Understanding and Treating Central Blood Pressure

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Approximately 1.5 billion people worldwide have high blood pressure, making hypertension the most common risk factor for cardiovascular disease, and the number of people affected by hypertension is expected to increase in the coming years. Despite every effort to diagnose and treat hypertension, less than one-third of hypertensive patients are adequately treated. Consequently, hypertension remains the leading cause of death and nonfatal events, especially in low-income countries, but also in well-developed countries.

The noninvasive method of measuring brachial blood pressure, proposed by Riva-Rocci in 1896 and refined by Korotkoff in 1905, has been used for more than a century because it has been shown to predict cardiovascular events, thus representing a very useful surrogate end point for assessing the risk associated with hypertension and the benefits of treatment. Measurement of brachial office blood pressure has limitations and, as Norman Kaplan noted, “the measurement of blood pressure is likely the clinical procedure of greatest importance that is performed in the sloppiest manner.”

Hemodynamic studies have shown that measuring systolic blood pressure in the aorta usually results in values that are lower than brachial blood pressure, especially when considering that the pulse wave is amplified when traveling from the heart to the periphery. As such, there is a need to measure central blood pressure because it reflects the true load imposed on target organs. In addition, it is now clear that central blood pressure values may be different among subjects with similar brachial blood pressure values. Central blood pressure predicts organ damage and future cardiovascular events, independent of brachial blood pressure, and antihypertensive drugs may have a different effect on central vs brachial blood pressure. In addition, target-organ damage during antihypertensive treatment is more closely related to central blood pressure than brachial blood pressure.
In this issue of *Dialogues in Cardiovascular Medicine*, Enrico Agabiti-Rosei and Maria Lorenza Muiesan discuss the theoretical and clinical background of central blood pressure assessment and examine the concept that measuring central blood pressure, with available noninvasive modern devices, may provide a more accurate and effective diagnosis and treatment of hypertension. However, they warn that, before introducing central blood pressure measurement in the everyday clinical management of hypertension, additional large, randomized clinical trials are needed to demonstrate that clinical outcomes may be improved by specifically reducing central blood pressure.

Stephane Laurent and Pierre Boutouyrie analyze the different methodologies currently used to measure central blood pressure, discuss the advantages and limitations of these methods, and examine the meaning of various parameters originating from the central pressure waveform.

The two subsequent articles discuss treatments that may answer the urgent need to achieve a higher blood pressure control rate in hypertensive patients.

Charalampos Vlachopoulos and Panagiotis Xaplanteris discuss the role of combination therapy in the treatment of hypertension, which guidelines now indicate should be the initial choice of treatment in patients at a high risk of cardiovascular disease and/or with markedly high baseline blood pressure values. In addition, combination therapy may favorably affect patients with mild-to-moderate hypertension and patients with comorbidities.

Lastly, Peter Sever analyzes the role of renal denervation for the treatment of resistant hypertension, and discusses the fact that, despite a large number of early positive studies, the first truly randomized, sham-controlled trial failed to show any benefit of renal denervation. Hence, further randomized, sham-controlled trials are needed, together with an attempt to identify the patients that respond to the procedure.

The diagnosis and treatment of hypertension remains difficult and further studies are needed to improve the present state of our knowledge and offer precise tools for a more appropriate treatment, with a subsequent reduction in the burden of cardiovascular diseases related to high blood pressure.
Understanding and treating central blood pressure

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The noninvasive measurement of blood pressure in the brachial artery predicts cardiovascular events; however, results of hemodynamic studies have shown that systolic blood pressure is usually lower when measured in the aorta compared with the brachial artery. These results indicate that there is a need to measure central blood pressure, as central blood pressure represents the load that directly influences the structure and function of target organs, such as the heart, brain, and kidneys. In addition, evidence indicates that central blood pressure, which may now be assessed noninvasively, is more strongly related to organ damage and future cardiovascular events than brachial blood pressure. In addition, antihypertensive drugs may have different effects on central vs brachial blood pressure. Hence, measuring central blood pressure with available noninvasive modern devices may provide a more accurate and effective diagnosis and treatment of hypertension. However, before introducing central blood pressure measurements in the routine management of hypertension, further studies are needed to demonstrate that clinical outcomes may be improved definitively by specifically lowering central blood pressure.

SELECTED ABBREVIATIONS AND ACRONYMS

<table>
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<th>Abbreviation</th>
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<tr>
<td>ASCOT</td>
<td>Anglo-Scandinavian Cardiac Outcomes Trial</td>
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<td>CAFE</td>
<td>Conduit Artery Function Evaluation</td>
</tr>
<tr>
<td>ICARe</td>
<td>Insufficienza Cardiaca negli Anziani</td>
</tr>
<tr>
<td>Dicomano</td>
<td>Residenti a Dicomano [study]</td>
</tr>
<tr>
<td>LIFE</td>
<td>Losartan Intervention For Endpoint reduction in hypertension [study]</td>
</tr>
<tr>
<td>REASON</td>
<td>pReterax in regression of Arterial Stiffness in a controLled double-bliNd study</td>
</tr>
<tr>
<td>SAFAR</td>
<td>noninvaSive Aortic ambulatory blood pressure monitoring For the detection of tARget organ damage [study]</td>
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brachial blood pressure. \(^8\) Central blood pressure can now be assessed noninvasively and the availability of modern and accurate devices permits a better evaluation of pressure load and an even more effective management of hypertension.

This review will discuss our present knowledge of central blood pressure. It will also discuss how central blood pressure may be used to help improve both risk stratification and pharmacological treatment of hypertensive patients.

**PHYSIOLOGICAL BACKGROUND**

The shape of the pressure waveform continuously changes along the arterial tree.\(^ {11,12} \) However, while mean and diastolic blood pressure remain relatively constant, systolic blood pressure may be up to 40 mm Hg lower in the aorta than in the brachial artery (Figure 1). This phenomenon is known as “pressure wave amplification,” and is mainly related to the increase in arterial stiffness (decreased compliance), as the pressure wave moves from the heart to the periphery.\(^ {11,13} \)

A two-element Windkessel model (resistance and compliance), with a central reservoir that fills during systole and empties during diastole, has been proposed to measure the hemodynamics of the arterial system. Subsequently, the prediction of pressure and flow throughout the entire cardiac cycle has improved with the addition of aortic characteristic impedance (three-element Windkessel model). However, these methods do not allow the wave transmission characteristics to be investigated.

The pressure wave, which is determined by the left ventricle ejection, travels along the arterial tree, where it is then reflected from sites of impedance mismatch (ie, arterial taper and differences in vessel stiffness), which often occur at bifurcations and possibly at the level of small resistance arteries.\(^ {14-16} \) Hence, the recorded pressure waveform represents the sum of the forward (incident) and backward (reflected) traveling waveforms. In normal subjects with healthy arteries, merging of the incident and reflected waves occurs in the proximal aorta during diastole, thus increasing diastolic blood pressure, and consequently, increasing coronary perfusion. On the contrary, in patients with stiff arteries and increased pulse wave velocity, merging of incident and reflected waves occurs during systole; therefore, there is a clear increase in systolic blood pressure, and consequently, greater left ventricular afterload and impaired ventricular relaxation and coronary filling.

Changes in central blood pressure are also the result of changes in the proportion of the incident wave that is reflected, which depends on the balance between vasoconstriction and vasodilatation in the peripheral circulation. The reflected wave is probably the sum of
numerous reflected “wavelets” that “augment” or increase systolic blood pressure in the central arteries. The extent of augmented pressure relative to the central pulse pressure is called “the augmentation index,” a complex measure with many interrelated determinants that provides information about the contribution of the amplitude and timing of reflected waves within the central arteries. Furthermore, timing depends on both the distance to the reflecting site and the pulse wave velocity. In addition, left ventricular ejection characteristics substantially modify the relations between reflected wave timing and amplitude with a change in the augmentation index. 17-20

There is substantial pressure amplification within the arterial tree, regardless of the mechanisms that result in changes to the shape of the waveforms (Figure 2). Pressure amplification is not fixed, either between or within individuals, since it depends on several variables, including age, heart rate, height, sex, and vascular diseases. In fact, central blood pressure is lower in young people (ie, ~20 to 30 mm Hg lower than blood pressure in the brachial artery). 21

Moreover, since pressure augmentation is inversely related to height and heart rate, central blood pressure is relatively higher in subjects with a shorter stature and in those with a lower heart rate. However, even using multivariable regression models, brachial blood pressure cannot provide an accurate prediction of central blood pressure (Table I). Recently, normalcy values have been published for central blood pressure and amplification in a very large number of subjects (>85 000 individuals), representing a healthy population who are free of traditional cardiovascular risk factors, according to age, sex, and brachial blood pressure (Figure 3, page 172). 27 In the same study, it was also concluded that amplification is significantly influenced by cardiovascular risk factors, but differently between men and women. 28 Interestingly, at any age or blood pressure category, men had greater pressure amplification than women. 27-29

### MEASURING CENTRAL BLOOD PRESSURE

Invasive measurement of central blood pressure cannot be routinely applied in asymptomatic patients; therefore, we must rely on noninvasive methods. 30 The noninvasive measurement of central blood pressure relates to the analysis of an arterial waveform by different methods and it is usually calibrated on brachial blood pressure. Applanation tonometry and oscillometric methods, using a standard brachial blood pressure cuff, are methods described for the arterial waveform analysis of the carotid or radial arteries.

Tonometry of the carotid or radial artery is directly performed with a hand-held piezoelectric probe or a tonometer, and it requires some skill and reasonable

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<td>34 Normotensives, 36 Hypertensives</td>
<td>Mobil-O-Graph (IEM GmbH)</td>
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<td>Luzardo et al, 2012</td>
<td>35 Normotensives at rest, 83 Normotensives at rest and during the daytime</td>
<td>Mobil-O-Graph (IEM GmbH)</td>
<td>Comparison of central BP measurement vs radial tonometry (Sphygmocor)</td>
</tr>
<tr>
<td>Weber et al, 2011</td>
<td>30 Subjects</td>
<td>Oscillometric/ARC Solver algorithm, Tonometry/transfer function</td>
<td>Validation vs invasive measurement</td>
</tr>
<tr>
<td>Williams et al, 2011</td>
<td>15 Subjects for the invasive study, 217 Volunteers for the comparison study</td>
<td>A-Pulse tonometer (N-point moving average), Sphygmocor (generalized transfer function)</td>
<td>Validation vs invasive measurement, Comparison of central systolic BP measurement with A-Pulse and Sphygmocor</td>
</tr>
<tr>
<td>Ott et al, 2012</td>
<td>52 Patients</td>
<td>BPPro device with A-Pulse, Sphygmocor</td>
<td>Validation vs invasive measurement</td>
</tr>
</tbody>
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Table 1. Central blood pressure measurement validation studies.
training for good-quality pressure waveform recordings. New devices have been developed to obtain an operator-independent recording of the arterial pressure waveform, based on applanation tonometry and oscillometry. When using radial tonometry, brachial blood pressure is measured using a conventional cuff-based device before the tonometry, while the patient is seated or supine, and a minimal amplification between brachial and radial arteries is assumed. When the cuff-based oscillometric method is performed, the brachial blood pressure measurement and the brachial arterial waveform acquisition are performed simultaneously, and in this case, the brachial-radial amplification may be overcome.

For the analysis of the arterial (carotid, radial, or brachial) waveform, three different approaches have been proposed: (i) the use of a generalized transfer function; (ii) the derivation of the inflection point on the descending slope of the systolic pressure wave, called the secondary systolic wave (SBP2) method; and (iii) the N-point moving average (NPMA) method. Both the oscillometric method with a generalized transfer function and the NPMA method allow for 24-hour central systolic blood pressure monitoring.

Several generalized transfer functions have been developed to derive the aortic waveform from the peripheral artery waveform. A transfer function encodes the alterations introduced by a system (arterial tree) on the original signal (radial waveform), which generates the output (aortic waveform), and assumes that the properties of the upper limb arteries are virtually identical between individuals. To date, most of the validation studies have been carried out in men undergoing diagnostic cardiac catheterization, and the accuracy of the transfer function in women, in individuals without coronary disease, after exercise, or in a supine rather than sitting position has been a matter of debate (Table I).

In a recent meta-analysis, 22 available studies were examined in order to systematically evaluate the accuracy of noninvasive applanation tonometry methods to estimate central blood pressure. The meta-analysis showed that when the acquired arterial pressure waveforms were calibrated to match invasive measurements of aortic mean blood pressure and diastolic blood pressure, the errors of estimated central blood pressure were small, with a mean and standard deviation of difference of $-1.1 \pm 4.1$ mm Hg for central systolic blood pressure, $-0.5 \pm 2.1$ mm Hg for central diastolic blood pressure, and $-0.8 \pm 5.1$ mm Hg for central pulse pressure. Contrarily, when acquired arterial pressure waveforms were calibrated to match the brachial blood pressure measured with a sphygmomanometer, the errors were higher: $-8.2 \pm 10.3$ mm Hg for central systolic blood pressure, $7.6 \pm 8.7$ mm Hg for central diastolic blood pressure, and $-12.2 \pm 10.4$ mm Hg for central pulse pressure. The results of this meta-analysis highlight the need to improve the measurement accuracy of central blood pressure when cuff blood pressure is used to calibrate the peripheral waveforms.

Amplification of systolic blood pressure from brachial to radial arteries is also likely to contribute to central systolic blood pressure underestimation when using the radial tonometry method. The calibration of radial artery waveforms on brachial systolic blood pressure represents another problem that leads to a systematic underestimation of the true central systolic blood pressure. The values of central systolic blood pressure become closer to the true aortic systolic blood pressure when the waveforms of peripheral arteries are calibrated using the oscillometric mean and diastolic blood pressure, as was clearly highlighted in the results of the SAFAR study (noninvasive Aortic ambulatory blood pressure monitoring For the detection of TArget organ damage).
Identification of the inflection point (SBP2) has been used to derive central aortic systolic blood pressure. SBP2, also defined as the late systolic shoulder of the peripheral pressure waveform, was shown to approximate central aortic systolic blood pressure.\(^{47-49}\) Mean blood pressure may be calculated from systolic and diastolic brachial blood pressure; central diastolic blood pressure may be calculated after derivation of central systolic blood pressure at the SBP2, assuming that peripheral mean blood pressure is substantially similar to the mean blood pressure in the aortic root.

However, identification of the second peak of aortic pressure may not be easy, especially in elderly subjects with stiff arteries or in young people with early peak systolic pressure in the absence of augmentation, representing an important limitation to its clinical use. The correct identification of the second peak may also be influenced by the acquisition of the arterial pressure waveform.\(^{50}\)

Finally, Williams et al showed that the NPMA method was capable of estimating central aortic systolic blood pressure.\(^{25}\) The NPMA is a mathematical low-pass filter that can smooth the high-frequency components and reveal the underlying peak of the central aortic systolic blood pressure. Each single point in the signal is summed up with its neighbors and divided by the number of considered data points; therefore, the more data points that are taken in the original formula, the smoother the signal. The NPMA method, with a common denominator of 4 (one-quarter of the acquisition sampling frequency), has been shown to accurately define central systolic blood pressure.\(^{25,51,52}\)

Recently, applying the NPMA method to a cuff-based technique, by integrating the NPMA into current oscillometric blood pressure monitors, was developed and validated.\(^{26,51,52}\)

Despite the widespread use of these techniques, there are still some methodological problems, possibly due to the use of different algorithms in different devices.\(^{53-55}\) Considering the problems relative to the feasibility and reproducibility of different methods proposed for central blood pressure evaluation, the issue of reference values for central blood pressure seems to be highly important.

In the last 10 years, technological progress has allowed for the development of some ambulatory blood pressure monitoring devices that measure central blood pressure or pulse wave velocity, continuously or intermittently. A few studies have been performed, showing that progress has been made in the evaluation of 24-hour ambulatory central aortic blood pressure (Table II).\(^{31,46,56-59}\) The 24-hour central systolic blood pressure monitoring may be performed by recording the brachial artery waveform using the oscillometric method, with a generalized transfer function,\(^{31}\) or the NPMA method for central blood pressure estimation.\(^{56}\)

The reliability of central blood pressure measurements obtained by the oscillometric method has been assessed in both invasive\(^{24,60}\) and noninvasive stud-

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Device</th>
<th>Study aim</th>
</tr>
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<tr>
<td>Jankowski et al,(^{31}) 2013</td>
<td>50 Normotensives 50 Hypertensives</td>
<td>BPro, HealthStats, Singapore</td>
<td>Monitor and measure 24-hour peripheral and central BP</td>
</tr>
<tr>
<td>Theilade et al,(^{59}) 2013</td>
<td>629 Patients with type 1 diabetes 86 controls</td>
<td>BPro, HealthStats, Singapore</td>
<td>Assess the correlation between central BP and diabetes-related complications</td>
</tr>
<tr>
<td>Freercks et al,(^{58}) 2014</td>
<td>74 Prevalent dialysis patients</td>
<td>BPro, HealthStats, Singapore</td>
<td>Correlate central BP values with vascular calcification</td>
</tr>
<tr>
<td>Protogerou et al,(^{57}) 2012</td>
<td>30 Consecutive hypertensives</td>
<td>Mobil-O-Graph (IEM GmbH)</td>
<td>Assess the reproducibility of the 24-hour BP recordings</td>
</tr>
<tr>
<td>Williams et al,(^{56}) 2013</td>
<td>171 Patients (AmCAP study)</td>
<td>BPro, HealthStats, Singapore</td>
<td>Determine the effect of antihypertensive treatment</td>
</tr>
<tr>
<td>Protogerou et al,(^{56}) 2014</td>
<td>229 Consecutive subjects (75% hypertensive)</td>
<td>Mobil-O-Graph (IEM GmbH)</td>
<td>Correlate LVH with 24-hour central and peripheral BP recordings</td>
</tr>
</tbody>
</table>

*Table II. Clinical studies using 24-hour central blood pressure recordings.*

*Abbreviations: BP, blood pressure; LVH, left ventricular hypertrophy.*
ies and compared with those recorded with the Sphygmocor device, which is widely known as the most commonly used approach for the noninvasive assessment of central aortic blood pressure. During daytime and nighttime hours, both methods have shown that peripheral pressure was higher than central blood pressure, with a lower nocturnal decline of central blood pressure vs peripheral blood pressure. The identification of a higher central nighttime blood pressure warrants further investigation.

