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Diagnostic Technology:
Estimating central blood pressure and arterial stiffness in primary care using non-invasive automated pulse wave analysis.

Clinical Question: What role can automated estimates of central blood pressure and arterial stiffness play in primary care?

Arterial stiffness: Increased arterial stiffness is associated with an increased risk of cardiovascular events. We can quantify arterial stiffness by measuring "pulse wave velocity" and assessing the "arterial pulse waveform".

Pulse wave velocity: The product of the distance and time taken for the arterial pulse wave to travel between two points: commonly measured between the carotid and femoral arteries.

Arterial pulse waveform: The arterial waveform has two components; the forward moving wave when the left ventricle contracts and the reflected wave returning from the periphery. When the reflected wave arrives back at the central arteries earlier this leads to an augmentation of central aortic pressure. The arrival time and degree of augmentation is depends on the stiffness of the arteries. This can be quantified through the augmentation pressure which is the difference between the forward and reflected systolic pulse wave peaks. When expressed as a percentage of the pulse pressure it is called *augmentation index*.

Details of Technology:
What are the potential methods to estimate stiffness of the arteries?

1. Tonometric/piezoelectric: A probe is placed on the skin overlying the carotid or radial artery and pressure is applied to distort, or applanate (flatten) the artery, this creates a signal which approximates arterial pressure. This method requires skill and training to use. Operator-independent devices using a wrist watch design are currently available.
2. Oscillometric: A standard BP cuff is used to record brachial artery pressure waveforms. The BP machine automatically applies a 'general transfer function' (a mathematical representation used in physics to describe relationships between systems) to the brachial pressure waveform which generates a corresponding aortic pressure waveform. This method uses familiar automated systems for brachial BP assessments, which are easy to use and operator-independent. They appear best suited for large studies or use in primary care.
3. Photoplethysmographic: The digital volume pulse is analysed using a finger clip. The digital volume pulse is characterised by 2 distinct waves; an early systolic peak and a 2nd peak caused by the pressure wave reflected at peripheral sites. Out of the three methods, this method appears to be most susceptible to errors.

Advantages over Existing Technology:
Automated pulse wave analysis devices provide non-invasive estimates of central (aortic) blood pressure and the stiffness of vascular structures, particularly the arteries. The most accurate method for measurement of central blood pressures and vascular structure remains direct assessment via invasive catheter at the aortic valve/root and Doppler/MRI imaging of large arteries (measuring for example intima media thickness of the carotid artery). However, these are invasive, time consuming, costly, and impractical in primary care. Applanation tonometry of the carotid and femoral arteries is the current gold-standard non-invasive measure of arterial stiffness (1). However, this too is inconvenient, expensive, requires specialised training and is not feasible in primary care. The ability to perform pragmatic pulse wave analysis in primary care from measures taken at the brachial site using a specialised blood pressure cuff has become available, with several devices on the market or currently undergoing trials of clinical validity. These new brachial pulse wave analysis devices

potentially could provide a greater user-independent, time efficient and more cost effective methods to assess arterial dysfunction which up until now has been impractical in the primary care setting.

Importance:
Hypertension is the most common chronic disease in primary care, affecting over 16 million people in the UK. The prevalence of high blood pressure in England is 32% amongst men and 29% amongst women (2).

The relationship between raised blood pressure and cardiovascular risk is well recognised (3). The WHO identified high blood pressure as one of the most important preventable causes of premature morbidity and mortality worldwide (4). There is a well-established continuous relationship between systolic and diastolic blood pressures with cardiovascular morbidity and mortality. There are also independent relationships between blood pressure with heart failure, peripheral arterial disease and end stage renal disease.

Marked differences between aortic and brachial systolic pressures have been observed during invasive cardiac catheterisation (5). There is also evidence that drugs used to lower peripheral blood pressure may have a differing effect on central blood pressure (6). Furthermore, aortic stiffness has been shown to be an independent predictor for coronary events (7). It may have utility as a predictor of other vascular events as large artery stiffening and wave reflections have been identified as the most important pathophysiological determinants of isolated systolic hypertension (8).

