

INTEGRATED NON-INVASIVE VASCULAR PHENOTYPING USING ANKLE-BRACHIAL INDEX (ABI) AND PULSE WAVE VELOCITY (PWV) FOR EARLY DETECTION OF SUBCLINICAL ATHEROSCLEROSIS. BRIDGING EVIDENCE FROM COMPREHENSIVE LITERATURE REVIEW AND CASE-BASED CLINICAL EVALUATION

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Abstract

Cardiovascular disease remains the leading global cause of morbidity and mortality, often preceded by a prolonged subclinical phase characterized by early vascular alterations. This study aims to evaluate the clinical utility of integrated non-invasive vascular phenotyping using ankle-brachial index (ABI) and pulse wave velocity (PWV) for the early detection of subclinical atherosclerosis, combining a comprehensive literature review with a case-based clinical evaluation.

A 36-year-old male with cardiometabolic risk factors, including smoking, physical inactivity, and dyslipidemia, underwent detailed vascular assessment using a four-limb oscillometric system (BPlab® with Vasotens®). Despite normal findings on conventional cardiovascular testing—including ECG, echocardiography, and exercise stress testing—advanced vascular evaluation revealed subtle abnormalities. ABI values were within the upper-normal range on the right (1.28) but elevated on the left (1.44), suggesting increased arterial stiffness rather than overt peripheral arterial disease. PWV analysis demonstrated mildly increased brachial-ankle and aortic PWV, while carotid-femoral PWV remained within normal limits, indicating early peripheral arterial stiffening. Central hemodynamic parameters were preserved, although wave reflection indices suggested early vascular functional changes.

These findings highlight the discordance between standard diagnostic approaches and advanced vascular biomarkers, emphasizing the added value of combined structural (ABI) and functional (PWV) assessment. The observed vascular phenotype is consistent with early vascular aging associated with cardiometabolic dysregulation.

In conclusion, integrated vascular phenotyping enhances early detection of subclinical vascular disease, improves cardiovascular risk stratification, and may guide timely preventive interventions, particularly in younger individuals with modifiable risk factors.

Keywords: Ankle-brachial index; Pulse wave velocity; Subclinical atherosclerosis; Arterial stiffness; Vascular phenotyping

Introduction

The cardiovascular disease remains the leading global cause of morbidity and mortality, with pathological vascular alterations developing insidiously and often undetected during a prolonged subclinical phase that may precede overt clinical events by many years (WHO, 2025; Fuster et al., 2024). In this instances identifying subclinical markers of atherosclerosis is essential for timely diagnosis and intervention.

Peripheral arterial disease (PAD) is a common manifestation of systemic atherosclerosis that affects over 200 million people worldwide, particularly older adults and those with diabetes, smoking history, or chronic kidney disease (Zemaitis et al., 2026). Nearly half (42.6%) residing in low- and middle-sociodemographic regions (GBD 2019 and Injuries collaborators, 2020).

The overall global prevalence is estimated at 1.52%, rising markedly with advancing age, reaching nearly 15% among individuals aged 80–84 years, and demonstrating a higher prevalence in females compared to males within the same age group (18.03% vs. 10.56%) (Lin et al., 2022; GBD 2019 Peripheral artery disease collaborators, 2023).

This condition results from progressive arterial narrowing and stiffness most often in the aortoiliac, femoropopliteal, and infrapopliteal segments, leading to reduced or impaired blood flow to the lower extremities and it is associated with a substantially increased risk of major adverse cardiovascular events (MACE), including myocardial infarction (MI), stroke and cardiovascular mortality, reflecting the diffuse nature of atherosclerotic disease. Early detection of vascular damage, arterial stiffness, subclinical atherosclerosis, and cardiovascular risk is critical for effective prevention and management of cardiovascular diseases (CVD), but PAD remains underdiagnosed and untreated, largely due to its frequently asymptomatic or atypical presentation. Consequently, early identification through non-invasive diagnostic tools, such as the ABI, is essential for timely risk stratification and implementation of preventive and therapeutic strategies.