Another interesting, but only partially addressed, aspect is the relationship between 24-hour ambulatory central vs brachial blood pressure and target-organ damage. The availability of ambulatory central blood pressure measurements will open a new field of research and a large number of issues will be of interest, such as the assessment of blood pressure variability, and obviously, the investigation of the effect of antihypertensive treatment on central blood pressure. The accuracy and reproducibility of all available devices need to be carefully evaluated, with simultaneous recordings of peripheral and central blood pressure, and the cost of the devices should be affordable.

### CLINICAL PROGNOSTIC VALUE OF MEASURING CENTRAL BLOOD PRESSURE

Several studies have clearly shown that central blood pressure, rather than brachial blood pressure, is more representative of the blood pressure acting on target organs. It has been shown that central hemodynamics are independently associated with organ damage, incident cardiovascular diseases, and clinical events, both in the general population and in several pathological states. Moreover, it has become evident that different antihypertensive drugs could have different effects on brachial vs central blood pressure.

### CENTRAL HEMODYNAMICS AND PRECLINICAL ORGAN DAMAGE

In cross-sectional studies, central blood pressure, rather than brachial blood pressure, is more closely related to accepted markers of preclinical organ damage, such as carotid intima-media thickness and left ventricular mass or wall thickness, independent of age and mean blood pressure. These conclusions have been further supported by several longitudinal observations. In the REASON study (pREterax in regression of Arterial Stiffness in a controlled double-blind study), treatment with atenolol was compared with a low-dose combination of the angiotensin-converting enzyme inhibitor perindopril and the diuretic indapamide. This study showed that reduction in left ventricular mass was more strongly related to the change in central vs brachial blood pressure. These observations were confirmed in a substudy of the ASCOT trial (Anglo-Scandinavian Cardiac Outcomes Trial). In addition, the reduction in carotid intima-media thickness during antihypertensive therapy is more related to a decrease in central vs brachial blood pressure. Moreover, in inflammatory disorders, such as systemic vasculitis, augmentation index is independently associated with levels of C-reactive protein, making it a good marker of disease activity.

### CENTRAL HEMODYNAMICS AND CARDIOVASCULAR EVENTS

The predictive value of central blood pressure has been assessed in several studies that were performed in either general populations or cohorts of patients with a variety of cardiovascular diseases. In nine out of eleven published studies, central blood pressure was independently related to future cardiovascular events. At a 5-year follow-up, data from the Strong Heart Study showed that noninvasively determined central pulse pressure predicts cardiovascular events better than the corresponding brachial blood pressure. Central blood pressure was also determined to be a strong independent predictor of all-cause and cardiovascular mortality in patients with end-stage renal failure. Central hemodynamics are also powerful and independent predictors of coronary events in patients with coronary artery disease and in patients after percutaneous coronary interventions.
Both the ICARe Dicomano study (Insufficienza Cardiaca negli Anziani Residenti a Dicomano), which was performed in a geriatric population in Italy,6 and a community-based study in Taiwan89 also observed a stronger relationship between cardiovascular events and central blood pressure rather than brachial blood pressure. In contrast, the Framingham Heart Study could not confirm these results and was unable to demonstrate any additional value of carotid blood pressure.91

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>N, population</th>
<th>Country</th>
<th>Duration</th>
<th>Parameter</th>
<th>End point</th>
<th>Outcome</th>
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<tr>
<td>Nakayama et al.93 2000</td>
<td>53, CAD-PTCA</td>
<td>Japan</td>
<td>3 mo</td>
<td>Invasive aortic pulsatility*</td>
<td>Restenosis</td>
<td>Pulsatility ratio independently associated with restenosis</td>
</tr>
<tr>
<td>Lu et al.85 2001</td>
<td>87, CAD-PTCA, stable angina</td>
<td>China</td>
<td>6 mo</td>
<td>Invasive aortic SBP, PP, and pulsatility</td>
<td>Restenosis</td>
<td>Aortic PP and pulsatility ratio independently associated with restenosis</td>
</tr>
<tr>
<td>Safar et al.8 2002</td>
<td>180, End-stage renal disease</td>
<td>France</td>
<td>1 y</td>
<td>Carotid PP</td>
<td>All-cause mortality (including CV mortality)</td>
<td>Carotid PP independently associated with all-cause mortality</td>
</tr>
<tr>
<td>Weber et al.87 2005</td>
<td>262, CAD-PTCA</td>
<td>Australia</td>
<td>2 y</td>
<td>AI</td>
<td>CV mortality and events</td>
<td>AI associated with CV mortality, MI, and restenosis</td>
</tr>
<tr>
<td>Chirinos et al.64 2005</td>
<td>324, Men with CAD</td>
<td>US</td>
<td>4 y</td>
<td>Invasive aortic SBP and PP</td>
<td>All-cause mortality and major CV events</td>
<td>Aortic PP independently associated with all-cause mortality</td>
</tr>
<tr>
<td>Dart et al.88 2006</td>
<td>484, Hypertensive women</td>
<td>Australia</td>
<td>4.1 y</td>
<td>Carotid SBP and PP</td>
<td>CV events and mortality</td>
<td>No predictive value of carotid systolic BP or PP</td>
</tr>
<tr>
<td>Williams et al.92 2006</td>
<td>2199, Hypertensives</td>
<td>UK</td>
<td>4 y</td>
<td>Aortic PP</td>
<td>CV mortality, events, and procedures</td>
<td>Aortic PP independently associated with CV events and procedures</td>
</tr>
<tr>
<td>Roman et al.7 2007</td>
<td>2403, Native Americans, Strong Heart Study</td>
<td>US</td>
<td>4.8 y</td>
<td>Aortic SBP and PP</td>
<td>CV mortality and events</td>
<td>Aortic systolic BP and PP independently associated with CV mortality and events</td>
</tr>
<tr>
<td>Jankowski et al.68 2008</td>
<td>1109, Angiography</td>
<td>Poland</td>
<td>4.5 y</td>
<td>Invasive aortic PP and pulsatility</td>
<td>CV mortality and events</td>
<td>Aortic PP and aortic pulsatility related to CV mortality/events</td>
</tr>
<tr>
<td>Pini et al.6 2008</td>
<td>173, Elderly subjects, Dicomano Study</td>
<td>Italy</td>
<td>8 y</td>
<td>Carotid SBP and PP</td>
<td>CV mortality and events</td>
<td>Carotid systolic BP and PP independently associated with CV events and carotid systolic BP with fatal CV events</td>
</tr>
<tr>
<td>Wang et al.94 2009</td>
<td>1272, General population</td>
<td>Taiwan</td>
<td>10 y</td>
<td>Carotid SBP and PP</td>
<td>All-cause and CV mortality</td>
<td>Carotid systolic BP predicted CV mortality</td>
</tr>
<tr>
<td>Mitchell et al.91 2010</td>
<td>2232, General population, Framingham Study</td>
<td>US</td>
<td>7.8 y</td>
<td>Carotid PP</td>
<td>Major CV events</td>
<td>No predictive value after adjustment for brachial systolic BP</td>
</tr>
</tbody>
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Table IV. Association between central pressures and outcomes.

Abbreviations: AI, augmentation index; CAD, coronary artery disease; CV, cardiovascular; MI, myocardial infarction; mo, month; PP, pulse pressure; PTCA, percutaneous angioplasty; pulsatility, ratio of pulse pressure to mean arterial pressure; SBP, systolic blood pressure; y, year.
In addition, it seems that the usefulness of a specific central blood pressure index does not necessarily apply to other indices. It should be noted that the studies performed so far are relatively underpowered to demonstrate that central blood pressure is superior to brachial blood pressure in predicting cardiovascular events, especially considering that there is a relatively close correlation between the two measurements. However, a meta-analysis of studies published before 2010 confirmed that central blood pressure has an independent predictive value and may be a better predictor of cardiovascular events.

Recently, Cheng et al validated central blood pressure thresholds for diagnosing hypertension based on the prediction of cardiovascular and stroke mortality. Optimal central blood pressure and “central hypertension” thresholds were estimated in a derivation cohort (n=1272) and then tested in a separate (validation) cohort (n=2501). Cardiovascular mortality was more strongly associated with both central pulse pressure and systolic blood pressure compared with brachial cuff blood pressure. The contribution of central blood pressure to the prediction of future cardiovascular and stroke mortality was in addition to brachial blood pressure and independently of traditional cardiovascular risk factors.

Although most of the studies indicate that central blood pressure provides incremental and independent prognostic value, clearly there is a need for additional studies in the general population and in a variety of disease states (Table IV, page 175).

**EFFECTS OF ANTIHYPERTENSIVE TREATMENT ON CENTRAL BLOOD PRESSURE**

The benefit of antihypertensive treatment is mostly related to the reduction in blood pressure per se, independently of the drugs used, which has been shown in a number of large randomized clinical trials and their meta-analyses. This conclusion has been accepted and confirmed in the recent European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines for the management of hypertension. However, the effect of different antihypertensive drugs on the regression in preclinical organ damage (eg, left ventricular hypertrophy, arterial and renal alterations, etc) is not the same. β-blockers, particularly atenolol, are less potent in this regard. Moreover, in randomized trials using combination regimens, including the LIFE study (Losartan Intervention For Endpoint reduction in hypertension) and the ASCOT trial, atenolol was found to be inferior to other major antihypertensive drug classes in preventing cardiovascular events. Interestingly, most of the differences in the effects of drugs on cardiovascular outcomes are related to effects on central vs brachial blood pressure.

Numerous studies have examined the effect of different antihypertensive drugs on central vs brachial blood pressure. However, most of these studies only included a small number patients, while among them, there was a consistent difference in the duration of the treatments and methods used to assess central blood pressure. Nevertheless, these studies have shown that conventional β-blockers do not lower central blood pressure as much as brachial blood pressure. This effect was clearly observed in the REASON trial, which showed a greater reduction in central blood pressure when using a combination-drug treatment (Figure 4). The different effects on central blood pressure might have accounted for the different reductions in left ventricular mass. In addition, the CAFE trial (Conduit Artery Function Evaluation), a substudy of the ASCOT trial, has shown that patients randomized to atenolol (+bendroflumethiazide, in most cases) had higher central blood pressure than those who received amlopidine (+perindopril, in most cases), despite having similar brachial blood pressure measurements (Figure 5). The different effects on central blood pressure are illustrated in Figure 4.

![Figure 4](image-url)

**Figure 4. Changes in left ventricular mass index and central blood pressure in the REASON study.**

Abbreviations: LVM, left ventricular mass; PP, pulse pressure; REASON, prEterax in regression of Arterial Stiffness in a controLled double-blINd study.

Based on data from reference 75.
Pressure could explain, at least in part, the differences in outcomes in the ASCOT trial.103 Newer β-blockers with vasodilating properties, such as nebivolol,97,104 carvedilol, and celiprolol,77,105 seem to be more effective101,106 in reducing wave reflections, and therefore, central blood pressure. Renin-angiotensin-aldosterone system (RAAS) blockers are the most effective in reducing central blood pressure.107 Combining RAAS blockers with calcium antagonists resulted in a superior efficacy vs other combinations (diuretic + β-blocker, β-blocker + calcium antagonist, diuretic + calcium antagonist) for lowering central hemodynamics.92,108,109 In addition, data suggest that nitrates, which are nitric oxide donors, may reduce central blood pressure more than brachial blood pressure. This offers an interesting therapeutic strategy,110-113 although nitrates do not represent classic antihypertensive drugs, mostly due to concerns regarding tolerance.

All of these results have been confirmed in a recent meta-analysis,114 which was performed on twenty-four randomized trials that measured brachial blood pressure, central blood pressure, and augmentation index (Table V). The conclusion was that β-blockers, diuretics, and combinations containing β-blockers tend to reduce central to brachial amplification, implying that the achievement of target brachial blood pressure may be associated with a lower reduction in central blood pressure with these drug regimens.

### FUTURE PERSPECTIVES

#### Methodological aspects

Currently, techniques for measuring central blood pressure are not perfect, which is partly due to variability in the performance of different devices, although brachial blood pressure measurements may have similar problems when assessed by monitors using different proprietary algorithms.
In a recent meta-analysis, it has been suggested that using radial tonometry for the calibration of waveforms with brachial systolic and diastolic blood pressure may lead to underestimation of central blood pressure. This could be related to both amplification of systolic blood pressure from brachial to radial arteries and underestimation of brachial systolic blood pressure using oscillometric or auscultatory methods. It has also been suggested that central blood pressure measurements could be improved, obtaining values closer to true (invasive) blood pressure values, when mean arterial blood pressure is used to calibrate peripheral arterial waveforms. In a cohort of 229 patients with hypertension, it has been recently shown that central blood pressure measurements, using waveforms calibrated from oscillometric mean arterial blood pressure and diastolic blood pressure, provide values that are more closely related to the left ventricular mass index than 24-hour brachial systolic blood pressure.

It is important to establish a standardized approach for the validation of old or new devices that can be obtained using accurate comparisons with either instruments that measure invasive aortic blood pressure or instruments that are already available on the market and commonly used. In order to solve all of these issues, further studies are needed to indicate the best methods for measuring central blood pressure that are possibly supported by an international consensus.

**Comparison with other forms of blood pressure measurement**

The clinical prognostic value of central blood pressure should be compared with that of other forms of blood pressure measurements, including 24-hour ambulatory blood pressure monitoring and home blood pressure monitoring. A recent study has suggested that the prediction of risk using office central blood pressure is comparable with the results provided by ambulatory blood pressure monitoring. Certainly, further studies are needed in order to settle the clinical value for all blood pressure measurements, including 24-hour central blood pressure monitoring, which may provide useful complementary information.

**“Normal values” of central blood pressure**

So far, cut-off values and thresholds for central blood pressure have not been fully established, since blood pressure has a normal distribution. However, recent reference values for central blood pressure, according to sex, age, and brachial blood pressure, and its amplification in a general healthy population have been reported. In order to establish “normal values,” we probably need well-designed clinical trials with end points in which treatment is guided by either office brachial blood pressure or central blood pressure. Whether amplification of blood pressure per se can provide further independent and useful clinical information remains to be demonstrated. It is also possible that various indices, in addition to central blood pressure, such as augmentation index or reflection magnitude, may have different prognostic values.

**CONCLUSION**

In recent years, it has been shown that central blood pressure differs from brachial blood pressure and represents an independent predictor of cardiovascular events. In fact, blood pressure load directly affects and damages target organs, such as the heart, brain, and kidneys. Antihypertensive drugs affect central blood pressure differently than brachial blood pressure. Thus, measuring central blood pressure may be useful to understand the pathophysiology of target-organ damage and the differential effects of antihypertensive drugs on organ damage regression. Therefore, large randomized clinical trials with central blood pressure-driven therapeutic strategies are needed to demonstrate that clinical outcomes are clearly improved by specific lowering of central blood pressure.

**REFERENCES**


4. Karamanoglu M, O’Rourke MF, Avolio AP, Kelly RP. 
An analysis of the relationship between central aortic and peripheral upper limb pressure waves in man. 

5. Vlachopoulos C, Aznaouridis K, Stefanadis C. 
Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. 

Central but not brachial blood pressure predicts cardiovascular events in an unselected geriatric population: the ICARediCamo Study. 

7. Roman MJ, Devereux RB, Kizer JR, et al. 
Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: the Strong Heart Study. 
*Hypertension.*, 2007;50:197-203.

Central pulse pressure and mortality in end-stage renal disease. 

Central blood pressure measurements and antihypertensive therapy: a consensus document. 

The effect of antihypertensive drugs on central blood pressure beyond peripheral blood pressure. Part II: evidence for specific class-effects of antihypertensive drugs on pressure amplification. 

Role of pulse pressure amplification in arterial hypertension: experts’ opinion and review of the data. 

12. Hirata K, Kawakami M, O’Rourke MF. 
Pulse wave analysis and pulse wave velocity: a review of blood pressure interpretation 100 years after Korotkov. 
*Circ J.*, 2006;70:1231-1239.

13. Gillebert TC. 
Central blood pressure and its amplification: a final breakthrough or do we need more? 

14. Nichols WW, O’Rourke MF. 
Aortic pulse wave velocity, reflection site distance, and augmentation index. 

15. Nichols WW, Denardo SJ, Wilkinson IB, McEniery CM, Cockcroft J, O’Rourke MF. 
Effects of arterial stiffness, pulse wave velocity, and wave reflections on the central aortic pressure waveform. 

16. Westerhof N, Sipkema P, van den Bos GC, Elzinga G. 
Forward and backward waves in the arterial system. 

17. Westerhof BE, Westerhof N. 
Magnitude and return time of the reflected wave: the effects of large artery stiffness and aortic geometry. 

The arterial reservoir pressure increases with aging and is the major determinant of the aortic augmentation index. 

Reservations on the reservoir. 

The aortic reservoir-wave as a paradigm for arterial haemodynamics: insights from three-dimensional fluid-structure interaction simulations in a model of aortic coarctation. 

Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). 

Oscillometric estimation of central blood pressure: validation of the Mobil-O-Graph in comparison with the Sphygmocor device. 

24-h ambulatory recording of aortic pulse wave velocity and central systolic augmentation: a feasibility study. 

Validation of a brachial cuff-based method for estimating central systolic blood pressure. 
*Hypertension.*, 2011;58:825-832.
25. Williams B, Lacy PS, Yan P, Hw ee CN, Liang C, Ting CM.
Development and validation of a novel method to derive central aortic systolic pressure from the radial pressure waveform using an n-point moving average method.

26. Ott C, Haetinger S, Schneider MP, Pauschinger M, Schmieder RE.
Comparison of two noninvasive devices for measurement of central systolic blood pressure with invasive measurement during cardiac catheterization.

Establishing reference values for central blood pressure and its amplification in a general healthy population and according to cardiovascular risk factors.
Eur Heart J. 2014;35:3122-3133.

The impact of cardiovascular risk factors on aortic stiffness and wave reflections depends on age: the Anglo-Cardiff Collaborative Trial (ACCT III).

Central blood pressure: variability and impact of cardiovascular risk factors: the Anglo-Cardiff Collaborative Trial II.

Central blood pressure: current evidence and clinical importance.

Twenty-four-hour profile of central blood pressure and central-to-peripheral systolic pressure amplification.

