NEW PAPERS

Noninvasive hemodynamic phenotyping in hypertension: Integrating ambulatory hemodynamics into a mechanism-based framework

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For decades, hypertension has been classified and treated primarily according to numerical blood pressure (BP) thresholds. This paradigm has contributed substantially to reductions in cardiovascular morbidity and mortality worldwide[1], despite persistently suboptimal BP control rates across many communities. Yet an important physiological question remains insufficiently addressed: why do patients with similar BP values exhibit distinct hemodynamic profiles and divergent risk trajectories?

Hypertension is traditionally staged according to office BP cut-offs.[1] Although risk stratification is essential, it does not explicitly account for the physiological determinants of arterial pressure. BP values reflect the interaction between cardiac output (CO), systemic vascular resistance (SVR), and arterial compliance. These determinants vary substantially among individuals meeting identical diagnostic criteria.[2] As classical hemodynamic studies demonstrated, elevated pressure may arise from different combinations of CO and SVR.[3]

Emerging evidence indicates that BP subtypes may originate from fundamentally different circulatory mechanisms. We have previously shown that isolated systolic hypertension and isolated diastolic hypertension differ markedly in total arterial compliance, SVR, and cardiac hemodynamics using validated noninvasive estimates derived from 24-hour ambulatory BP monitoring (ABPM), without pulse waveform analysis.[2] Thus, comparable BP levels may reflect distinct physiological substrates, reinforcing the need for a mechanism-based framework.

ABPM offers a practical platform to operationalize this heterogeneity (4). Beyond refining diagnosis and risk stratification, ABPM captures the temporal dimension of BP regulation – circadian variation, dipping patterns, variability, and morning surge.[5] We hypothesized that routinely collected ABPM variables contain sufficient physiological information to derive reproducible circulatory phenotypes.

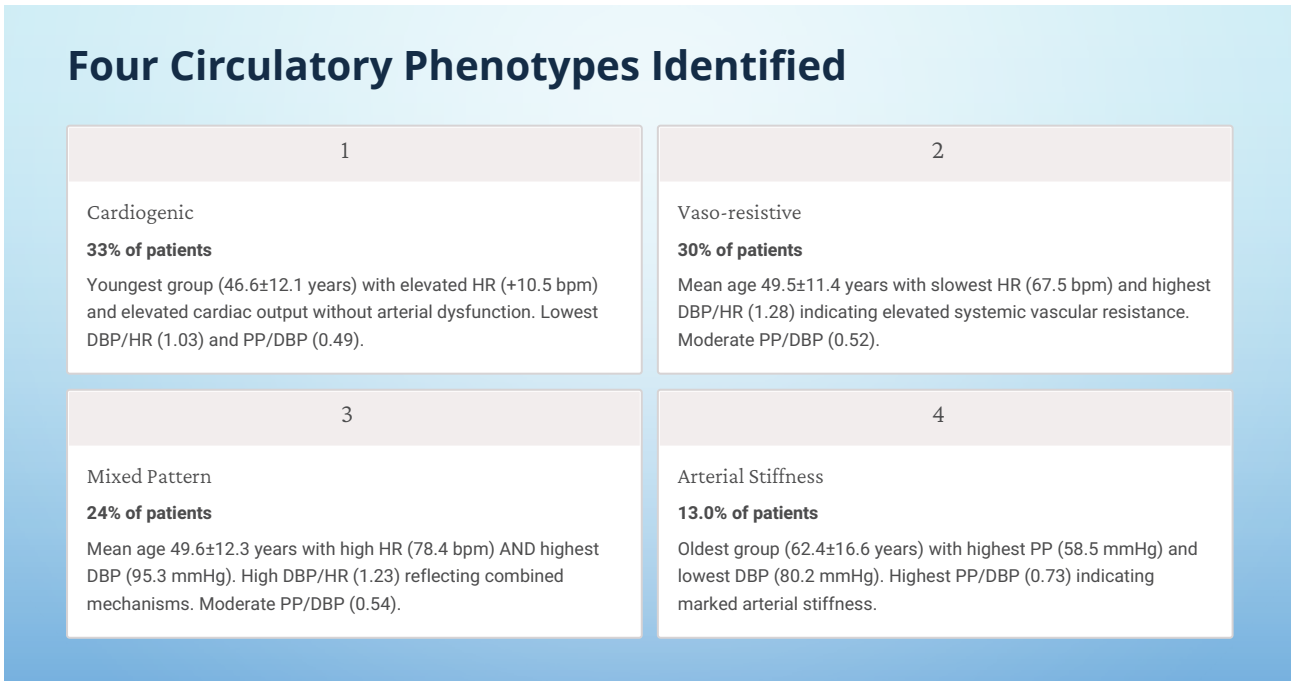
Hemodynamic Phenotypes Derived from ABPM

