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SPECIAL ISSUE ARTICLE

Noninvasive central hemodynamic monitoring in the primary care setting: improving prevention and management of cardiovascular diseases

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Abstract

Background: Although cardiovascular disease (CVD) has markedly declined since the early 1960s due to medical advances and better management, this condition persists as the most critical and preventable cause of death in the US. For that reason, the identification and application of more sensitive, specific, validated, and noninvasive biomarkers of cardiovascular functioning in the primary care setting for the early identification of CVD risk at the subclinical level are warranted.
Aim: The goal of the present review is twofold: first, to familiarize the primary care practitioner with noninvasive aortic hemodynamic parameters, including how these could be integrated into primary care services and patient management, and second, to propose a model for earlier detection of CVD based on the noninvasive hemodynamic parameters in the primary care setting.
Relevance for Patients: Implementation of noninvasive hemodynamic monitoring in a primary care setting could help in the identification of heart disease risk at the early onset thus preventing the need for expensive treatment or death at later stages.

1. Introduction

It is well established that a higher-than-expected percentage of young adults have undetected early vascular aging or asymptomatic atherosclerosis, which may conceal undiagnosed cardiovascular disease (CVD) [1-3]. Early stages of CVD manifested as vascular damage for example endothelial dysfunction, arterial wall stiffening, and loss of vascular elasticity often go undetected during a routine clinical evaluation in the primary care setting that exclusively utilizes brachial (peripheral) blood pressure and blood chemistry values [4,5]. Expensive and more invasive tests such as carotid ultrasound, echocardiogram, coronary CT scan, and angiogram are generally not indicated in asymptomatic patients or those without a family history, leading to a delay in diagnosis of asymptomatic atherosclerosis and further disease progression.

Although CVD has markedly declined since the early 1960s, mostly owing to medical advances and better management, this condition persists as the primary cause of death in the US [6]. For that reason, the identification and application of more sensitive and specific validated noninvasive markers of cardiovascular functioning in the primary care setting are warranted for the early identification of impaired vascular function and atherosclerosis at the subclinical level. Nevertheless, primary care physicians do not have routine access to the devices or receive the training to interpret non-invasive

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aortic hemodynamic parameters in medical school or residency, representing a significant educational gap.

2. Discussion

2.1. Central hemodynamic parameters: Technical considerations and measurement

There are various commercially available devices capable of measuring central hemodynamic parameters non-invasively, including aortic pulse wave velocities (PWVao) such as SphygmoCor® (Atcor, Illinois, US), Mobil-O-Graph® (I.E.M., Stolberg, Germany), and Arteriograph (TensioMed, Budapest, Hungary). Although the main algorithms to calculate parameters may vary by manufacturer, the latest brachial cuff technology is a simple, noninvasive, and rather inexpensive way to measure vascular arterial stiffness, which can easily be used in primary-care settings where prevention efforts are most effective.

In general, the noninvasive aortic hemodynamics devices (NAH) first measure peripheral blood pressure (or BP). Next, the devices decompress the cuff. In a few seconds, the machine starts inflating the cuff again, first to the measured diastolic pressure and then, the suprasystolic (SBP > 35 mmHg) pressure. NAH records the signals for approximately 8 – 10 s at both cuff pressure levels. All the signals received by the NAH are transmitted wirelessly to a mobile device or personal computer to be analyzed by the device's software. These reports become readily available to the primary care practitioner and are securely transferred or integrated into the electronic medical record for easily accessible managed care documentation.

Pulse Wave Analysis (PWA) and PWVao measurements are tests that reveal central blood pressure, augmentation index (AIx), and arterial stiffening, respectively (Figure 1 and Table 1) [7,8]. The PWA and PWVao derived from noninvasive measurements such as those taken by the NAH devices mentioned earlier have been used in clinical practice and research for decades and validated as surrogates for invasive, catheter-derived central pressure measurements [5,9-12]. During systole, the blood volume ejected into the aorta generates a pulse wave (early systolic peak, P1). The P1 travels down the aorta and reflects from the peripheral circulation, including the bifurcation of the aorta, creating a second wave known as late systolic peak (P2) [13]. Both P1 and P2 peaks are obtained at suprasystolic pressure and recorded as pulse waves. The time between the observed peaks of the P1 and P2 waves is equal to the time (Return Time (RT)) of the travelling the initial pulse pressure wave (P1) to the aortic bifurcation and reflecting as P2.