Estimation of central aortic waveform pressure by mathematical transformation of radial tonometry pressure. Validation of generalized transfer function.

33. Fetics B, Nevo E, Chen CH, Kass DA.
Parametric model derivation of transfer function for noninvasive estimation of aortic pressure by radial tonometry.

34. Hope SA, Tay DB, Meredith IT, Cameron JD.
Use of arterial transfer functions for the derivation of aortic waveform characteristics.

35. Hope SA, Meredith IT, Cameron JD.
Arterial transfer functions and the reconstruction of central aortic waveforms: myths, controversies and misconceptions.

36. Karamanoglu M, Feneley MP.
Derivation of the ascending aortic-carotid pressure transfer function with an arterial model.

37. Hope SA, Meredith IT, Cameron JD.
Effect of non-invasive calibration of radial waveforms on error in transfer-function-derived central aortic waveform characteristics.

38. Segers P, Mahieu D, Kips J, Van Bortel LM.
The use of a generalized transfer function: different processing, different results!
J Hypertens. 2007;25:1783-1787.

39. Papaioannou TG, Protoperou A, Stefanadis C.
Comparison between Mobil-O-Graph and the SphygmoCor device for central systolic blood pressure estimation: consensus is required for “validation protocols.”

40. Pauca AL, O’Rourke MF, Kon ND.
Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform.

41. Hope SA, Tay DB, Meredith IT, Cameron JD.
Comparison of generalized and gender-specific transfer functions for the derivation of aortic waveforms.

Individualizing the aorto-radial pressure transfer function: feasibility of a model-based approach.

43. Payne RA, Teh CH, Webb DJ, Maxwell SR.
A generalized arterial transfer function derived at rest underestimates augmentation of central pressure after exercise.

44. Vrachatis D, Papaioannou TG, Konstantopoulou A, et al.
Effect of supine versus sitting position on noninvasive assessment of aortic pressure waveform: a randomized cross-over study.


Aortic pressure augmentation predicts adverse cardiovascular events in patients with established coronary artery disease.
**Hypertension.** 2005;45:980-985.

Arterial wave reflections and incident cardiovascular events and heart failure: MESA (Multiethnic Study of Atherosclerosis).
**J Am Coll Cardiol.** 2012;60:2170-2177.

Central aortic reservoir-ware analysis improves prediction of cardiovascular events in elderly hypertensives.
**Hypertension.** 2015;65:629-635.

Excess pressure integral predicts cardiovascular events independent of other risk factors in the conduit artery functional evaluation substudy of Anglo-Scandinavian Cardiac Outcomes Trial.
**Hypertension.** 2014;64:60-68.

Pulsatile but not steady component of blood pressure predicts cardiovascular events in coronary patients.
**Hypertension.** 2008;51:848-855.

69. Roman MJ, Okin PM, Kizer JR, Lee ET, Howard BV, Devereux RB.
Relations of central and brachial blood pressure to left ventricular hypertrophy and geometry: the Strong Heart Study.

70. Roman MJ.
Association of central and peripheral pulse pressure with intermediate cardiovascular phenotypes.
**J Hypertens.** 2012;30:834-835.

71. Roman MJ, Devereux RB.
Association of central and peripheral blood pressures with intermediate cardiovascular phenotypes.
**Hypertension.** 2014;63:1148-1153.

72. Ott C, Raff U, Harazny JM, Michelson G, Schmieder RE.
Central pulse pressure is an independent determinant of vascular remodeling in the retinal circulation.
**Hypertension.** 2013;61:1340-1345.

Relationship of wall-to-lumen ratio of retinal arterioles with clinic and 24-hour blood pressure.
**Hypertension.** 2014;63:1110-1115.

Pulsatile hemodynamics and microcirculation: evidence for a close relationship in hypertensive patients.
**Hypertension.** 2013;61:130-136.

75. de Luca N, Asmar RG, London GM, O'Rourke MF, Safar ME; REASON Project Investigators.
Selective reduction of cardiac mass and central blood pressure on low-dose combination perindopril/indapamide in hypertensive subjects.

Differences in the magnitude of wave reflection account for differential effects of amiodipine- versus atenolol-based regimens on central blood pressure: an Anglo-Scandinavian Cardiac Outcome Trial substudy.
**Hypertension.** 2009;54:724-730.

Local pulse pressure and regression of arterial wall hypertrophy during long-term antihypertensive treatment.
**Circulation.** 2000;101:2601-2606.

CRP and ASAS are associated with future elevated arterial stiffness, a risk marker of cardiovascular disease, in patients with ankylosing spondylitis: results after 5-year follow-up.

The association between aortic augmentation index and cardiovascular risk factors in a large unselected population.
**J Hum Hypertens.** 2012;26:476-484.

**Hypertension.** 2010;56:30-43.

Inflammatory markers and growth in South Asian and European origin infants in Britain: the Manchester Children’s Growth and Vascular Health Study.
**Atherosclerosis.** 2009;207:227-231.

Relations of inflammatory biomarkers and common genetic variants with arterial stiffness and wave reflection.
**Hypertension.** 2008;51:1651-1657.


102. Asmar RG, London GM, O'Rourke ME, Safar ME; REASON Project Coordinators and Investigators.
Improvement in blood pressure, arterial stiffness and wave reflections with a very-low-dose perindopril/indapamide combination in hypertensive patients: a comparison with atenolol.

Role of blood pressure and other variables in the differential cardiovascular event rates noted in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA).

A comparison of atenolol and nebivolol in isolated systolic hypertension.

Local pulse pressure and regression of arterial wall hypertrophy during antihypertensive treatment: the CELIMENE study [in French].

106. Pucci G, Battista F, Schillaci G.
Effects of antihypertensive drugs on central blood pressure: new evidence, more challenges.

107. Laurent S, Boutouyrie P; Vascular Mechanism Collaboration.
Dose-dependent arterial destiffening and inward remodeling after olmesartan in hypertensives with metabolic syndrome.
_Hypertension_. 2014;64:709-716.

Destiffening effect of valsartan and atenolol: influence of heart rate and blood pressure.

Amlodipine-valsartan combination decreases central systolic blood pressure more effectively than the amlodipine-atenolol combination: the EXPLOR study.

110. Stokes GS, Ryan M, Brnabic A, Nyberg G.
A controlled study of the effects of isosorbide mononitrate on arterial blood pressure and pulse wave form in systolic hypertension.
_J Hypertens_. 1999;17:1767-1773.

111. Stokes GS, Barin ES, Gilfillan KL.
Effects of isosorbide mononitrate and AII inhibition on pulse wave reflection in hypertension.
_Hypertension_. 2003;41:297-301.

112. Stokes GS, Barin ES, Gilfillan KL, Kaesemeyer WH.
Interactions of l-arginine, isosorbide mononitrate, and angiotensin II inhibitors on arterial pulse wave.

113. Kelly RP, Gibbs HH, O'Rourke MF, et al.
Nitroglycerin has more favourable effects on left ventricular afterload than apparent from measurement of pressure in a peripheral artery.
_Eur Heart J_. 1990;11:138-144.

114. Manisty CH, Hughes AD.
Meta-analysis of the comparative effects of different classes of anti-hypertensive agents on brachial and central systolic blood pressure, and augmentation index.


Reference values for central blood pressure [letter to the editor].
Understanding and Treating Central Blood Pressure

Expert Answers to Three Key Questions

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1

What is the best method to evaluate central blood pressure?

*S. Laurent, P. Boutouyrie*

---

2

What is the role of combination therapy in treating hypertension?

*C. Vlachopoulos, P. Xaplanteris*

---

3

What is renal denervation’s place in the management of treatment-resistant hypertension?

*P. Sever*
In recent years, the concept of central blood pressure has gained support after a large number of studies showed that central blood pressure, rather than brachial blood pressure, reflects the true load imposed on target organs, explaining the occurrence of cardiovascular events in hypertensive patients.

During the last two decades, major methodological developments validated and simplified the evaluation of central blood pressure. This article will review the general principles of central hemodynamics to understand the various parameters originating from central pressure waveforms, analyze the various methodologies currently used to evaluate central blood pressure, and discuss the advantages and limitations of these methods.

**What is the best method to evaluate central blood pressure?**

**Stephane Laurent, MD, PhD**

**Pierre Boutouyrie, MD, PhD**

**IN THE GOLD STANDARD FOR MEASURING BLOOD PRESSURE (BP) AND DIAGNOSING HYPERTENSION IS THE BRACHIAL CUFF, WHICH FAVORS A DISTAL SITE THAT IS ACCESSIBLE TO NONINVASIVELY MEASURE BP. HOWEVER, AN INCREASING NUMBER OF PHYSIOLOGICAL, PATHOPHYSIOLOGICAL, EPIDEMIOLOGICAL, AND PHARMACOLOGICAL STUDIES HAVE HIGHLIGHTED THE IMPORTANCE OF MEASURING NOT ONLY BRACHIAL SYSTOLIC BP AND PULSE PRESSURE (PP), BUT ALSO CENTRAL SYSTOLIC BP AND PP.**

This concept has been demonstrated between central BP and end-organ damage, (iii) central BP predicts cardiovascular events and mortality, independent of brachial BP, (iv) antihypertensive medications influence central and brachial BP differently, and (v) end-organ changes after antihypertensive therapy are more strongly related to central BP than brachial BP.

This article will review the general principles of central hemodynamics to understand the various parameters originating from central pressure waveforms, analyze the various methodologies currently used to evaluate central BP, and discuss the advantages and limitations of these methods.

**GENERAL PRINCIPLES OF CENTRAL HEMODYNAMICS**

Central hemodynamics correspond to the absolute value of systolic and diastolic BP at the site of central arteries and several measured or calculated parameters that provide complementary information on the nature of central pulsatile hemodynamics. During ventricular contraction, part of the stroke volume is forwarded directly to the peripheral tissues and the other part is momentarily stored in the aorta and central arteries, thereby stretching the arterial walls and raising local BP (Figure 1, page 188). Part of the energy produced by the heart...
is diverted for distension of arteries and is “stored” in the vessel walls. During diastole, the “stored” energy recoils the aorta, squeezing the accumulated blood forward into the peripheral tissues, and ensuring a continuous blood flow (Figure 1). To reduce cardiac work during ventricular ejection, the energy necessary for arterial distension and recoil should be low (ie, for a given stroke volume, the increase in pressure should be as low as possible). 4,5

**Pressure wave propagation**

The ejection of blood into the aorta generates a wave that propagates along the aorta toward the peripheral arterial tree. The velocity of wave propagation along the aorta (ie, pulse wave velocity) is dependent on factors that determine: (i) the displacement of blood along the axis of the vessel, with inertia being the most important effect in large arteries; and (ii) the transverse displacement of the vessel wall (ie, the stiffness of the vessel [the stiffer the arterial wall, the higher the pulse wave velocity]). 4 The centrally measured arterial pressure waveform is a composite of the forward pressure wave created by ventricular contraction and the reflected wave. 4,5 Indeed, the arterial tree is not a simple tube, but a complex structure with wave reflections at the distal end. From the heart toward the periphery, arteries continuously decrease in diameter (ie, geometric taper), increase in stiffness (ie, elastic taper, also called the “arterial stiffness gradient”), and form branches, which together, lead to an increase in the global arterial surface. 8,9

**Forward and reflected waves**

The stiffness gradient, together with the geometric taper, local arterial branching, and lumen narrowing, creates an impedance mismatch that results in partial reflections of forward pressure waves traveling back to the central aorta (reflected wave). 4,10 The wave reflections will considerably change the pressure wave amplitude and shape along the arterial tree. 9,11 Forward and reflected pressure waves overlap and the final amplitude and shape of the PP wave are determined by the phase relationship (ie, timing) between the component waves. 4,5 The overlap between the two waves depends on the site where the pressure is recorded along the arterial tree. Peripheral arteries are close to reflection sites and the reflected wave occurs simultaneously with the impact of the forward wave (ie, the waves are in phase and produce an additive effect). The ascending aorta and central arteries are distant from reflecting sites; therefore, the return of the reflected wave is variably delayed depending on pulse wave velocity and traveling distances. 4,9-11 In the aorta or central arteries, the forward and reflected waves are not in phase. In subjects with a low pulse wave velocity, reflected waves have an impact on central arteries during end-diastole, which increases the aortic pressure in early diastole, but not during systole. 4,9-11 This is physiologically advantageous because the increased diastolic pressure boosts coronary perfusion without increasing the left ventricular pressure load. 4,9-11
Pressure waves are reflected from the periphery, mainly at branch points or sites of impedance mismatch. The reflection pattern is complex, but may be seen as a "net" or "effective" reflection pattern, where all the forward and backward traveling waves seem to add up to one single forward and backward wave, representing the global effect of all reflections present.\(^{12,13}\) The inflection point is the point in time that coincides with the peak of the flow wave in the artery.\(^{12,13}\) Augmentation index (AIx) is used to assess the proportion of reflected pressure waves and is defined as the difference between the first (P1) and second (P2) systolic peaks (Augmentation pressure [AP]=P2-P1), and it is expressed as a percentage of PP.\(^{12,13}\) As AIx is calculated as a ratio, it is dimensionless and usually expressed as a percentage, and it does not depend on absolute pressure.

**Figure 2. The phenomenon of wave reflection can be quantified using the augmentation index.**

AIx is defined as the difference between the first (P1) and second (P2) systolic peaks (AP=P2-P1), and it is expressed as a percentage of PP: AIx=AP/PP. The inflection point is the point in time that coincides with the peak of the flow wave in the artery. AP is measured above the reflection point.\(^{12,13}\) Abbreviations: AIx, augmentation index; AP, augmentation pressure; PP, pulse pressure.

**Central blood pressure evaluation - Laurent and Boutouyrie**

**Figure 3. Central-to-peripheral amplification.**


Wave reflections occur distant from the microcirculation and return at a low pulse wave velocity to the aorta during diastole. Thus, the reflected waves arrive back at the aortic root during late systole. However, at the site of the peripheral artery (ie, brachial artery), the pressure waves travel rapidly, and the reflected waves (from peripheral branching sites and small arteries) arrive at the recording site in early systole, which increases brachial systolic BP. This means that central systolic BP is lower than distal systolic BP, which leads to the so-called “central-to-peripheral pressure amplification.” In contrast, when the stiffness gradient disappears or is inverted (aortic pulse wave velocity > peripheral pulse wave velocity), pulsatile pressure is not sufficiently dampened at the central level and the central-to-peripheral pressure amplification is attenuated.

By favoring early wave reflections, arterial stiffening increases peak-and end-systolic pressures in the ascending aorta, which increases myocardial pressure load (ie, left ventricular hypertrophy) and oxygen consumption and decreases diastolic BP and subendocardial bloodflow. In elderly subjects, central systolic BP is higher than in young subjects due to increased aortic stiffening, and it is closer to the brachial systolic BP value. At the
site of the brachial artery, arterial stiffness is not influenced by age, and the timing of forward and reflected waves is similar to those in younger subjects. Central-to-peripheral pressure amplification can be expressed as either an absolute value (peripheral systolic BP-central systolic BP; peripheral PP-central PP) or a relative value (peripheral systolic BP/central systolic BP; peripheral PP/central PP).

**Reflection magnitude**

The pulse waveform analysis (PWA) is a time-domain analysis of the pulse waveform that quantifies the effect of pressure wave reflections on the central arterial waveform. Determining forward and reflected waveforms requires a pressure-flow analysis in the time domain (Figure 4).16,17 Wave reflections are absent in early systole, thus early systolic BP and flow can be interpreted according to a simple model originally proposed by Westerhof et al.3

“The standard” Windkessel model for the systemic circulation is calculated as follows: \( Zc = \Delta \text{pressure}/\Delta \text{flow} \), where \( Zc \) is characteristic impedance, \( \Delta \text{pressure} \) and \( \Delta \text{flow} \) are calculated when the flow and pressure reach 95% of their peak value.16,17 Due to the superimposition of forward (incident) and backward (reflected) waves in early systole, measured pressure equals the sum of forward and backward pressures and measured flow equals the sum of forward and backward flows (backward flow has a negative sign). Pressure and flow waves can be quantitatively related to each other using \( Zc \). A procedure, commonly called wave separation analysis (Figure 4),16,17 can be used to decompose the pressure signal into its forward (\( P_f \)) and backward (\( P_b \)) components: \( P_f = (|P+Q|/Zc)/2 \), and \( P_b = (|P-Q|/Zc)/2 \), where \( P \) is pressure and \( Q \) is flow. In practice, this way of calculating \( P_f \) and \( P_b \) is not very different from applying the formulas for each individual harmonic and then adding all harmonics together.13,16-18 The ratio of their amplitudes is known as the reflection magnitude (RM): \( \text{RM} = P_b \text{ amplitude}/P_f \text{ amplitude} \).

**Methods currently used for evaluating central blood pressure**

Several commercial techniques have been available to noninvasively estimate central BP19 and they can be described according to where the pressure waveform is measured (radial, brachial, or common carotid artery). Table I details several methods, described below, that are used under resting conditions. Ambulatory BP measurements will be addressed at the end of this review.

**Sites of measurement**

Many reviews have recommended adequately measuring central BP1,2,10,19 Arterial pressure waveforms can be recorded peripherally, but should be transformed into central pressure waveforms. As detailed below, the arterial pressure waveforms can also be determined directly at the site of the common carotid artery (Figure 5). In practice, measurements at the common carotid artery and the ascending aorta are similar.

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**Figure 4. Wave separation analysis.**

Once \( Zc \) is known (see text), pressure and flow waves can be quantitatively “scaled” in the vertical axis (Panel A) to identify the difference in their waveforms (gray area), which is assumed to be the result of wave reflections. Pressure can be separated into forward and backward pressures (\( P_f \) and \( P_b \)), and the amplitude ratio of \( P_b/P_f \) (reflection magnitude) can be computed (Panel B).

**Abbreviations:** \( P_b \), backward pressure wave; \( P_f \), forward pressure wave; \( \text{RM} \), reflection magnitude; \( Zc \), characteristic impedance.

Radial artery pressure waveform

The basic operating procedure is that radial artery pressure waveforms are recorded by applanation tonometry, and a central BP waveform is synthesized using a generalized mathematical transfer function.