Non-invasive vascular biomarkers such as the ABI, PWV (including aPWV (aortic), baPWV (brachial-ankle) and cfPWV (carotid-femoral)), central aortic pressure (CAP), and related arterial stiffness parameters have emerged as valuable tools for identifying individuals at increased risk before overt clinical disease develops.

- **Ankle–Brachial Index (ABI)** is calculated as the ratio of systolic blood pressure at the ankle to that at the brachial artery on each side. It is highly specific for PAD diagnosis when measured by Doppler ultrasound but can also be assessed using oscillometric or automated devices with varying sensitivity/specificity (Fendrik et al., 2023; Stone et al. 2023). Normal ABI ranges from 0.90 to 1.40 and PAD is defined as an ABI of 0.90 or less (Mazzolai et al., 2024; Aboyans et al., 2012). Patients with ABI 0.70 to 0.90 are categorized as mild PAD and typically are asymptomatic or present with intermittent claudication (Birkett et al., 2021). Those with ABI 0.50 to 0.70 have moderate PAD and typically present with more frequent claudication and reduced walking distance (Gommans et al., 2014). An ABI of less than 0.50 indicates severe PAD or chronic limb-threatening ischemia (CLTI) and often presents with ischemic rest pain, non-healing wounds, or tissue loss (Sprengers et al., 2010). Values greater than 1.40 may indicate non-compressible, calcified arteries, often seen in patients with diabetes or chronic kidney disease (Zemaitis et al., 2026; Mazzolai et al., 2024). In such cases, the ABI value is unreliable, and alternative testing like for example the toe-brachial index (TBI) or duplex ultrasound, is required to evaluate for PAD (Aboyans et al., 2012; Collins et al., 2007). The TBI, which is less affected by arterial calcification, provides a more accurate assessment; a TBI of less than 0.70 suggests the presence of PAD (Mazzolai et al., 2024; Collins et al., 2007; Suzuki et al., 2024).
- **Pulse Wave Velocity (PWV)** is an important and well-established measure of arterial stiffness that is strongly associated with aging and the faster the pulse wave travels between two points (e.g., carotid-femoral or brachial-ankle), the stiffer the arteries (Laurent et al., 2006). PWV, particularly cfPWV and baPWV, is widely recognized as a gold-standard measure of arterial stiffness and an independent predictor of CVD events across diverse populations (Zemaitis et al., 2026 ; Fendrik et al., 2023; Kim et al., 2019). In a landmark study by the Reference Values for Arterial Stiffness' Collaboration in 2010, normative values for pulse wave velocity (PWV) were established in a large population-based cohort (Reference Values for Arterial Stiffness' Collaboration, 2010). The authors reported a mean PWV of 6.0 m/s (95% CI 5.8–6.1), demonstrating a significant increase in PWV with advancing age and higher blood pressure categories (both $p < 0.001$). While no sex-related differences were observed in normotensive individuals, women exhibited significantly higher PWV values compared to men in the hypertensive subgroup ($>140/90$ mmHg;

$p=0.005$). Additionally, interpercentile ranges were narrower in individuals younger than 55 years, whereas greater variability and higher upper limits of PWV were observed in participants aged ≥ 55 years, particularly among those with elevated blood pressure (Reference Values for Arterial Stiffness' Collaboration, 2010); Van Hout et al., 2021). Beyond its role as a marker of arterial stiffness, PWV has substantial clinical relevance. Evidence indicates that increased PWV is independently associated with subclinical target organ damage, including coronary artery calcification, cerebral white matter hyperintensities, and albuminuria (Reference Values for Arterial Stiffness' Collaboration, 2010); ; Kim et al., 2019; Van Hout et al., 2021). Importantly, PWV also predicts future cardiovascular events and all-cause mortality, even after adjustment for traditional cardiovascular risk factors (Fuster et al., 2024; Zemaitis et al., 2026; Vlachopoulos et al., 2019; Ohkuma et al., 2017; Claessens et al., 2023).

In parallel, growing attention has been directed toward central hemodynamic parameters. **Central aortic systolic blood pressure** provides a more direct estimate of left ventricular afterload compared with peripheral blood pressure measurements (Williams et al., 2006). Furthermore, pulse wave analysis enables the assessment of additional indices such as the **augmentation index** and **reflected wave transit time (RWTT)**, which reflect the timing and magnitude of wave reflections and are associated with early vascular alterations (Mitchell et al., 2010). However, their routine clinical application still requires further validation in large-scale prospective studies.