Measuring the amplitudes of the systolic waves (P1 and P2) allows for measuring other hemodynamic parameters such as central systolic blood pressure (SBPc), aortic Augmentation Index, and return time (RT) of the wave reflection. The aortic Augmentation Index is defined as the augmented pressure (AP = P2-P1) expressed as a percentage of the aortic pulse pressure, while the return time (RT) of the wave reflection, which is the time it takes for the pulse wave to travel from the aortic root to the bifurcation and back [9,13]. An additional derived variable that can be obtained are systolic pressure-time index (STI; left ventricular work); diastolic pressure-time index (DTI; coronary perfusion), the ratio of DTI to STI expressed as a percentage (SVI; surrogate of subendocardial blood flow and coronary flow reserve) [14,15]. The markers, as mentioned earlier, are altered by acute psychological and physiological stressors, and more importantly, are sensitive markers of early CVD [16-18].

2.2. Central hemodynamics and cardiovascular disease risk Identification and stratification

Both PWV and PWA parameters have been demonstrated to be more sensitive markers of cardiovascular functioning than brachial blood pressure and superior predictors of cardiovascular mortality [19-21]. However, current guidelines for the treatment of hypertension (HTN), the most prevalent risk factor for CVD, neither consider central blood pressure values nor arterial stiffness parameters in the risk stratification or treatment of HTN [22]. Strikingly, the current guidelines may overlook asymptomatic atherosclerosis and vascular calcification which can be easily

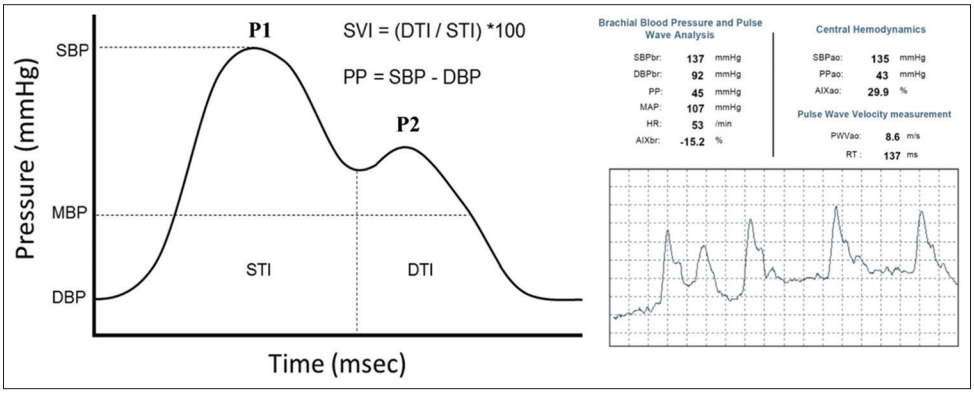

Figure 1. illustrates the main components of the aortic pressure waveform and associated clinical parameters. Adapted from (Sanchez-Gonzalez *et al.*, 2015). SBP: Systolic blood pressure; MAP: Mean arterial pressure; DBP: Diastolic blood pressure; P1: First systolic peak; P2: Second systolic peak; STI: Systolic time interval; DTI: Diastolic time interval; SVI: Subendocardial viability index; PP: Pulse pressure; SBPbr: Brachial systolic bloop pressure; DBPbr: Brachial diastolic blood pressure; HR: Heart rate; AIXbr: Brachial augmentation index; SBPao: Aortic systolic blood pressure; PPao: Aortic pulse pressure; AIXao: Aortic augmentation index; PWVao: Aortic augmentation index; RT: Return time of the systolic wave.

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Table 1. Non-invasive hemodynamic parameters and their corresponding descriptions

