25.

doi: 10.3892/mi.2025.267

155. Basri AM, Turki AF. Evaluating Heart Rate Variability as a Biomarker for Autonomic Function in Parkinson's Disease Rehabilitation: A Clustering-Based Analysis of Exercise-Induced Changes. *Medicina (Kaunas)*. 2025;61(3) doi:10.3390/medicina61030527

156. Sabino-Carvalho JL, Falquetto B, Takakura AC, Vianna LC. Baroreflex dysfunction in Parkinson's disease: integration of central and peripheral mechanisms. *J Neurophysiol*. 2021;125(4):1425-1439.

doi: 10.1152/jn.00548.2020

157. Lenarczyk R, Zeppenfeld K, Tfelt-Hansen J, *et al*. Management of patients with an electrical storm or clustered ventricular arrhythmias: a clinical consensus statement of the European Heart Rhythm Association of the ESC-endorsed by the Asia-Pacific Heart Rhythm Society, Heart Rhythm Society, and Latin-American Heart Rhythm Society. *Europace*. 2024;26(4)doi:10.1093/europace/euae049

158. Spona DC, Haugan KJ, Graff C, *et al*. Circadian patterns of atrial fibrillation and disease progression assessed by implanted loop recorders. *Eur Heart J*. 2025;46(47):5160-5173.

doi: 10.1093/eurheartj/ehaf386

159. Scheid MR, Friedmann B, Oppenheim M, Hirsch JS, Zanos TP. Development and validation of a clinical wearable deep learning based continuous inhospital deterioration prediction model. *Nat Commun*. 2025;16(1):9513.

doi: 10.1038/s41467-025-65219-8

160. Yadav A, Dandu H, Parchani G, *et al*. Early detection of deteriorating patients in general wards through continuous contactless vital signs monitoring. *Front Med Technol*. 2024;6:1436034.

doi: 10.3389/fmedt.2024.1436034

161. Fraser RA, Walker RJ, Campbell JA, Ekwunife O, Egede LE. Integration of artificial intelligence and wearable technology in the management of diabetes and prediabetes. *NPJ Digit Med*. 2025;8(1):687.

doi: 10.1038/s41746-025-02036-9

162. Xiang JZ, Wang QY, Fang ZB, Esquivel JA, Su ZX. A multi-modal deep learning approach for stress detection using physiological signals: integrating time and frequency domain features. *Front Physiol*. 2025;16:1584299.

doi: 10.3389/fphys.2025.1584299

163. Contreras M, Silva B, Shickel B, *et al*. Real-time prediction of intensive care unit patient acuity and therapy requirements using state-space modelling. *Nat Commun*. 2025;16(1):7315.

doi: 10.1038/s41467-025-62121-1

164. Hinrichs N, Roeschl T, Lanmueller P, *et al*. Short-term vital parameter forecasting in the intensive care unit: A benchmark study leveraging data from patients after cardiothoracic surgery. *PLOS Digit Health*. 2024;3(9):e0000598.

doi: 10.1371/journal.pdig.0000598

165. Widatalla N, Younis SA, Khandoker A. Heart rate transition patterns reveal autonomic dysfunction in heart failure with renal function decline: a symbolic and Markov model approach. *BioData Min*. 2025;18(1):45.

doi: 10.1186/s13040-025-00460-x

166. Beauchamp MK, D'Amore C, Raina P, *et al*. Establishing global standards on wearable technology for measuring mobility in ageing populations: an international consensus exercise. *Age Ageing*. 2026;55(1).

doi: 10.1093/ageing/afaf376

167. Chodankar D, Raval TK, Jeyaraj J. The role of remote data capture, wearables, and digital biomarkers in decentralized clinical trials. *Perspect Clin Res*. 2024;15(1):38-41.

doi: 10.4103/picr.picr_219_22

168. Collins GS, Moons KGM, Dhiman P, *et al*. TRIPOD+AI statement: updated guidance for reporting clinical prediction models that use regression or machine learning methods. *BMJ*. 2024;385:e078378.