The combined assessment of ABI and PWV enhances risk stratification for adverse cardiovascular outcomes compared with either marker alone. This integrated approach is particularly valuable in high-risk populations, including patients with diabetes mellitus or acute myocardial infarction, where the coexistence of structural (atherosclerotic burden) and functional (arterial stiffness) vascular abnormalities confers additive prognostic significance. In the context of the present case, this dual evaluation allowed a more nuanced interpretation of vascular status, highlighting the interplay between PAD and increased arterial stiffness, which may otherwise remain underrecognized if assessed in isolation.

Beyond this, a comprehensive vascular phenotyping strategy incorporating ABI, PWV, central aortic pressure and RWTT enables simultaneous evaluation of macrovascular obstruction and arterial stiffness. This multidimensional approach improves early detection of subclinical vascular disease and refines cardiovascular risk prediction beyond traditional factors. In our patient, the integration of these parameters provided a more detailed characterization of vascular function and structure, offering clinically relevant insights that may inform individualized preventive and therapeutic strategies.

Such findings underscore the potential value of incorporating advanced vascular assessment into routine clinical practice, particularly in complex or high-risk cases where conventional evaluation may underestimate the true burden of vascular disease.

Case presentation

A 36-year-old male patient presented for cardiovascular evaluation with intermittent left lower limb tingling and episodic palpitations, described as brief, self-limited, and not previously documented on electrocardiography. His cardiovascular risk profile included active smoking, physical inactivity, and overweight status (BMI 26.7 kg/m²).

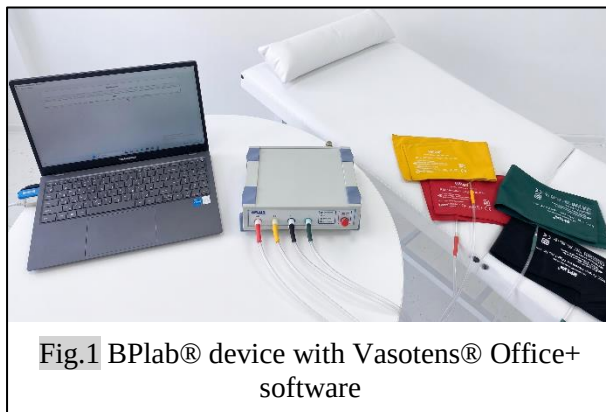
On physical examination, vital parameters were within normal limits: blood pressure 128/77 mmHg, heart rate 94 bpm, and oxygen saturation 97%. No signs of overt cardiovascular or peripheral vascular disease were observed on routine clinical examination. Resting 12-lead ECG demonstrated sinus rhythm, left axis deviation, and a PR interval of 0.20 s (upper limit of normal), with normal QRS duration, isoelectric ST segments, and normal QT interval.

Ambulatory rhythm monitoring (Holter ECG) revealed a second-degree atrioventricular block (Mobitz type I, Wenckebach) occurring during sleep, a finding generally considered benign and often associated with increased vagal tone, particularly in physically conditioned individuals. Exercise stress testing was clinically and electrically negative for ischemia, with the patient achieving maximal predicted workload. Isolated ventricular extrasystoles (VES) were observed during the recovery phase without clinical significance.

Transthoracic echocardiography demonstrated normal cardiac structure and function, with a preserved left ventricular ejection fraction (LVEF) of 67%, normal chamber dimensions, and no evidence of diastolic dysfunction. A localized chronic pericardial thickening, more pronounced at the apical region, was noted without hemodynamic compromise.

Laboratory findings revealed largely preserved metabolic and organ function parameters, with some notable findings: Glucose: 6.6 mmol/L (borderline elevated), HbA1c: 5.7% (upper-normal range, suggestive of prediabetes), Triglycerides: 4.2 mmol/L (elevated), HDL cholesterol: 1.0 mmol/L (low), LDL cholesterol: 3.1 mmol/L, Uric acid: 421 μ mol/L (borderline elevated), ALT: 64 U/L and GGT: 149 U/L (elevated, suggestive of possible hepatic/metabolic involvement), Inflammatory markers (CRP), renal function (creatinine 77 μ mol/L), electrolytes, and hematological indices were within normal limits. These findings indicate a metabolic risk profile consistent with early cardiometabolic dysfunction.

