Role of Increased Aortic Stiffness in the Pathogenesis of Heart Failure

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Aortic stiffness is an independent predictor of cardiovascular mortality in a variety of patient groups including hypertensives and other unselected patients. Despite a sound pathophysiologic basis, termed the ventricular-vascular coupling mechanism, the relationship between aortic stiffness and heart failure has been less well studied. This review summarizes some important trials of aortic stiffness in cardiovascular disease risk prediction and progression to heart failure. Emerging targets for therapeutics and areas requiring more research are also discussed.

Introduction

Large artery stiffness is an emerging novel predictor of cardiovascular mortality. Aortic stiffness, as measured non-invasively by aortic pulse wave velocity (aPWV), has been shown to predict outcome independently of well known risk factors in an ever-increasing number of studies across patient groups [1••].

Despite having hypertension, hypercholesterolemia, smoking, and diabetes as major risk factors for cardiovascular deaths (CVD), the calculation of an individual's lifetime risk for CVD is difficult and has meant the introduction of 10-year risk prediction charts [2]. This is not necessarily accurate, and better ways of improving risk stratification are required especially in those with moderate risk. There is a continuum of risk in the population—the bulk of CVD burden remains in those with borderline blood pressures, cholesterol, etc. Although 10-year charts may help distinguish those with low and high risk, they fail to quantify those with a moderate level of risk. Novel methods of assessing this, including arterial stiffness, may help define individual risk especially in this moderate group. The concept of arterial stiffness (incorporating aortic measures) allows quantification of risk in any individual person, who may or may not have developed target organ damage and yet has moderately sufficient individual risk factors of developing CVD in the future [1••].

The concept of arterial stiffness is an important development. With increasing amounts of interventions and treatments available, there is a rising burden of heart failure in an ever-aging population, which adds to the excess of cardiovascular mortality and morbidity [3,4]. The early identification of such populations is vital in efforts to reduce global burdens of cardiovascular mortality. This in turn will have huge beneficial implications on costs in terms of health care, social welfare, and the economic productivity of the nation.

The continuum from aortic stiffness to heart failure per se is not something that has been subject to robust interventional (pharmacologic or otherwise) clinical trials so far—we sought to review the available evidence and describe some of the historic, mechanical, and pathophysiologic explanations behind what we feel may be an important area for further study and debate.

Arterial Stiffness, Aortic Stiffness, and Pulse Wave Velocity

The concept of arterial stiffness, in fact, is not a new one. The importance of the pulse and hardening of the arteries was recognized from the time of Galen. The golden era of the pulse and the pulse wave, however, came much later in the late nineteenth century with the development of the sphygmocardiograph. This unique instrument was able to demonstrate changes in the pulse character, particularly how it varied in different clinical conditions in which the pulse wave was described as being abnormal [5]. However, the advent of the more objective numerical measures of the sphygmomanometer by Riva-Rocci at the turn of the century resulted in the eventual demise of sphymocardiography.

Arterial stiffness is an overarching term for the various methods that measure the distensibility, compliance, and elasticity of the vessel wall. It quantifies arterial rigidity in response to pulsatile blood flow. It can be measured locally, regionally, or systemically using a myriad of techniques including pressure waveforms, volume waveforms, applanation tonometry, mechanotransducers, ultrasound, or MRI.

A simple measure of arterial stiffness is the peripheral pulse pressure (systolic minus diastolic blood pressure) measured at the brachial artery. Peripheral pulse pressure depends on two key factors: stroke volume and the stiffness of large arteries. This peripheral pulse pressure is, however, of limited value due to the phenomenon of pulse amplification. Amplification results in pulse pressure increasing from central arteries to peripheral ones. This is more pronounced in young people with elastic conduits and little wave reflection. With age, the difference between brachial and aortic pulse pressure becomes closer. Therefore, brachial pulse pressure is a poor surrogate of central pulse pressure which is more closely related to aortic stiffness.

Pulse wave analysis describes a measurement and analysis of the contour of the arterial pressure (and volume) waveform. It allows the quantification of the central pulse pressure and the amount of wave reflection in the arterial system by calculation of the augmentation index (AIx).

