Should the blood pressure or the blood vessel be the target of therapy?


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Measured blood pressure is an insensitive and moderately nonspecific guide to the presence of vascular or cardiac diseases likely to progress to cardiovascular morbid events. Since the goal of the diagnosis and treatment of hypertension is to prevent or forestall such morbid events, blood pressure measurements should be supplemented by studies of the health of the cardiovascular system in defining the syndrome of hypertension and in monitoring its response to therapy.

**Keywords:** atherosclerosis • blood pressure • endothelial dysfunction • large arteries • small arteries

Variability of blood pressure

Cuff blood pressure readings vary from moment to moment and from day to day. Patients and healthcare providers are well aware of this variability and are taught to not put much stock in individual readings. Readings are sometimes averaged over time to calculate a mean value. Sometimes home readings and even ambulatory blood pressure readings are utilized in an attempt to gain further insight into the average daily blood pressure. Thus, readings that determine the diagnosis of hypertension and readings to document the effectiveness of therapy must be interpreted in context and often with inadequate insight.

The result of the uncertainty as to which measurement or measurements to use in diagnosing hypertension and which measurements to use to gauge the effectiveness of therapy leads to widely divergent practices. Some medical practitioners are reluctant to make the diagnosis of hypertension and initiate antihypertensive therapy in the face of this variability, instead advising patients to lose weight or to undertake modest lifestyle changes. Even when drugs are initiated, low doses are often not uptitrated because of uncertainty of the reliability of the casual readings taken in the clinic and the unwillingness of the physician or patient to accept the idea that additional therapy is required. Therefore, undertreatment of blood pressure is a common phenomenon in practice, even when the healthcare provider is attentive and motivated [1].

Control of blood pressure

Mean blood pressure is determined by the product of cardiac output and total systemic vascular resistance, which is affected by the tone and structure of small arteries and arterioles. The systolic and diastolic pressures are further dependent on the stiffness or compliance of the large conduit arteries. These simple physiologic principles are well known to all medical practitioners, but are often forgotten in the focused quest to measure and control blood pressure. Blood pressure is therefore not an independent entity. An elevated blood pressure must reflect either an elevated cardiac output or a heightened vascular resistance. When blood pressure falls it must reflect a change in either the output or the tone or structure of the vasculature.

Physiologic stresses such as exercise, anxiety and pain will produce a rise in blood pressure owing to either an increase in cardiac output or an inappropriate level of peripheral resistance. Such physiologic blood pressure elevations do
not necessarily reflect an abnormality of the vasculature and should not lead to a diagnosis of hypertension. Determining the difference between physiologic blood pressure elevation and a pathological process called "hypertension" is a challenge to primary care providers and is not adequately addressed in any guidelines.

In patients with established hypertension, the cardiac output is no higher than that in normotensive individuals. Therefore, an elevated pressure is related to a persistent change in tone or structure of the small arteries that control vascular resistance [2]. Transient changes in tone occur continuously in normal individuals and account, in part, for the physiologic fluctuations in blood pressure. Structural changes, including wall thickening and decreases in luminal cross-sectional area, are hallmarks of the hypertensive state. These structural changes of hypertension may exist in individuals with modest rises in blood pressure, well below the threshold that we identify as hypertension. The temporal relationship between small artery changes and blood pressure elevations is controversial, since some insist that the vascular changes precede the pressure elevation and others claim that the blood vessel changes are a result of the blood pressure elevation [3]. However, a sustained rise in blood pressure cannot occur unless the vascular resistance is inappropriately elevated.

Effect of blood pressure on arteries

Functional and structural changes also occur in the small and large arteries in response to an elevation in pressure. Constriction of the small arteries is attributed to an autoregulatory process [4]. The physiological rationale for this process is an effort by the body's regulatory apparatus to prevent an increase in blood flow to regional vascular beds as a consequence of the rise in perfusion pressure. A heightened vascular resistance accompanies the increase in tone of the small arteries and arterioles.

Structural changes involve vascular smooth muscle changes and changes in the interstitium. Vascular smooth muscle may undergo hypertrophy or hyperplasia, while collagen growth and elastin fragmentation may characterize changes in the media and adventitia. Some of these functional and structural changes may be induced by a decrease in nitric oxide bioavailability resulting from endothelial dysfunction [5], others may be a direct consequence of the rise in blood pressure itself (Figure 1).