Vascular Assessment, ABI and Pulse Wave Analysis protocol



A comprehensive vascular evaluation was performed using the BPlab® device with Vasotens® Office+ software, which enables simultaneous non-invasive assessment of ankle-brachial index (ABI), pulse wave velocity (PWV), central blood pressure, and wave reflection indices. The system is consisted of a measurement module, four cuffs, four hoses, power supply unit, USB cable, dongle, and TensOffice+ software. The system was connected to a PC via USB, with the software activated using the

supplied dongle. After connecting the hoses according to the device markings, correct system readiness was confirmed by the green indicator lights (see figure 1).

The patient was examined in a supine position, barefoot, with both arms and ankles exposed (fig.2). Before cuff placement, upper-arm and ankle circumferences were measured to ensure correct cuff size. Arm cuffs were positioned with the arrow directed toward the brachial artery, ensuring they were neither too tight nor too loose. Ankle cuffs were then applied according to the measured ankle circumference.

In the first step of the protocol anthropometric distances were measured according to the device protocol, including the distance from the sternal notch to the os pubis (La), sternal notch to the middle of the brachial cuff (Lb), from the sternal notch to the femoral artery (Lc), and from the femoral artery to the middle of the ankle cuff (Ld) (fig. 3). The patient remained resting in the supine position for several minutes before measurement. Speaking or movement during the procedure was avoided, as these may affect signal quality and cause erroneous results, particularly in the presence of arrhythmia.



Fig.2 Patient stays relaxed in a supine position and the 4 cuffs placed in a correct order by protocol.

In the first measurement phase, arm and ankle cuffs were inflated simultaneously on both sides. The system recorded: *systolic blood pressure, diastolic blood pressure, ankle-brachial index, ABI classification, reflected wave transit time, aortic blood pressure, and aortic pulse wave velocity.*

In the second phase, simultaneous pulse wave analysis of all four limbs was performed using volume sphygmography. The target cuff pressure corresponded to the previously measured diastolic pressure of each limb. Pulse waves were recorded online until satisfactory signal quality was achieved. This phase provided right and left brachial-ankle pulse wave velocity, estimated carotid-femoral pulse wave velocity, and estimated aortic pulse wave velocity.

After completion, the software generated a detailed editable medical report, including ABI and arterial stiffness parameters (fig.5).

Examination procedure form

Step 1
Enter patient data

Examination
Examination number: CF88A51-DC00-45CD-89DD-35BE71BD8BCD
Date and time: [] [] [] [] [] []

Patient
Family name: [] [] [] [] [] [] [] []
First name: [] [] [] [] [] [] [] []
Middle name: [] [] [] [] [] [] [] []
Sex: ☒ M ☐ F ☐ X
Age (years): [] [] [] []
Height (cm): [] [] [] [] [] []
Weight (kg): [] [] [] [] [] []

La. Aorta length (cm): 64
Lb. Distance from sternal notch to the middle of brachial cuff (cm): 29
Lc. Distance from sternal notch to femoral artery (cm): 71
Ld. Distance from femoral artery to the middle of ankle cuff (cm): 52

Attention! During the study, a patient should be in a supine position, relaxed and motionless.

Diagram for distances measurement and cuff application

The diagram shows a human figure with measurement points and distances labeled: L_b (sternal notch to the middle of the brachial cuff), L_c (sternal notch to the femoral artery), L_a (sternal notch to the os pubis), and L_d (from the femoral artery to the middle of the ankle cuff).

Fig.3 Measuring anthropometric distances before initiating the procedure according to the device protocol. L_a (distance from the sternal notch to the os pubis) L_b (sternal notch to the middle of the brachial cuff), L_c (sternal notch to the femoral artery), and L_d (from the femoral artery to the middle of the ankle cuff).

