Ventricular Arterial Stiffening
Integrating the Pathophysiology

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Abstract—Vascular stiffening of the large arteries is a common feature of aging and is exacerbated by many common disorders such as hypertension, diabetes, and renal disease. This change influences the phasic mechanical stresses imposed on the blood vessels that in turn is important to regulating smooth muscle tone, endothelial function, and vascular health. In addition, the heart typically adapts to confront higher and later systolic loads by both hypertrophy and ventricular systolic stiffening. This creates altered coupling between heart and vessel that importantly affects cardiovascular reserve function. In this overview, I discuss the notion of a coupling disease in which stiffness of both heart and arteries interact to limit performance and generate clinical symptoms. This involves changes in the mechanical interaction of both systems, changes in signaling within the arteries themselves, and alterations in coronary flow regulation. Lastly, I briefly review recent development in de-stiffening strategies that may pave the way to treat this syndrome and its clinical manifestations. (Hypertension. 2005;46:185-193.)

Key Words: arteries ■ compliance ■ ventricular function

Widening of the arterial pulse is common in the elderly and is generally a reflection of arterial stiffening. It is a dominant circulatory hemodynamic risk factor for cardiac disease and stroke.1-3 Pulsatility of blood flow and pressure is also an intrinsic feature of the circulation. For example, during aerobic exercise, the arterial pulse can increase >100% in peripheral arteries and by ≈50% in central arteries (Figure 1A).4 Short-term widening of the pulse pressure under these circumstances might be considered physiological and not a source for vascular or ventricular disease. One might even anticipate increased pulsatile mechanical stimulation of the arteries to enhance endothelial regulation of vascular tone to improve blood flow where needed. As discussed later in this review, there is a growing body of data supporting such signaling and its role in enhancing organ perfusion. However, this may require normal vascular distensibility and thus may be compromised in stiff arteries. In contrast, chronic increases in pulse pressure (Figure 1A) caused by age-related arterial damage and/or diseases that stimulate vascular stiffening (eg, diabetes, renal disease) worsen cardiovascular risk.

When considering the pathophysiologic implications of vascular stiffening, it is important not to overlook the role played by the heart to which the blood vessels are coupled. Evidence shows that ventricular systolic and diastolic stiffness also increase with age, which increase in tandem with large-artery stiffening.5,6 This is likely linked to the interaction of heart and vascular load, and also by intrinsic changes in the heart itself, and common comorbidities such as diabetes, hypertension, renal disease, and neurohumoral stress that impact both systems. Importantly, such combined stiffening alters how the heart–arterial system interacts at rest, but particularly under stress by exertional demands, salt loading, and abrupt changes in heart function. In this broad sense, combined ventricular–arterial stiffening potently impacts on cardiovascular reserve, blood pressure lability and diastolic dysfunction, coronary and peripheral flow regulation, endothelial function, and mechanical signaling, and undoubted other factors. It is in this broader context that I propose the concept of stiff heart artery coupling disease. These changes occur to some extent with aging5 and may be particularly prominent in patients with cardiac hypertrophy in whom heart failure symptoms develop despite having a preserved ejection fraction.6 In this review, I discuss the pathophysiology of coupling disease and suggest some novel approaches to treating it.

Ventricular–Arterial Stiffening
Age-dependent increases in vascular stiffening are well established with evidence from multiple large cross-sectional studies involving various ethnicities.7,8 Mechanisms underlying this stiffening, methodologies to assess it, and new approaches to treat it have all been subjects of recent reviews9-11 and are not discussed here. What has been only more recently revealed is that age-related vascular stiffening is also accompanied by changes in the left ventricle (LV) that increase end-systolic chamber stiffness.5 This does not require renal disease and/or cardiac hypertrophy to be present.5

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although both play important roles in vascular and ventricular stiffening. Importantly, this combination of ventricular–arterial stiffening alters the way in which the cardiovascular system can respond to stress demands and changes in volume and pressure loading. Furthermore, it appears common in patients with heart failure and preserved ejection fraction and may importantly contribute to the clinical features of this disorder.

Figure 1B shows example pressure–volume (PV) relations measured invasively in a young and elderly individual, with neither having any demonstrable clinical heart disease at the time of study. Each set of loops was obtained by transient obstruction of venous return, with the baseline condition reflected by the most rightward loop of the set. The two relations depicted are the end-systolic PV relation and slope (Ees) and the ratio of end-systolic pressure to stroke volume—or effective arterial elastance (Ea). These are often equal in absolute magnitude, a combination yielding optimal and efficient matching of heart and artery. However, the elderly patient displays marked increases in both elastances, with Ea reflecting vascular stiffening and Ees LV systolic stiffening. The change in loop shape (trapezoidal) in the elderly subject reflects stiff arteries with a wider pulse pressure. The diastolic PV relation (lower boundary of the loops) is also somewhat steeper. As reported by Chen et al, Ea, Ees, and diastolic stiffness increase with age and correlate with one another. Figure 1C shows such an inverse relation between Ees and total arterial compliance, with the latter a component of Ea (Ea increases as compliance declines). Patients with low arterial compliance display increased Ees.