These changes in the function and structure of the vasculature can be identified and monitored. Small artery elasticity or stiffness can be derived noninvasively from pulse contour analysis [6], and small arteries can be examined histologically by buttock biopsy [7]. Large conduit artery structural changes can be identified by ultrasound examination of the carotid arteries [8], and the resultant increase in large artery stiffness can be quantitated by pulse contour analysis [6] or by measurement of central pulse wave velocity [9]. Augmentation of a second systolic peak in the waveform recorded from a brachial or radial artery provides insight into the combination of small and large artery stiffening [10]. All of the noninvasive tests listed are suitable for use in clinical screening.

Blood pressure & morbid events

Epidemiologic studies have demonstrated a linear relationship in populations between the level of blood pressure and the frequency of cardiovascular morbid events [11]. This population data is usually interpreted as evidence that blood pressure defines the disease (hypertension), and that the higher the level of blood pressure the more severe the disease. This concept has then been adopted by clinical practitioners who are encouraged to define and treat hypertension in individuals with blood pressures above a somewhat arbitrary threshold.

An alternate explanation of the population relationship between blood pressure and morbid events is equally plausible: blood pressure levels in a population define the frequency of abnormal vascular function and structure, but not the presence or absence of hypertension. For example, a blood pressure of 120/80 mmHg is usually defined as normal, but some individuals with that blood pressure experience cardiovascular morbid events. By contrast, a blood pressure of 140/90 mmHg is defined as hypertensive, but some of these individuals never experience morbid events. However, the frequency of morbid events is higher with higher pressure. A simple explanation is that pressure levels define the frequency of the vascular disease in a population. A larger percentage of individuals in the 140/90 mmHg group will have early vascular disease than individuals with pressures of 120/80 mmHg. However, to use the blood pressure alone to define the disease will result in unnecessary treatment for some individuals in the 140/90 mmHg group and undertreatment of some individuals in the 120/80 mmHg group.

Drug therapy, blood pressure & arteries

The focus on blood pressure to evaluate the response to antihypertensive therapy is based on the apparent simplicity of its measurement and the evidence from trials that a reduction of blood pressure is predictive of a favorable effect on morbid events [12]. Since lower pressure in a population is associated with fewer morbid events, studies have been carried out in an effort to document that a lower therapeutic target pressure is associated with improved outcomes. These studies have not been consistently positive, with some showing evidence that targeting a lower blood pressure yields better results [13] and some failing to demonstrate a difference [14,15]. Since we know that having a lower blood pressure is predictive of fewer morbid events, why does the therapeutic response of blood pressure not mirror the epidemiologic data?

If blood pressure was the disease and morbid events were a direct consequence of the blood pressure elevation, then any safe intervention to lower blood pressure should produce an incremental benefit on outcome. But if the blood vessel is the site of disease, and blood pressure elevation in part a consequence of that disease, then the benefit of the blood pressure reduction will be dependent on the reversal of that vascular abnormality. Thus, the abnormal vascular function and structural characteristics of hypertension will raise blood pressure, but pharmacologic reduction of blood pressure will not necessarily restore the abnormal vasculature to normal. The fact that blood pressure itself is a
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An improved diagnostic & therapeutic strategy

The convenience of blood pressure measurements makes healthcare workers reluctant to abandon them as a guide to the diagnosis and treatment of hypertension. Guidelines have recognized the need for modification in the traditional approach by introducing the concept that blood pressures below the traditional threshold for hypertension may identify an abnormal state [1]. However, by labeling this condition 'prehypertension' they cling to the notion that blood pressure levels define the disease and those with lower pressures do not yet have it. In reality, these prehypertensive patients experience the majority of cardiovascular morbid events in any population, even before their blood pressure rises to levels defined as hypertension.

Are there diagnostic and monitoring techniques that could improve on the specificity and sensitivity of blood pressure in defining the vascular abnormalities that lead to morbid events? Endothelial dysfunction, which produces modest blood pressure rises within the normal range [18], may be the first stage of the vascular abnormalities that lead to atherothrombotic morbid events. Invasive and noninvasive techniques are available to assess endothelial dysfunction, but most are not suitable for efficient clinical screening. Measurement of small artery elasticity using a radial artery pulse wave is a simple screening method that has been demonstrated to identify endothelial dysfunction and to respond to therapy designed to reverse it [18,19]. By supplementing blood pressure measurement with small artery elasticity measurement, it is possible to identify prehypertensive individuals likely to progress to hypertension and to identify individuals likely to experience morbid cardiovascular events [20]. The usefulness of this measurement to identify a favorable long-term therapeutic response must be documented by prospective trials.