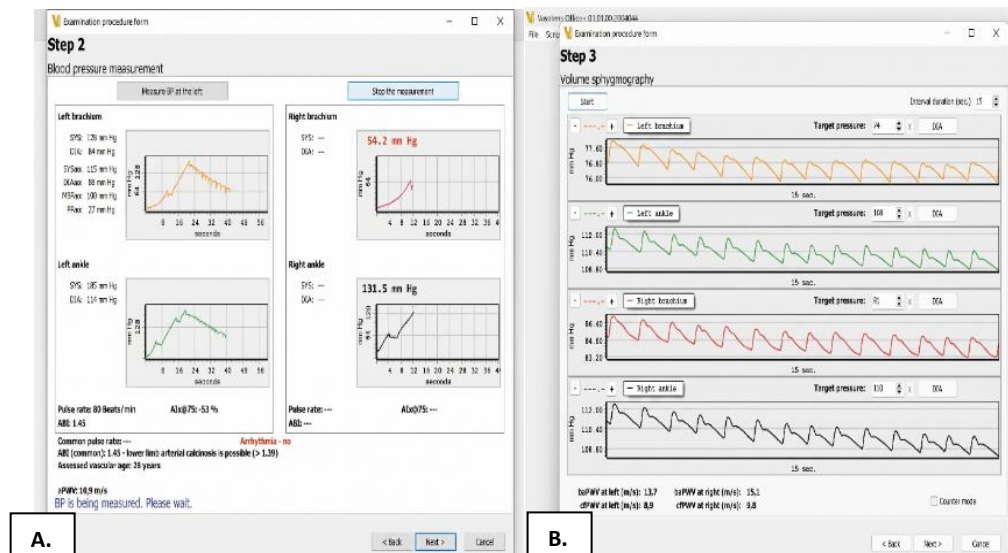


Fig.4 (A) Step 2, simultaneous four-limb blood pressure measurement. (B) Step 3, pulse waveforms from all four limbs indicating reliable volume sphygmography.

Hemodynamic and vascular parameters were assessed using simultaneous four-limb oscillometric measurement. Brachial blood pressure values were within the normotensive range, measuring 113/74 mmHg on the right arm and 111/78 mmHg on the left arm, with no clinically significant inter-arm difference (Δ SYS = 2 mmHg), normal peripheral and central blood pressure values, with preserved inter-arm symmetry, indicating the absence of significant proximal arterial obstruction, while ankle systolic asymmetry reached 15 mmHg.