Patient Group and Use:
- Assessment of cardiovascular risk in the general population
- Assessment of cardiovascular risk in specific patient groups, including those with diabetes and renal impairment
- Monitoring anti-hypertensive treatment
- Routine monitoring of blood pressure in pregnancy

Previous Research
1. Invasive, Doppler and tonometric/piezoelectric methods:
Two recently published systematic reviews have calculated quantitative estimates of the predictive value of both aortic pulse wave velocity and central pressure, as estimated by pulse wave analysis, from studies using invasive, Doppler or tonometric methods. The review of pulse wave analysis included 11 studies, with a total of 5,648 subjects. Four of these studies assessed patients with coronary artery disease undergoing angioplasty, three studies assessed patients with end-stage renal disease and three studies were community–based, recruiting mixed populations of normotensive and hypertensive individuals (9). The review which assessed the evidence for pulse wave velocity included 17 studies and 15,877 subjects in total (7). These studies varied in their populations, including end-stage renal failure in four studies, known hypertensives in three studies, diabetics, elderly patients and patients with chest pain, and participants from the general population (7). The studies included in these reviews reported risk values from invasive catheterisation or applanation tonometry at the carotid-femoral arteries, or the radial artery using mathematical modelling (general transfer function).

The reviews demonstrate that both pulse wave velocity and central pressures independently predict future cardiovascular events and all-cause mortality by similar amounts (7, 9). The risk of a cardiovascular event increases by 9% for every 10 mmHg increase in central BP. An increase of central pulse pressure by 10 mmHg increases the risk of a cardiovascular event by 14%. An increase in augmentation index of 10% increases the risk of a cardiovascular event by 32% and increases the risk of death from all causes by 38%.

The same study performed an analysis of four studies comparing the predictive ability if central and brachial BP for clinical events. Meta-analysis revealed central SBP and brachial SBP provided similar risk estimates (RR = 1.23 vs. 1.20, respectively, $P = 0.62$). However, in a separate analysis central pulse pressure was marginally but not significantly better at predicting clinical events compared with brachial pulse pressure (1.32 vs. 1.19, respectively, $P = 0.057$).

In the second review, an increase in pulse wave velocity of 1m/s corresponded to an increased risk of 14%, 15%, and 15% for total cardiovascular events, cardiovascular mortality, and all-cause mortality, respectively. An increase in aortic pulse wave velocity by 1 SD was associated with respective increases of 47%, 47%, and 42%.

These data compare favourably to risk associated with peripheral and central BP above and indicate PWV as an additional risk factor, particularly in patients with a high baseline CV risk (patients with coronary artery disease, renal disease, hypertension, or diabetes).

Table 1 Relative risk and 95% confidence interval of cardiovascular events in various populations according to changes in pulse wave analysis and velocity parameters.

Outcome	Central BP (10 mmHg↑)	Central pulse pressure (10 mmHg↑)	Augmentation index (10 %↑)	Pulse wave velocity (high vs. low)	Pulse wave velocity (1 m/s)	Pulse wave velocity (1 SD)
Total CV events	1.09 (1.04 – 1.14)	1.14 (1.06 – 1.215)	1.32 (1.09 – 1.59)	2.26 (1.89 – 2.70)	1.14 (1.09 – 1.20)	1.47 (1.31 – 1.64)
CV mortality	No data	No data	No data	2.02 (1.68 – 2.42)	1.15 (1.09 – 1.21)	1.47 (1.29 – 1.66)
All cause mortality	No data	No data	1.38 (1.19 – 1.60)	1.90 (1.61 – 2.24)	1.15 (1.09 – 1.21)	1.42 (1.29 – 1.58)

CV – cardiovascular; ↑ Increase; m/s – millisecond; SD – standard deviation

Studies have also shown anti-hypertensive agents may affect peripheral and central pressure differently. In the Conduit Artery Function Evaluation (CAFÉ) study, individuals randomized to atenolol had a 4.3 mmHg higher central BP than those receiving amlodipine, despite identical peripheral pressures (6).

In terms of the technologies themselves, a recent paper debated the validity of measures from the most widely used non-invasive tonometric device (SphygmoCor). Reporting on five studies, the SphygmoCor demonstrated unacceptably high mean and SD of error, ranging from 2 ± 11 mmHg to 13 ± 15 mmHg across the five studies (10). This study also critiques the reconstruction of central waveforms from non-invasive radial waveform assessment via transfer functions, suggesting that they are simply producing a radial waveform that has been passed through a mathematical transformation.