Parameter (abbreviation; units)	Description
Aortic Pulse Wave Velocity (PWVao; m/s)	Arterial compliance, elasticity or stiffness. Pulse Wave Velocity of the aorta (PWVao) is determined by the characteristics of the aortic wall (see RT). The stiffer the aortic wall, the faster the PWVao. A result <9.0 m/s indicates normal range, moderate to high increased is >9 m/s. Increased PWVao values are related to increased CV risk and atherosclerotic organ damage.
Return Time of the Direct Forward Systolic Wave (RT; msecs)	Return Time of the aortic pulse wave. RT reflects the characteristics of the aortic wall. The stiffer the aortic wall, the lower the RT. RT is normal above 124 msec <124 msecs may be a predictor of future cardiac events.
Augmentation Index (AIx; %)	The Augmentation index (AIx) is defined as the difference between the first and second systolic peaks divided by the pulse pressure and multiplied by 100. The AIx is considered a marker of wave reflection. Aortic (central) Augmentation Index mainly determines the peripheral arterial tone (resistance) of the small arteries and arterioles, which is influenced by endothelial nitric oxide (NO) synthesis. AIx aortic is normal under 33%.
Central Systolic Blood Pressure (SBPao; mmHg)	In a normal case, aortic (central) systolic blood pressure (SBPao) should be physiologically lower than the peripheral (brachial) SBP. SBPao is normal under 140 mmHg and 10 mmHg below the brachial systolic BP reading.
Aortic (central) Pulse Pressure (PPao; mmHg)	Aortic (central) Pulse Pressure (PPao) is the difference between the central systolic and diastolic pressure. PPao is normal under 50 mmHg.
Brachial Blood Pressure (SBP/DBP; mmHg)	High blood pressure should be treated earlier with lifestyle changes and in some patients with medication – at 130/80 mm Hg.
Ankle Brachial Index (ABI)	Ankle Brachial Index (ABI) <0.9 indicates increased risk of peripheral vascular disease. ABI >1.0 is normal.
Systolic Area Index (SAI; %)	In normal, resting situation with normal heart rate, the Systolic Area Index (SAI) is usually <50%. SAI is considered a surrogate of ventricular work.
Diastolic Area Index (DAI; %)	Pressurizing the cuff to the diastolic blood pressure generates volumetric signals. The area under the curve is taken as 100%, and then divided into SAI and Diastolic Area Index (DAI) area and expressed as the percentage of the total (100%). In normal, resting situation with normal heart rate the SAI is usually <50% and the DAI >50%. If the lower third of the DAI is under 46%, this is considered abnormally low. DAI is a surrogate of coronary perfusion.

measured using noninvasive hemodynamic parameters of arterial stiffness and central blood pressure [23-25]. This is worth noting because many individuals who appear healthy would be better stratified in the higher CVD risk categories based on more sensitive and easily accessible parameters such as PWV [25,26].

Despite the demonstrated superiority of central hemodynamic parameters, including SBPc, DBPc central BP, PWV, and AIx, these are not currently included in the clinical guidelines as cut-off indicators or for the development of targets for therapeutic or pharmacologic interventions. In this vein, many patients are not getting optimized management of their CVD prevention and management. Even more concerning when measuring traditional risk factors is the potential to overlook patients appearing normal who have underlying cardiovascular abnormalities and subclinical atherosclerosis and/or CVD. Standard techniques' usual methods to evaluate cardiovascular and metabolic disorders in primary care may underestimate or simply cannot identify actual cardiovascular risk [5,6,21,27,28].

Even with the advent of 24-h ambulatory blood pressure monitoring (ABPM), it still only measures peripheral blood pressure, missing the central pressure measurements that are a critical markers of arterial stiffness central pressure load, that leads to potential organ damage, and left ventricular hypertrophy (LVH) [5,21]. If physicians are provided information about their patients' central blood pressure, such as central pulse pressure (PPao), PWVao, SBPc, and aortic AIx, they can better evaluate the overall vascular health of their patients and determine if a more aggressive diagnostic evaluation or treatment is warranted [29].

2.3. Central hemodynamics, cardiometabolic risk factors, and risk stratification

The National Cholesterol Education Program Adult Treatment Panel issued revised guidelines concerning strategies for treating dyslipidemia to prevent cardiovascular disease [30,31]. These guidelines focus on recognizing metabolic syndrome and diabetes as disorders in need of more aggressive treatment. Based on these guidelines, millions of additional individuals may be considered eligible for drug therapy. Therefore, a more aggressive approach to identifying at-risk patients using noninvasive central hemodynamic parameters may lower BP, blood lipid, and body composition thresholds through pharmacologic and therapeutic lifestyle interventions earlier in the disease progression. A considerable challenge for physicians, especially in primary care, exists to identify patients who do not yet meet the criteria for drug therapy but would nevertheless benefit from more aggressive treatment. This large group of patients is usually identified as intermediate risk, assessed by statistical risk scoring methods such as Framingham risk score and coronary artery calcium (CAC) score [32,33]. The previously mentioned arteriography device, which requires only a single brachial cuff and produces accurate noninvasive central pressure measurements, offers clinical

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Table 2. A proposed cardiovascular risk stratification and management model using PWVao cut-off values related to therapeutic targets