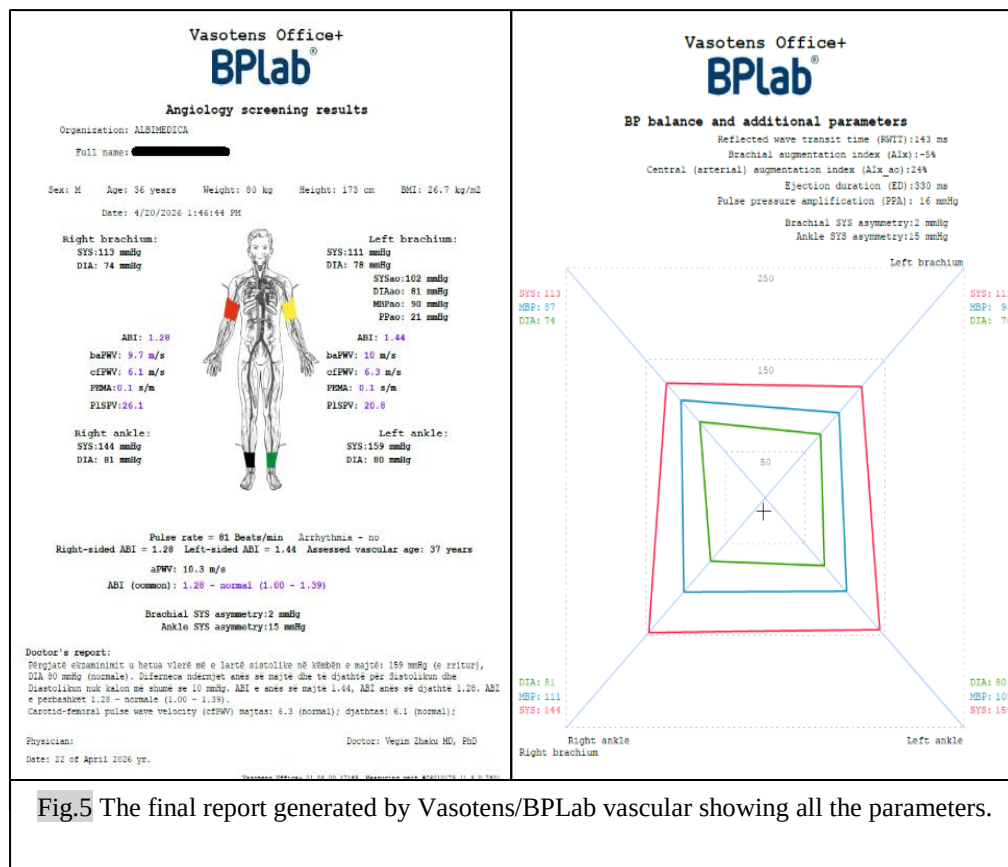


Fig.5 The final report generated by Vasotens/BPLab vascular showing all the parameters.

- **ABI results**

Ankle systolic blood pressure was higher compared to brachial measurements, as expected physiologically, with values of 144/81 mmHg on the right side and 159/80 mmHg on the left side. The calculated ABI was 1.28 on the right and 1.44 on the left, yielding a mean ABI of 1.28. While the right-sided ABI fell within the normal range (1.00–1.39), the left-sided ABI exceeded the upper normal threshold suggesting increased arterial stiffness, potentially reflecting early medial arterial calcification rather than obstructive peripheral arterial disease.

- **PWV results**

The PWV analysis demonstrated brachial–ankle PWV (baPWV) values of 9.7 m/s on the right and 10.0 m/s on the left (mildly increased values relative to expected norms for age). Estimated carotid–femoral PWV (cfPWV) values were 6.1 m/s and 6.3 m/s for the right and left sides, respectively which is within the normal limits. The calculated aortic PWV (aPWV) was 10.3 m/s. This pattern is consistent with early functional vascular alterations predominantly affecting peripheral arterial segments.

- **Central hemodynamic parameters**

Central hemodynamic parameters (SYSao: 102 mmHg; DIAao: 81 mmHg; PPao: 21 mmHg) were within normal physiological limits, with preserved pulse pressure amplification (PPA: 16 mmHg), suggesting maintained central arterial compliance.

Wave reflection indices revealed a RWTT of 143 ms, consistent with normal arterial elasticity. The brachial augmentation index (AIx: −5%) was within expected values for age, while the central augmentation index (AIx_{ao}: 24%) was within the normal-to-mildly elevated range. Ejection duration (330 ms) was appropriate for the recorded heart rate.

Additional indices (PEMA: 0.1 s/m bilaterally; PISPV: 20.8–26.1) were within expected ranges, although their clinical interpretation remains supplementary due to limited standardization.

Overall, the findings are consistent with preserved central hemodynamics and absence of overt peripheral arterial disease, with evidence of early peripheral arterial stiffening, particularly reflected by elevated left-sided ABI and mildly increased baPWV/aPWV values.

Discussion

This case reinforces the concept that subclinical vascular dysfunction may be present despite normal findings on conventional cardiovascular testing, highlighting the limitations of standard diagnostic approaches in detecting early-stage vascular disease. The integration of ABI, PWV, central hemodynamics, and wave reflection indices allowed identification of early vascular remodeling, supporting the paradigm that vascular alterations precede overt clinical manifestations of atherosclerosis by years or even decades.

A central observation in this patient is the discordance between an overall normal ABI and a borderline elevated left-sided ABI (1.44). While ABI values above 1.40 have traditionally been associated with arterial incompressibility, recent evidence suggests that such findings may reflect functional and structural vascular changes related to increased arterial stiffness, even in younger populations without advanced calcific disease (McDermott et al., 2010; Ix et al., 2010). Moreover, asymmetrical ABI elevation may indicate regional vascular heterogeneity, a phenomenon increasingly recognized as an early manifestation of vascular dysfunction rather than simply a measurement artifact.