2. Oscillometric method:

The **ARCSolver (Mobil-o-graph)** uses an oscillometric method with a common cuff to determine augmentation index and aortic systolic BP and has been compared to invasive and non-invasive gold standard methods (11,12). Estimates of aortic systolic pressure showed good agreement (mean bias -0.3 ± 4.5 mmHg) with invasive measures (11). Similarly good agreement was demonstrated for aortic systolic BP (mean bias -0.1 ± 3.1 mmHg [12]; -0.5 ± 4.6 mm Hg [11]) and augmentation index (1.2 ± 7.9% [12]) compared with a widely used non-invasive method (SpygmoCor)(11,12). Estimates were within current regulatory body (e.g. Association for the advancement of medical instrumentation [AAMI] SP10) guideline thresholds and indicate realistic estimations of central systolic BP and augmentation index.

The **Arteriograph** uses an oscillometric occlusive technique to measure aortic pulse wave velocity, central systolic pressure and augmentation index at the brachial artery. Studies have shown a strong correlation between invasively measured aortic augmentation index and brachial augmentation index and a correlation between invasive and non-invasive central systolic BP (13)

The **Vicorder** uses an oscillometric technique to measure pulse wave velocity. Two studies have shown the device is unsuitable for accurate measurements of pulse wave velocity, particularly at higher velocities, due to an under- (14) and over-estimation (15) by the Vicorder device respectively.

The **PulseCor** is a model based estimation of aortic pulse pressure using suprasystolic brachial pressure waveforms. The agreements between actual (invasive) and estimated central systolic pressure exceed AAMI SP10 thresholds (16).

3. Photoplethysmographic method:
A comparison of a photoplethysmograph (Micro Medical) with carotid-femoral transit time, via non-invasive applanation tonometry (Millar and SphygomoCor) demonstrated significant but modest correlation between the digital volume pulse and the carotid-femoral pulse wave velocity ($r=0.65$, $P<0.0001$) (17). The study was supported by a grant from Micro Medical. There has been no comparison of this method with invasive measures.

The **PulseTrace** estimates stiffness index by analysing photoplethysmographic waves acquired on the finger-tip. The PulseTrace had relatively poor correlation with pulse wave velocity when compared to the reference method ($r = 0.55$), which measured the time delay between the pulse waves at the carotid and femoral pulse using tonometry (18).

Research Questions:
There is a growing body of evidence demonstrating a significant prognostic role for central pressures. Moreover, antihypertensive treatment may differentially affect central and peripheral pressures. However, to date no RCTs have assessed whether treatment based on central rather than peripheral pressure offers superior outcomes, or whether effects are drug class dependent. A number of research questions are presented:

- Will knowledge of central BP and arterial stiffness parameters improve prediction of cardiovascular risk and clinical outcomes in primary care compared to current practice?
- Do different antihypertensive agents have different effects on peripheral and central blood pressures?
- Do changes in peripheral and central pressures affect prognostic outcome differently?

Suggested next steps:
A systematic review of the measurement accuracy, reliability and validity of non-invasive pulse wave analysis and pulse wave velocity technologies in primary care settings.
A review of the predictive and monitoring capacity of central blood pressure and arterial stiffness in comparison with peripheral blood pressure.
Cohort studies assessing the predictive capacity for cardiovascular outcomes from estimates of central BP and arterial stiffness in primary care.
RCTs of treatment for patients with hypertension based on central versus peripheral blood pressure, and the effects of different antihypertensive agents on these two parameters in primary care settings.

Expected outcomes:
If the reliability and validity of peripheral measurement devices can be confirmed, and predictive and monitoring value greater than that of existing measures, then assessment of central blood pressures and arterial stiffness could potentially provide better diagnosis, management and outcomes in patients with hypertension and better cardiovascular risk assessment in general populations within primary care.

Clinical implications:
Data in Table 1 demonstrate the predictive capacity of pulse wave analysis and pulse wave velocity measures. Current clinical practice bases cardiovascular risk prediction on peripheral (brachial) BP values. Whether cardiovascular risk prediction from central BP and arterial stiffness parameters is better still remains to be determined. Large cohort studies would allow assessment of the predictive capacity of these measures and evaluate potential improvements over current risk prediction and/or risk factor management in primary care. Moreover, treatment strategies based on consecutive assessment of central BP and arterial stiffness, have the potential to improve hypertensive control in high risk populations such as the elderly and those with uncontrolled hypertension.

Guidelines:
European Society of Cardiology/Hypertension 2007 guidelines for the management of arterial hypertension state that non-invasive assessment of arterial stiffness through measurement of carotid-femoral pulse wave velocity has been shown to

have independent predictive value for all cause mortality and cardiovascular morbidity. Currently the assessment of arterial stiffness is largely limited to research settings; however its wider clinical use may add further precision to the assessment of cardiovascular risk.

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