

The Growing Burden of Cardiovascular Disease: Role of the Arterial-Cardiac Interaction

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Introduction

World Heart Day was inaugurated to increase global awareness that cardiovascular disease (CVD) is the world's leading cause of death, claiming, according to the World Heart Federation website, 17.1 million lives each year.¹ Control of risk factors such as hypertension, diabetes mellitus, dyslipidemia, tobacco use, and physical inactivity, are obviously critical in reducing the burden of morbidity and mortality from heart disease and stroke.² In addition to these conventional risk factors, several blood biomarkers have been identified as either surrogate indicators of the presence of CVD or predictors of future CVD events. These include high sensitivity C-reactive protein, homocysteine, lipoprotein (a), small, dense low-density lipoprotein and leukocyte count. The litany of novel biomarkers is ever expanding – recently published data on community cohorts suggest possible roles for B-type natriuretic peptide, cardiac troponins and growth-differentiation factor 15.^{3,4}

It has also become clear that diseases of both conduit and peripheral arteries may in themselves, increase the burden of cardiac disease, and indeed be instrumental in the pathogenesis of a broad spectrum of cardiovascular conditions. Physicians treating patients with CVD should be aware of the under-emphasized interaction of arterial and ventricular function, and holistic CVD management should encompass the increasingly evident direct or indirect roles of arterial stiffening.

Clinical and experimental work in the past few decades has increased our understanding of the pathophysiology of vascular disease, including the pathways involved in atherogenesis and its progression.⁵ These complex events which include foam cell migration, vascular smooth muscle cell proliferation, inflammation, matrix fragmentation, collagenization and glycation eventuate in endothelial dysfunction, and plaque formation. Additionally, in the thoracic aorta and major central elastic arteries, age-related medial degeneration leads to the loss of elastin and increase in the collagen content which, in turn, lead to progressive stiffening, a process exacerbated by repetitive pulsations which fatigue and fracture the elastin lamellae.⁶ Alterations in the biophysical properties of these conduit arteries have

detrimental circulatory effects which are only gradually becoming appreciated.

Putative Role of Vasculopathy and Ventricular-Arterial Stiffening in the Pathogenesis of Common Cardiac Conditions

The human arterial system performs a cushioning function, receiving pulsatile flow from the left ventricle (LV), as well as a conduit function, distributing this as steady flow through peripheral capillaries.⁷ Increasing arterial stiffness promotes earlier return of peripheral wave reflections from the smaller muscular arteries to the heart. This alters the contour of the central aortic pressure (CAP) wave, creating a late systolic peak and attenuating the diastolic component.⁸ The resultant augmentation of central aortic pulse pressure increases LV load and leads to hypertrophy with its attendant sequelae.

Thus, among older subjects with systolic hypertension and increased pulse pressure, the ability to reduce the magnitude of peripheral wave reflection and CAP may help regress LV hypertrophy. Antihypertensives which exert differential effects on CAP, including vasodilators which act on muscular arteries, may therefore confer theoretic benefits. In the Conduit Artery Function Evaluation (CAFE) study, patients who were randomised to receive amlodipine-based therapy had greater reduction in CAP compared to those taking atenolol-based treatment, despite similar brachial systolic blood pressure.⁹ Additionally, higher CAP was associated with a composite outcome of total cardiovascular events and development of renal impairment. Differential effects of antihypertensive agents on CAP have also been reported by others.¹⁰ These data provide a rational explanation for why agents such as atenolol are less effective in preventing CVD events,¹¹ and imply that CAP may provide more useful information about prognosis and treatment efficacy than brachial blood pressure.

Increased arterial and systolic LV stiffness also promote load-dependent changes in diastolic function¹² and may underlie diastolic heart failure or more appropriately,

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heart failure with preserved ejection fraction (HFPEF), a syndrome which accounts for between 40% to 71% of all heart failure cases in epidemiologic studies.¹³ The concept of conduit artery disease as a fundamental perturbation in HFPEF is supported by studies which show a correlation between LV relaxation and arterial stiffness markers.^{14,15} and also increased wave reflection among women, who consistently constitute a majority of HFPEF cases.^{13,16} In the Olmsted County community-based study, advancing age and female gender were associated with combined ventricular-vascular stiffening even in the absence of CVD.¹⁷ However, in this predominantly white population, HFPEF and hypertensive controls had similarly increased arterial and LV end-systolic elastance compared with healthy controls but more impaired relaxation and increased diastolic stiffness than either control group.¹⁸ It should be noted that the indices of vascular resistance and pulsatility in these studies were derived and not directly measured. Further investigation into the role of ventricular-vascular stiffening in HFPEF is warranted since determination of specific mechanisms is the key to effective treatment, for which there is glaringly little evidence base.¹⁹

Increased arterial stiffness has also been implicated in the pathogenesis of non-valvular atrial fibrillation (AF), the commonest sustained arrhythmia which is attaining epidemic proportions in the ageing population and responsible for considerable morbidity and mortality. Although a genetic basis for common variant AF is recognised, there are well-known environmental triggers such as hypertension which increase haemodynamic stress on the LV. Indeed, the presence and severity of LV diastolic dysfunction are independently predictive of first documented AF.²⁰ Prospective, observational data from the Framingham Heart Study also incriminate pulse pressure as an important independent risk factor for incident AF among participants aged 35 years and older.²¹ These data suggest, therefore, that conduit arterial stiffening may be a proximate cause of AF in predisposed individuals.

Besides the aforementioned conditions, vascular ageing and stiffening may also have a direct pathophysiological role in coronary artery disease,²² stroke,²³ kidney disease,²⁴ and dementia,²⁵ all of which are leading causes of morbidity and/or mortality in both the developed and developing world.

Noninvasive Assessment of Arterial Stiffening

Parameters of stiffness such as two-point pulse wave velocity, CAP and augmentation index are readily obtained noninvasively using applanation tonometry.²⁶ More recently, ultrasonic tracking of pulsatile distension of the elastic carotid artery walls has been used to generate automatic measurements of compliance, elastic modulus, beta-stiffness

index and single-point pulse wave velocity.²⁷ Arterial stiffness can also be estimated from an ambulatory blood pressure recording by computing the regression slope of diastolic on systolic blood pressure.²⁸ “Abnormal” measures may have better prognostic value than conventional biomarkers as they denote vascular disease which may be subclinical. Their validity is strengthened by a consistent ability, particularly of pulse wave velocity, to predict adverse cardiovascular outcomes in community-based^{29,30} and clinical cohorts.³¹

Management Strategies

Having detected stiff arteries, what should physicians advise? The evidence base is limited presently but aggressive vascular risk factor control is sensible, given their documented association with stiffness markers.³² As mentioned, reduction of smooth muscle vascular tone in the distributing arteries by either vasodilator drugs or exercise may reduce the magnitude of wave reflection and CAP.^{9,10} While animal and small scale human studies suggest that statins can increase aortic pulse wave velocity, larger and long-term trials are needed to evaluate the effects of statin-induced vascular remodeling on arterial elasticity. Ligands for peroxisome proliferator-activated receptor γ appear to have beneficial effects on the arterial wall in atherosclerosis, possibly via an anti-inflammatory mechanism. One recent study showed that long-term pioglitazone treatment could lower aortic wall stiffness, aortic pressure and LV hypertrophy in a rat model of elastocalcinotic arteriosclerosis.³³ Claims of similar benefit have also been made for some traditional remedies.³⁴ Further research is clearly needed to examine the mechanistic effect of these interventions, and whether improved arterial compliance can prevent remote microvascular damage and improve long-term cardiovascular prognosis. The last word in this promising field will not be written for many years yet.

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