Review Article

The Constellation of Hypertensive Heart Disease

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A World Health Organisation report has underscored the importance of blood pressure as a risk factor for cardiovascular disease, identifying high blood pressure as one of the most important preventable causes of premature morbidity and mortality in developed and developing countries.[1] In addition, systemic hypertension is one of the most common causes of diastolic dysfunction and was a major contributor to the pathogenesis of a large proportion of heart failure cases in a population-based sample.[2] Along with diastolic dysfunction and/or heart failure, several other pathological conditions are usually present with hypertension, such as left ventricular hypertrophy, myocardial fibrosis, ischaemia, intrinsic myocyte impairment, apoptosis, endothelial dysfunction and increased arterial stiffness. This constellation of abnormalities often forms a vicious circle and represents the phenotypic portrait of hypertensive heart disease. This review surveys the above constellation, providing a new perception of hypertensive disease beyond the mere numerical value of blood pressure measurement, and outlines how patients' global risk might be assessed in the near future.

Diastolic dysfunction

The diastole is defined as the period of the cardiac cycle when the myocytes return to their previous "relaxed" state. The term diastolic dysfunction implies that the myofibrils do not rapidly or completely return to their resting length; the ventricle cannot accept blood at low pressures, and ventricular filling is slow or incomplete unless atrial pressure rises.

A number of factors may influence the diastolic function in systemic hypertension. Of these, extracellular and perivascular fibrosis, intrinsic myocyte impairment, structural ventricular hypertrophy, myocardial ischaemia, loading conditions, endothelial dysfunction and increased arterial stiffness are most often implicated.

Myocardial fibrosis

An exaggerated interstitial and perivascular deposition of fibrillar collagen has been demonstrated in myocardial hypertrophy due to hypertension.[3]

Mechanical stress forces and humoral substances, such as the components of the renin-angiotensin-aldosterone system, catecholamines, endothelin, nitric oxide and growth factors, have been implicated in mediating myocardial fibrosis.[4] In addition, morphometrically determined myocardial interstitial and perivascular fibrosis, and not hypertrophy, has been found to be responsible for abnormal myocardial diastolic stiffness in rats with genetic hypertension.[5] Two other clinical studies[6,7] confirmed the same findings in patients, and administration of an angiotensin-converting enzyme inhibitor decreased collagen content and improved diastolic function. The evidence of myocardial fibrosis has also been confirmed by a pathologo-

anatomical study in humans,[8] showing that the volumetric fraction of fibrosis in healthy control hearts was 6.5%, whereas the volume fractions in hypertensive hearts increased progressively according to heart weight up to 31.1%.

Angiotensin II and aldosterone can directly induce cardiomyocyte hypertrophy and fibrosis, even without an increase in vascular resistance or cardiac afterload.[9] Other humoral factors, in addition to angiotensin II and aldosterone, can also affect the phenotype and function of cardiac fibroblasts. These include endothelin, the basic fibroblast growth factor, transforming growth factor-b, catecholamines and insulin-like growth factor-1. Activated fibroblasts (myofibroblasts) produce extracellular matrix proteins and proteinases, as well as autocrine/paracrine factors, and mediate tissue remodeling processes.[10]

Intrinsic myocyte impairment

Not only myocardial fibrosis, but also intrinsic myocyte impairment, can be responsible for many of the functional alterations encountered in hypertensive disease. An association between impaired left ventricular filling and subnormal high-energy phosphate metabolism has been demonstrated in hypertensive patients, even in the absence of evident left ventricular hypertrophy.[11]

The intrinsic contractile properties of myocytes have also been found to be altered during hypertension.[12] Calcium movement abnormalities have been described in hypertensive rat myocytes. These abnormalities have been linked to the endothelin and renin-angiotensin systems, which account, at least in part, for the ventricular dysfunction that gradually develops in hypertrophy. In the presence of induced hypertension, diastolic dysfunction and hypertrophy may not develop in the absence of the angiotensin receptor.[13] A significant relationship has also been found between the beta-adrenergic receptor density in myocytes and segmental early diastolic velocity derived by tissue Doppler.[14]

