Journal of
HYPERTENSION RESEARCH
www.hypertens.org/jhr

Invited Review
J Hypertens Res (2021) 7(4):131-134

The role of ambulatory blood pressure monitoring in the diagnosis of pheochromocytoma

Sofia **Lider** [1, 2], Corin **Badiu** [1, 2] *

[1] Department of Endocrinology 2, CI Parhon National Institute of Endocrinology, Bucharest, Romania
[2] Department of Endocrinology, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

Received: September 24, 2021, Accepted: November 14, 2021

Abstract

Pheochromocytoma and paraganglioma (PPGL) represent a group of rare disorders associated with secondary hypertension. With more than 50% of cases with a genetic cause, the current management of these patients includes adrenal imaging, functional investigation, and surgical treatment. While some cases bring a full clinical picture, many patients are oligo- or asymptomatic. In order to bring catecholamine hypertension into focus, ambulatory monitoring of blood pressure (ABPM) is a useful approach. In this review, we discuss the role of ABPM in the management of PPGL in diagnosis, preparation for surgery and further follow-up. Cut-off levels for normal variations as well as response to pharmacological treatment are also debated.

Keywords: pheochromocytoma, ambulatory blood pressure monitoring, paraganglioma, adrenal tumor.

Catecholamine-secreting tumors that arise from chromaffin cells of the adrenal medulla and the sympathetic ganglia are referred to as "pheochromocytomas" (PHEOs) and "catecholamine-secreting paragangliomas"(PGLs), respectively [1]. The pattern of catecholamine secretion from the tumor can be continuous, episodic, or both, and the symptoms can be precipitated by physical activity (exercise, postural change) or tumor manipulation. However, it is still unknown and difficult to predict when and how many catecholamines each particular tumor will secrete during each secretory episode.

* Correspondence to: Corin BADIU,
CI Parhon National Institute of Endocrinology, 34-38 Aviatorilor Ave., District 1, 11863, Bucharest, Romania.
Phone: +40722524002; E-mail: badicrin@yahoo.co.uk

Symptoms are present in approximately 50% of patients, and when present, they are typically paroxysmal [2]. The classic triad involves a triad of symptoms in patients with a PHEO consisting of episodic headache, sweating, and tachycardia. However, most patients with PHEO do not have the three classic symptoms.

Sustained or paroxysmal hypertension is the most common sign of PHEO; approximately one-half have paroxysmal hypertension, and most of the rest have either primary hypertension (formerly called "essential" hypertension) or normal blood pressure [3]. PHEOs are found in 0.2–0.6% of the subjects with hypertension. Certain foods or beverages with high concentrations of tyramine (cheeses, beers, and wines), drugs (histamine, phenothiazine, or tricyclic antidepressants), and operative procedures with/without anesthesia can cause paroxysmal hypertension in patients with PHEO [4].

The clinical phenotype of the hypertensive syndrome depends on multiple factors, including adrenal content of catecholamines, as well as the pattern and nature of their secretion. While the cellular content can be enormous, intracellular processing can divert significant amounts into metabolites, an apparent clinical paradox of normal or near-normal plasma catecholamines and significantly elevated metanephrines. Sustained hypertension strongly correlates with high levels of plasma norepinephrine continuously released from the tumor. It was also reported that patients with tumors that predominantly and continuously secreted norepinephrine had higher 24-hr, daytime, and night-time blood pressure compared to patients with tumors that secreted only epinephrine [5].

On rare occasions, patients present with a condition termed pheochromocytoma crisis or pheochromocytoma multisystem crisis. These individuals may have either hypertension or hypotension, hyperthermia (temperature >40°C), mental status changes, and other organ dysfunction. Patients with spells (defined as a sudden onset of a symptom or symptoms that are recurrent, self-limited, and stereotypic in nature) that relate to paroxysmal elevations in blood pressure should be evaluated for PHEO. However, the clinician should recognize that most patients with spells do not have a PHEO [3, 4].

Signs of secondary hypertension are the onset of hypertension at a young age (e.g., <20 years), paroxysmal hypertension, resistant hypertension, or hypertension with new-onset or atypical diabetes mellitus (e.g., new onset of apparent type 2 diabetes in a slender person). Due to the non-specificity of the PHEO-associated symptoms and the fact that one of the differential diagnoses is a panic attack, the first step is to confirm the sign and symptoms described by the patient when a patient accuses symptoms related to PHEO.