The pressure waveform can be recorded noninvasively with a pencil-type probe that incorporates a high-fidelity Millar strain gauge transducer (SPT-301, Millar Instruments, USA). The most widely used approach is to perform radial artery tonometry and then apply a transfer function (eg, SphygmoCor, AtCor Medical, Australia) to calculate the aortic pressure waveform from the radial pressure waveform. Also, the radial artery is well supported by bony tissue, making it easier to achieve optimal applanation measurements.

Generalized inverse transfer functions are applied to reconstruct the aortic pressure waveform from radial waveforms.

Figure 5. Applanation tonometry for the measurement of radial or carotid pressure waveforms.

Table I. Device and methods used for estimating central blood pressure, classified by the arterial segment used for pressure wave recording.

<table>
<thead>
<tr>
<th>Year of first publication</th>
<th>Device</th>
<th>Method</th>
<th>Company</th>
<th>Parameters</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radial artery pressure waveform</td>
<td>1990</td>
<td>SphygmoCor®*</td>
<td>Tonometer, GTF</td>
<td>AtCor Medical</td>
<td>cSBP, cPP, cAlx</td>
</tr>
<tr>
<td>1997</td>
<td>Cardiovascular Engineering, Inc®*</td>
<td>Tonometer, cardiac echo, impedance</td>
<td>Cardiovascular Engineering, Inc</td>
<td>cSBP, cPP, cAlx, Zc, Pr, Pb</td>
<td>16</td>
</tr>
<tr>
<td>2004</td>
<td>PulsePen®</td>
<td>Tonometer, direct</td>
<td>DiaTecne</td>
<td>cSBP, cPP, cAlx</td>
<td>36</td>
</tr>
<tr>
<td>2009</td>
<td>Omeron HEM-9001At®</td>
<td>Tonometer</td>
<td>Omeron Healthcare, Inc</td>
<td>cSBP, rAlx</td>
<td>29,30</td>
</tr>
<tr>
<td>2012</td>
<td>BPro</td>
<td>Tonometer</td>
<td>HealthSTATS</td>
<td>rAlx</td>
<td>37</td>
</tr>
<tr>
<td>Brachial artery pressure waveform</td>
<td>2010</td>
<td>Arteriograph®</td>
<td>Oscillometric, Add. Infl.</td>
<td>TensioMed</td>
<td>cSBP, cPP, cAlx</td>
</tr>
<tr>
<td>2010</td>
<td>Mobil-O-Graph®</td>
<td>Oscillometric, ARCSolver, PWV</td>
<td>IEM</td>
<td>cSBP, cPP, cAlx, Zc, P1, Pb</td>
<td>31,32,34</td>
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<td>2010</td>
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<td>BPLab</td>
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<td>2012</td>
<td>Centron cBP301</td>
<td>Oscillometric</td>
<td>Centron Diagnostics</td>
<td>cSBP, cPP, cAlx</td>
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<td>2012</td>
<td>CardioScope II</td>
<td>Oscillometric, Add. Infl.</td>
<td>Pulsocor</td>
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<td>40</td>
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<td>2013</td>
<td>Vicorder®</td>
<td>Oscillometric</td>
<td>Skidmore Medical</td>
<td>cSBP, cPP, cAlx</td>
<td>41</td>
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<tr>
<td>Carotid artery pressure waveform</td>
<td>1984</td>
<td>Millar strain gauge®*</td>
<td>Tonometer, direct</td>
<td>Millar</td>
<td>cSBP, cPP, cAlx</td>
</tr>
<tr>
<td>2004</td>
<td>PulsePen®</td>
<td>Tonometer, direct</td>
<td>DiaTecne</td>
<td>cSBP, cPP, cAlx</td>
<td>36</td>
</tr>
</tbody>
</table>

*Apparatus used in pioneering epidemiological studies showing the predictive value of central BP for cardiovascular events.
diastolic tonometry (Figure 6), which is possible due to a consistent relationship between radial and aortic pressure waveforms under different conditions. The transfer function is generated by first determining, in the frequency domain, the individual transfer function between the pressure waves at the different arterial sites and relating the modulus and phase of the corresponding harmonic components (Figure 6). Then, a generalized representation of the transfer function is constructed by pooling the individual transfer functions.

In clinical practice, using a generalized inverse transfer function means that the peripheral pressure waveform must be first transformed into a series of simultaneously present sine waves (harmonics) that are all traveling at the same speed (pulse wave velocity), with their own amplitude and phase, period, frequency, and wavelength. Then, a specific mathematical transformation (ie, a “generalized” transfer function) is applied to each of the main har-

Figure 6. Generalized transfer function.

A pressure waveform can be regarded as a series of simultaneously present sine waves (harmonics) that are all traveling at the same speed (pulse wave velocity), with their own amplitude and phase, period, frequency, and wavelength, but all traveling at the same speed (pulse wave velocity). Using a transfer function on a peripheral pressure waveform in order to reconstruct a central pressure waveform consists of applying specific mathematical transformations to each of the main harmonics and then reconstructing the resulting pressure wave.

monics, and finally, the resulting pressure wave is reconstructed using an “inverse” transfer function.

This method has received several criticisms. First, the generalized transfer function may not apply to most conditions of clinical practice. However, the algorithm was robust for accurately determining central BP even during hemodynamic perturbations that may be caused by exercise, performing a Valsalva maneuver, taking nitroglycerin, stimulating the β-adrenergic receptor, and increasing angiotensin II and noradrenaline. Second, peripheral waveforms are typically calibrated to brachial systolic and diastolic cuff pressures. Brachial cuff systolic BP is lower than invasive brachial (ie, intra-arterial) systolic BP, therefore, this tends to underestimate both brachial systolic BP and invasive aortic systolic BP. However, it is the brachial cuff BP, rather than invasive brachial BP, that is recommended for the routine diagnosis and treatment of hypertension and is used as a surrogate end point for cardiovascular events. In addition, errors in the estimation of central BP are equivalent to errors in brachial cuff sphygmomanometry. Third, radial waveforms are calibrated to brachial cuff systolic and diastolic BP, thus the brachial-to-radial amplification in systolic BP can exaggerate the underestimation of central systolic BP. Recent studies suggest that calibration should be performed with brachial mean pressure (ie, the equivalent of the area under the pressure curve) and diastolic BP. Fourth, the accuracy of the transfer function for determining aortic AIx has been disputed. Indeed, measuring AIx is dependent on higher frequency signals than BP measurements and the transfer function appears to be less accurate at high frequencies, with a greater variability between subjects. Fifth, the use of a transfer function should be limited to the upper limb, where elastic properties remain relatively constant with age and disease. Despite these limitations, radial tonometry remains popular since it is simple to perform, well tolerated, and has provided consistent results in many physiological, pathophysiological, epidemiological, and pharmacological studies.

Instead of determining the whole pressure waveform at the central site, other methods try to determine, using an automated detection system, the discrete value of central systolic BP from the radial pressure waveform (Table I). Indeed, it is possible to estimate central systolic BP from the second systolic peak on the radial pressure waveform without a transfer function.

### Brachial cuff pressure waveform

Novel methods to measure brachial pressure waveforms using brachial cuff-based devices have been developed. The brachial pressure waveforms are generally obtained using pulse wave velocity (PWV) and then scaled to the measured brachial cuff pressure. As seen above, the time-domain analysis of the pulse waveform (ie, PWA) quantifies the effects of pressure wave reflections on the central arterial waveform. As the measurements of AIx, AP, and the amount of wave reflections in PWA are dependent on the magnitude and timing of wave reflections, alternative methods have been developed, including wave separation analysis.

As discussed above, wave separation analysis requires a simultaneous determination of pressure and flow waves at the same location in order to separate the pressure wave into its forward and backward components. However, in the clinical, routine and accurate measurements of flow are time consuming and not trivial. To overcome the difficulties associated with a non-invasive assessment of ventricular flow, several methods have been proposed, using either a Windkessel model or a triangular analysis of the pressure wave in order to get a flow wave. However, triangular flow is somewhat different from the physiological flow curve. Weber et al developed ARCSolver, an aortic blood flow model based on the higher order Windkessel theory, which compared reasonably well against conventional Doppler echocardiography and triangular analysis for determining forward and backward pressure waves, although some variability was observed between patients and methods.

Table I details the recent methods and devices that use volumetric cuff displacement techniques to determine brachial artery pressure waveforms and compute indices of central pulsatile hemodynamics.

These methods calibrate pressure waveforms from classic measurements of systolic and diastolic BP through oscillometric measurements. Algorithms are currently available for estimating central BP from any classic brachial BP measurement, either as a proprietary or published algorithm. Therefore, any oscillometric device that measures brachial BP has the possibility to estimate central BP. However, only the Arteriograph and Mobil-O-Graph have been used in pathophysiological, epidemiological, and pharmacological studies and these measurements have been validated by showing that there are significant correlations between central BP and target organ damage, cardiovascular risk profile,
Central blood pressure evaluation - Laurent and Boutouyrie

Cardiovascular events, or changes after pharmacotherapy. The other methods should demonstrate an ability to provide similar data; however, until now, most have only shown repeatability and reproducibility data.

In addition, volumetric cuff displacement techniques provide signals that are inherently more damped than the signals obtained by applanation tonometry, potentially affecting parameters reliant on higher frequency components of the pulse waveform. Indeed, parameters relying on the low frequency components of the peripheral waveform, such as central systolic BP, have a better agreement between cuff-based devices than parameters that rely on higher frequency waveform components, such as central AIx.43

Common carotid pressure waveform

Aortic pressure waveforms can also be applied externally to the common carotid artery in order to applanate the arterial conduit and record the internal BP. This requires a higher degree of technical expertise44,45 than at the radial artery site, since bones beneath the arterial conduit are quite far. However, a transfer function is not necessary since the ascending aorta and common carotid artery are very close and the waveforms are similar.19

Although the pressure waveform can be accurately determined, a calibration is required. This can be done according to the methods suggested by Van Bortel et al19 and Verbeke et al27 (Figure 7). Calibration of the artery tonometer pressure wave is based on the observation that mean BP is constant throughout the large artery tree and that diastolic BP does not change substantially. In practice, BP is measured at the reference artery (generally the brachial artery) with a validated BP device, and PP equals systolic BP - diastolic BP. Generally, in clinical practice, the most accepted approach to calculate mean BP is where mean BP = diastolic BP + (PP/3), but, according to Van Bortel et al, it can also be calculated as diastolic BP + (0.4*PP).19 Subsequently, or simultaneously, applanation tonometry is performed at the site of the common carotid artery. At the carotid site, mean BP is calculated from the area under the carotid pressure waveform, which is set equal to brachial mean BP. Carotid systolic PP and brachial artery PP are then computed from the diastolic BP and the position of mean BP on the carotid pressure wave (Figure 7).

Alternatively, mean BP can be calculated in a subsequent applanation tonometry at the radial artery site, from the area under the pressure waveform. This procedure is more accurate than the rough calculation of mean BP described above, but requires calibration. Thus, the radial artery pressure waveforms have to be calibrated with brachial systolic and diastolic BP, which is determined with an oscillometric apparatus. During this last step, the investigator may choose to use either the true value of brachial systolic BP or the brachial-radial amplification.27

Finally, carotid systolic BP and PP can be indirectly estimated from carotid distension waveforms, which
are obtained with echotracking techniques (Walltrack and Artlab Systems). Carotid distension waveforms provide high-quality recordings that parallel pressure, with minimal compression-distension waveforms. Central BP values derived from such echographic distension waveforms have been validated against invasive measurements and applanation tonometry. A large number of pathophysiological and pharmacological studies have been published using carotid artery pressure waveforms. The local measurement of carotid PP is particularly interesting when dealing with carotid mechanics analyzed by echotracking. However, direct central BP measurements at the common carotid artery are not always possible. A transfer function may be useful when applanation tonometry cannot be applied at the site of the carotid artery, for instance, in obese patients or patients with major atherosclerotic plaques or calcified arteries, in whom this method may not be free from risk.

**Standardization of methods**

Although the above methodologies make their own hypotheses of central hemodynamics based on the laws of physics, and have their own physiological rational, mathematical processing, and proprietary software, their measurements should theoretically be interchangeable. Validation studies have demonstrated significant correlations between two, and sometimes three, different methods, with small systematic errors in Bland-Altman plots.

To our knowledge, only one attempt was made to cross-calibrate several methodologies, and this was performed during the Reference Value for Arterial Measurement Collaboration Study. The goal of the study was to determine the reference values for central BP, and included up to 82,000 subjects originating from 53 centers worldwide (Figure 8).

A major requirement was the standardization of various methodologies, such as the SphygmoCor device (AtCor Medical, Australia), the Omron HEM-9000AI device (Omron, Japan), the Walltrack & Artlab systems (both Esaote, Italy), the PulsePen device (Diactecne, Italy), and direct carotid tonometry (high-fidelity Millar strain gauge transducer in a pencil-type probe). To estimate correction factors, the authors first calculated the weighted mean difference for each technique between invasive aortic and estimated values, and then, centered those values on the weighted mean of SphygmoCor-estimated central systolic BP and Omron SP2, which represented 90% of the data. When central PP was provided and central systolic BP was not, brachial diastolic BP was assumed to be equivalent to carotid or aortic diastolic BP in order to convert central PP to central systolic BP values. As expected, invasive brachial pressures were higher than noninvasive ones. Noninvasively estimated central BP calibrated with noninvasive cuff brachial BP was considered to be the reference.

**Ambulatory central blood pressure monitoring**

Several devices that use the brachial cuff methodology (detailed above) were described to reliably measure central BP over 24 hours; however, none of the devices convincingly demonstrated that the BP values, which were recorded under ambulatory conditions, truly reflected central BP. Although most devices have been validated against invasive BP under resting conditions, today it is not possible to use similar invasive procedures as the gold standard for comparison.
CONCLUSION

In recent years, the concept of central BP has gained support after a large number of studies showed that central BP, rather than brachial BP, reflects the true load imposed on target organs, explaining the occurrence of cardiovascular events in hypertensive patients. During the last two decades, major methodological developments validated and simplified the evaluation of central BP. Although noninvasive measurements of central BP now appear to be a major tool for clinical and pharmacological research, outcome studies are needed in order to establish central BP as a true surrogate end point deserving to be listed among the various parameters of the routine workup in hypertensive patients.

REFERENCES


43. Butlin M, Alqahtani A, Qasem A, Turner M, Avolio AP. 
Aortic systolic pressure values but not indices derived from waveform features are consistent between brachial cuff-based devices used for estimation of central aortic pressure [abstract 6A.07]. 
*J Hypertens.* 2015;33(suppl 1):e74-e75.

Association between local pulse pressure, mean blood pressure, and large-artery remodeling. 

Amiodipine-valsartan combination decreases central systolic blood pressure more effectively than atenolol-amiodipine combination: the EXPLOR study. 

Arterial remodeling associates with CKD progression. 

Effect of celiprolol on prevention of cardiovascular events in vascular Ehlers-Danlos syndrome: a prospective randomized, open, blinded-endpoints trial. 

Dose-dependent inward arterial remodeling and destiffening after olmesartan in hypertensives with metabolic syndrome. 
*Hypertension.* 2014;64:709-716.

49. Adji A, O’Rourke MF. 
Brachial artery tonometry and the Popeye phenomenon: explanation of anomalies in generating central from upper limb pressure waveforms. 
What is the role of combination therapy in treating hypertension?

Charalambos Vlachopoulos, MD, PhD, FESC; Panagiotis Xaplanteris, MD, PhD

Hypertension remains the leading cause of cardiovascular morbidity and mortality worldwide. European countries have a higher prevalence (60%) and lower hypertension control rate compared with Canada and the US.1 In spite of the availability of novel diagnostic modalities that detect target organ damage at a very early stage and the introduction of drugs that can efficiently reduce blood pressure (BP) levels, the percentage of hypertensive patients that achieve the guidelines’ recommended BP goals is suboptimal. According to the 2007-2008 National Health and Nutrition Examination Survey (NHANES), approximately 29% of the 42,856 participants (representative of the US population) were hypertensive. Of the 29% of hypertensive patients, most were aware of their condition (80.7%; 95% CI, 78.1% to 83.0%) and many were on an antihypertensive drug regimen (72.5%; 95% CI, 70.1% to 74.8%), but only half (50.1%; 95% CI, 46.8% to 53.5%) succeeded in reaching their target BP values (Figure 1, page 200).2 Race, ethnic background, and income status affect the rate of hypertension control and other cardiovascular risk factors. The control rates are even worse among patients with comorbidities.

**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
</tr>
<tr>
<td>ARB</td>
<td>angiotensin receptor blocker</td>
</tr>
<tr>
<td>BP</td>
<td>blood pressure</td>
</tr>
<tr>
<td>CCB</td>
<td>calcium channel blocker</td>
</tr>
<tr>
<td>FDC</td>
<td>fixed-dose combination</td>
</tr>
<tr>
<td>NHANES</td>
<td>National Health and Nutrition</td>
</tr>
<tr>
<td>RAAS</td>
<td>renin-angiotensin-aldosterone system</td>
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**STUDY ACRONYMS**

<table>
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<tr>
<th>Acronym</th>
<th>Description</th>
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<tr>
<td>ACCOMPLISH</td>
<td>Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension [trial]</td>
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<tr>
<td>ASCOT</td>
<td>Anglo-Scandinavian Cardiac Outcomes Trial</td>
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<tr>
<td>CAFE</td>
<td>Conduit Artery Function Evaluation</td>
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<tr>
<td>ONGTARGET</td>
<td>ONGoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial</td>
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<tr>
<td>VALUE</td>
<td>Valsartan Antihypertensive Long-term Use Evaluation</td>
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Keywords: adherence; combination therapy; dual combination; hypertension; persistence; single pill; triple combination

Address for correspondence:
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such as chronic kidney disease, diabetes, stable angina, acute coronary syndromes, or left ventricular dysfunction; therefore, the term “hypertension paradox” has been coined to describe the combination of a still uncontrolled disease despite improved pharmacological therapy.  