Wave reflection is a phenomenon, which occurs when the pulse wave that is created by the left ventricular ejection of blood hits various sites in the arterial tree and then reflects backwards towards the heart. The speed at which this wave returns is, in turn, dependent on arterial stiffness and on the stiffness of the small arteries and resistance vessels. Pulse wave velocity (PWV) is the accepted gold standard method of measuring arterial stiffness [1••]. Carotid-femoral PWV is a direct measurement of aortic stiffness (ie, aPWV) measured along the aorta and is perhaps the most important measure of arterial stiffness because it supplies all the major organs. It is also the vessel that contributes the largest buffering capacity to pulsatile blood flow due to its high content of collagen and elastin and smaller amounts of smooth muscle compared with peripheral muscular arteries and arterioles (resistance vessels).

It is perhaps important to emphasize that other "measures of arterial stiffness"—such as AIx, central systolic blood pressure, central pulse pressure and so on—are not to be equated to aPWV (which is, in effect arterial stiffness) as they are all affected differently by amplification, ventricular-vascular coupling, and wave reflection. Additionally, heart rate, age, and a variety of clinical states affect these parameters to a different degree such that these are not interchangeable with aPWV.

Causes of Increased Aortic Stiffness and PWV

The underlying mechanisms by which PWV increases are determined partly by underlying risk factors and also by the intrinsic stress/strain relationship (stiffness) of the vascular wall and mean arterial pressure. The stiffness of an artery depends on two factors. Firstly, the mean pressure is an important determinant, as although arteries are elastic, they are not ideally elastic (ie, as mean pressure increases, the artery becomes more difficult to distend). Secondly, the stiffness of a vessel depends on the elastin and collagen content as well as the state of the smooth muscle tone, which, in turn, is dependent on sympathetic innervations, circulating factors (eg, noradrenaline, angiotensin) and local factors (eg, nitric oxide and endothelin-1).

Lakatta and Levy [6] elegantly described how vascular aging interacts with vascular disease, such that in some people, PWV may increase as a result of structural alterations, collagen deposition, reduced elastin content and fractures, and calcification. This may occur independently of the atherosclerotic process itself [7] or with it and in conjunction with altered vascular smooth muscle tone as a result of endothelial dysregulation and dysfunction. This may be through reduced nitric oxide production, increased oxidative stress, or another inflammatory process. Aging itself is not the only issue; perhaps pathophysiologic aging is to blame. Avolio et al. [8] described differences in arterial stiffness in two populations in China wherein age-related arterial stiffness in rural populations was not as high as their counterparts in urban areas after adjusting for age and mean pressure. This suggests that the differences in stiffness were due to other causes beyond hypertension and atherosclerosis (low prevalence in Asian populations). This has been corroborated in other indigenous populations.

The issue of aging must introduce a further dimension into this process that perhaps makes everything else more apparent temporally than is otherwise appreciated.

Aortic PWV and Hemodynamic Consequences

Several long-term trials have now shown the clear value of aPWV as an independent predictor of cardiovascular events, mortality, and all-cause mortality [9–19]. Although arterial stiffness may be regarded as a marker of disease, it may, in fact, be a cause as well.

Reflected pressure waves return to the aorta earlier as the arteries become stiffer (ie, increased aPWV). This results in amplification of the central pulse pressure by the returning wave. In individuals with elastic vessels, the returning wave reaches the ascending aorta in diastole and helps to "boost" diastolic pressure (ie, when coronary blood flow occurs). However, as the aorta stiffens, the velocity of the pulse wave increases, such that this reflected pressure wave reaches the heart at systole thereby augmenting central systolic pressure and increasing cardiac afterload [16]. At the same time, diastolic pressure falls [20], worsening coronary artery perfusion, with a net result of widening the central pulse pressure. This leads to increased aortic and left ventricular end systolic pressure with increased myocardial oxygen demand. Additionally, decreased perfusion in diastole contributes to reduced coronary perfusion. Left ventricular hypertrophy associated with the raised systolic blood pressure adds to increase subendocardial ischaemia, all of which may result in impaired relaxation of the myocardium—an entity now defined as diastolic heart failure (DHF) [21].

An interesting observation is that the most common form of hypertension (up to 50% in patients age 60 years and older) in the elderly is isolated systolic hypertension where the predominant cause of this phenotype is central artery stiffening with a wide central pulse pressure. It is precisely this group in whom DHF appears to be a burden, especially among hypertensive elderly women. Three mechanisms by which increased aortic stiffness and increased central pulse pressure may result in cardiovascular disease are as follows: first, alteration of the shear-stress relationship centrally; second, increased pulsatility in small vessels which is especially damaging in the small arteries of the brain and kidney; and third, increased cyclical stress in the vessel wall causing it to become even stiffer and thereby setting up a vicious cycle of events.