doi: 10.1136/bmj-2023-078378

169. de Kanter E, Kaul T, Heus P, *et al*. Adherence to TRIPOD+AI guideline: an updated reporting assessment tool. *J Clin Epidemiol*. 2025;191:112118.

doi: 10.1016/j.jclinepi.2025.112118

170. Moons KGM, Damen JAA, Kaul T, *et al*. PROBAST+AI: an updated quality, risk of bias, and applicability assessment tool for prediction models using regression or artificial intelligence methods. *BMJ*. 2025;388:e082505.

doi: 10.1136/bmj-2024-082505

171. Bijlani N, Maldonado OM, Nilforooshan R, *et al*. Utilizing graph neural networks for adverse health detection and personalized decision making in sensor-based remote monitoring for dementia care. *Comput Biol Med*. 2024;183:109287.

doi: 10.1016/j.compbiomed.2024.109287

172. Nakano T, Fujino M, Miyata M, Yoshikawa T. A Clinically Oriented Framework for Real-Time Heart Rate Variability Analysis: A Novel Approach To Personalized and Robust Monitoring. *J Med Syst*. 2026;50(1):13.

doi: 10.1007/s10916-026-02342-z

173. Olesen JB, Torp-Pedersen C, Hansen ML, Lip GY. The value of the CHA2DS2-VASc score for refining stroke risk stratification in patients with atrial fibrillation with a CHADS2 score 0-1: a nationwide cohort study. *Thromb Haemost*. 2012;107(6):1172-9.

doi: 10.1160/TH12-03-0175

174. Han S, Jia R, Cen Z, *et al*. Early rhythm control vs. rate control in atrial fibrillation: A systematic review and meta-analysis. *Front Cardiovasc Med*. 2023;10:978637.

doi: 10.3389/fcvm.2023.978637

175. Kirchhof P, Camm AJ, Goette A, *et al*. Early Rhythm-Control Therapy in Patients with Atrial Fibrillation. *N Engl J Med*. 2020;383(14):1305-1316.

doi: 10.1056/NEJMoa2019422

176. Brignole M, Moya A, de Lange FJ, *et al*. 2018 ESC Guidelines for the diagnosis and management of syncope. *Eur Heart J*. 2018;39(21):1883-1948.

doi: 10.1093/eurheartj/ehy037

177. Dani M, Dirksen A, Taraborrelli P, *et al*. Orthostatic hypotension in older people: considerations, diagnosis and management. *Clin Med (Lond)*. 2021;21(3):e275-e282.

doi: 10.7861/clinmed.2020-1044

178. Fedorowski A, Ricci F, Hamrefors V, *et al*. Orthostatic Hypotension: Management of a Complex, But Common, Medical Problem. *Circ Arrhythm Electrophysiol*. 2022;15(3):e010573.

doi: 10.1161/CIRCEP.121.010573

179. Jasinski SR, Presby DM, Grosicki GJ, Capodilupo ER, Lee VH. A Novel method for quantifying fluctuations in wearable derived daily cardiovascular parameters across the menstrual cycle. *NPJ Digit Med*. 2024;7(1):373.

doi: 10.1038/s41746-024-01394-0

180. Wang BX, Brennand E, Le Page P, Mitchell ARJ. Heart rate variability in cardiovascular disease diagnosis, prognosis and management. *Front Cardiovasc Med*. 2025;12:1680783.

doi: 10.3389/fcvm.2025.1680783

181. Bayoumy K, Gaber M, Elshafeey A, *et al*. Smart wearable devices in cardiovascular care: where we are and how to move forward. *Nat Rev Cardiol*. 2021;18(8):581-599.

doi: 10.1038/s41569-021-00522-7

182. Varma N, Han JK, Passman R, *et al*. Promises and Perils of Consumer Mobile Technologies in Cardiovascular Care: JACC Scientific Statement. *J Am Coll Cardiol*. 2024;83(5):611-631.