ADHERENCE AND CARDIOVASCULAR EVENTS: A VICIOUS CYCLE

Adherence (or compliance) to medication refers to the degree of conformity with the recommendations regarding the proper intake of daily medications (eg, timing, dosage, frequency). In essence, it is a metric of the patients’ fidelity to the prescription given by a health care professional. On the other hand, medication persistence refers to the act of continuing the treatment for the prescribed duration. Thus, it is the duration of time from initiation to discontinuation of therapy. The two terms are not synonymous, but are frequently used interchangeably in the literature. In lay terms, nonadherent patients are “bad users” and nonpersistent patients are “discontinuers,” with the latter being more difficult to tackle. The low rates of BP control in real life can be attributed to physicians, patients, and the health care system. Low adherence to treatment is a critical determinant of this outcome. Among the patients who are still on therapy at the end of the first year, following the initial diagnosis of hypertension and initiation of treatment, 50% stop therapy within the next 2 years.

Figure 1. Clinical epidemiology of hypertension.

Data include prevalence, awareness, treatment, treatment and controlled, and controlled from the National Health and Nutrition Examination Survey (NHANES) cohort. Data are presented as means with 95% confidence intervals (error bars). From reference 2: Egan et al. JAMA. 2010;303:2043-2050. © 2010, American Medical Association.
The fact that nonadherence increases future cardiovascular events is intuitive and has been ascertained by both retrospective and prospective studies. When newly diagnosed hypertensive patients from a large Italian registry were assessed 6 months after the initiation of therapy, only 8.1% had a high adherence with the therapy (proportion of days covered ≥ 80%). High adherence to antihypertensive therapy was associated with a multiple-drug treatment, presence of dyslipidemia, diabetes mellitus, and obesity; and combination therapy. The latter signified a 29% higher chance of having a high adherence with the therapy. By increasing adherence, the risk of cardiovascular events decreased. Patients with high levels of adherence had a 50% lower risk of cardiovascular events compared with those with low levels of adherence. The link between adherence and cardiovascular risk reduction has been subsequently confirmed in the ONTARGET trial (ONGoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial). In this study, only high adherers had a decreased risk for cardiovascular events compared with those with low adherence and cardiovascular risk reduction has been subsequently confirmed in the ONTARGET trial (ONGoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial). In this study, only high adherers had a decreased risk for cardiovascular events (hazard ratio [HR], 0.62; 95% CI, 0.40-0.96). An increased risk of nonpersistence with study medications was associated with older age, female sex, black ethnicity, smoking, history of diabetes mellitus, previous stroke/transient ischemic attack, and history of depression. Conversely, the persistence rate was higher in Asians, in individuals reporting regular physical activities, and in previous users of angiotensin-converting enzyme (ACE) inhibitors.

The interplay between adherence and cardiovascular events is a two-way relationship, i.e., patients may become nonadherent after they have survived a nonfatal cardiovascular event, and merits further investigation. This puzzling reaction can be explained by distrust in medications following an adverse event. Indeed, data from the ONTARGET trial show that patients are more likely to discontinue treatment after a nonfatal event. Nonpersistence rapidly increased within the first year after nonfatal events, such as myocardial infarction (HR, 3.37; 99% CI, 2.72-4.16), stroke (HR, 3.25; 99% CI, 2.59-4.07), and hospitalization for heart failure (HR, 3.67; 99% CI, 2.95-4.57).

Persistence was poorer with more frequent and earlier events. Patients stopping medication after an event were at a greater risk of subsequent events. Interestingly enough, the development of new-onset diabetes mellitus had the opposite effect and subsequently increased persistence, which may be attributed to a more intensive medical communication between the patient and care provider.

Therefore, nonadherence, poor BP control, and cardiovascular events are closely linked and should not be viewed in isolation. Their interplay is a vicious cycle that can be disrupted by effective therapeutic interventions, and from a pharmacological standpoint, combination antihypertensive therapy has this potential (Figure 2).

**COST-EFFECTIVENESS**

From an economical perspective, the added medical cost of high adherence cannot be disentangled from the health care costs related to cardiovascular risk modification. A retrospective analysis incorporating administrative claims data and medical/drug utilization showed that high adherence levels are cost-effective, which was driven by lower hospitalization rates that eventually reduced all-cause medical costs. Therapeutic drug monitoring has been proposed as a tool for the detection of nonadherence and effective BP control. This approach has been shown to be a potential cost-effective intervention. Simpler methods, such as the widespread implementation of guideline recommendations, would similarly improve cost-effectiveness. In the US, the full implementation of the new hypertension guidelines would result in approximately 56 000 fewer cardiovascular events and 13 000

![Figure 2. The vicious cycle of adherence to drug therapy and cardiovascular events.](image-url)
fewer deaths, which would result in overall cost savings. Impressively enough, even if treatment costs doubled, antihypertensive therapy would still be cost-effective for patients with cardiovascular disease and men with stage 2 hypertension, but no cardiovascular disease.12

**IMPROVING ADHERENCE**

Different methods to improve adherence at patient, drug-treatment, and health-system levels have been suggested in the 2013 European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines for the management of arterial hypertension.5 Regarding drug treatment, simplifying the drug regimen and reminder packaging have been shown to boost adherence. The former approach is linked to the daily intake of fewer pills, which can rarely be achieved by switching to a more potent drug, or usually, to the use of polypills, which are essentially standard fixed-dose combinations (FDC).

The use of antihypertensive drug combinations started in the 1960s with hydrochlorothiazide, which was combined with the potassium-sparing diuretic triamterene, and has expanded with the addition of newer and different combinations over the subsequent decades. A number of trials have studied the combined use of different classes of antihypertensive drugs, taking advantage of their complementary actions. ACE inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), thiazide diuretics, and α- and β-blockers are the most commonly used classes of antihypertensive agents. Available combinations involve using an ACE inhibitor or ARB with a diuretic or an ACE inhibitor with a CCB. The majority of currently available standard FDCs contain a diuretic. Newer formulations with a triple combination of a diuretic, CCB, and a renin-angiotensin-aldosterone system (RAAS) blocker have been introduced in recent years.

Meta-analysis data from cohort studies and randomized clinical trials (n=30 295 hypertensives) suggest that the use of standard FDCs is associated with a 29% increase in the combined end point of compliance and persistence with therapy compared with free-drug combinations (Figure 3).13-18 The reduction in pill burden through the use of standard FDCs is important in the subgroups of patients with lower adherence, and who, as a consequence, have difficulties maintaining BP control. Black patients are more likely to have stage 2 hypertension, require ≥2 classes of drugs to maintain BP control, and have a lower adherence compared with white patients. In this population, standard FDCs improve adherence and may reduce racial differences in hypertension control and the time to control hypertension.19

### COMBINATION THERAPY VS UPTITRATED MONOTHERAPY

Compelling evidence from clinical trials and meta-analyses has shown that combination therapy is superior to up titration of the monotherapy for achieving BP goals. A meta-analysis comparing a higher dose of valsartan alone (320 mg) with the standard FDC of valsartan/hydrochlorothiazide (160 mg/12.5 mg) has shown that the standard FDC was superior in achieving target BP values.20 A meta-analysis of 42 trials with 11 000 participants highlighted the fact that BP reduction from combination therapy can be predicted on the basis of additive effects. Importantly, the extra BP reduction from combination therapy is approximately 5 times greater than doubling the dose of a single drug (Figure 4).21

Escalating doses of monotherapy raise concerns about more frequent side effects. It has been demonstrat-

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**Table 3. Meta-analysis of studies on compliance/persistence with therapy associated with the use of a fixed-dose combination of two antihypertensive agents vs the corresponding free-drug combination.**

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dezi,14 2000</td>
<td>1.19 (0.83, 1.71)</td>
</tr>
<tr>
<td>Dezi,14 2000</td>
<td>1.22 (0.85, 1.75)</td>
</tr>
<tr>
<td>Jackson et al,13 2006</td>
<td>2.84 (1.67, 4.83)</td>
</tr>
<tr>
<td>Taylor and Shoheiber,16 2003</td>
<td>1.09 (0.80, 1.51)</td>
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<tr>
<td>Gerbino and Shoheiber,17 2004</td>
<td>1.28 (0.93, 1.75)</td>
</tr>
<tr>
<td>Dickson and Plauschinat,18 2008</td>
<td>1.29 (0.89, 1.89)</td>
</tr>
<tr>
<td><strong>Overall (I-squared=49.2%; P=0.080)</strong></td>
<td><strong>1.29 (1.11, 1.50)</strong></td>
</tr>
</tbody>
</table>

Favors free combination 0.5 1.5 2 Favors FDC

---

**Figure 3. Meta-analysis of studies on compliance/persistence with therapy associated with the use of a fixed-dose combination of two antihypertensive agents vs the corresponding free-drug combination.**

Fixed-effect model used due to lack of heterogeneity.

**Abbreviations:** FDC, fixed-dose combination; OR, odds ratio.

ed that side effects at half-standard doses are 80% lower than standard doses, albeit with a concomitant reduction (≈20%) in their BP-lowering effects (Table I). Therefore, the prevalence of adverse effects from a two-drug combination at half-standard doses would be lower than with a single drug at standard doses. Low-dose combination therapy has the potential for reducing side effects, which are frequently dose-related, with the exception of ACE inhibitors. The tolerability of combination therapy has been proven in retrospective, propensity-matched analyses and randomized

clinical trials. Nevertheless, it remains unclear if these results can be extrapolated to different subgroups, including the elderly and patients with comorbidities. Though preliminary insights can be deducted from retrospective analyses and meta-analyses, the safe use of combination therapy in such subgroups mandates specifically designed and randomized clinical trials. A position paper of the American Society of Hypertension (ASH) suggests combination therapy for uncomplicated stage 1 hypertension, especially when one drug will mitigate the side effects of the other.

The superior efficacy of combination therapy is mainly attributed to the synergistic BP-lowering effect of its components in different tissues. Diuretics inhibit sodium reabsorption in the kidney; β-blockers inhibit β-adrenergic stimulation, decrease contractility and heart rate, and directly suppress renin release. ACE inhibitors remove the angiotensin II effect (eg, vasoconstriction, stimulation of aldosterone secretion) and enhance kinin-mediated vasodilatation, and ARBs antagonize angiotensin II at the vascular and myocardial level by directly blocking the angiotensin I receptor.

### Table I. Adverse effects of drugs.

<table>
<thead>
<tr>
<th>Category of drug</th>
<th>No. of trials</th>
<th>Percentage (95% CI) with symptoms (treated minus placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Half-standard dose</td>
</tr>
<tr>
<td>Thiazides</td>
<td>59</td>
<td>2.0 (−2.2 to 6.3)</td>
</tr>
<tr>
<td>β-blockers</td>
<td>62</td>
<td>5.5 (0.3 to 10.7)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>96</td>
<td>3.9 (−3.7 to 11.6)</td>
</tr>
<tr>
<td>Angiotensin II receptor antagonists</td>
<td>44</td>
<td>−1.8 (−10.2 to 6.5)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>96</td>
<td>1.6 (−3.5 to 6.7)</td>
</tr>
</tbody>
</table>

Percentage of people with one or more symptoms that is attributable to treatment, according to the category of drug and dose, in randomized trials. The most common side effects include the following: thiazides can cause dizziness, impotence, nausea, and muscle cramps; β-blockers can cause cold extremities, fatigue, and nausea; ACE inhibitors can cause coughing; and calcium channel blockers can cause flushing, ankle edema, and dizziness.

Abbreviations: ACE, angiotensin-converting enzyme.

In addition, combination therapy offers synergy at the clinical level. Different drug classes offer protection from distinct outcomes; therefore, when they are combined, their beneficial effects accrue. ACE inhibitors protect against coronary artery disease and CCBs protect against stroke, so a combined use of the two is advantageous. The ACCOMPLISH trial (Avoiding Cardiovascular events through COMBination therapy in Patients Living with Systolic Hypertension) lent support to the concept of clinical synergy of the aforementioned combination. For the same BP reduction, the ACE inhibitor/CCB combination led to a 20% greater reduction in cardiovascular morbidity and mortality compared with the ACE inhibitor/thiazide combination. Further appraisal of the literature demonstrates that not all combinations are created equal with regard to outcome. In the ASCOT trial (Anglo-Scandinavian Cardiac Outcomes Trial), the amiodipine/perindopril treatment was more effective in reducing cardiovascular events than an atenolol/thiazide regimen, despite a similar reduction in BP. An explanation for this finding was offered by the CAFE study (Conduit Artery Functional Evaluation), a sub-study of the ASCOT trial, which was based on the concept that central (aortic) BP is a better predictor of cardiovascular events than traditional peripheral (brachial) BP. Indeed, a preferential reduction in central (aortic) BP with amiodipine/perindopril treatment was shown in the CAFE study, despite a similar effect on peripheral (brachial) BP.

**STANDARD FIXED-DOSE COMBINATIONS VS SEPARATE FREE-DRUG COMPONENTS**

Combination therapy can be applied by either using a single pill containing a fixed-dose combination of drugs or multiple pills, ie, separate free-drug components. The choice between the two is dictated by their relative effectiveness, safety, and compliance. Regarding effectiveness, the previously mentioned meta-analysis on combination therapy reported that the final BP reduction is an additive effect of the drugs that constitute the combination. The finding was in line with a subsequent meta-analysis that compared the outcomes of standard FDCs with multiple pills. Thus, a standard FDC is equal to separate free-drug components in terms of antihypertensive potency.

In a similar fashion, the safety of the two methods is comparable. In five trials (n=1775), adverse effects for standard FDCs did not differ compared with free-drug combinations (odds ratio [OR], 0.80, 95% CI, 0.58-1.11). In contrast, compliance appears to be better with the use of standard FDCs. The meta-analysis by Gupta et al highlighted that the use of standard FDCs was associated with significantly better compliance (OR, 1.21; 95% CI, 1.03-1.43) and a nonsignificant improvement in treatment persistence (OR, 1.54; 95% CI, 0.95-2.49). Therefore, standard FDCs have a similar profile to a separate free-drug regimen regarding efficacy and safety, but standard FDCs result in better compliance. The logical claim that this will eventually translate into better cardiovascular outcomes, given the interplay of compliance and cardiovascular risk, is tempting, yet remains an extrapolation that should be put to test in trials.

**COMBINATION THERAPY: A VALID INITIAL CHOICE?**

Traditionally, single-agent regimens were advocated as the first approach to therapy, with the addition of different drug classes being reserved at later stages for patients unable to maintain a good BP control. This stepwise approach was advocated in order to minimize the number of drugs used; thereby, avoiding overtreatment and side effects. This notion has been repeatedly challenged, as it results in prolonged periods of insufficient BP control. Clinical trial data have highlighted that the time to BP control is an important determinant of long-term outcomes, a concept that is contained within the motto “the earlier, the better.” In the VALUE trial (Valsartan Antihypertensive Long-term Use Evaluation), which compared valsartan-based regimens with amiodipine-based regimens, the 5-year cardiovascular risk was significantly lower in those patients that achieved earlier BP control irrespective of the drug used; moreover, an earlier BP response (within 1 month) was predictive of a better outcome. This was subsequently corroborated by data from trials exploring the effect of initial combination therapy. In hypertensive patients with a metabolic syndrome, the combination of valsartan and amiodipine resulted in faster BP control compared with an initial valsartan monotherapy. Further support for combination therapy, as an initial choice, was provided by the retrospective analysis by Grady et al. After 6 months of therapy, more patients who were initiated with a combination therapy achieved BP control compared with monotherapy. This translated into a significant 23% reduction in cardiovascular events and death compared with monotherapy (HR, 0.77; 95% CI, 0.61-0.96). Of note, the beneficial effect was more pronounced in patients with a prior acute myocardial infarction and heart failure. The finding that initial combination therapy resulted in a lower use of health care resources (eg, urgent care, out-
patient treatment, etc) is an indirect argument downplaying concerns regarding the impact of the side effects of combination therapy.

**COMBINATION THERAPY FOR MILD-TO-MODERATE HYPERTENSION**

Combination therapy remains an attractive initial choice, even for patients with mild-to-moderate hypertension. In a cohort of patients with mild-to-moderate hypertension treated with perindopril 3.5 mg/amlopidine 2.5 mg once daily, the combination was shown to be superior to either component given singly and noninferior to both components given singly at their lowest clinically approved doses. Adverse events relating to peripheral edema were less frequent with the combination than with amlopidine alone.

These salutary outcomes were further strengthened by data from a randomized clinical trial comparing the single-pill combination of perindopril and amlopidine to a stepped-care strategy of valsartan monotherapy with titration to valsartan and amlopidine after 2 months. Initial combination therapy resulted in rapid and improved achievement of BP control at 1 month and greater reductions from baseline, with comparable safety outcomes.

**COMBINATION THERAPY FOR PATIENTS WITH COMORBIDITIES**

Patients with comorbidities (eg, diabetes mellitus, chronic kidney disease) that call for aggressive and efficient BP control and those with markedly elevated BP levels are candidates for combination therapy. In a recent network meta-analysis, which analyzed the efficacy and safety of blood pressure-lowering agents in patients with type 2 diabetes mellitus and chronic kidney disease, no drug regimen was more effective than placebo in reducing mortality. Nonetheless, end-stage renal disease was significantly reduced (OR, 0.62; 95% CI, 0.43-0.90) after RAAS blockade in combination with both an ARB and an ACE inhibitor. The authors report that no regimen significantly increased hyperkalemia or acute kidney injury, although combined ACE inhibitor and ARB treatment resulted in border-line increases in the estimated risks.

The aforementioned intriguing findings should be put in a broader context, given their contrast with the recommendations from the 2013 ESH/ESC guidelines for the management of arterial hypertension, which advise against an ARB/ACE inhibitor combination and were based on the outcomes of the ONTARGET trial.

The therapy for patients with comorbidities is further perplexed by the concomitant use of drugs for diabetes mellitus, dyslipidemia, coronary and/or peripheral artery disease, and chronic kidney disease. Polypharmacy, defined as the use of four or more medications, is frequent in the elderly population, increases adverse drug reactions and interactions, and is associated with a decreased quality of life. Combination antihypertensive therapy can reduce pill burden in these patients. The introduction of a polypill that contains a statin, an antiplatelet agent, and an antihypertensive drug has been proposed and tested for the reduction in multiple risk factors and cardiovascular risk.