Myocardial ischaemia with normal coronary arteries

Myocardial ischaemia has been shown to play a key role in hypertensive disease, and to be responsible for functional and structural alterations, even without arteriographic signs of coronary vascular lesions.[15] The main causes of ischaemia-induced lesions in systemic hypertension appear to be decreased coronary flow reserve and subendocardial and microvascular ischaemia resulting from:

1. Coronary arteriolar constriction due to perivascular and interstitial fibrosis.[16]
2. Dysfunction of endothelium-mediated relaxation of coronary resistance vessels.[17]
3. Abnormal ratio between coronary lumen area and regional left ventricular mass.[18]
4. Increased wall stress.[19]
5. Decreased subendocardial/subepicardial blood flow ratio.[20]
6. Impairment of early diastolic coronary arterial inflow.[21]
7. Decreased subendocardial capillary density.[22]

Coronary flow reserve

Several observations have found early alterations in coronary flow reserve and left ventricular diastolic function in arterial hypertension, even before the development of left ventricular hypertrophy.[23,24] Functional abnormalities in coronary vasomotion, such as reduced coronary reactivity and reduction in coronary flow reserve, were found even in young, healthy and asymptomatic men fulfilling the World Health Organisation's criteria for borderline hypertension.[25]

The maximal flow response to physiological or pharmacological stimuli may also be limited in hypertension by a reduction in the overall maximal cross-sectional area of the microcirculatory bed that is induced by vascular changes in the intramyocardial coronary arteries, increased coronary arteriolar tone, inadequate angiogenesis in left ventricular hypertrophy, endothelial dysfunction, or by extravascular compression.[26-28]

It has also been shown that endothelial vasodilator dysfunction is not confined only to atherosclerotic epicardial conductance vessels, but may also extend into the coronary resistance vasculature, even in the absence of obstructive epicardial artery disease. Since, in the absence of obstructive lesions within epicardial conductance vessels, coronary blood flow is regulated by the resistance vasculature, defective endothelium-mediated dilation of the resistance coronary arteries may contribute to abnormal coronary blood flow regulation, even in early stages of coronary atherosclerosis commonly encountered in hypertensive patients.[29-31]

Impaired coronary flow reserve capacity of penetrating intramyocardial coronary arteries has also been associated with myocardial fibrosis in hypertensive patients with chest pain and normal coronary angiogram results,[34] and with the appearance of diastolic dysfunction.[32]

Loading

Hypertension, by definition, consists of a high loading condition responsible for important functional and structural alterations. Increased afterload increases mechanical stress, which in turn, through internal transduction mechanisms and local secretion of angiotensin II and endothelin-1, provokes hypertrophy and increases collagen synthesis.[33] Although increased loading has specific influences on myocardial systolic function, as described by the well known Frank-Starling mechanism, diastolic function can also be directly affected by high loading states.[34,35]

Load-dependent diastolic dysfunction occurs in normal hearts facing heavy afterload and in severely diseased hearts even with normal haemodynamic parameters. This dysfunction can be reversed by decreasing systolic pressures or by decreasing venous return.[36]

Ventricular hypertrophy

The Framingham study found left ventricular hypertrophy to be an independent risk factor for cardiovascular mortality: for every 50 g increment in echo left ventricular mass the relative risk was 1.73 in men and 2.12 in women, even after correction for risk factors such as blood pressure.[37]

Two major proximal triggers for hypertrophy are biomechanical stress and neurohumoral factors. Left ventricular hypertrophy is generally regarded as an "adaptive" process to increased afterload. Laplace's law dictates that an afterload-induced increase in systolic wall stress is offset by increased wall thickness,[38] the major characteristic of hypertensive disease.

