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Review Article

Emerging Role of ambulatory ECG monitoring in the Diagnosis of resistant hypertension

Nakamura R^{1*}, Suzuki S² and Yamamoto S³

¹Department of Cardiovascular Medicine, Nile Institute of Cardiology, Taiwan

²Division of Cardiovascular Medicine, Fraser Academy of Cardiovascular Medicine, Taiwan

³Department of Cardiology, Congo Research Center for Cardiology, Malaysia

*Address for Correspondence: Ryo Nakamura, Department of Cardiovascular Medicine, Nile Institute of Cardiology, Taiwan; E-mail: ryo.nakamura@nile.edu

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Abstract

Background: Office measurement misclassifies many patients labeled as resistant hypertension, since white-coat effect inflates cuff readings while masked hypertension conceals poor control.

Objective: This review examines ambulatory blood pressure monitoring, paired with ambulatory ECG surveillance, in confirming true treatment-resistant hypertension and identifying candidates for escalation.

Methods: We synthesized outcome cohorts, diagnostic-accuracy studies, and guidelines addressing ambulatory monitoring, white-coat and masked phenomena, dipping patterns, and ambulatory ECG correlates in resistant hypertension.

Findings: Ambulatory monitoring reclassifies roughly a third of apparent resistant cases as white-coat or masked hypertension, non-dipping and reverse-dipping carry elevated risk, and ambulatory ECG strain and heart-rate-variability changes track ambulatory pressure load more closely than office readings.

Conclusions: Ambulatory blood pressure monitoring, integrated with ambulatory ECG where cardiac risk stratification is needed, should precede diagnostic labeling and escalation of therapy in suspected resistant hypertension.

Keywords: resistant hypertension; ambulatory blood pressure monitoring; masked hypertension; white-coat effect; ambulatory ECG

1. Introduction

Resistant hypertension is conventionally defined as office blood pressure above goal despite three complementary antihypertensive classes, one typically a diuretic, or pressure controlled only with four or more agents. The diagnosis carries substantial prognostic weight: patients labeled treatment resistant face markedly higher rates of stroke, heart failure, renal decline, and cardiovascular death than patients who respond to standard therapy [1]. The label is unreliable, however, when it rests on office cuff readings alone. A clinic reading can be inflated by an alerting reaction, the white-coat effect, or can understate a patient's true burden when pressure is worst outside the clinic, termed masked hypertension [2]. Twenty-four-hour ambulatory blood pressure monitoring (ABPM), sampling pressure across waking and sleeping hours, addresses both distortions directly.

ABPM has accumulated three decades of outcome data showing it predicts cardiovascular events more accurately than office measurement, across general hypertensive populations, older patients with isolated systolic hypertension, and patients labeled treatment resistant [3,4,5]. It also captures information a single office reading cannot: nocturnal dipping, the morning surge, and, when paired with simultaneous ambulatory ECG, the rhythm and repolarization abnormalities that track sustained pressure load rather than a momentary clinic value. This review synthesizes evidence for integrating ambulatory blood pressure and ECG monitoring into the diagnostic pathway for resistant hypertension: the scale of misclassification from white-coat and masked phenomena, the prognostic importance of dipping patterns, the correlation between ambulatory pressure load and ambulatory ECG findings, and implications for escalated therapy.

2. The scale of misclassification from office measurement alone

When patients labeled treatment resistant by office

criteria undergo confirmatory ABPM, a substantial fraction are reclassified. de la Sierra and colleagues, studying 8295 patients referred for resistant hypertension, found only around 62% had ambulatory pressures confirming true resistance, while roughly 37% had controlled ambulatory pressures despite elevated office readings, consistent with white-coat resistant hypertension [6]. Pierdomenico and colleagues, distinguishing responder, masked, false-resistant, and true-resistant categories in a treated cohort, found event rates tracked ambulatory rather than office classification, with false-resistant patients faring similarly to well-controlled responders [7]. Judd and Calhoun's review situates these findings in context, estimating that white-coat effect accounts for a large minority of apparent treatment failure and that skipping out-of-office confirmation risks substantial overtreatment [8].

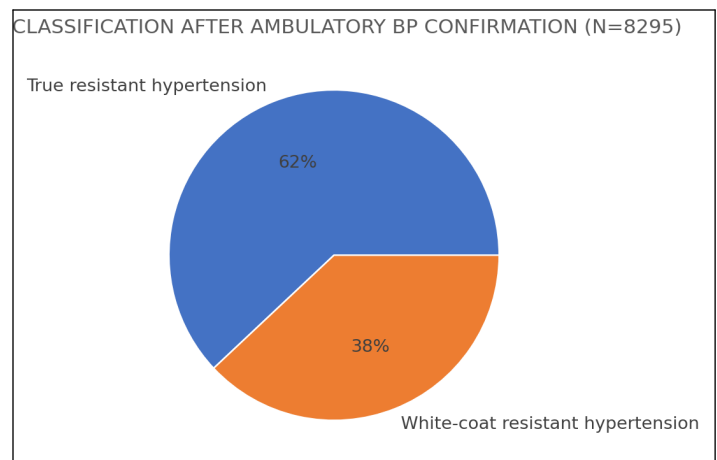


Figure 1: Reclassification of 8295 patients referred for apparent office-defined resistant hypertension after confirmatory 24-hour ambulatory blood pressure monitoring, distinguishing true resistant hypertension from white-coat resistant hypertension [6].