**CURRENT STATUS IN THE GUIDELINES**

In light of these data, European guidelines recommend initiating combination therapy for patients with markedly high baseline BP or those with a high cardiovascular risk. For the vast majority of patients, effective BP control can only be achieved by combining at least two antihypertensive drugs. The advantage of initiating with a combination therapy is a faster response in a larger number of patients, a greater probability of achieving the target BP in patients with higher BP values, and a lower probability of discouraging patient adherence. These ultimately lead to a reduction in cardiovascular risk. Regarding standard FDCs, the 2013 ESH/ESC guidelines for the management of arterial hypertension state that "combinations of two antihypertensive drugs at fixed doses in a single tablet may be recommended and favored because reducing the number of daily pills improves adherence, which is low in patients with hypertension" (Class of recommendation, IIb, level of evidence, B).

In the US, the recommendation for achieving BP control does not favor initial combination therapy, but advocates a gradual approach, according to the 2014 guidelines for the management of high BP in adults (Eighth Joint National Committee, JNC8). It should be noted that, according to the panel of authors, this is the only recommendation in the guidelines that is not based on a review of the literature, but solely on expert opinion. Thus, they suggest that if goal BP is not reached within 1 month of treatment, then the clinician should increase the dose of the initial drug or add a second drug. If goal BP cannot be reached with two drugs, then they should add and titrate a third drug from the list provided. In the previous iteration of the guidelines (Seventh Joint National Committee, JNC7), an initial two-drug combination for most patients with stage 2 hypertension (systolic BP > 160 mm Hg or diastolic BP > 100 mm Hg)
was advocated, and the guidelines acknowledged the fact that most patients with hypertension will require two or more antihypertensive medications to achieve the goal BP.

A scientific statement by the American Heart Association/American College of Cardiology/American Society of Hypertension (AHA/ACC/ASH) regarding treatment of hypertension in patients with coronary artery disease has been recently issued. According to the statement, patients with hypertension and chronic stable angina should be treated with the combination of a β-blocker (in patients with a history of a prior myocardial infarction), an ACE inhibitor or ARB (if there is a prior myocardial infarction, left ventricular systolic dysfunction, diabetes mellitus, or chronic kidney disease), and a thiazide or thiazide-like diuretic.  

**WHY IS COMBINATION THERAPY UNDERUTILIZED IN CLINICAL PRACTICE?**

Despite the guidelines’ recommendations for initiating combination therapy in patients with marked BP elevation (at least 20/10 mm Hg above the goal) or those with a high cardiovascular risk, the implementation in clinical practice remains low. A number of reasons can account for such hesitancy. Therapeutic inertia following the diagnosis of hypertension, which can be attributed to both patients and physicians, is common due to the initial lack of symptoms. The false impression that hypertension “grants time,” increases cardiovascular risk in the long run and has led constituent bodies to put emphasis on the timely initiation of treatment. In current guidelines, “the earlier, the better” approach has superseded the “the lower, the better” approach. Clinicians are concerned over issues of tolerability and side effects. However, current evidence puts such concerns to rest, for instance, in the ACCOMPLISH trial, initial combination therapy was discontinued by only 8.8% of patients during the first 90 days of treatment.

**CONCLUSION**

Combination therapy for the treatment of hypertension increases adherence, achieves faster BP control, and reduces cardiovascular risk. The extra BP reduction from combination therapy can be as much as five times greater than doubling the dose of one drug. Combination therapy should be the initial choice in patients with markedly high baseline BP or those with a high cardiovascular risk, and it may be considered for mild-to-moderate hypertension and for patients with comorbidities.

**REFERENCES**


What is renal denervation’s place in the management of treatment-resistant hypertension?

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Early proof-of-concept studies in patients were encouraging and pilot studies showed that decreases in systolic blood pressure >30 mm Hg could be achieved using renal denervation (RDN) in the management of treatment-resistant hypertension. Numerous uncontrolled observational studies followed, with similar benefits. In some studies, accompanying metabolic and cardiovascular changes supported the outcomes. Regrettably, the concept of a proper, blinded, randomized controlled trial escaped the attention of many investigators and sponsors, and RDN was accepted worldwide. However, the first randomized, sham-controlled trial (Symplicity HTN-3) showed no overall benefits of RDN. Few have focused on the indisputable fact that poor adherence to drug therapy is a major issue for patients with treatment-resistant hypertension. Further randomized sham-controlled trials are needed and, until the role of RDN has been clarified, there should be a moratorium on its use.

The unrivalled enthusiasm for a novel intervention, following the first reports of a substantial reduction in blood pressure associated with renal denervation (RDN) in patients with treatment-resistant hypertension, deserves comment. Apparent treatment-resistant hypertension is common in clinical practice, responses to drugs are frequently suboptimal, and residual cardiovascular risk from myocardial infarction, stroke, and heart failure remain high. Based on good scientific theory, RDN was a novel intervention that was potentially safe and capable of dramatically reducing systolic blood pressure by 30 mm Hg or more.1,2

Interventionalists (mainly cardiologists who had not previously shown, hitherto in the author’s experience, much interest in hypertension) could not get their hands on RDN catheters fast enough as they were ready to capitalize on these early results and extend treatment to the patient population labeled as treatment-resistant hypertensives, for which there now appeared an opportunity to control blood pressure. Device companies were quick to respond, and overnight, RDN became a big worldwide business.

History dictates the unbelievable naivety and uncritical acceptance of these early results, especially in a patient population where the complexity is well known, where heterogeneity in relation to cause is manifest, and most of all, where poor adherence to drug treatment is probably the rule rather than the exception.

Treatment-resistant hypertension is defined as blood pressure remaining above the goal despite the concurrent use of three different classes of antihypertensive drugs. Ideally, one of these drugs should be a diuretic and all drugs should be prescribed at optimal doses. The true prevalence of treatment-resistant hypertension is unknown, but figures as high as 20% to 30% have
been reported. Observational studies and clinical trials suggest that it is a common clinical problem. In an analysis of the National Health And Nutrition Examination Survey (NHANES) of participants being treated for hypertension, only 53% reached a blood pressure <140/90 mm Hg, however, in those with diabetes or chronic kidney disease, the percentage was considerably lower. Similar figures (65%) for all treated patients have recently been reported by the Health Survey of England, but of course, many of the participants in these surveys were not receiving optimal treatment for their hypertension.

Treatment-resistant hypertension comprises a heterogeneous group of patients, including those with undiagnosed secondary hypertension, inaccurate blood pressure measurement, white coat hypertension, and poor adherence to prescribed medication. In the author’s experience, true treatment-resistant hypertension is uncommon. Thus, in the evaluation of patients with apparent treatment-resistant hypertension, a comprehensive management algorithm should be applied to rule out secondary causes, confirm that appropriate treatments have been prescribed (drugs and doses), including the diuretic spironolactone, and assess drug adherence. This should include observing drug intake in the clinic, followed by blood pressure monitoring for up to 4 hours, and then 24-hour ambulatory blood pressure monitoring (ABPM) thereafter. The 4-hour period of observation after intake in the clinic is a precaution for cases where substantial decreases in blood pressure occur in the hitherto nonadherent or poorly adherent patients. If the facility is available, urinary drug screening can provide additional information on nonadherence. True treatment-resistant hypertension can only be diagnosed with confidence after a diligent exclusion of the majority of patients who are referred with so-called treatment-resistant hypertension.

In a pilot study, 37 patients were referred to a specialist clinic. Patients claimed to be taking their medications as prescribed. Additionally, any secondary causes of hypertension were eliminated and it was confirmed that all patients had been prescribed an optimal treatment, including a trial with spironolactone. In this study, the patient’s drugs were administered under observation. Following observed drug intake and 24-hour ABPM, 60% of these patients achieved a blood pressure <140/90 mm Hg and 80% achieved a blood pressure <150/90 mm Hg. The original series has now been extended to over 100 patients and the outcomes will be available soon, but the preliminary results are similar to those observed in the pilot study.

Therefore, it is manifest that poor drug adherence is the major contributing factor to apparent treatment-resistant hypertension, and without its systematic evaluation, treatment-resistant hypertension will be grossly overdiagnosed and the outcome of interventions will be influenced by variations in drug adherence.

**RENAI DENERVATION**

From the mid-20th century, there has been an interest in the role of the sympathetic nervous system in hypertension, which is supported by two important historical facts. First, prior to the onset of antihypertensive drug treatment, surgical sympathectomy produced profound decreases in arterial pressure in patients with severe or malignant hypertension. Second, many of the earliest antihypertensive drugs had, as their primary site of action, a central (alpha-methyl DOPA) or peripheral (ganglion blockers, adrenergic neuron blockers) interruption of the sympathetic nervous system. A plethora of studies in the 1970s and 1980s attempted to assess sympathetic nervous system activity directly using a variety of biochemical and physiological methods. Assessment of catecholamines in biological fluids (eg, plasma and urine) and radiochemical spill-over techniques to measure noradrenaline release from several organs (eg, heart, brain, and kidneys) have provided some insight into the role of the sympathetic nervous system in the pathogenesis of hypertension. Results from these assessments strongly suggested that the sympathetic nervous system had an important role in 40% to 65% of hypertensive patients. Also, activation of the renal sympathetic outflow was particularly pronounced in treatment-resistant hypertension. Direct recording of sympathetic muscle nerve activity and physiological studies on heart rate variability also supported the notion of an overactive sympathetic activity in many hypertensive patients.

The interpretation of these studies was challenging and the outcomes hotly debated. Suffice it to say, the agenda moved on with increasing interest in other biological systems, particularly the renin-angiotensin-aldosterone system.

However, despite the evolution of antihypertensive drug therapy and the increased use of combinations of antihypertensive drugs, even "optimal" therapy failed to control blood pressure in a group of so-called treatment-resistant patients, who represented around 20% of hypertensive patients receiving treatment. The proposed sympathetic
nervous system renaissance probably arose from a belief that contemporary treatments failed to target the underlying pathophysiology of treatment-resistant hypertension (although few of its proponents ever considered that drug adherence was a major problem in this group!), and that a new device-based therapy targeting the sympathetic nervous system was needed, including surgically implanted baroreflex-stimulation devices and catheter-based RDN by radiofrequency ablation.11,12

The case for RDN was supported by the knowledge that renal nerves promote renal tubular reabsorption of sodium, stimulate renin secretion from the kidneys, and cause renal vasoconstriction—all mechanisms that may elevate blood pressure. Combined with evidence that renal sympathetic outflow was increased in hypertensive patients and that, in experimental animals, surgical RDN lowered blood pressure,13 it was proposed that essential hypertension might be treated with a renal nerve ablation catheter. This concept was patented by Levin and Gelfand in the US in 2002.14 The first catheters were developed by Ardian/Medtronic, and the first human trials were initiated in June 2007 and conducted by Esler et al in Melbourne, Australia.

In the studies Symplicity HTN-1 (an uncontrolled study)1 and Symplicity HTN-2 (a prospective, randomized, noninterventional controlled study),2 impressive reductions in clinical systolic blood pressure (≈30 mm Hg) were reported following RDN, and these reductions were maintained during an extended follow-up period (up to 3 years). Other European centers reported similarly impressive reductions in blood pressure in uncontrolled studies.15 A meta-analysis has been published,16 however, only 18 out of 294 studies merited inclusion into a further meta-analysis.17 There have been additional reports that the reductions in blood pressure were accompanied by decreases in plasma catecholamines,18 improvements in insulin sensitivity,19 reductions in plasma renin (although this has not been a consistent finding),20 and regression in left ventricular hypertrophy.21

Despite the fact that several factors could have contributed to the fall in blood pressure in many of these trials (eg, placebo effect, regression to the mean, better drug adherence following recruitment into and intense follow-up of patients during the trial, and the notorious Hawthorne effect), there have been few words of caution against the hype surrounding RDN.22 Others have suggested that because Symplicity HTN-2 was an open trial, the trial was vulnerable to patient-, physician-, and sponsor-related biases.23 None of the Symplicity studies comprehensively screened patients for poor adherence or nonadherence. Only one in five had received a trial of spironolactone, which, in our experience, decreases blood pressure almost to the same levels as observed with RDN.24

In a subgroup of patients from the Symplicity HTN-2 trial, the reduction in blood pressure with ABPM following RDN was only 11/7 mm Hg, a far smaller reduction than anticipated from the clinic recordings. As Howard et al pointed out,23 in drug trials without randomization or blinding, blood pressure reductions in the clinic were substantially greater than the reductions in blood pressure when assessed using ABPM. However, with randomization and blinding, reductions measured in the clinic and by ABPM are remarkably similar. Howard et al predicted that, in Symplicity HTN-3, the first randomized, controlled, sham-operated trial of RDN, the reduction in systolic blood pressure would be closer to 10 mm Hg rather than the 30 mm Hg observed in earlier studies.

In a small series of patients undergoing RDN with treatment-resistant hypertension, Fadl Elmula et al reported that, after observing the intake of medication and ABPM, no decrease in blood pressure measured in the clinic or by ABPM occurred after RDN.25 In a subsequent paper, Fadl Elmula et al report that, after excluding poor drug compliance, adjusting the drug treatment was more effective than RDN in lowering blood pressure in true treatment-resistant hypertensive patients.26

While a minority may have urged caution over the widespread and often uncritical application of RDN to suspected cases of treatment-resistant hypertension, RDN has been extensively adopted by cardiologists and interventional radiologists in many countries, with a proliferation of device manufacturers entering an anticipated, rapidly expanding, and lucrative market. By 2015, more than 20 000 procedures had been conducted worldwide.

Following the earlier trials, guidelines on the application of RDN for treatment-resistant hypertension were published by the British Hypertension Society27 and other organizations,28 but the strict criteria recommended prior to qualification for RDN have, in international practice, been systematically ignored.

The Symplicity HTN-3 trial was the first prospective, randomized, sham-controlled trial of RDN. Over 500 patients with treatment-resistant hypertension participated in the study. The primary efficacy end point was the change in office systolic
blood pressure at 6 months; a secondary efficacy end point was the change in mean 24-hour ambulatory systolic blood pressure. The trial failed to meet its primary end point. The difference in office systolic blood pressure between the intervention arm and the sham-operated arm was only 2.4 mm Hg, and the change in mean 24-hour ambulatory blood pressure was only 2 mm Hg. Neither benefit was statistically significant. Obviously, this was a far less impressive outcome than many would have anticipated from the earlier observational and nonsham-controlled trials. The authors, however, confirmed that the procedure was safe, with few complications—an outcome similar to earlier trials of RDN.

Various explanations have been proposed to explain why RDN in the Symplicity HTN-3 trial was ineffective compared with sham operations. Several groups have highlighted the possibility that RDN was ineffective due to inadequacies in the denervation procedure, which is discussed in a comprehensive review by Epstein and de Marchena. This is an entirely possible explanation, largely accounted for by inexperienced investigators and inadequate denervation. However, to show no significant blood pressure reduction, it would seem, to me, that a large majority of the attempted denervation procedures must have been ineffective. However, it is extremely unlikely that the majority of the RDN procedures failed, especially given the substantial reductions in blood pressure reported in earlier studies. This means that there would have to be an additional explanation. I would suggest that if RDN does work (perhaps in a limited number of patients), then the true benefit is a much smaller reduction in blood pressure than initially reported.

This raises further issues. First, can the adequacy of RDN be determined? By measuring renal noradrenaline overflow, a technique that could be incorporated (albeit in a very limited number of centers) in further trials on RDN, the answer is probably yes, however, this may provide information on renal efferent sympathetic activity. Whether this gives any relevant information on renal afferent nerve activation, which is probably more important based on interpretation of earlier scientific studies, remains uncertain. Second, are there defined subgroups of patients in which the technique works and others in whom it does not? This suggestion is not unreasonable given that the concept holds for responses to antihypertensive drugs. It is claimed that the large proportion of African-Americans recruited into Simplicity HTN-3 could have influenced the outcome. If they, as a subgroup, were less responsive than white patients were to RDN. Again, this is a possible explanation, but it cannot totally explain the negative results of the trial, unless the real benefits of RDN are much smaller than we were initially led to believe from the previous trials. Finally, imbalance between the denervation group and the sham-operation group in medications pre- and postprocedure has also been postulated as an explanation for the lack of effect of RDN in the trial, but again, this seems unlikely.

A more recent French trial, DENER-HTN (renal DENERvation for resistant HyperTensioN), adds further insight to our current understanding. This carefully conducted trial also reported more modest reductions in blood pressure following RDN, and therefore, it deserves further comment. Over more than 1400 patients with treatment-resistant hypertension were screened for eligibility for the trial, but only 106 were eventually randomized to treatment—that is about 7%. Patients were randomly assigned to renal denervation + standardized stepped-care antihypertensive treatment (SSAHT) or SSAHT alone (the latter included spironolactone).

The primary end point—change in daytime systolic blood pressure measured by 24-hour ABPM—was reduced by 6 mm Hg in the denervation + SSAHT group compared with those receiving SSAHT alone at the 6-month follow-up. While this trial meets several of the criticisms leveled at earlier studies, in the absence of a sham-controlled comparator group, we cannot be sure that these conservative benefits following RDN were solely attributable to the procedure. It is important to note that only a small proportion of those initially considered for the trial were eventually subject to randomization. Given that there were no records of blood pressure following observed drug intake prior to recruitment, those eligible could have been further reduced to a small percentage of cases with treatment-resistant hypertension. A summary of more recent prospective and randomized studies is shown in Table I (page 212). Therefore, as has been previously suggested, substantial reductions in blood pressure in previous RDN trials could have been explained by better adherence to drug therapy following the procedure and during the intensive follow-up under close observation by the physicians. Without a doubt, from our observations in patients with treatment-resistant hypertension and from studies on drug concentrations in urine, compliance with medications is a major problem in this group of patients. In the context of a formal trial, particularly when RDN is con-
trolled by a group undergoing a sham procedure, it is entirely possible that improved drug compliance postprocedure would be similar in the two groups.

**FUTURE**

The scientific background and work leading up to RDN was sound and the innovative work by Esler et al commendable.\(^{33}\) The early trials of RDN in humans certainly reawakened interest in the role of the sympathetic nervous system in the pathophysiology of hypertension in general, and more specifically, in treatment-resistant hypertension. However, after Symplicity HTN-3, we need to take a big step backward to reevaluate RDN. The Joint UK Societies have recommended a moratorium on RDN until the Symplicity HTN-3 outcomes have been appropriately analyzed and digested.\(^{34}\)

Shock waves ran through the device companies, and plans for the development and marketing of newer catheters for RDN revised. There is a clear need for a sham-controlled trial with a large number of subjects, where inclusion is restricted to those with true treatment-resistant hypertension and after an evaluation following observed drug intake. Only when such a study has been conducted, can we begin to establish the future role of RDN in treatment-resistant hypertension.