doi: 10.1016/j.jacc.2023.11.024

183. Healey JS, Lopes RD, Granger CB, *et al*. Apixaban for Stroke Prevention in Subclinical Atrial Fibrillation. *N Engl J Med*. 2024;390(2):107-117.

doi: 10.1056/NEJMoa2310234

184. Kirchhof P, Schotten U, Zapf A. Anticoagulation with Edoxaban in Patients with Atrial High-Rate Episodes. Reply. *N Engl J Med*. 2023;389(24):2302-2303.

doi: 10.1056/NEJMc2312837

185. Lewandowska K, Medrzycka-Dabrowska W, Miklas M, Wujtewicz M. Improving alarm management to reduce alarm fatigue in critical care: a mixed-methods study. *Intensive Crit Care Nurs*. 2026;93:104254.

doi: 10.1016/j.iccn.2025.104254

186. Michels EAM, Gilbert S, Koval I, Wekenborg MK. Alarm fatigue in healthcare: a scoping review of definitions, influencing factors, and mitigation strategies. *BMC Nurs*.

2025;24(1):664.

doi: 10.1186/s12912-025-03369-2

187. Ganguli I, Simpkin AL, Lupo C, *et al*. Cascades of Care After Incidental Findings in a US National Survey of Physicians. *JAMA Netw Open*. 2019;2(10):e1913325.

doi: 10.1001/jamanetworkopen.2019.13325

188. Senoo K. Atrial Fibrillation Screening: Burden or Benefit for Patients and the Healthcare System. *J Cardiovasc Electrophysiol*. 2025.

doi: 10.1111/jce.70153

189. Khera R, Oikonomou EK, Nadkarni GN, *et al*. Transforming Cardiovascular Care With Artificial Intelligence: From Discovery to Practice: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2024;84(1):97-114.

doi: 10.1016/j.jacc.2024.05.003

190. Tsai WC, Hung TC, Kusayama T, *et al*. Autonomic Modulation of Atrial Fibrillation. *JACC Basic Transl Sci*. 2023;8(10):1398-1410.

doi: 10.1016/j.jacbts.2023.03.019

191. Khan MS, Javaid SS, Mentz RJ, *et al*. Heart rate variability in patients with cardiovascular diseases. *Prog Cardiovasc Dis*. 2025;91:67-79.

doi: 10.1016/j.pcad.2025.06.003

192. Chen X, Zhang X, Fang X, Feng S. Association of inflammatory markers with clinical outcomes in atrial fibrillation: a meta-analysis. *Front Cardiovasc Med*. 2025;12:1504163.

doi: 10.3389/fcvm.2025.1504163

193. Shitole SG, Heckbert SR, Marcus GM, *et al*. Assessment of Inflammatory Biomarkers and Incident Atrial Fibrillation in Older Adults. *J Am Heart Assoc*. 2024;13(24):e035710.

doi: 10.1161/JAHA.124.035710

194. Svihrova R, Dei Rossi A, Marzorati D, Tzovara A, Faraci FD. Designing digital health interventions with causal inference and multi-armed bandits: a review. *Front Digit Health*. 2025;7:1435917.

doi: 10.3389/fdgth.2025.1435917

195. Liu S, Cui Y, Chen M. Heart rate variability: a multidimensional perspective from physiological marker to brain-heart axis disorders prediction. *Front Cardiovasc Med*. 2025;12:1630668.

doi: 10.3389/fcvm.2025.1630668

196. Olivieri F, Biscetti L, Pimpini L, Pelliccioni G, Sabbatinelli J, Giunta S. Heart rate variability and autonomic nervous system imbalance: Potential biomarkers and detectable hallmarks of aging and inflammaging. *Ageing Res Rev*. 2024;101:102521.