Higher ventricular and arterial stiffness has important implications to blood pressure lability and loading sensitivity. This is shown by example in Figure 1D, with the data derived from the same set of PV loops shown in Figure 1B. Decreasing preload results in only a modest decline in systolic blood pressure in the younger individual but a much greater change in the older subject. As previously reported, the slope of such relations is determined by both arterial and ventricular stiffness and increases with age.

Another implication of combined ventricular–arterial stiffening is that exertional capacity can be limited and this may play a role in patients with heart failure and normal-range ejection fraction. An example from the recent study of Kawaguchi et al is shown in Figure 2A. This patient has increased Ees and Ea at baseline, and on performance of sustained hand-grip exercise (solid loop) displayed a marked hypertensive response and elevated diastolic pressures. The steep basal Ees means that contractile reserve, normally reflected by further increases in Ees, is limited, whereas pressure-loading changes are amplified. Evidence that such pathophysiology likely contributes to exertional intolerance was reported by Hundley et al (Figure 2B). There is a direct relation between arterial distensibility (ie, compliance) and peak oxygen consumption during exercise testing. Patients with cardiac failure symptoms and preserved ejection fraction (EF) are shown by the white triangles and have the stiffest arteries. This study did not determine whether these patients also had increased Ees, although a more recent study found such elevations that exceeded that predicted from age alone in
such patients. Gender differences in ventricular arterial stiffening may also impact exercise performance.

Cardiac relaxation is delayed when hearts are exposed to elevated systolic pressure during ejection (ie, increased afterload), as occurs with vascular stiffening or enhanced systemic resistance. As noted in Figures 1 and 2A, ventricular–vascular stiffening exacerbates the load–pressure interaction, worsening the potential impact on diastole. A correlation between greater prolongation of diastolic relaxation and ventricular vascular (VV) stiffening was found in a recent study. Underlying mechanisms for load-dependence of relaxation have been previously unclear, although recent murine studies in which protein kinase A–phosphorylation sites on troponin I were constitutively active has yielded new insights. As shown in Figure 2C, normal mice show marked relaxation delay when cardiac afterload is increased by partial aortic constriction, whereas the mutant animals display little effect, highlighting a key role of TnI-PKA phosphorylation state as a coupler between load and relaxation.

Impact of Blood Flow Pulsatility

A major hemodynamic consequence of arterial stiffening is widening of the arterial pulse, which also increases cyclic changes of arterial flow. In studies performed over the past decade, we and other investigators have found that such pulsatility itself triggers vasodilator responses and contributes to flow reserve. In vitro studies suggest this may be blunted by loss of wall distension (ie, vascular stiffening), although this has not yet been tested in vivo.

The initial observation that enhancing flow pulsatility itself triggers vasodilation in vivo came in an experiment testing effects of systemic vascular stiffening on cardiac function and mechanoenergetics. In canine hearts ejecting into a stiff conduit substituting for the thoracic aorta, total compliance was reduced and central arterial pulse pressure increased 2- to 3-fold. At matched cardiac oxygen consumption, hearts ejecting into this stiff load displayed \( \approx 15\% \) increase in mean coronary blood flow. Subsequent studies using a servo-controlled perfusion pump to selectively vary pulse pressure...
in a given vascular bed confirmed this and clarified the biochemical mechanisms. Figure 3A shows the effect of altering pulse pressure in a coronary artery and consequent changes in phasic flow. Diastolic flow increased slightly with the higher pulse pressure despite a decline in mean pressure during this period, and there was a greater increase in flow during the systolic period. Net flow increased by 15%, confirmed by both coronary sinus and microsphere flow, and is not associated with changes in regional function or metabolic demand.

A 15% change in coronary flow from higher perfusion pulsatility, although significant, was not large, raising doubts that such a mechanism would play an important physiological role. However, the situation changed markedly when distal vascular tone is modestly lowered by adenosine involving activation of ATP-sensitive potassium channels (Figure 1B). Under such conditions, the same augmentation of pulse pressure results in a marked increase in mean flow, with a peak response nearly doubling flow over that at the normal (40 mm Hg) pulse pressure. This was specific to vasodilators that were active in the distal microvessels (ie, <150 μm) by mechanisms involving activation of K<sub>ATP</sub> channels (adenosine, pinacidil). Alternative dilators operating on more proximal vessels (calcium channel blockers, acetylcholine, bradykinin) did not replicate this synergistic interaction with perfusion pulsatility.