This whole episode in the history of hypertension management raises interesting issues. There are few fields of medicine where the investigaton of therapeutic interventions has been conducted so thoroughly, with a history of clinical trials in hypertension dating back more than 50 years. Very early on, the substantial effects of placebo were recorded, and invariably with the introduction of placebo-controlled trials of antihypertensive drugs, the true blood pressure–lowering effect of the drugs was substantially lower than that observed in open, uncontrolled studies. A review of many of these trials revealed a systolic blood pressure–lowering effect for placebo to be around 15 mm Hg and a true drug effect of no more than 6 to 10 mm Hg.\(^{35}\) Many trials of add-on or combination therapy fell into the same trap, with a lack of a placebo control for the phase of the trial containing the combination, and again, unwarranted claims were often made for the added blood pressure–lowering effect of the combination, which failed to take into account the lack of a placebo control.

Therefore, it is extraordinary that the uncontrolled studies of RDN were viewed so uncritically not only

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### Table I. Characteristics and results of five prospective and randomized studies investigating blood pressure–lowering effects of renal sympathetic denervation.

**Abbreviations**: +, Δ in favor of control group; -, ΔRDN control in favor of renal denervation group; ΔFU-6 mo, 6-month follow-up; BP, blood pressure; DENER-HTN, renal DENERvation for resistant HyperTension [trial]; HTN, hypertension; RDN, renal denervation; SBP, systolic blood pressure.


<table>
<thead>
<tr>
<th>Variable</th>
<th>Symplicity HTN-2</th>
<th>Oslo RDN</th>
<th>HTN-3</th>
<th>PRAGUE-15</th>
<th>French DENERHTN</th>
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*Baseline ambulatory BP values were not given in this study

**Results given just for the difference between 20 patients in the renal denervation group and 25 patients in the control group**
Renal denervation’s place in the management of treatment-resistant hypertension

Surely, we should have been led by our knowledge of history rather than by the naked emperor from Hans Christian Andersen’s “The Emperor’s New Clothes”! For any novel intervention, including RDN, there is a necessity for properly controlled, randomized clinical trials to be carried out prior to the widespread uptake in clinical practice. This is required for any new antihypertensive drug, so why would we not demand that similar stringent processes be adopted prior to the introduction of a novel blood pressure-lowering device? This must apply to other devices that are currently being developed, including baroreceptor-activation devices and arteriovenous fistula creation, both of which have also been accepted with the same level of uncritically achieved notoriety by publication in major journals.11,37 There is also the recognition of the enormous problem of poor adherence with drug therapy in hypertensive patients in general and treatment-resistant patients in particular. The cost of poor adherence to health providers is substantial in terms of drug waste, the need for repeated clinical visits and investigations, and the residual morbidity and mortality associated with uncontrolled blood pressure. Drug assays on urine samples are inexpensive, cost-effective, and expose poor adherence. In addition, measuring blood pressure after observed drug intake is simple and important for eliminating poor adherence. Just because a patient says they take their medications is no reason to believe them. These techniques should be used routinely in the workup of patients with treatment-resistant hypertension.

Ultimately, there may be a place for RDN in the management of treatment-resistant hypertension where drug adherence is problematic due to side effects or other causes of noncompliance, but further controlled trials in such subgroups would be mandatory. The natural history of RDN mimics the late Desmond Lawrence’s teaching on new drugs to generations of British medical students—unrivalled enthusiasm, followed by total rejection, and then an ultimate place for use in a restricted number of patients (although we still have a long way to go before we can say with confidence in which patients the technique might be applied). Guidelines, such as the National Institute for Health and Care Excellence (NICE) guidelines, will clearly define the place of RDN in the UK health care system. It is hoped that national and international guidelines will be equally conservative and restrictive to its acceptance and use until we have more information and trial outcomes.

Let us not forget that other interventional procedures, which are well established in clinical practice (e.g., tonsillectomy and knee arthroscopy with washout) ultimately have been shown to be of little value when objectively evaluated. Based on the evidence to date, I put the following question to both the physicians and their patients with “treatment-resistant” hypertension—Who’s kidding whom?

REFERENCES


Renal denervation’s place in the management of treatment-resistant hypertension - Sever
30. Epstein E, de Marchena E. Is the failure of SYMPPLICITY HTN-3 trial to meet its efficacy endpoint the “end of the road” for renal denervation? J Am Soc Hypertens. 2015;9:140-149.


Understanding and Treating Central Blood Pressure

Summaries of Ten Seminal Papers

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Dialogues Cardiovasc Med. 2015;20:217-227

1. La tecnica sfigmomanometrica
   S. Riva-Rocci. Gazz Med Torino. 1897

2. Forward and backward waves in the arterial system
   N. Westerhof and others. Cardiovasc Res. 1972

3. An analysis of the relationship between central aortic and peripheral upper limb pressure waves in man
   M. Karamanoglu and others. Eur Heart J. 1993

4. Arterial wave reflections and survival in end-stage renal failure
   G. M. London and others. Hypertension. 2001

5. Improvement in blood pressure, arterial stiffness and wave reflections with a very-low-dose perindopril/indapamide combination...
   R. G. Asmar and others. Hypertension. 2001

6. Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity...
   C. M. McEniery and others. J Am Coll Cardiol. 2005

7. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes...
   B. Williams and others. Circulation. 2006

8. Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: the Strong Heart Study
   M. J. Roman and others. Hypertension. 2007

9. Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis
   C. Vlachopoulos and others. Eur Heart J. 2010

10. Establishing reference values for central blood pressure and its amplification in a general healthy population...
    A. Herbert and others. Eur Heart J. 2014

Selection of seminal papers by M. Lorenza Muiesan, MD
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Highlights of the years by Sherri Smith, PhD
Publications office
Scipione Riva-Rocci’s original article describes an instrument for the measurement of blood pressure. He first illustrates the concept of “lateral pressure” (which we now call mean blood pressure) and of “total or “terminal pressure.” “To evaluate the pressure exerted on the arterial walls, it is necessary to know what in hydraulics is called pressure loading, and the best way to determine this, in theory, is by the application of a piezometer to the artery when you wish to measure the pressure…”

In a conduction system of elastic conduits, an increase in the fluid’s velocity may be perceptible only over a certain short distance. With each increase in the pressure loading, the elastic wall dilates and part of the total load is stored as elasticity under pressure. The energy is then stored in the interval between two successive increases. The wall stretches and subsequently relaxes to keep the velocity constant, ie, to maintain a steady outflow of fluid with rhythmic movements of the tube walls—the phenomenon of the pulse.

After an accurate description of available sphygmomanometers, he proposed his own sphygmomanometer, an instrument that provides a measure of total pressure loading. Finally, Riva-Rocci gives detailed instructions for “how to use” the sphygmomanometer and he finally concludes:

It is hardly necessary to add that it will be possible to compare only blood pressure data obtained under exactly the same conditions, such as surroundings, position, time, time since the last meal, walking, etc. This observation is perhaps superfluous for the researchers, but useful to doctors for whom haste is sometimes the cause of time wasting. If the procedures given here are followed, sphygmomanometry could become genuinely useful in the clinical practice.

John J. McDermott beats 14 men to win the first Boston Marathon; the Klondike Gold Rush begins when the first successful prospectors arrive in Seattle; and Sir Ronald Ross demonstrates the transmission mechanism of Plasmodium, the malaria parasite
The real site of wave reflections has been a matter of debate. In this paper, Westerhof et al describe the phenomena of wave reflections in the arterial system as reported in previous studies and try to clarify the confusing situation of forward (incident) and backward (retrograde) flow and pressure.

The experiments, performed in 7 mongrel dogs, were conducted by implanting an electromagnetic flow probe in the ascending aorta, and after 10 days, both common carotid arteries were isolated and loosely ligated, while a balloon catheter was introduced in the aorta and a catheter-tip manometer was placed in the aorta. Pressure and flow, measured in the ascending aorta, could be separated into a (composite) wave traveling from the heart toward the periphery (the forward wave) and a (composite) wave traveling in the opposite direction (the backward wave). The calculations were carried out in the frequency domain, via Fourier analysis and the addition of harmonics. A set of four examples was used to show the forward and backward traveling waves in the ascending aorta together with the measured pressure and flow waves and include: (i) a reference or control condition; (ii) a condition of increased resistance, obtained by the ligation of both common carotid arteries; (iii) a condition of decreased resistance, induced by emptying a balloon occluding the aorta; and (iv) a condition of complete occlusion of the aorta, generated by filling the balloon with liquid. For all of these conditions, Westerhof et al calculated the global reflection coefficients (ie, the ratio of the composite backward wave [resulting from many individual waves that return from different locations and are all combined into this backward wave] to the forward wave, in the frequency domain). The global reflection coefficient includes damping of the waves while they travel along the system, and without more information, does not distinguish between damping of waves and (local) reflections.

The plot of reflection coefficients, as a function of frequency, clearly showed that, for high frequencies, most reflection coefficients are different; reflection coefficients have higher values when the aorta is occluded (high-resistance conditions) and lower values in low-resistance conditions as compared with the control conditions. It seems likely that, at bifurcations of large arteries, a constant amount of reflection contributes to the reflection coefficient and that a varying amount of reflection is added to this fixed amount in the peripheral part of the system.

In the case of low resistance, a low reflection coefficient suggests that the reflections occurring at large bifurcations, with a constant amount of reflection, are very small. In the other cases, including the control situation, a high reflection coefficient at low frequencies shows that the contribution of the periphery to the reflection coefficient is quite large. The authors concluded that the considerable influence of the periphery on the reflection coefficient, shown in this study, provides doubt about using models that are based only on reflections at bifurcations of large arteries (and exclude the periphery).

1972
The first scientific handheld calculator is introduced; Maurice Auguste Chevalier, a French singer and actor, dies at age 83; and the immunosuppressive effect of cyclosporine is discovered
An analysis of the relationship between central aortic and peripheral upper limb pressure waves in man

M. Karamanoglu, M. F. O'Rourke, A. P. Avolio, R. P. Kelly

Eur Heart J. 1993;14:160-167

Initially, the values of systolic and diastolic blood pressure, measured at the brachial artery, were assumed to be similar throughout the whole arterial tree and reflect the true left ventricular afterload. However, this clearly failed to recognize the differences in pressure wave forms between central and peripheral arteries; these differences are related to the forward-traveling pulse wave and backward reflection along the arterial system. The amplification of the pressure pulse between central and peripheral arteries renders pressure values in the upper limb an inaccurate measure of ascending aortic pressure, therefore, an improvement in accuracy could be obtained by taking this amplification into account.

Karamanoglu et al more accurately examined the relationship between central aortic and peripheral brachial or radial pressure transfer functions and compared the results with those previously obtained. A total of 14 patients were studied during diagnostic cardiac catheterization, and a high fidelity (Millar micromanometer) recording of pressure waves in the brachial and ascending aorta was obtained under both control conditions and after sublingual administration of nitroglycerin. In addition, the radial artery pressure wave pulse was recorded by applanation tonometry, simultaneously with the ascending aortic pressure, before and after sublingual administration of nitroglycerin.

Transfer functions were determined for pressures between the ascending aorta and the brachial artery and for pressures between the ascending aorta and the radial artery. There were no significant differences in the brachial artery transfer function under control conditions or after the administration of nitroglycerin; the same was true for the radial artery transfer function, so the results were pooled. The results confirmed that a substantial difference occurs in the amplitude and contour of pressure waves measured in the ascending aorta or in the brachial or radial arteries, as observed previously, and these differences were larger after nitroglycerin administration.

Frequency-dependent changes in the modulus and phase of both the brachial artery transfer function and the radial artery transfer function were attributable to wave travel and reflections in the upper limb. Finally, authors compared brachial and radial artery transfer functions with both published transfer functions and transfer functions derived from an analysis of aortic and brachial or radial pressure waves in previous publications, with similar results. The brachial and radial artery transfer functions obtained in this study were then used to synthesize ascending aorta pressure waves from published peripheral pulses, with a close correspondence, especially for systolic pressure. The difference between radial or brachial systolic pressure was 20.4 mm Hg ($P < 0.0001$), on average, whereas synthesized aortic systolic pressure was, on average, just 2.4 mm Hg ($P > 0.005$) different.

The results indicated that, in adult humans, a single generalized transfer function can be used with acceptable accuracy to determine central from peripheral pressure under different conditions. These results represent an important advancement in starting to measure central blood pressure by applanation tonometry, which has been integrated into the SphygmoCor system (Artcor, Australia).
Epidemiological studies have shown that, in end-stage renal failure patients, arterial stiffness of large elastic-type arteries is increased and the wave-reflection effect is more pronounced. The consequences of these alterations are the development of myocardial hypertrophy, an increase in oxygen consumption, and changes in coronary blood flow distribution, which favors the occurrence of cardiovascular events. London et al. have already shown that aortic stiffening, determined by measuring aortic pulse wave velocity, was an independent predictor of all-cause and cardiovascular mortality in end-stage renal failure patients; however, the impact of wave reflections on clinical outcomes and mortality remained to be demonstrated. Therefore, London et al. examined, from 1990 to 2000, 180 patients with end-stage renal failure undergoing hemodialysis treatment, with an average follow-up and monitoring period of 52 months.

During the follow-up, 70 deaths occurred, including 40 cardiovascular and 30 noncardiovascular deaths. In addition to standard clinical and biochemical analyses, all patients underwent aortic pulse wave velocity measurement and determination of arterial wave reflection by applanation tonometry on the common carotid artery, which was expressed as the augmentation index.

Cox analyses demonstrated that the main factors associated with an increased risk of all-cause and cardiovascular mortality were age, aortic pulse wave velocity, low diastolic blood pressure, preexisting cardiovascular disease, and an increased augmentation index. Angiotensin-converting enzyme inhibitors had a favorable effect on survival. After adjustment for all confounding factors, the risk ratio for every 10% increase in augmentation index was 1.51 (95% CI, 1.23 to 1.86, \( P = 0.0001 \)) for all-cause mortality and 1.48 (95% CI, 1.16 to 1.90, \( P = 0.0001 \)) for cardiovascular mortality. Most importantly, the predictive value of the augmentation index was independent of pulse wave velocity, once more highlighting the need for assessing both parameters for a comprehensive evaluation of arterial stiffness and central hemodynamic abnormalities.

In the discussion, the authors described the pathophysiological mechanisms explaining the association between augmentation index increase and the occurrence of cardiovascular events, including cardiac hypertrophy, systolic and diastolic dysfunction, and coronary hypoperfusion. However, as highlighted in the discussion, the relationship between mortality and increase in augmentation index does not imply direct causation, and in order to clarify the causality of the association, it would be necessary to demonstrate that an intervention aimed at reducing the augmentation index would be associated with a reduction in mortality or morbidity.

The Azote Fertilisant chemical factory explodes, killing 29 and seriously wounding over 2500; the first Harry Potter film, *Harry Potter and the Sorcerer’s Stone*, is released, grossing $975.8 million worldwide; and the Beatles’ George Harrison dies at the age of 58 from metastatic non–small cell lung cancer.
Improve in blood pressure, arterial stiffness and wave reflections with a very-low-dose perindopril/indapamide combination in hypertensive patients: a comparison with atenolol


Hypertension. 2001;38:922-926

Asmar et al examined the different effects of antihypertensive treatment on aortic stiffness and central hemodynamic parameters. The authors randomized 471 patients with essential hypertension to either the very-low-dose combination perindopril (2 mg) and indapamide (0.625 mg) (perindopril/indapamide) or the β-blocking agent atenolol (50 mg) and monitored all patients for 1 year. In each patient, aortic pulse wave velocity (by automatic measurements) and wave reflections (by pulse wave analysis and applanation tonometry) were measured.

After the 1-year follow-up, the brachial pulse pressure and brachial systolic, diastolic, and mean blood pressures decreased significantly in the two treatment groups. The decrease in diastolic blood pressure was the same in each treatment group, whereas the perindopril/indapamide combination had a more marked reduction in brachial pulse pressure and brachial systolic, diastolic, and mean blood pressures compared with atenolol. The decrease in carotid and aortic blood pressures was significantly more pronounced with the perindopril/indapamide combination than with atenolol. The blood pressure–effect profile clearly differed between perindopril/indapamide, which induced a similar effect on central (carotid and aortic) and peripheral (brachial) blood pressure, and atenolol, which had an even smaller effect on central vs peripheral blood pressure.

The two antihypertensive agents decreased pulse wave velocity to a similar degree, but only perindopril/indapamide significantly attenuated carotid wave reflections, identifying a hemodynamic profile that is possibly favorable for an improvement in survival for hypertensive patients. Three possible hemodynamic factors have been suggested as possible explanations for the more marked decrease in central blood pressure with perindopril/indapamide than atenolol, including (i) alterations in ventricular ejection time (due to the different effect on heart rate), (ii) reduction in aortic pulse wave velocity, and (iii) modification in the site or intensity of wave reflections (possibly related to the effect on changes in the vascular structure and/or function of the arterioles). A subanalysis of the results of this study demonstrated that the greater change in left ventricular mass, measured by echocardiography, observed in patients treated with the perindopril/indapamide combination was linked to central, but not brachial, blood pressure.

The publication of the CAFE study (Conduit Artery Function Evaluation), 5 years later, confirmed the differential impact of different antihypertensive drugs (and drug combinations) on peripheral and central hemodynamics.
Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT)

C. M. McEniery, Yasmin, I. R. Hall, A. Qasem, I. B. Wilkinson, J. R. Cockcroft; ACCT Investigators

J Am Coll Cardiol. 2005;46:1753-1760

Recently, it has been recognized worldwide that age is the most important determinant of stiffening and dilatation of large arteries. In previous studies, pulse wave velocity, an index of large artery stiffening, increased linearly with age and mainly occurred later in life. A linear correlation between age and augmentation index, a composite measure that depends on the site and degree of wave reflection, has also been observed, although data from invasive studies suggest that the intensity of wave reflection becomes less marked in old age.