In a cohort of over nine thousand untreated hypertensive individuals, we applied unsupervised clustering to three minimally collinear ABPM-derived variables: diastolic BP (DBP), pulse pressure (PP), and heart rate (HR). These parameters reflect SVR, arterial compliance, and cardiac response. Distinct and reproducible clusters emerged, corresponding to recognizable physiological patterns.[6]

Four principal phenotypes were identified:

1. **Cardiogenic (hyperdynamic)** (33%); elevated HR and DBP with preserved PP, consistent with increased CO and preserved compliance.
2. **Vaso-resistive** (30%); markedly elevated DBP with lower HR, suggesting increased SVR.
3. **Mixed** (24%); elevated HR and DBP, reflecting combined increases in CO and SVR.
4. **Stiffness-predominant** (13%); widened PP with lower DBP, consistent with reduced arterial compliance and increased pulsatile load.

Figure: the four circulatory phenotypes identified. See reference 6.



These phenotypes are grounded in cardiovascular physiology.[7] Mean arterial pressure is largely determined by CO and SVR, whereas PP reflects arterial stiffness and wave reflections.[8] DBP, particularly relative to HR, provides insight into the arterial time constant (τ = compliance × resistance) and diastolic runoff. Importantly, this mechanistic interpretation requires no additional testing beyond standard ABPM.

ABPM Reveals a Time-Structured Circulatory Response

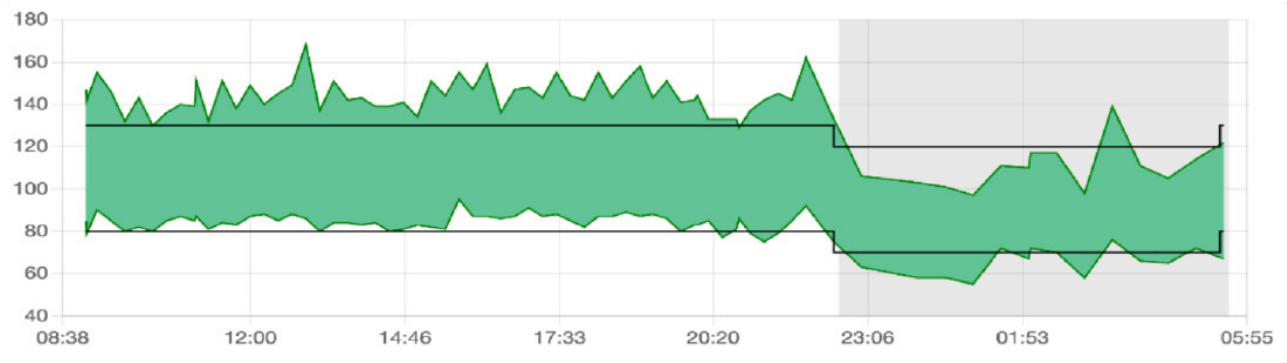
ABPM further reveals that hypertension is not a static value but a temporally structured physiological state. Reduced nocturnal dipping, exaggerated morning surge, and increased short-term variability independently predict adverse outcomes.[5]

Clinical Illustration:

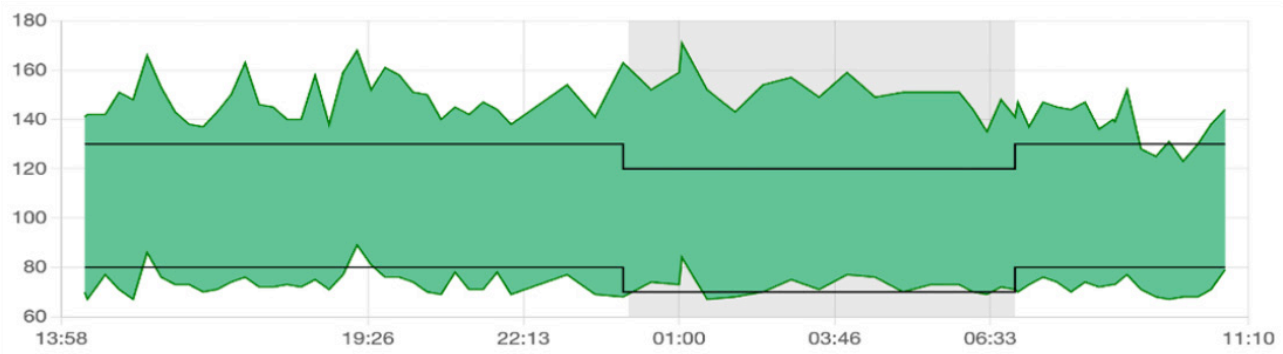
Table X. Distinct 24-Hour Hemodynamic Signatures in Hypertension Revealed by Ambulatory Monitoring