PWVao	AIx	SBPao and PPao	Brachial BP	Blood Lipids	Diabetes	Obesity	Waistline	Tobacco use	Exercise
<8.4 ms	<33% normal >33%, focus attention on all other risk factors. Also consider age, gender, ethnicity, psychosocial, behavioral, cognitive, disability, family history, health literacy and socio economic status. Preventive counseling, education if no other risk factors are identified	Normal if <130 mmHg and 10 mmHg <brachial systolic BP, PPao <50 mmHg >130 mmHg consider follow-up check or 24 h ABPM confirmation	Normal if <140/90 >140/90, consider 24 h ABPM confirmation Treat per guidelines	Treat per guidelines if: LDL >130 or HDL <40 or >60 TG >200	Yes, treat per guidelines. Pre diabetes, Yes target 5–7% weight loss and TLC. Met syndrome, yes, target 10% weight loss and TLC. If diabetes, measure ABI Abnormal if <0.9	BMI >25 and <29.9, if BF% >25 (m) or >30 (f), target <23 (m) <25 (f) BF% If BMI >30 weight loss, target <30 and BF% <23% (m) <25 (f)	If BMI <25 Target (m) ≤90 cm (w) ≤80 cm If BMI >26 <29.9 Target (m) ≤100 cm (w) ≤90 cm If BMI >30 <34.9 Target (m) ≤110 cm (w) ≤105 cm If BMI >35 Target (m) ≤125 cm (w) ≤115 cm	If yes, cease immediately	150 (200 if diabetes) min/week of moderate exercise or 75 min/week of vigorous exercise. Add some resistance exercises. Especially if pre diabetes, diabetes, Met Syndrome add resistance exercises.
>8.5 ms and <9.0 ms Vitamin K2 supplementation If post-menopausal women, weigh-up calcium medication for osteoporosis versus CVD risk.	<33% normal >33%, focus attention on all other risk factors. Also consider age, gender, ethnicity, psychosocial, behavioral, cognitive, disability, family history, health literacy and socio economic status. Aggressive preventive counseling and education if no other risk factors are identified.	Consider treatment (CCB, ACEI versus BB) and closer monitoring if >130 mmHg, (24 h ABPM confirmation.) and/or PPao >50 mmHg, treatment, close and regular monitoring. Target SBPao <130 mmHg Target PPao <50 mmHg	>130/80 consider 24 h ABPM confirmation. Treat per guidelines if >140/90 Target <135/85	Treat per guidelines if: LDL >120 or HDL <40 or >60 TG >175	Yes, treat per guidelines. Pre diabetes, Yes target 5 – 7% weight loss and aggressive TLC. Met Syndrome, yes, target 10% weight loss & TLC. If BMI >35 and Age <60 years consider metformin. Reduce A1C by at least 0.2%. If diabetes, Measure ABI Abnormal if <0.9	BMI >25 and <29.9, if BF% >25 (m) or >30 (f), target <18 (m) <20 (f) BF%. BMI >30, aggressive TLC, weight loss, target <28 and BF% <23% (m) <25 (f). and If BMI >35 and Age <60 years consider metformin	If BMI <25 Target (m) ≤90 cm (w) ≤80 cm If BMI >26 <29.9 Target (m) ≤100 cm (w) ≤90 cm If BMI >30 <34.9 Target (m) ≤110 cm (w) ≤105 cm If BMI >35 Target (m) ≤125 cm (w) ≤115 cm	If yes, cease immediately	150 (200 if diabetes) min/week of moderate exercise or 75 min/week of vigorous exercise. Add some resistance exercises. Especially if pre diabetes, diabetes, Met Syndrome add resistance exercises.
>9.1 ms order Carotid Ultrasound, if positive, order Coronary CT scan. *+ve tests seek cardiovascular specialist opinion*. Alcohol ≤2 drinks for male and ≤1 drink for female	≤ & ≥ 33% Aggressive preventive counseling and education. Measure ABI Abnormal if <0.9	Consider treatment (CCB, ACEI versus BB) and close monitoring if >130 mmHg, (24 h ABPM confirmation) and/or	>130/80 consider 24 h ABPM confirmation. Treat per guidelines Target <130/80	Treat per guidelines if: LDL >110 or HDL <40 or >60 TG >150	Yes, treat per guidelines. Pre diabetes, Yes target 10% weight loss and aggressive TLC. Met syndrome, yes consider metformin Reduce A1C by at least 0.2%	Target BMI≤28, aggressive TLC, weight loss, BF% target <18% (m) <20 (f). If BMI >30 and Age <60 years consider metformin	If BMI <25 Target (m) ≤90 cm (w) ≤80 cm If BMI >26 <29.9 Target (m) ≤100 cm (w) ≤90 cm If BMI >30 <34.9 Target	If yes, cease immediately	200 min/week of moderate exercise including 40 min of vigorous intensity exercise three to four times a week. Add resistance exercises

(Cont'd...)