Masked uncontrolled hypertension is the mirror-image problem, and easier to miss since office readings look reassuring. Franklin and colleagues found masked hypertension carries cardiovascular risk approaching that of sustained hypertension [9], a gradient Fagard and Cornelissen's meta-analysis quantified directly: roughly twice the risk of true normotension, while white-coat hypertension carried only modest excess risk [10]. Bobrie

and colleagues found masked uncontrolled hypertension common even among patients believed well controlled, and independently associated with worse prognosis [11]. Bangash and Agarwal extended these findings to chronic kidney disease, where both phenomena are disproportionately prevalent and masked hypertension tracks accelerated renal decline [12]. Office measurement alone, in either direction, is an unreliable gatekeeper for the resistant hypertension diagnosis.

3. Ambulatory blood pressure monitoring as the confirmatory standard

The prognostic superiority of ambulatory over office measurement is established across enough independent cohorts that guideline bodies now recommend ABPM, or validated home monitoring, before finalizing a resistant hypertension diagnosis. Verdecchia and colleagues showed ambulatory pressure independently predicted cardiovascular morbidity in essential hypertension [3]; Staessen and colleagues confirmed the same in older patients with isolated systolic hypertension (Syst-Eur) [4]; and Dolan and colleagues' Dublin Outcome Study confirmed superiority for mortality prediction over a decade of follow-up [5]. Segal and colleagues' PAMELA study extended the finding to a general population sample [13]. Hansen and colleagues isolated nighttime ambulatory pressure as the strongest independent mortality predictor among ambulatory-derived metrics [14], echoed by Fagard and colleagues' analysis distinguishing daytime and nighttime predictive value [15].

Table 1: Key outcome studies establishing the prognostic superiority of ambulatory over office blood pressure measurement.		
Study	Population	Key finding
[3]	Essential hypertension cohort	Ambulatory pressure independently predicts cardiovascular morbidity
[4]	Older patients, isolated systolic hypertension (Syst-Eur)	Ambulatory pressure outperforms office pressure for risk prediction

Study	Population	Key finding
[5]	Community-referred cohort (Dublin Outcome Study)	Ambulatory pressure superior for predicting all-cause and cardiovascular mortality
[13]	General population (PAMELA study)	Ambulatory and home readings outperform office pressure as mortality predictors
[14]	Population-based cohort	Nighttime ambulatory pressure carries strongest mortality association

These data underpin the European Society of Hypertension's position paper and practice guidelines, which specify standardized ABPM protocols and recommend it as the confirmatory step before labeling hypertension resistant [16,17]. The 2013 ESH/ESC and 2017 ACC/AHA guidelines converge on the same principle, recommending secondary-cause screening only after ambulatory confirmation excludes pseudoresistance [18,19]. Redon and colleagues' earlier study of refractory hypertension found ambulatory, not office, pressure predicted subsequent events in a cohort selected for apparent resistance [20]. Muxfeldt and colleagues showed nocturnal reduction on ABPM, independent of daytime control, predicted outcomes within resistant hypertension specifically [21]. Rimoldi, Scherrer, and Messerli's review situates ABPM confirmation as the necessary gate before resource-intensive secondary-cause workup, since much apparent resistance resolves once ambulatory confirmation is obtained [22].

4. Circadian dipping patterns and nocturnal risk

Beyond confirming or excluding resistance, ABPM characterizes the circadian pressure profile, invisible to office measurement. Normal physiology produces a nocturnal dip of roughly 10-20%; patients dipping less than 10% are non-dippers, and those with nighttime pressure exceeding daytime are reverse dippers. Ohkubo and colleagues' Ohasama study established that a blunted nocturnal decline predicted cardiovascular mortality independently of 24-hour pressure level [23]. Salles and colleagues' ABC-H meta-analysis confirmed both non-dipping and reverse-dipping carry independently

elevated risk, with reverse dippers highest [24]. Ben-Dov and colleagues similarly identified nocturnal pressure as the strongest mortality predictor among ambulatory-derived parameters [25].

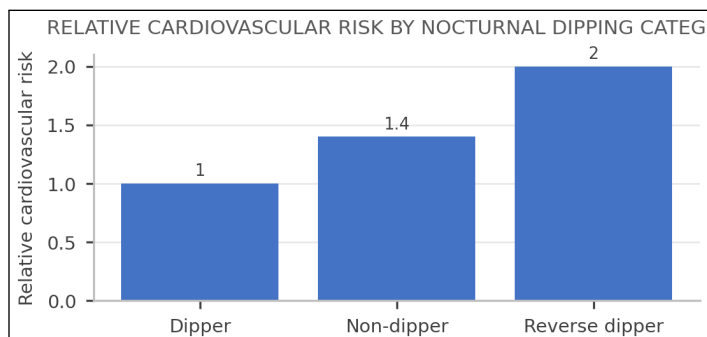


Figure 2: Relative cardiovascular risk by nocturnal dipping category on ambulatory blood pressure monitoring, pooled across cohorts in the ABC-H meta-analysis, with reverse dippers carrying the highest excess risk [24].