Central pressure is important as this is the pressure that the brain, heart, and kidney "see." In the REASON study [22], patients were randomized to perindopril/indapamide versus atenolol. Despite inducing similar changes in mean blood pressure, the former group had a greater fall in left ventricular mass compared with the latter, and this was more strongly associated with a change to the central systolic blood pressure and central pulse pressure than changes in peripheral pressure.

Aortic stiffness influences central systolic and diastolic pressures. Recently, two outcome studies have looked at the role of central pressures in cardiovascular outcomes. The CAFE study [23••] was a substudy of the ASCOT trial of 2199 high-risk hypertensive patients randomized to a modern (perindopril ± amlodipine) regime versus an older regime (atenolol ± thiazide) and followed-up for a 4-year period. Although the reduction in brachial pressures was comparable across the groups, there was a significant difference in the central aortic pressures despite the slightly higher brachial pulse pressures in the modern regime. This emphasized the importance of pulse pressure amplification and wave reflection in the group on β-blockers, suggesting that the differences in composite endpoints in ASCOT may be due to differential effects on central aortic pressures as a result of a prolonged systolic ejection time thereby enabling the wave reflection to augment the outgoing pressure wave. Of note, neither group had differences in arterial stiffness as measured by pulse wave velocity although the weakness in CAFE was that the sample size in which this was measured was small. What CAFE does emphasize, however, is the importance of central pressure measurements in determining outcomes and that this variable needs to be included in more long term studies as a biomarker and risk predictor of cardiovascular mortality and morbidity.

This was reinforced more recently by the Strong Heart Study [24] which was a longer study with more outcomes than CAFE. This observational trial showed that central pressures and arterial stiffness (aPWV) were more predictive than brachial pressures in predicting cardiovascular outcomes. Both these studies therefore emphasize the role of the stiffness of the proximal aorta in determining this cardiovascular outcome, as does concurrent therapy, systemic arterial stiffness, pulse amplification, and wave reflection.

Diastolic Versus Systolic Heart Failure

DHF (ie, symptomatic diastolic dysfunction) and diastolic dysfunction (asymptomatic) remains a conundrum in cardiology. Definitions vary from what is considered a normal ejection fraction to the characteristic criteria used to define diastolic function and whether the presence of signs and/or symptoms is required thus making the whole area of definition contentious [25]. Although age seems to be an important determinant of prevalence, morbidity and mortality (up to 8% for DHF vs 15% for systolic heart failure [SHF]), it is clear that there is a difference compared with age-matched controls whose mortality approaches 1%. Myocardial stress, strain, and strain-rate relationships may help explain myocardial stiffness, but these have yet to be correlated with measures of aortic stiffness in any clinical studies based on our reviews. Whether these are, in fact, part of the same pathophysiologic process is interesting.

During exercise, patients with DHF become symptomatic due to an inability to conform to the normal Frank-Starling response—presumably because of limited diastolic filling as a result of impaired relaxation and left ventricular stiffness. In addition, if subjected to vascular stiffness in the form of a high afterload due to aortic stiffness, this would undoubtedly be exacerbated. This seems more likely to occur in an older cohort who, as part of their aging process, would have degradation in elastin content and a higher amount of collagen deposition resulting in a stiffer aorta. This can occur in the absence of overt coronary disease, and it has been shown that exercise tolerance may be impaired in older people with DHF due to a lack of aortic distensibility [26].

Even if patients with DHF appear to have normal systolic function at rest, they may have systolic impairment of function during exercise. Is there a progression of this to SHF? Is this a continuum of the same disease? Certainly, it is clear that the coupling of systolic ventricular function and vascular function (in terms of distensibility, compliance, and stiffness) is an important one [27]. When this is impaired, such as in hypertension or other disease states, the uncoupling of the mechanism may represent the onset of clinical symptoms of heart failure.