In this relevant study, McEniery et al assessed the precise relationship between increasing age and changes in both the stiffening of large arteries and central hemodynamics in 10,096 subjects ranging in age from 18 to 90 years (i.e., the ACCT trial [Anglo-Cardiff Collaborative Trial]). Subjects were selected from local general practice lists and open-access cardiovascular risk assessment clinics across East Anglia and Wales. For the current study, all subjects with hypertension, diabetes, or previous cardiovascular disease and those receiving treatment were excluded, and 4001 individuals, mainly Caucasian, were considered. For each subject, applanation tonometry and pulse wave analyses were performed, and central blood pressure, augmentation pressure, and augmentation index were determined. In addition, aortic and brachial pulse wave velocities were measured in a subset of 998 subjects.

As expected, peripheral blood pressure, central pulse pressure, augmentation pressure, augmentation index, aortic and brachial pulse wave velocity increased significantly with age. In addition to age, male sex and mean arterial pressure were the most important determinants of the central hemodynamic indexes, such as augmentation index, augmented pressure, and pulse pressure amplification. However, the changes in augmentation index observed across the age categories were not linear, with a steep increase from 20 to 50 years of age, both in men and women; at all ages, central augmentation index was higher in women, possibly due to a shorter average height. In addition, the age-related increase in pulse wave velocity was not linear and was more marked from 45-50 to 90 years, with no significant differences between men and women.

These findings highlight a different sensitivity between augmentation index and pulse wave velocity as markers of arterial vascular aging for central hemodynamic parameters; augmentation index is a more appropriate index in younger individuals and aortic pulse wave velocity is a better measure in older individuals. In younger individuals, the increase in augmentation pressure may be due to an increase in the magnitude of wave reflection, rather than to an increase in wave velocity, while in older individuals, the increase in augmentation pressure may be due to an earlier return of the reflected wave and a less compliant aorta, rather than predominant changes in the magnitude of wave reflection.

The authors also described an association between heart rate and both augmentation index and augmentation pressure that accounted for about 10% of the variance in each parameter. This small effect on heart rate would exclude the idea that age-related changes in heart rate are involved in the increase in central hemodynamic parameters in the different age strata. The important clinical implication is that obtaining and integrating all markers may possibly be used to improve risk prediction.

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2005

American comedian Richard Pryor dies at age 65 after a heart attack; Cosmonaut Sergei Krikalev breaks the world record for the most days spent in space while onboard the International Space Station; and Didier Delsalle becomes the first person to land a helicopter on the summit of Mount Everest.
The CAFE study (Conduit Artery Function Evaluation), a substudy of the ASCOT trial (Anglo-Scandinavian Cardiac Outcomes Trial), was designed to examine the impact of two different blood pressure–lowering regimens (atenolol ± thiazide-based vs amlopidine ± perindopril-based therapy) on derived central aortic pressures and hemodynamics.

After 1 year of randomization into the ASCOT trial, 2,199 patients (from 5 ASCOT centers) were recruited into the CAFE study, meaning that patients were studied after titration of treatment and after reducing blood pressure for 1 year. In addition to all the parameters assessed during the main ASCOT study, patients participating in the CAFE study underwent radial artery applanation tonometry and pulse wave analysis using a commercially available system (SphygmoCor) on repeated visits (up to 4 years) in order to collect at least 2 measurements for each participant in the CAFE study over the course of the ASCOT follow-up. Central aortic blood pressure, augmentation pressure, augmentation index, and pulse pressure amplifications were derived and calculated from the applanation tonometry and pulse wave analysis. Most patients received combination therapy throughout the study; the mean follow-up after the initial tonometry was 3 years and the mean number of tonometry measurements was 3.4.

The results of the CAFE study show that no significant differences in brachial systolic blood pressure changes were observed between the two groups of atenolol-based and amlopidine-based treatments (Δ between treatments, 0.7 mm Hg, 95% CI, -0.4 to 1.7, P = 0.2), while central aortic pressure changes in the amlopidine regimen were much higher compared with those observed in the atenolol group (Δ between treatments for central systolic blood pressure, 4.3 mm Hg, 95% CI, 3.3 to 5.4, P < 0.0001 and Δ between treatments for central pulse pressure, 3.0 mm Hg, 95% CI, 2.1 to 3.9, P < 0.0001). Augmentation pressure and index were increased by atenolol ± thiazide-based therapy compared with the amlopidine ± perindopril-based therapy. The increase in central systolic blood pressure and pulse pressure observed during the treatment with atenolol ± thiazide-based therapy could be a consequence of an increased pressure wave reflection from distal reflection sites due to the much higher central aortic systolic pressure wave augmentation and augmentation index vs amlopidine ± perindopril-based therapy.

An additional aim of the study was to correlate the changes in central hemodynamics observed between the two treatment regimens with the occurrence of cardiovascular events. According to Cox proportional-hazards modeling, central pulse pressure was significantly associated with a post hoc–defined composite outcome of total cardiovascular events/procedures and the development of renal impairment in the CAFE cohort (unadjusted, P < 0.0001, adjusted for baseline variables, P < 0.05). Therefore, central aortic pulse pressure could represent a determinant of clinical outcomes and Williams et al extrapolated these results to the main ASCOT study, suggesting that the differences in central aortic pressures may be a potential mechanism to explain the different clinical outcomes between the blood pressure–treatment arms with β-blocker/diuretic or calcium channel blocker/angiotensin-converting enzyme inhibitor combinations in the ASCOT trial.

The main clinical implication of the CAFE study is that antihypertensive treatment with different blood pressure–lowering drugs may affect central aortic pressures and hemodynamics, despite a similar effect on brachial blood pressure.

Differential impact of blood pressure–lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study

B. Williams, P. S. Lacy, S. M. Thom, K. Cruickshank, A. Stanton, D. Collier, A. D. Hughes, H. Thurston, M. O’Rourke; CAFE Investigators, ASCOT Investigators, CAFE Steering Committee and Writing Committee

Circulation. 2006;113:1213-1225
Central aortic blood pressure reflects the loading conditions of the left ventricular myocardium, coronary arteries, and cerebral vasculature better than brachial blood pressure; therefore, cardiovascular target organ damage and cardiovascular events should correlate better with central aortic pressures than with brachial pressures. Similarly, the measurement of pulse wave velocity integrates the vascular damage secondary to aging, hypertension, and diabetes better than brachial or even central aortic blood pressure.

In this study, Roman et al explored the relations of carotid artery hypertrophy (intimal-medial thickness and vascular mass), extent of atherosclerosis (plaque score), and incident cardiovascular events with both brachial and central pressures in the Strong Heart Study, a population-based study in North America Indians. Central pressures were calculated using radial applanation tonometry, while carotid intima-media thickness and plaques were assessed by carotid ultrasound. Among the 3520 participants, central and brachial pulse pressures were more strongly related to vascular hypertrophy and the extent of atherosclerosis than systolic pressures. Most importantly, central pulse pressure was more strongly related to intima-media thickness, vascular mass, and plaques in the carotid arteries than brachial pulse pressure. The majority of these patients were receiving antihypertensive treatment, but the association of central blood pressure with carotid structural alterations remained statistically significant after considering the effect of treatment.

When the relation between central and brachial pressures and clinical outcomes was evaluated in a subgroup of 2403 participants free of overt cardiovascular disease, central pulse pressure was more strongly predictive of cardiovascular events than brachial pulse pressure, independently of age, sex, current smoking, body mass index, ratio of total cholesterol to high-density lipoprotein, creatinine, fibrinogen, diabetes, and heart rate. The same result was true when the analysis was further adjusted for the presence of carotid atherosclerosis. These results have been obtained in a sample of North American Indians and are not easily applicable to other subjects or patients; however, subjects participating in the Strong Heart Study are characterized by a high prevalence of obesity and diabetes and might be representative of the increasing number of high-risk patients.

The results of this study provide an important contribution to the assessment of the relationship between target organ damage and aortic central pressure, confirming the concept that central pressure is more strictly related to carotid atherosclerosis. Consequently, the use of antihypertensive treatments targeted to reduce central blood pressure could reduce the development of cardiovascular structural changes and favor their regression, improving the patient's cardiovascular prognosis.

Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: the Strong Heart Study


Hypertension. 2007;50:197-203

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South Africa wins the Rugby World Cup after defeating England, the 2003 defending champions; Boris Yeltsin dies of congestive heart failure at age 76; and the I-35W Mississippi River Bridge, an eight-lane, steel truss arch bridge in Minneapolis, MN, US, suddenly collapses, killing 13 people and injuring 145
central pressures and indices have been shown, in several studies, to predict future events, but the findings have not always been consistent. Therefore, Vlachopoulos et al wanted to provide an overview of relevant studies and an overall quantitative estimate of the ability of central pressures and derived indices to predict cardiovascular outcomes and all-cause mortality. In this meta-analysis, Vlachopoulos et al performed a systematic review of the literature to clarify the correlation between central hemodynamics and the occurrence of future cardiovascular disease. In addition, the eventual superiority of the central indices vs peripheral blood pressure values to predict future cardiovascular disease was tested.

Published in 2010, this landmark systematic review has been helpful to investigators and clinicians in the field. Vlachopoulos et al performed an admirable job given the difficulty of assessing 528 potential studies. In the end, 11 longitudinal studies that had measured central hemodynamics were selected, resulting in an analysis involving 5,648 subjects with a mean follow-up of 45 months. In the selection of eligible studies, no exclusion criteria were imposed with regard to the type of population studied (eg, healthy subjects, general population, or populations with risk factors or disease), the size of the population, or the duration of follow-up. All longitudinal studies included in the meta-analysis were prospective studies.

The CAFE study (Conduit Artery Function Evaluation), a sub-study of the ASCOT trial (Anglo-Scandinavian Cardiac Outcomes Trial), was excluded because of its design (interventional, randomized trial assessing two different combinations of antihypertensive medications) and because central hemodynamic measurements were performed 1 year after randomization and were lacking at baseline. The authors used the aggregate data as reported or calculated in published articles and did not use the data from individual patients.

The age- and risk-factor-adjusted pooled relative risk of total cardiovascular events was assessed for an increase in central systolic blood pressure in three studies, for central pulse pressure in six studies, and for augmentation index in five studies. The age- and risk-factor-adjusted pooled relative risk of total cardiovascular events was 1.088 (95% CI, 1.040-1.139) for a 10 mm Hg increase in central systolic blood pressure and 1.137 (95% CI, 1.063-1.215) for a 10 mm Hg increase in central pulse pressure. The risk associated with a 10% absolute increase in central augmentation index was 32% for total cardiovascular events and 38% for all-cause mortality. In five studies, the risk of cardiovascular events was reported for both central and brachial pulse pressure. The cumulative analysis of these studies showed that central pulse pressure was associated with a marginally, but not significantly, higher relative risk of clinical events (P=0.057) compared with brachial pulse pressure.

Despite the fact that the analysis neither evaluated individual data nor accounted for potential methodological problems of the original studies, the study's conclusion supports the concept that central pressure components and indices independently predict future clinical events. In particular, the augmentation index predicts clinical events independently of peripheral pressures, while the effect is only marginal for central blood pressure. The results of ongoing studies should provide data on a wider range of populations and disease states. In addition, the results should be analyzed to continue assessing the ability of central indexes to discriminate, calibrate, and reclassify the risk of patients in clinical practice.

2010

Dave Crisp discovered the Frome Hoard, a hoard of 52,503 Roman coins (AD 253-305), one of the largest in the UK; Ky Fan, a Chinese-American mathematician and theorist, dies at age 95; and Jessica Watson, a 16-year-old sailor, completes a solo voyage around the world.
Establishing reference values for central blood pressure and its amplification in a general healthy population and according to cardiovascular risk factors

A. Herbert, J. K. Cruickshank, S. Laurent, P. Boutouyrie; Reference Values for Arterial Measurements Collaboration

Eur Heart J. 2014;35:3122-3133

In recent years, central blood pressure (ie, pressure at the aortic root) has gained popularity as a potentially useful measurement of the “true” pressure affecting target organs that have been damaged by arterial hypertension (ie, the heart, brain, and kidneys). Central blood pressure can now be noninvasively estimated using a variety of validated techniques. In addition, the association between an increase in central blood pressure and subsequent cardiovascular events and mortality has become more evident, highlighting the clinical importance of estimating central systolic blood pressure and amplification. However, no reference values are available, despite having used different devices to measure central systolic blood pressure and amplification for at least 25 years.

In this study, Herbert et al aimed to establish reference values for a worldwide general population and standardize the most frequently used methods of measurement. Using a validated tonometry or calibrated distension wave technique, the authors analyzed all the data collected in population surveys and clinical trials for people >14 years old. Out of a total number of 82,990 subjects participating in 77 studies from 53 centers, 45,436 subjects were included in the analysis and divided into the following 4 groups: (i) normal population of healthy subjects, ie, subjects without cardiovascular risk factors (18,183), (ii) subjects with cardiovascular risk factors (15,831), (iii) subjects with essential hypertension, but no other cardiovascular risk factors (10,122), and (iv) reference population, ie, essential hypertensive subjects with other cardiovascular risk factors (10,410). Included subjects were apparently healthy, not being treated for hypertension or dyslipidemia, and free from overt cardiovascular disease and diabetes. Reference values for central systolic blood pressure and amplification were calculated as percentiles for “normal” and “reference” populations. Values of central systolic blood pressure and amplification were stratified by brachial blood pressure categories and age decade in turn, and both were stratified by sex.

Along with the calculation of reference values, the main determinants of pulsatile hemodynamic parameters were examined in detail. Risk factors affected normotensives and hypertensives differently, all risk factors, except glucose, had a statistically significant impact on central systolic blood pressure in normotensives, whereas only smoking, male sex, and heart rate were significantly related to central systolic blood pressure in hypertensives. Male sex was associated with a lower central systolic blood pressure in hypertensives, and the opposite was observed in normotensives, indicating a strong interaction between age, sex, and blood pressure.

Amplification decreased with age, but to a different degree in males and females. Sex was the most powerful factor associated with amplification, with a 6.6 mm Hg (5.8 to 7.4) higher amplification in males than females, possibly due to the influence of height. Amplification was marginally, but significantly influenced by cardiovascular risk factors. Smoking and dyslipidemia decreased amplification, whereas hyperglycemia increased amplification.

The availability of reference values for central systolic blood pressure and amplification in a healthy population and a population free from traditional cardiovascular risk factors, according to age, sex, and brachial blood pressure, with a wide geographical representation, provides an important tool to continue evaluating whether central blood pressure or amplification are needed for a more accurate risk stratification.

At the age of 16, Lewis Clarke from Bristol, UK becomes the youngest person to trek to the South Pole; a previously unknown copy of Shakespeare’s the First Folio (1623) is discovered in northern France; and an underground city estimated to be around 5000 years old is discovered in Turkey.
Understanding and Treating Central Blood Pressure

Bibliography of One Hundred Key Papers

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<td>Hirata K, Kawakami M, O’Rourke MF.</td>
<td>Pulse wave analysis and pulse wave velocity: a review of blood pressure interpretation 100 years after Korotkoff.</td>
<td><em>Circ J.</em> 2006;70:1231-1239.</td>
</tr>
<tr>
<td>Hope SA, Meredith IT, Cameron JD.</td>
<td>Arterial transfer functions and the reconstruction of central aortic waveforms: myths, controversies and misconceptions.</td>
<td><em>J Hypertens.</em> 2008;26:4-7.</td>
</tr>
<tr>
<td>Hope SA, Meredith IT, Cameron JD.</td>
<td>Effect of non-invasive calibration of radial waveforms on error in transfer-function-derived central aortic waveform characteristics.</td>
<td><em>Clin Sci (Lond).</em> 2004;107:205-211.</td>
</tr>
<tr>
<td>Kelly RP, Gibbs HH, O’Rourke MF, et al.</td>
<td>Nitroglycerin has more favourable effects on left ventricular afterload than apparent from measurement of pressure in a peripheral artery.</td>
<td><em>Eur Heart J.</em> 1990;11:138-144.</td>
</tr>
<tr>
<td>Reference</td>
<td>Title</td>
<td>Journal</td>
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Millasseau SC, Patel SJ, Redwood SR, Ritter JM, Chowienczyk PJ.  
Pressure wave reflection assessed from the peripheral pulse: is a transfer function necessary?  
*Hypertension.* 2003;41:1016-1020.

Arterial stiffness and cardiovascular events: the Framingham Heart Study.  
*Circulation.* 2010;121:505-511.

Muiesan ML, Salvetti M, Rizzoni D, et al.  
Pulsatile hemodynamics and microcirculation: evidence for a close relationship in hypertensive patients.  

Central aortic reservoir-wave analysis improves prediction of cardiovascular events in elderly hypertensives.  
*Hypertension.* 2015;65:629-635.

Nichols WW, Denardo SJ, Wilkinson IB, McEniery CM, Cockcroft J, O’Rourke MF.  
Effects of arterial stiffness, pulse wave velocity, and wave reflections on the central aortic pressure waveform.  

Nichols WW, O’Rourke MF.  
Aortic pulse wave velocity, reflection site distance, and augmentation index.  

Inflammatory markers and growth in South Asian and European origin infants in Britain: the Manchester Children’s Growth and Vascular Health Study.  

Ott C, Haetinger S, Schneider MP, Pauschinger M, Schmieder RE.  
Comparison of two noninvasive devices for measurement of central systolic blood pressure with invasive measurement during cardiac catheterization.  
*J Clin Hypertens (Greenwich).* 2012;14:575-579.

Ott C, Raff U, Harazny JM, Michelson G, Schmieder RE.  
Central pulse pressure is an independent determinant of vascular remodeling in the retinal circulation.  

Papaioannou TG, Protogerou A, Stefanadis C.  
Comparison between Mobil-O-Graph and the Sphygmocor device for central systolic blood pressure estimation: consensus is required for validation protocols.  

Pauca AL, Kon ND, O’Rourke MF.  
The second peak of the radial artery pressure wave represents aortic systolic pressure in hypertensive and elderly patients.  

Pauca AL, O’Rourke MF, Kon ND.  
Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform.  

Pini R, Cavallini MC, Palmieri V, et al.  
Central but not brachial blood pressure predicts cardiovascular events in an unselected geriatric population: the ICARe Dicomano Study.  
*J Am Coll Cardiol.* 2008;51:2432-2439.
### Bibliography of One Hundred Key Papers

<table>
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<tr>
<th>Author(s)</th>
<th>Title</th>
<th>Journal</th>
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