Non-dipping and reverse-dipping are disproportionately common in resistant hypertension, reflecting sympathetic overactivity, obstructive sleep apnea, and chronic kidney disease. Kario and colleagues showed an exaggerated morning surge independently predicted silent and clinical cerebrovascular events in elderly hypertensives [26], and Kario and Pickering identified morning hypertension as the strongest independent stroke risk factor among ambulatory parameters studied [27]. Kabutoya and colleagues linked morning surge magnitude to autonomic activity and cardiac remodeling, bridging the circadian pressure profile to changes ambulatory ECG can detect directly [28].

5. Ambulatory ECG correlates of blood pressure load

Ambulatory ECG obtained concurrently with ambulatory blood pressure adds a cardiac-specific dimension office pressure and standalone ABPM cannot provide. Left ventricular hypertrophy correlates more closely with 24-hour ambulatory pressure than office pressure, and Verdecchia and colleagues showed hypertrophy, associated with strain patterns detectable on ambulatory ECG, independently predicted acute cerebrovascular

events [29]. A subsequent meta-analysis confirmed reduction in left ventricular mass under treatment tracked with reduced risk, reinforcing remodeling as a meaningful intermediate endpoint [30].

Heart-rate variability, readily derived from ambulatory ECG, is a second correlate of ambulatory burden. Kikuya and colleagues found reduced variability carried independent prognostic significance alongside ambulatory pressure level [31]. Palatini and colleagues found elevated ambulatory heart rate independently predicted mortality in elderly systolic hypertension, most pronounced with concurrently elevated pressure load [32]. These findings matter because resistant hypertension is disproportionately associated with sympathetic overactivity, and ambulatory ECG offers a practical window onto that overactivity already available during ambulatory pressure evaluation.

6. Implications for escalation to device-based and combination therapy

Once ambulatory confirmation establishes true resistance, the ambulatory profile informs escalated therapy. Williams and colleagues' PATHWAY-2 trial showed spironolactone superior to bisoprolol and doxazosin as fourth-line therapy for confirmed resistant hypertension, using out-of-office measurement to establish eligibility and response [33]. Renal denervation trials followed a similar arc: the sham-controlled Symplicity HTN-3 trial, with ambulatory and office pressure as co-primary endpoints, did not meet its primary endpoint [34], while later trials with stricter ambulatory confirmation of true resistance, such as RADIANCE-HTN SOLO, demonstrated significant ambulatory pressure reduction versus sham [35].

Guideline bodies have converged on integrating ambulatory confirmation into the resistant hypertension pathway. The American Heart Association's scientific statement specifies ambulatory or home monitoring as required before secondary-cause workup or device

therapy [1], and the 2017 ACC/AHA and 2013 ESH/ESC guidelines incorporate the same principle into their definitions of resistant and apparent treatment-resistant hypertension [19,18]. The resulting pathway begins with ambulatory confirmation, incorporates ambulatory ECG where cardiac risk stratification is indicated, characterizes the dipping profile, and only then proceeds to secondary-cause screening and escalated therapy.

Table 2: Trials informing fourth-line pharmacologic and device-based therapy in ambulatory-confirmed resistant hypertension.

Trial	Intervention	Ambulatory blood pressure role	Outcome
[33]	Spironolactone vs bisoprolol vs doxazosin (PATHWAY-2)	Home/ambulatory confirmation of eligibility and response	Spironolactone superior as fourth-line agent
[34]	Renal denervation vs sham (Symplicity HTN-3)	Co-primary ambulatory and office endpoints	No significant ambulatory pressure reduction vs sham
[35]	Endovascular ultrasound renal denervation vs sham (RADIANCE-HTN SOLO)	Ambulatory confirmation of true resistance at entry	Significant ambulatory pressure reduction vs sham

7. Conclusion

Office measurement alone is an unreliable foundation for diagnosing resistant hypertension: white-coat effect inflates apparent resistance in a substantial minority of referred patients, while masked hypertension conceals genuinely elevated risk in others [6,9]. Ambulatory blood pressure monitoring resolves this ambiguity, outperforms office measurement as a predictor of cardiovascular events, and characterizes dipping and morning-surge patterns identifying the highest-risk patients [5,24,26]. Concurrent ambulatory ECG adds a complementary cardiac-specific dimension through left ventricular remodeling and heart-rate variability changes that office assessment cannot detect [29,31]. Integrating ambulatory blood pressure and, where indicated, ambulatory ECG monitoring into the diagnostic pathway before escalating therapy allows clinicians to distinguish true resistant

hypertension from its pseudoresistant mimics and to direct fourth-line therapies toward patients most likely to benefit [33,35].

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