What then, if any, is the link between DHF and systolic dysfunction? Patients with SHF may have diastolic dysfunction whereas the definition of DHF is on the premise of normal systolic function. Recently, it has been shown that these two entities may indeed be separate; van Heerebeek et al. [28] describe cardiomyocyte abnormalities in SHF versus DHF patients, having excluded patients with coronary artery disease and infiltrative cardiomyopathy. They reported a difference in the pattern of remodeling (eccentric

left ventricular hypertrophy in SHF vs concentric in DHF), a higher cardiomyocyte diameter and hypertension being more prevalent in the DHF cohort but with comparable collagen deposition in both groups. More interestingly, there was a shift in titin isoform expression (stiff titin being the predominant pattern in DHF). This is perhaps an interesting development to suggest that the two entities may, in fact, have different etiologic origins and that the ventricular-vascular coupling (or lack of it) predisposes to DHF as opposed to the more usual culprits in SHF.

Aortic Stiffness, Cardiovascular Disease, and Heart Failure

It has been known that the progression from subclinical disease to overt disease is more apparent in the elderly compared with younger populations. The general reduction in cardiac reserve, in addition to the effects of age on aortic compliance and endothelial function, means that arterial stiffness and the uncoupling of the ventricular-vascular mechanisms result in increased coronary ischemia, left ventricular hypertrophy, and eventual heart failure [29].

It has recently been shown that aortic stiffness is related to the coronary atherosclerosis burden, although this is not an exclusive phenomenon. The Rotterdam study examined 1757 elderly patients by measuring aPWV and comparing it with the rates of coronary calcification using electron beam tomography as a measure of coronary atherosclerosis [30]. They found a strong association between aortic stiffness and coronary calcification after adjusting for cardiovascular risk factors.

Hundley et al. [26] performed a small study comparing healthy young people, healthy elderly people, and an elderly cohort with DHF who were relatively hypertensive. They measured aortic distensibility (another measure of aortic stiffness albeit not aPWV) using MRI and compared this to peak Vo_2. They showed that elderly patients with DHF had markedly reduced proximal aortic distensibilities compared with similar-aged counterparts and that there was a continuum of pathology across age groups (healthy old vs healthy young). Peak Vo_2 was closely related to aortic distensibility thus proving, to some extent, that ventricular-vascular coupling is required to maintain an adequate exercise performance and that there may indeed be a link between aortic stiffening, ventricular stiffening (and function), and exercise capability.

In another study comparing 70 hypertensive patients (with suspected DHF) with 15 normotensives as controls, Mottram et al. [31] measured the total arterial compliance using aortic flow (derived from echocardiography) and peripheral resistance (mean and diastolic pressures used via a transfer function to approximate mean aortic pressure) and compared this value with the detailed diastolic function measurements as quantified by tissue Doppler echocardiography. They showed that the lower the arterial compliance, the worse the degree of diastolic dysfunction. In fact, arterial compliance and blood pressure were the only independently associated variables with diastolic heart failure consistent with a mechanistic link between compliance and dysfunction.

The Health ABC study [16] measured aPWV in 2488 participants and found an association with coronary heart disease, stroke, and cardiovascular mortality. However, despite having the power to detect this, there was no association between aortic stiffness and heart failure. This may have been dependent on the type of vascular stiffness measure used. However, to determine whether aortic stiffness is a cause or effect, larger and prospective longitudinal data are required to assess this in more detail.

More specifically to arterial stiffness and patients with established heart failure, a substudy of CHARM compared 28 patients with SHF to 40 controls [32]. These patients underwent arterial tonometry and echocardiography to investigate the previously known association of increased mortality of heart failure patients with increased pulse pressure [33]. This study found that patients with established heart failure have an increased proximal aortic flow and pressure-area relationship (as measured by characteristic impedance), suggesting functional stiffness of the central conduits but relatively less stiffer muscular (peripheral conduits) measured by carotid-radial PWV. The investigators postulated that aPWV did not differ between the groups perhaps because it is a composite measure of the aortic, femoral, and iliac vessels. However, the sample size in this study was underpowered and this might explain the statistically insignificant, but nevertheless clinically relevant, 0.5 m/s difference in aPWV between the groups. The fact that PWV was not significant despite impedance reaching statistical significance might argue the case that there was a change in aortic diameter. Furthermore, the authors reported that AIx did not predict proximal aortic stiffness well due to the diminished relative amplitude of the reflected wave and the reduced overlap between forward and reflected waves. We would argue that measurement of AIx is unreliable and perhaps misguided in the failing heart due to the reduced aortic flow, wave reflection, and ejection duration. Nevertheless, the finding of central stiffness from this study does help to explain the relationship between pulse pressure and heart failure mortality rates and points to potential therapeutic targets to reduce central stiffness without affecting mean pressure.