The exact mechanisms through which biomechanical stress initiates a hypertrophic response are not clear. Stretch-sensitive ion channels are present in the cardiac myocytes' plasma membrane. An interactive continuum, from integrins at the cell surface to the contractile apparatus and the nucleus, seems to be responsible for cardiac myocytes' response to mechanical stress. In addition, myocyte stretch induces the synthesis and secretion of a number of growth factors, including insulin-like growth factor-I, angiotensin II and endothelin-1, and each of these humoral factors is sufficient to induce hypertrophic growth of cardiac myocytes.[39] Furthermore, mechanical stretch can activate cardiomyocyte angiotensin II receptors directly, without the involvement of angiotensin II.[40]

In addition to mechanical wall stress, humoral factors such as angiotensin II, aldosterone, noradrenaline and endothelin are directly implicated in the genesis of a hypertrophic state, and are related to the maladaptive process of increased myocardial fibrosis in hypertrophic ventricles.[41,42]

Arterial stiffness

Arterial stiffness is an independent predictor of all-cause and cardiovascular mortality in patients with essential hypertension.[43] Arterial stiffening is the end result of multiple interactions between stable and dynamic changes in structural and cellular elements of the vessel wall, along with influences from haemodynamic forces and "extrinsic factors" such as hormones, salt and glucose regulation.[44]

Vascular remodelling, as expressed by hypertrophy of large vessels, constitutes a characteristic feature of many models of animal and human hypertension, and is primarily due to an increase of both smooth muscle mass and extracellular matrix collagen fibers, an environment that favours arterial stiffening.[45]

Imbalance between the two prominent scaffolding proteins, collagen and elastin, in the vascular wall, caused by stimulation of excessive collagen production due to increased luminal pressure, has been proposed as the fundamental mechanism of arterial stiffening in hypertension.[46] It has also been shown that in systemic hypertension, not only rearrangement of the arterial wall material through the cell-matrix connection,[47] but also systemic inflammation, as depicted by tumour necrosis factor-α, interleukin-6 and high-sensitivity C-reactive protein,[48] is associated with evidence of increased arterial stiffness.

Increased vascular smooth muscle cell tone, modified by mechanostimulation or by paracrine mediators such as angiotensin II, endothelin, oxidant stress, nitric oxide and endothelial dysfunction, has also been proposed as a cause of arterial stiffening in hypertension.[49-51] Angiotensin II, aldosterone and endothelin-1 are also directly implicated in increased vascular collagen formation, matrix remodelling and vascular hypertrophy, resulting in increased arterial stiffness.[49,52,53] Increased stiffness of conduit arteries is associated with higher velocity transmission of the pulse wave generated by left ventricular ejection. Early return of reflected waves from the periphery, which arrive back at the heart during left ventricular systole, may augment the amplitude of the central aortic pressure wave, thus increasing left ventricular afterload and central pulse pressure.[54] Increased afterload may promote myocyte hypertrophy along with functional

and structural abnormalities, as already mentioned.

The concomitant reduction in central diastolic blood pressure because of the reflected waves' early return may also compromise coronary perfusion, which in association with myocytic hypertrophy and increased afterload, may exacerbate subendocardial and microvascular ischaemia. This can further impair myocardial relaxation and promote interstitial and replacement fibrosis, reducing left ventricular compliance.[55] Increased ventricular stiffness in association with arterial stiffening has recently been shown in patients with overt diastolic heart failure, and interactions between these processes may be important in the clinical expression of heart failure.[56]

The role of pulse wave velocity, an index of arterial stiffening, has been recently acknowledged as a measure of subclinical target organ damage, important for the evaluation and management of the hypertensive patient.[57]

Endothelial dysfunction

Endothelial dysfunction, the hallmark of essential hypertension, was first described in human hypertension in the forearm vasculature in 1990.[58] Impaired vasodilation in hypertension has been confirmed by many studies in different vascular beds, including small resistance vessels.[59,60] In stage I essential hypertension, it has been shown that ~60% of patients exhibit impaired small artery vasodilation when this is studied *in vitro* in vessels dissected from gluteal subcutaneous biopsies.[61]

Impairment of nitric oxide (NO) bioavailability, which plays a major role in regulating blood pressure, is an important characteristic of endothelial dysfunction.[62] NO is a simple but pluripotent molecule, synthesised predominantly in the vascular endothelium, which vasodilates the vascular smooth muscle cells, prevents platelet adhesion and aggregation, and exerts anti-inflammatory, antiproliferative and antimigratory effects on leukocytes, endothelial cells and vascular smooth muscle cells.