	Case 1	Case 2	Case 3
ABPM features	Elevated daytime mean arterial pressure (MAP) Widened pulse pressure (PP) during active hours Preserved nocturnal dipping with near-normal nighttime BP	Disproportionately elevated systolic BP (SBP) Low diastolic BP (DBP) troughs Persistently widened PP across the 24-hour cycle with blunted nocturnal normalization	Parallel elevations of SBP and DBP A narrower PP Preserved nocturnal dipping
Interpretation	Widened PP occurs mainly during periods of elevated pressure load and normalizes overnight, suggesting pressure-dependent (functional) rather than structural arterial stiffening. Increased daytime CO and/or SVR raises distending pressure, shifting the arterial wall toward a stiffer segment of the pressure–diameter curve.	The widened PP persists independent of circadian modulation, suggesting intrinsic reductions in arterial compliance (i.e., significant arterial stiffness). This reflects structural vascular remodeling with increased pulsatile load and reduced Windkessel function.	This pattern reflects increased SVR as the dominant driver of BP elevation. The preserved temporal modulation suggests intact circadian regulation despite elevated baseline vascular tone.
Phenotypic Alignment	Often reflecting a hyperdynamic or mixed phenotype.	Stiffness-predominant phenotype	Vaso-resistive phenotype.

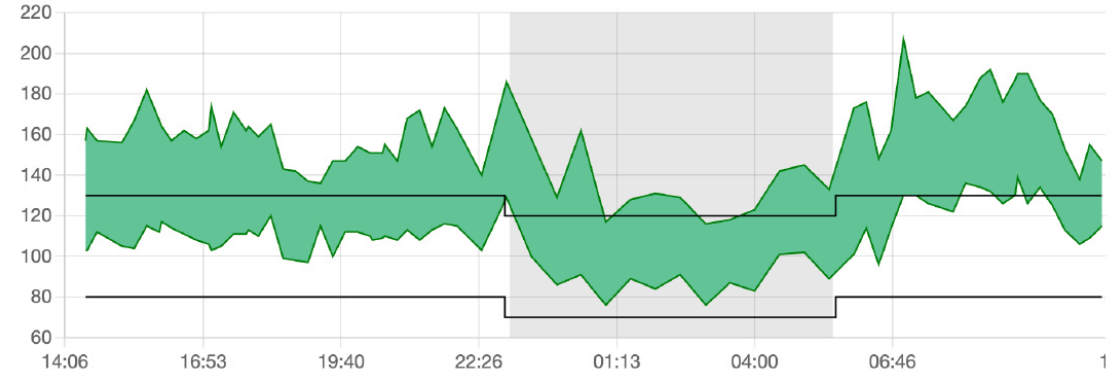
Case 1



Case 2



Case 3



These temporal patterns reflect the interplay among renal volume control, sympathetic activity, neurohormonal modulation, and vascular structure.[9] Persistent nighttime elevation may signal impaired circulatory adaptation, whereas increased variability may indicate diminished buffering capacity or heightened autonomic fluctuation.

Thus, interpreting 24-hour BP profiles allows movement beyond static thresholds toward a physiologically grounded understanding of circulatory adaptation – or maladaptation – to internal and environmental demands.

Regulatory Axes and Mechanistic Overlays

Primary hypertension is multifactorial. Renal sodium handling, sympathetic activation, and vascular remodeling act as interacting regulatory axes. The observed phenotype represents the surface expression of these underlying mechanisms.

This layered interpretation complements, rather than replaces, guideline-based care. Threshold-based treatment remains foundational.[1] However, recognizing mechanistic diversity may help explain differential therapeutic responses and provide additional insight into resistant or refractory hypertension.