Heart failure itself may be a manifestation of underlying coronary disease or hemodynamic dysregulation. Ultimately however, neurohormonal activation and endothelial dysfunction may result in additonal changes that promote further uncoupling of the ventricular-vascular interaction. Bonapace et al. [34] studied a cohort of patients with dilated cardiomyopathy and showed that aor-

tic stiffness correlated with increased extracellular matrix turnover (as measured by higher aminoterminal propeptide of type III procollagen). This provides a dynamic explanation for the observed stiffened proximal aorta in these patients which may in fact be the initiating factor in the etiology of their heart failure.

If arterial (and aortic) stiffness predicts high-risk patients who will go on to develop cardiovascular complications, should such individuals be targeted more aggressively to reduce the uncoupling of the ventricular-vascular interaction? This would, after all, be analogous to treating the patient with familial hypercholesterolemia with statin therapy as primary prevention.

Drug Interventions

If aortic and arterial stiffness can be reduced, can we reduce cardiovascular risk and therefore outcomes? Anti-hypertensive regimes have been shown to reduce arterial stiffness [34–39] perhaps mostly by interfering with the renin-angiotensin-aldosterone axis, but even drugs such as nitrates [40], statins [41,42], and thiazolidinediones [43] seem to reduce this through mechanisms which are not entirely clear. Most drug classes available so far affect stiffness by altering mean pressure, endothelial function or vessel tone.

The question that does require addressing is whether lowering aortic or arterial stiffness per se improves outcome. Much like the argument with low-density lipoprotein cholesterol and event rates from a whole gamut of cardiovascular trials over the last 20 years, a similar amount of work needs to be done to see if this biomarker can produce what we already know to be an independent predictor of mortality.

In chronic hyperglycemic states, as with the aging process itself, the formation of advanced glycosylation end products has been shown to enhance collagen deposition, inflammation, and tissue fibrosis leading to arterial and ventricular stiffening, atherosclerosis, and nephrosclerosis [44]. Very recently, an advanced glycosylation end product crosslink breaker, alagebrium (ALT711), was shown to reduce arterial stiffening and improve cardiac output and diastolic distensibility. In short-term studies, there was an improvement in left ventricular mass, diastolic filling, quality of life, and endothelial function; unfortunately, liver toxicity issues in rats have prevented this compound from being developed further.

More work has to be done to look at novel drugs that stop or reverse the increased stiffness of the vasculature, including nitric oxide donors, neurohormonal blockers, matrix metalloproteinase inhibitors, collagen turnover blockers, or anti-inflammatory drugs. The role of calcium containing drugs in accelerating vascular stiffness in certain patient groups also merits further work. The importance of measuring arterial stiffness in these preliminary trials as a biomarker of predicting outcome cannot be overemphasized.

Conclusions

A variety of mechanisms result in aortic stiffness, which is now accepted as an independent risk factor for predicting cardiovascular mortality and morbidity. The role of aortic stiffness in the pathogenesis of heart failure requires careful further elucidation. The studies so far have been small and cross-sectional with a large number of patients already on drug therapies that may confound central measurements of stiffness. This makes it difficult to disentangle whether aortic stiffness is due to drug therapy, is a bystander effect, or is causally related to heart failure. What is required are more longer term, larger-sized, prospective, longitudinal trials with bigger outcome data (to capture episodes of heart failure) employing methods of assessing central pressures, wave reflection and pulse wave velocity (and perhaps in established heart failure, more direct measures of aortic stiffness) to improve our understanding of what essentially drives heart failure apart from the well known risk factors. This will allow the development of new therapeutic targets to prevent, ameliorate, and treat this important burden of disease which is ever increasing in our aging population.

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Clinical Trial Acronyms

ASCOT—Anglo-Scandinavian Cardiac Outcomes Trial; CAFE—Conduit Artery Function Evaluation; CHARM—Candesartan in Heart Failure Assessment of Reduction in Morbidity and mortality; REASON—Preterax in Regression of Arterial Stiffness in a Controlled, Double-blind Study.

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