Table 2. *(Continued)*

PWVao	AIx	SBPao and PPao	Brachial BP	Blood Lipids	Diabetes	Obesity	Waistline	Tobacco use	Exercise
Remove stress		PPao >50 mmHg, treatment, close and regular monitoring. Target SBPao <130 mmHg Target PPao <50 mmHg					(m) ≤110 cm (w) ≤105 cm If BMI >35 Target (m) ≤125 cm (w) ≤115 cm		

BMI: Body mass index; CVD: Cardiovascular disease; SBPao: Aortic systolic blood pressure; PPao: Aortic pulse pressure

evidence that can be utilized to identify younger, apparently healthy patients who are silently at cardiovascular risk [34].

The matrix provided in Table 2 uses a proposed PWVao cut-off values model, <8.4 m/s, 8.5 – 9.0 m/s, and >9.1 m/s adapted from predictive models and modified risk scores for cardiovascular mortality [23,24,35,36]. Additional categories to evaluate other CVD markers such as peripheral BP, blood lipids, diabetes, tobacco use, exercise, and body composition threshold limits for early intervention are also included. Furthermore, waist circumference and intra-abdominal (trunk or visceral) fat have been significant predictors of disease. Android fat distribution is also an essential and independent determinant of arterial stiffness [37]. Notably, individuals with increased central fat deposits have increased circulating levels of pro-inflammatory cytokines and other inflammatory molecules (e.g., C-reactive protein) associated with insulin resistance, cardiovascular disease, lipid abnormalities, and hypertension [38]. It has also been shown that as an individual's android fat mass increases over time, so does their arterial stiffness and endothelial dysfunction [39]. Taken together, this evidence suggests that the higher the PWVao risk category, the more aggressive the proposed pharmacologic and therapeutic intervention programs could be.

2.4. Using non-invasive hemodynamics in the primary care setting: Practical considerations

Routine capture of central pressure and arterial stiffness measurement during regular vitals check-ups could provide further information to assist the clinician in concocting diagnostic and therapeutic approach for their patients. NAH devices that offer standardized oscillometric brachial blood pressure measurement and aortic PWA measurements during the same procedure, could further assist clinicians in optimizing their patient encounters promptly, potentially avoiding unnecessary specialty referrals or underdiagnosing silent, underlying conditions. In today's modern clinical environment, blood pressure devices are being designed such that they are connected to and securely stored patient's data in the cloud, enabling the routine integration of other patient self-reported data, such as behavioral and lifestyle health risk information. With both the regular patient-derived data and more sensitive arterial stiffness information, physicians could make more specific clinical decisions, especially regarding preventive advice and education tailored to their individual patient's circumstances. Future use of cloud-based central pressure and arterial stiffness monitoring devices could also be extended to patient homes for remote patient physiologic and therapeutic monitoring and collection of information in more "normal" scenarios reducing white coat syndrome or "masked" hypertension effect and providing further confidence in prescribing or adjusting treatment.

3. Conclusion

While researchers and the scientific community support the need for ongoing extensive population-based studies, the abundance of literature and growing empirical evidence enable physicians to make sound clinical decisions, especially warranting non-harmful

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yet aggressive therapeutic lifestyle change in otherwise unidentified at-risk patients. Many physicians recognize that medicine is individualized but not systematically so across medical entities. Single-subject trials have significant precedent in educational and behavioral settings but have not yet gained a high level of interest in clinical settings [40]. Known as n-of-1 trials, these consider an individual patient as the sole unit of observation and focus on the objective determination of the optimal therapy. These trials may improve outcomes by preserving some homogeneity while stratifying care among patients. Hopefully, with this information, combined non-pharmacologic lifestyle changes in young people associated with multiple drug combinations in adults diagnosed with CVD will effectively slow down (or reverse) early vascular aging and premature cardiovascular events.

This review by no means comprehensively covers the topic, rather than provides a lucid introduction of the topic followed by its applications and practical considerations. Author's training and practice experience can also lead to a bias.

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Conflicts of Interest

The authors report no conflict of interest.

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