Other noninvasive tests to document the presence of early cardiovascular disease in asymptomatic individuals are now readily available. Ultrasound assessment of carotid artery intima—medial thickness [21], imaging of calcium in the coronary vasculature [22], detection of microalbuminuria [23], optic fundus photography, left ventricular ultrasound and biomarker assessment are all available. Use of these tests, especially in combination [24], shows promise in providing a more sensitive and specific means of identifying the early disease in need of treatment. Targeting the early disease rather than the blood pressure for treatment decisions should improve outcomes by treating those with abnormalities in function or structure, regardless of blood pressure, and withholding treatment in those with a normal vasculature. Follow-up testing to document the continued health of the cardiovascular system would be a necessary component of this strategy. Clinical trials to document the efficacy of this approach and its cost—effectiveness are urgently needed. Furthermore, the use of these tests to monitor therapeutic response has the potential to greatly streamline trials that now depend on morbid events for documentation of efficacy.

Contemporary insight into the mechanisms of cardiovascular morbid events and the poor correlation between these events and blood pressure mandate a revision of our traditional approach to the diagnosis and treatment of hypertension. Blood pressure can no longer serve as the sole diagnostic criterion nor the sole target for therapy. It is time to begin the process of modernizing our clinical approach to hypertension.

Expert commentary

The present convention of using casual blood pressure readings as the sole criterion for the diagnosis of hypertension and as the sole goal for antihypertensive therapy assumes that the blood pressure and not the blood vessel is the site of the disease. By contrast, abundant evidence now emphasizes the discrepancy between the measured blood pressure and the vascular and cardiac disease that leads to morbid events. Focusing on the blood pressure alone leads to undertreatment of many patients with advancing atherosclerosis and overtreatment of some without structural disease abnormalities. A new approach to individualized diagnosis and management of hypertension is needed through the focusing on markers of vascular and cardiac functional and structural abnormalities that lead directly to morbid events.

Five-year view

Growing recognition of the importance of early intervention, often before blood pressure reaches hypertensive levels, will emphasize that thresholds of blood pressure cannot serve as the sole criterion for therapy. Abnormalities of the vasculature in prehypertension will lead to pharmacotherapy that can no longer be linked to absolute blood pressure levels. This shift in emphasis will demand that clinically useful techniques for evaluating the health of the vasculature and heart become part of routine medical evaluation and management.
Financial & competing interests disclosure
Jay N Cohn is an inventor of the CVProfiler®, a device manufactured by Hypertension Diagnostics, Inc. and in worldwide use for assessing arterial elasticity. He also has an equity position in Cardiovascular Centers, an entity dedicated to developing screening centers for detecting early cardiovascular disease. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Key issues

- Blood pressure elevation is a manifestation of functional and structural alterations in the small and large arteries.
- These abnormalities may be present and progressive when blood pressures are below the traditional threshold for the diagnosis of hypertension.
- Not all pharmacologic agents that lower blood pressure produce the same changes in the function and structure of the arterial wall or the same benefit on morbidity events.
- The health of the vasculature and heart should be the focus of the diagnosis of hypertension and of its response to therapy.
- This change of emphasis is necessary for individualized care that can more effectively reduce mortality than the present strategy of targeting blood pressure alone.

References

Papers of special note have been highlighted as:

* of interest


3 Cohn JN. Is it the blood pressure or the blood vessel? J. Amer. Soc. Hypertens. 1(1), 5–16 (2007).


* A very large database demonstrating a continuous relationship between blood pressure and morbidity events.


* Trial evidence that all blood-pressure-lowering regimens do not protect the arteries equally.


* Further evidence for the differential benefit of blood pressure lowering regiments.


* Documentation that stiffening of small arteries is a sensitive marker for endothelial dysfunction.

19 Cohn JN, Wilson DJ, Neutel J et al. Co-administered amldopine and atorvastatin produces early improvements