Toward Precision Without Added Complexity

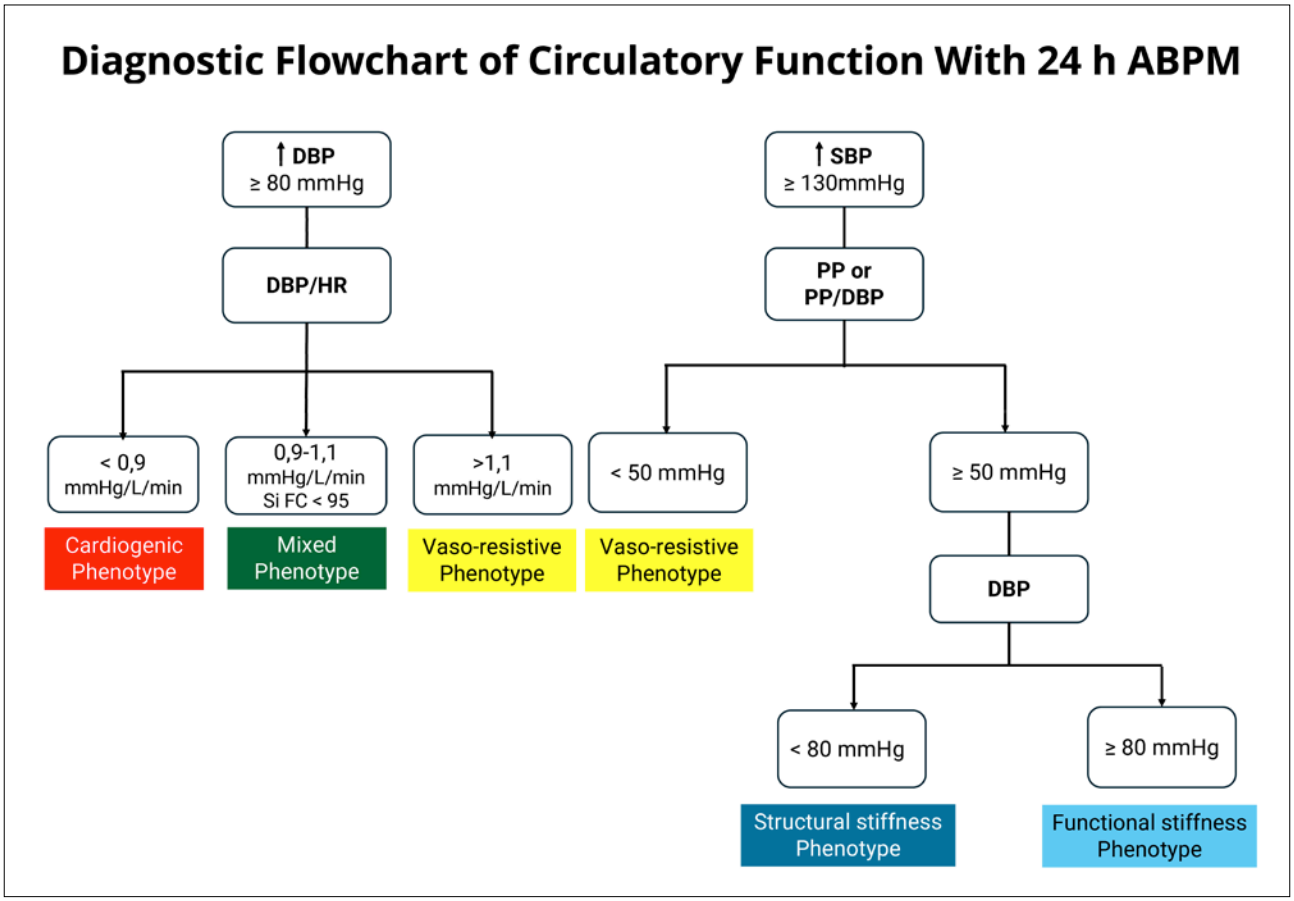
The appeal of a phenotype-informed framework lies in its practicality. ABPM is already recommended in clinical guidelines.[10] Systematic interpretation of HR, DBP, and PP patterns across 24 hours allows inference of dominant hemodynamic drivers without additional testing.[6]

A hyperdynamic phenotype may favor rate-modulating strategies. A stiffness-predominant profile may emphasize interventions targeting arterial compliance. A resistance-predominant pattern may align with renin–angiotensin system modulation or volume-directed therapy. The aim is precision without added complexity, a refinement rather than a paradigm shift.

Conclusion

Hypertension has long been managed through threshold-based staging.[1] Yet BP elevation represents the hemodynamic surface of interacting regulatory mechanisms.[9] ABPM captures both steady-state levels and temporal modulation,[6] enabling derivation of reproducible circulatory phenotypes.

In this framework, hypertension is reframed not as a single static number, but as a dynamic circulatory state – one that reflects how the heart and arterial system respond, adapt, and at times maladapt to physiological demands.



Diagnostic Flowchart of Circulatory Function Using 24-Hour ABPM

In predominantly diastolic hypertension, the relationship between heart rate (HR) and diastolic blood pressure (DBP) helps identify the dominant hemodynamic mechanism. If HR exceeds DBP by ≥10%, a hyperdynamic (cardiac output–mediated) phenotype is predominant. If DBP exceeds HR by ≥10%, a resistance-mediated phenotype driven by elevated systemic vascular resistance is more likely. A high pulse pressure (PP) >50 mmHg indicates a stiffness-predominant phenotype.

The 24-hour day–night BP profile further characterizes the severity of circulatory dysfunction and complements phenotypic classification as illustrated in the clinical ABPM examples (Figure x). Abbreviations: DBP, diastolic blood pressure; HR, heart rate; PP, pulse pressure.

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