Twenty-four-hour ambulatory blood pressure monitoring (ABPM) is the preferred method for confirming the diagnosis of hypertension and white coat hypertension but has limited availability in routine clinical practice. In 1964, Kain *et al.* demonstrated the benefits of ABPM and the attractive possibility of measuring blood pressure during patients' daily activities [5].

ABPM records the blood pressure at present intervals (usually every 15 to 20 minutes during the day and every 30 to 60 minutes during sleep). ABPM can identify or confirm white coat and masked hypertension and can also be used to confirm normal blood pressure readings obtained by self-monitoring at home. It is also the only method of blood pressure measurement that can reliably obtain nocturnal readings. These blood pressures are recorded on the device, and a computer calculates the average day (diurnal) or night (nocturnal) pressures. The percentage of blood pressure readings exceeding the upper limit of normal can also be determined [6].

Most experts agree that an average 24-hour blood pressure <115/75 mmHg is probably normal and that an average 24-hour blood pressure ≥125/≥75 mmHg is probably abnormal [7]. Measuring blood pressure outside the office setting with ABPM captures the effects of normal daily activities on blood pressure, provides information on blood pressure behavior during sleep and provides a greater number of readings than can be obtained during a typical office encounter.

In the case of pheochromocytoma, ABPM can identify the frequency and the intensity of the hypertension paroxysm, the response to alfa-receptors blockade medication, the effects of normal daily activities on blood pressure, the time when the patient has a hypertensive crisis which allows to associate the hypertensive paroxysm with a life situation and avoiding the situation further.

The ABPM can confirm:

- Nocturnal dipping of blood pressure – dipping is the proportional decrease in night-time compared with daytime blood pressure (reported as the percentage decline). The normal "dip" in systolic pressure is 10 to 20%. The prognostic implications of dipping are discussed below.
- Morning surge – Morning surge is defined as the difference between the night-time blood pressure and the average early morning blood pressure. Although there is no standardized method of calculating the morning surge, the average blood pressure from the first two hours after awakening minus the average night-time blood pressure may be the most reproducible. Patients with a more significant surge from night-time to early morning blood pressure may have a greater risk of future cardiovascular events.
- Systolic blood pressure load – Systolic blood pressure load is the proportion of time during the day in which the systolic blood pressure is above the threshold for elevated daytime blood pressure. This value provides insight into the duration and lability of elevated blood pressure. A patient whose systolic pressure is above the threshold for ≥40% of daytime measurements is generally considered to have an excessively high systolic blood pressure load. However, systolic blood pressure load does not provide additional prognostic information beyond the mean systolic blood pressure.
- Diastolic blood pressure load – similarly, diastolic blood pressure load is the proportion of time during the day in which the diastolic blood pressure is above the threshold for elevated daytime blood pressure. Like the systolic blood pressure load, this value provides insight into the duration and lability

of elevated blood pressure but does not provide independent prognostic information.
- Ambulatory arterial stiffness index (AASI) – AASI is determined by plotting a regression of all the diastolic blood pressure values with the simultaneous systolic blood pressure values and subtracting the slope of this line from 1. Higher values generally correspond to stiffer blood vessels and a higher risk of cardiovascular disease [8–10].

Sometimes, ABPM and office-based measurements are discordant. If office-based measurements are above the threshold of hypertension but out-of-office measurements are normal:
- Whitecoat hypertension is present in a patient who is not being treated for hypertension;
- Whitecoat effect is present in a patient already being treated with antihypertensive medication;
- If office-based measurements are normal but out-of-office measurements demonstrate elevated blood pressures, then masked hypertension is present.

Multiple studies suggest that all-cause mortality and cardiovascular events correlate more closely with 24-hour, daytime, or night-time ABPM than with the office-based blood pressure measurement and that an elevated 24-hour blood pressure predicts these outcomes even after adjusting for office-based blood pressure. As an example, in a prospective study of 1963 treated hypertensive patients, a 24-hour ambulatory systolic pressure ≥135 mmHg was associated with an increased risk for new cardiovascular events after adjusting for office-based blood pressure (relative risk 1.74, 95% CI 1.15-2.63) compared with <135 mmHg [8]. ABPM is also a superior prognostic indicator of future cardiovascular disease in patients with resistant hypertension.

In addition to cardiovascular risk prediction, ambulatory blood pressure, and particularly night-time blood pressure, might be a stronger marker of kidney disease progression and development of end-stage kidney disease (ESKD) than office-based blood pressure.