doi: 10.1016/j.arr.2024.102521

197. Boussen S, Benard-Tertrais M, Ogea M, *et al*. Heart rate complexity helps mortality prediction in the intensive care unit: A pilot study using artificial intelligence. *Comput Biol Med*. 2024;169:107934.

doi: 10.1016/j.compbiomed.2024.107934

198. Zamora-Justo JA, Campos-Aguilar M, Beas-Jara MDC, *et al*. Utility of nonlinear analysis of heart rate variability in early detection of metabolic syndrome. *Front Physiol*. 2025;16:1597314.

doi: 10.3389/fphys.2025.1597314

199. Jing Z, Wang G, Li Z, Wu S, Qiu X, Huang R. Association of blood pressure variability with target organ damage in older patients with essential hypertension. *Chronic Dis Transl Med*. 2023;9(4):320-328.

doi: 10.1002/cdt3.73

200. Kulkarni S, Parati G, Bangalore S, *et al*. Blood pressure variability: a review. *J Hypertens*. 2025;43(6):929-938.

doi: 10.1097/HJH.0000000000003994

201. Zhou X, Yuan Q, Yuan J, Du ZM, Zhuang X, Liao X. The impact of visit-to-visit heart rate variability on all-cause mortality in atrial fibrillation. *Ann Noninvasive Electrocardiol*. 2024;29(1):e13094.

doi: 10.1111/anec.13094

202. Biczuk B, Zurek S, Jurga S, Turska E, Guzik P, Piskorski J. Sleep Stage Classification Through HRV, Complexity Measures, and Heart Rate Asymmetry Using Generalized Estimating Equations Models. *Entropy (Basel)*. 2024;26(12) doi:10.3390/e26121100

203. Gronwald T, Kock H, Roglin L, *et al*. Recovery of Linear and Nonlinear Heart Rate Variability Metrics After Short-Term Moderate versus Vigorous Intensity Exercise: A Cross-Sectional Randomized Cross-Over Study. *Eur J Sport Sci*. 2025;25(11):e70077.

doi: 10.1002/ejsc.70077

204. Eilertsen RK, Midtbo H, Nawaz B, Fromm A, Waje-Andreassen U, Gerdts E. Associations of short-term blood pressure variability with presence and progression of organ damage over five years in ischaemic stroke survivors: the Norwegian Stroke in the Young Study. *Blood Press*. 2025;34(1):2521523.

doi: 10.1080/08037051.2025.2521523

205. Kelters IR, Koop Y, Young ME, Daiber A, van Laake LW. Circadian rhythms in cardiovascular disease. *Eur Heart J*. 2025;46(36):3532-3545.

doi: 10.1093/eurheartj/ehaf367

206. Addleman JS, Lackey NS, DeBlauw JA, Hajduczok AG. Heart Rate Variability Applications in Strength and Conditioning: A Narrative Review. *J Funct Morphol Kinesiol*. 2024;9(2) doi:10.3390/jfmk9020093

207. Riganello F, Cortese MD, Vatrano M, Lucca LF, Soddu A. Autonomic heart rate variability trends predict outcome in disorders of consciousness. *Sci Rep*. 2025;15(1):33148.

doi: 10.1038/s41598-025-18615-5

208. Shen Y, Fang Z, Zhang T, Yu F, Xu Y, Yang L. Heart rate variability with circadian rhythm removed achieved high accuracy for stress assessment across all times throughout the day. *Front Physiol*. 2025;16:1535331.

doi: 10.3389/fphys.2025.1535331

209. Sagris D, Georgiopoulos G, Pateras K, *et al*. Atrial High-Rate Episode Duration Thresholds and Thromboembolic Risk: A Systematic Review and Meta-Analysis. *J Am Heart Assoc*. 2021;10(22):e022487.

doi: 10.1161/JAHA.121.022487

210. Wu L, Yuan Z, Zeng Y, *et al*. Routinely available inflammation biomarkers to predict stroke and mortality in atrial fibrillation. *Clinics (Sao Paulo)*. 2025;80:100610.