Endothelial-dependent vasodilation caused by elevated perfusion pulsatility has been confirmed in vascular beds other than the coronary arteries. For example, Nakano et al reported that augmenting pulse perfusion in skeletal muscle triggers primary nitric oxide (NO)-dependent vasodilation. More recently, studies using external muscle compression to enhance central coronary blood flow revealed enhanced endothelial-dependent flow dilation in upper arm vascular beds exposed to the resulting higher perfusion pulsatility.

Steady shear stress induces vasodilation largely by activating NO synthase (NO release) and by stimulating factors that induce hyperpolarization. Although the precise mediators for the latter remain unclear and likely vary with the vascular tissue and site, they commonly stimulate calcium-dependent potassium channels (K<sub>Ca</sub>) and can be inhibited by K<sub>Ca</sub>-blocking toxins. Both NO and K<sub>Ca</sub> signaling are involved with pulse perfusion-mediated dilation as shown by Paolocci et al (Figure 3C). Inhibiting either pathway alone reduced the pulse perfusion response by half, whereas when combined this response was virtually eliminated.
Although normally compliant arteries can dilate in response to pulse perfusion, in the coronary circulation, this is also coupled to changes in the phasic pattern of flow, as noted in Figure 3A, and this has potentially detrimental consequences on cardiac reserve. Normal coronary perfusion is principally diastolic, and reducing systolic pressure has less impact on mean flow. However, this may not hold in hearts ejecting into a stiff arterial system with consequent increases in flow during systole. This shift can render the heart more sensitive to a decline in systolic pressure as occurs with loading changes or acute dysfunction (eg, myocardial infarction). An example is shown in Figure 3D. On the right are data from an in vivo heart ejecting into a stiff arterial system resulting in high arterial pulsatility. Acute coronary occlusion led to a rapid decline in LV pressure and marked chamber dilation (LV volume), ultimately triggering cardiac demise. After full resuscitation, the experiment was repeated but with the same heart now ejecting into the compliant vascular system. The magnitude of cardiac dysfunction was markedly attenuated (data from Kass et al²⁴). Thus, high perfusion pulsatility can benefit vascular tone yet have detrimental effects on myocardial flow regulation. As discussed in the next section, the benefits may diminish in vessels that are not compliant, so that the net balance tips further toward pathophysiology in such settings.

**Role of Wall Distensibility**

Another feature of ventricular–arterial stiffening is that it changes the mechanical forces to which endothelial cells and arterial smooth muscle cells are exposed. Because these mechanical forces play key roles in regulating wall tone, atherogenesis, angiogenesis, and other features of vascular homeostasis, understanding their impact is important. Using perfusion systems that expose cultured endothelial cells to controlled levels of phasic flow with or without distension, studies have revealed effects of pulsatility on NO synthase gene expression,²⁵–²⁷ endothelin, and other signaling cascades²⁸ that tend to favor a vasorelaxant response.
Arterial and Ventricular Destiffening Strategies

- Reduce smooth muscle tone
- Nitrates, ACE inhibitors, ARBs, calcium channel blockers
- Enhance endothelial function/relaxation
- Exercise
- Antioxidants
- Tetrahydrobiopterin
- Statins
- Rho kinase inhibitors
- Alter structural properties
- Reduce fibrosis (ARBs, aldosterone blockers, TGF-β1 inhibitors)
- Limit or reverse hypertrophy
- Advanced glycation end-product cleavage
- Enhance elasticity (elastin, fibrillin, etc)

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; TGF, transforming growth factor.

Recent studies used more physiological waveforms (Figure 4A) and assessed post-translational changes in signaling proteins. Endothelial cells cultured on the inner surface of distensible tubes were exposed to pulse perfusion with the degree of wall distensibility varied. These studies found important differences in signaling related to distensibility (Figure 4B and 4C). The enzyme Akt is stimulated in response to mechanical shear stress and cyclic stretch, and by receptor-coupled growth factors (eg, IGF-1). Activated Akt phosphorylates NO synthase to enhance NO release and stimulates proteins controlling vasomucosal, endothelial cytoprotection, and apoptosis. When cyclic stretch and shear were combined in normally compliant tubes, Akt was activated much more than with steady shear alone (Figure 3B). This was lacking if wall compliance was reduced, however. Downstream targets of Akt such as NO synthase also displayed this differential activation. (Figure 3C). This is further supported by data showing enhanced NO release from endothelial cells grown in distensible tubes exposed to pulsatile flow from external compression.