The PWV profile further supports this interpretation. The preservation of cfPWV within normal limits, contrasted with mildly elevated baPWV and aPWV values, reflects a differential involvement of central versus peripheral arterial segments. This pattern aligns with contemporary evidence demonstrating that peripheral muscular arteries may exhibit functional stiffening earlier than central elastic arteries, particularly in individuals with cardiometabolic risk factors (Townsend et al., 2015; Tomizama et al., 2003). Such findings underscore the importance of multi-site PWV assessment, as reliance on a single parameter may underestimate early vascular changes.

Central hemodynamic measurements in this patient were within normal limits; however, the analysis of wave reflection indices provides additional pathophysiological insight. The RWT of 143 ms and central augmentation index (AIx_{ao}: 24%), while within expected ranges, may reflect early alterations in arterial wave reflection dynamics, which are sensitive to changes in vascular tone, endothelial function, and arterial geometry (Vlachopoulos et al., 2011; Chirinos et al., 2012). Notably, the relatively low brachial AIx (−5%) is consistent with the patient's age and heart rate, but does not exclude the presence of early vascular dysfunction.

The observed ankle systolic asymmetry (15 mmHg), although not diagnostic of peripheral arterial disease, may represent an early marker of localized vascular impairment. Emerging data suggest that even subclinical inter-limb differences are associated with increased cardiovascular risk and may reflect early atherosclerotic or functional vascular changes (Su et al., 2014). This reinforces the importance of bilateral assessment in vascular screening protocols.

From a broader perspective, the vascular phenotype observed in this patient is consistent with early vascular aging (EVA), a condition characterized by accelerated arterial stiffening relative to chronological age. EVA has been strongly linked to modifiable risk factors such as smoking, sedentary lifestyle, dyslipidemia, and insulin resistance, all present in this case. Importantly, EVA is increasingly recognized as a critical intermediate stage in cardiovascular disease progression and a potential target for early (Nilson P, 2008; Benetos et al., 2019).

The metabolic abnormalities identified in this patient further support this interpretation. Elevated triglycerides, reduced HDL cholesterol, borderline glycemic status, and hepatic enzyme abnormalities are indicative of early cardiometabolic dysregulation, which is known to contribute to endothelial dysfunction, oxidative stress, and vascular remodeling. These processes play a central role in the pathogenesis of arterial stiffness and subclinical atherosclerosis (Saklayen M, 2018).

Clinically, this case highlights the incremental value of combining structural and functional vascular markers. ABI provides information on arterial obstruction and vessel compressibility, while PWV and wave reflection indices capture arterial stiffness and hemodynamic load. When integrated, these markers offer a comprehensive vascular phenotype, improving early risk stratification beyond traditional scoring systems.

However, several limitations must be acknowledged:

1. The interpretation of novel indices such as PEMA and PISPV remains constrained by limited validation and lack of standardized reference values.
2. Variability between measurement devices and algorithms may affect reproducibility.
3. The clinical significance of mild asymmetries and borderline abnormalities requires further confirmation in longitudinal studies.

And finally, while this case demonstrates early vascular changes, the absence of long-term follow-up limits conclusions regarding prognostic implications.

Conclusion

This case demonstrates that integrated non-invasive vascular phenotyping provides a sensitive approach for detecting early vascular alterations that are not captured by conventional cardiovascular assessment.

Despite normal routine investigations, the patient exhibited evidence of early peripheral arterial stiffening, vascular asymmetry, and subtle alterations in wave reflection, consistent with an early vascular aging phenotype associated with cardiometabolic risk factors.

These findings emphasize the importance of adopting a multimodal vascular assessment strategy, particularly in younger individuals with modifiable risk profiles. Early identification of subclinical vascular dysfunction offers an opportunity for timely intervention, including lifestyle modification, metabolic optimization, and targeted cardiovascular prevention.

Future research should focus on:

- standardization of emerging vascular indices
- validation of inter-limb asymmetry as a prognostic marker
- integration of vascular phenotyping into routine clinical practice
- and evaluation of cost-effectiveness and outcome-driven strategies

Ultimately, comprehensive vascular assessment has the potential to significantly enhance early detection, risk stratification, and prevention of cardiovascular disease.

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