doi: 10.1016/j.clinsp.2025.100610

211. Saiz-Vivo J, Chakravarthy N, Ho WHH, *et al*. Artificial intelligence for atrial fibrillation prediction while in sinus rhythm: a narrative review. *Eur Heart J Digit Health*. 2026;7(2):ztaf144.

doi: 10.1093/ehjdh/ztaf144

212. Salbach C, Yildirim M, Milles BR, *et al*. Improvement in risk prediction for patients with atrial fibrillation and intermediate-risk CHA2DS2-VASc score utilizing highly sensitive cardiac troponin T. *PLoS One*. 2025;20(8):e0330164.

doi: 10.1371/journal.pone.0330164

213. Xing LY, Diederichsen SZ, Hojberg S, *et al*. The ABC-Stroke Risk Score and Effects of Atrial Fibrillation Screening on Stroke Prevention: Results From the Randomized LOOP Study. *J Am Heart Assoc*. 2024;13(4):e032744.

doi: 10.1161/JAHA.123.032744

214. Short SAP, Wilkinson K, Hald E, *et al*. Improving stroke risk prediction in atrial fibrillation with circulating biomarkers: the CHA(2)DS(2)-VASc-Biomarkers model. *J Thromb Haemost*. 2025;23(10):3160-3172.

doi: 10.1016/j.jtha.2025.06.007

215. Asmuje NF, Mat S, Goh CH, Myint PK, Tan MP. Increased Beat-to-Beat Blood Pressure Variability Is Associated With Impaired Cognitive Function. *Am J Hypertens*. 2022;35(12):998-1005.

doi: 10.1093/ajh/hpac107

216. Lohman T, Sible I, Engstrom AC, *et al*. Beat-to-beat blood pressure variability, hippocampal atrophy, and memory impairment in older adults. *Geroscience*. 2025;47(1):993-1003.

doi: 10.1007/s11357-024-01303-z

217. Webb AJS, Lawson A, Wartolowska K, Mazzucco S, Rothwell PM. Progression of Beat-to-Beat Blood Pressure Variability Despite Best Medical Management. *Hypertension*. 2021;77(1):193-201.

doi: 10.1161/HYPERTENSIONAHA.120.16290

218. Ahluwalia N, Abbass H, Hussain A, *et al*. Patient-Led Smartwatch ECG Follow-Up Strategy After AF Ablation: Clinical Trial Design and Implementation. *JACC Adv*. 2026;5(2):102534.

doi: 10.1016/j.jacadv.2025.102534

219. Steinhubl SR, Waalen J, Edwards AM, *et al*. Effect of a Home-Based Wearable Continuous ECG Monitoring Patch on Detection of Undiagnosed Atrial Fibrillation: The mSToPS Randomized Clinical Trial. *JAMA*. 2018;320(2):146-155.

doi: 10.1001/jama.2018.8102

220. Bellfield RAA, Hormiga PR, Olier I, *et al*. AI-driven clustering and visualization of electrocardiogram signals to enhance screening for atrial fibrillation: The supermarket/hypermarket opportunistic screening for atrial fibrillation study. *Heart Rhythm O2*. 2025;6(10):1601-1612.

doi: 10.1016/j.hroo.2025.07.003

221. Syan J, Joshi M, Beard J, Attebery J, Ng FS, Khan S. Wearable Continuous Vital Sign Monitoring Study (WARD-AMS) to Detect Clinical Deterioration in Postoperative General Surgery Patients: Protocol for a Randomized Controlled Trial. *JMIR Res Protoc*. 2025;14:e81558.

doi: 10.2196/81558

222. Zahrieh D, Croghan IT, Inselman JW, Mandrekar SJ. Guidelines for Data and Safety Monitoring in Pragmatic Randomized Clinical Trials Using Case Studies. *Mayo Clin Proc*. 2023;98(11):1712-1726.

doi: 10.1016/j.mayocp.2023.02.019