Destiffening Strategies

Past and evolving strategies to counter vascular stiffening have been recently reviewed and are summarized in the Table. To date, the major emphasis has been on inhibitor smooth muscle tone, working through the NO/cGMP pathway, or by blocking neurohormones such as angiotensin-converting enzyme and angiotensin II. Calcium channel blockers have also been used. For example, verapamil has been shown to acutely lower ventricular systolic stiffness and arterial stiffness and, in association with these changes, improve aerobic exercise capacity in aged volunteers. This exercise benefit was not reproduced when smooth muscle tone only was reduced using an intravenous nitrate. Ongoing studies using angiotensin II receptor-blocking agents in patients with heart failure and normal-range EF may help clarify the role of such drugs for this disorder. Previous data from the substudy CHARM (Preserved) trial found only slight clinical benefits but the study population was not really representative.

Exercise remains an important factor and has been shown to reduce vascular stiffening with aging. Whether it can also lower ventricular systolic stiffening remains unknown. There is increasing interest in the use of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins). Studies have shown that statins augment Akt activity in vessels, improve blood flow by increasing NO synthase activation, and may reduce vascular stiffening. Statins also inhibit small GTP-binding proteins Rac1 and RhoA and thereby may impede development of cardiac hypertrophy. Other strategies may involve enhancing NO synthase signaling by increasing substrate availability (arginase inhibition) or its cofactor tetrahydrobiopterin (BH4).

Another tactic gaining interest is to reduce fibrosis and/or modify structural proteins thought linked to stiffness. Drugs that inhibit angiotensin II and particularly aldosterone are intriguing in this regard. Both may have the added advantages to targeting both vascular and ventricular changes. Efforts to enhance elastin by blocking neutrophil elastase have yielded very exciting results in both the heart and vasculature. However, translation to human trials has remained limited by the toxicity of these drugs, and this avenue remains one under investigation.

A different strategy that may also target both heart and arteries relates to the cleavage of advanced glycation end-products (AGEs). AGEs are highly stable glucose—protein links that accumulate with normal aging but are enhanced in settings of glucose excess (diabetes) and/or molecular stress such as from oxidation. These cross links form in collagen and other long-lived structural molecules resulting in reduced turnover by metalloproteinases and likely increased tissue stiffness. Proof for the involvement of AGEs in structural stiffness remains fairly indirect but has been fueled by animal and a recent clinical trial found that a breaker of AGE (ALT-711) improves vascular distensibility and perhaps ventricular diastolic distensibility (Figure 5A).

Last, we recently reported that enhancement of protein kinase G activation by inhibiting PDE5a may provide a novel approach to ventricular–arterial stiffening. PDE5a is the enzymatic target of sildenafil, which is widely used to treat erectile dysfunction. In the vasculature, PDE5a inhibition increases cGMP to activate protein kinase G-I, leading to reduced vascular tone. PDE5a inhibitors also appear to lower vascular stiffness, although the extent to which this is independent of mean pressure remains somewhat unclear. cGMP plays an important role as a negative modulator of vascular proliferation and fibrosis. Similarly, increasing cGMP/PKG activation in the heart reduces fibrosis and can be anti-hypertrophic. In mice, PDE5a inhibition markedly inhibits the development of cardiac hypertrophy and fibrosis while improving ventricular function despite sustained ventricular afterload increase (Figure 5B). Furthermore, this treatment reversed hypertrophy and fibrosis once established (Figure 5C). It remains to be determined whether this strategy will prove efficacious for treating humans with ventricular–vascular stiffening (coupling disease).

Perspectives

This brief review is meant to place recent studies regarding pulsatile perfusion, arterial, and ventricular stiffening in
Although many previous reviews have focused on stiffening of the arteries themselves, and much of this special issue highlights this pathophysiology, such changes have major ramifications on the heart and the manner in which it interacts with the rest of the body. Cardiac maladaptations such as hypertrophy and increased ventricular end-systolic elastance make the net effects of vascular stiffening even worse, particularly from the standpoint of net cardiovascular reserve, blood pressure regulation, and blood volume distribution. It is in the context of the coupling between these altered systems that one best understands the physiological manifestations observed in many affected patients. New de-stiffening strategies are needed, and some are presently undergoing development and entering clinical trials. Greater appreciation of the impact of coupling disease in the elderly should help us apply even the known therapies with better focus and hopefully improve our approach to this disorder.

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