Self-monitoring blood pressure (SMBP) readings obtained at home or at work, which correlate more closely with the results of 24-hour or daytime ABPM than with office-based blood pressure, might also be more predictive of adverse outcomes (e.g., stroke, ESKD) than blood pressure obtained in the clinic [9–11].

However, ABPM is unavailable in most clinicians' offices. This is due to a combination of factors, including lack of knowledge regarding its utility, the expense, and lack of reimbursement by third-party payers.

In the case of a PHEO, after confirming the hypertension diagnosis, it is necessary to evaluate the plasmatic and urinary catecholamine metabolites metanephrine (MN) and normetanephrine (NMN) levels. It is generally admitted that plasmatic MN, NMN have a better specificity. If the MN/NMN levels are high, the next step in diagnosing PHEO is to perform imaging of the adrenals. A computed tomography (CT) scan indicates the presence/absence of an adrenal tumor. If the adrenal tumor is not confirmed but the patient has high levels of catecholamine metabolites, the clinician should search for PGLs with a cervical-thoracic-abdominal and pelvic CT. If the diagnosis of PHEO/PGL is made, the patient should be prepared for surgery with the alfa-adrenergic blockade (7–14 days before surgery). After satisfactory arterial control of blood pressure, the surgery can be performed. Another ABPM for monitoring the arterial blood pressure values under alfa-blockade could be used.

Conclusions

Identifying patients with abnormal blood pressure and accurately diagnosing any hypertension type is crucial for both health care providers and patients.

The clear data supporting ABPM as the most accurate method for the diagnosis of hypertension should be an argument for a more personalized implementation of ABPM to evaluate borderline office readings for initial hypertension diagnoses. Furthermore, an ABPM system should be available in every health care facility.

Pheochromocytoma is a life-threatening disease; high circulating levels of catecholamines can lead to severe hypertension and devastating effects on multiple body systems (e.g., cardiovascular, cerebrovascular) and can lead to death if untreated. Therefore, fast identification of the symptoms is essential. Although surgical treatment represents the only modality of ultimate cure, pharmacological pre-operative treatment remains the mainstay of a successful outcome and good control of blood pressure.

Conflict of Interest

The authors confirm that there are no conflicts of interest.

References

1. Guerrero MA, Schreinemakers JM, Vriens MR, *et al.* Clinical spectrum of pheochromocytoma. J Am Coll Surg 2009; 209:727.

2. Neumann HPH, Young WF Jr, Eng C. Pheochromocytoma and Paraganglioma. N Engl J Med 2019; 381:552.
3. Bravo EL. Pheochromocytoma: new concepts and future trends. Kidney Int 1991; 40:544.
4. Kudva YC, Young WF Jr, Thompson GB, *et al.* Adrenal incidentaloma: An important component of the clinical presentation spectrum of benign sporadic adrenal pheochromocytoma. The Endocrinologist 1999; 9:77.
5. Kain HK, Hinman AT, Sokolow M. Arterial blood pressure measurements with a portable recorder in hypertensive patients. I. Variability and correlation with "casual" pressures. Circulation. 1964;30:882–892.
6. Muntner P, Einhorn PT, Cushman WC, *et al.* Blood Pressure Assessment in Adults in Clinical Practice and Clinic-Based Research: JACC Scientific Expert Panel. J Am Coll Cardiol 2019; 73:317.
7. Piper MA, Evans CV, Burda BU, *et al.* Diagnostic and predictive accuracy of blood pressure screening methods with consideration of rescreening intervals: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2015; 162:192.
8. Townsend RR. Out-of-Office Blood Pressure Monitoring: A Comparison of Ambulatory Blood Pressure Monitoring and Home (Self) Monitoring of Blood Pressure. Hypertension 2020; 76:1667.
9. Dolan E, Stanton A, Thijs L, *et al.* Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: the Dublin outcome study. Hypertension 2005; 46:156.
10. Shimbo D, Abdalla M, Falzon L, *et al.* Studies comparing ambulatory blood pressure and home blood pressure on cardiovascular disease and mortality outcomes: a systematic review. J Am Soc Hypertens 2016; 10:224.
11. Staessen JA, Byttebier G, Buntinx F, *et al.* Antihypertensive treatment based on conventional or ambulatory blood pressure measurement. A randomized controlled trial. Ambulatory Blood Pressure Monitoring and Treatment of Hypertension Investigators. JAMA 1997; 278:1065.