Hypertensive subjects generate increased reactive oxygen species, which scavenge NO thereby reducing its bioavailability.[63] Oxidative stress, which refers to excessive production of reactive oxygen species, appears not only to be the major cause of impaired NO bioactivity,[64] but also to be correlated with an increased risk of cardiovascular events.[65]

Potential mechanisms for the pathogenic link between impaired NO and hypertension include defects in the l-arginine/NO pathway, leading to decreased NO production; genetic polymorphisms in eNOS; reduced availability of cofactors essential to NO formation; increased levels of circulating NO inhibitors; and destruction of NO by reactive oxygen species.[64,66-68]

Angiotensin II is also implicated in the pathophysiology of endothelial dysfunction, as it has been shown that infusion of angiotensin II induces endothelial dysfunction in rats.[69] In hypertensive humans, interruption of the renin-angiotensin system with angiotensin-converting enzyme inhibitors appears to restore endothelial function.[70]

Inflammation

Recent evidence suggests that low-grade inflammation may be implicated in systemic hypertension and that C-reactive protein levels may be associated with the future development of hypertension.[71] There are several potential mechanisms that may account for the observed relationship between blood pressure and inflammation. Increased blood pressure *per se* may promote vascular inflammation by modulation of biomechanical stimuli from pulsatile blood flow. Cyclic strain has been shown to increase soluble intercellular adhesion molecule-1 and vascular cellular adhesion molecule-1 expression by endothelial cells[72] and to upregulate endothelial cell secretion of monocyte chemoattractant protein-1.[73] These changes, in turn, result in increased monocyte adhesion to the endothelium. Hormonal stimuli may also contribute to vascular inflammation via non-haemodynamic mechanisms. Rat models of hypertension induced by angiotensin II or aldosterone are characterised by early vascular infiltration by monocytes and macrophages and increased expression of inflammatory mediators, such as monocyte chemoattractant protein-1, cyclooxygenase-2, and osteopontin.[74,75]

Accumulated evidence suggests that C-reactive protein may directly quench the production of nitric oxide by endothelial cells.[76] This, in turn, could lead to disturbance of vasomotor tone and unopposed vasoconstriction. Furthermore, C-reactive protein has also been shown to augment the production of endothelin-1, a potent endothelium-derived constrictor, and may induce the expression of monocyte chemoattractant protein-1 and soluble intercellular adhesion molecule-1 via endothelin-1 and interleukin-6 dependent pathways.[77]

Apoptosis

Apoptosis represents a process in which a death program (programmed cell death) is activated by internal

or external stimuli. Apoptosis related to hypertensive disease has been demonstrated in the left ventricle of animal models.[78] Increased apoptosis has been shown in the hypertrophied left ventricle of spontaneously hypertensive rats compared with their normotensive control animals.[79] In clinical studies, cardiomyocyte apoptosis has been found to be abnormally stimulated in the hypertrophied heart of patients with essential hypertension, no angiographic evidence of coronary artery disease, and normal cardiac function.[80]

A transition from compensated hypertrophy to failure in spontaneously hypertensive rats has been documented and has been associated with increased numbers of apoptotic cells,[81] suggesting that apoptosis may play an important role in the transition from compensated left ventricular hypertrophy to failure in pressure-overloaded hearts, although most of the underlying mechanisms are still unclear. Pressure overload, angiotensin II, aldosterone, oxidative stress and ischaemia have been suggested as being potentially involved with increased apoptosis.[82]

In another study, cardiomyocyte apoptosis increased in angiotensin II-infused hypertensive Sprague-Dawley rats, and blockade of the angiotensin II type 1 receptor with losartan prevented this effect, despite the persistence of increased blood pressure.[83]

Transition to failure

Although hypertrophic growth is believed to have a compensatory role that diminishes wall stress and oxygen consumption, the Framingham[84] and other studies have established ventricular hypertrophy as a marker for increased risk of developing chronic heart failure, suggesting that hypertrophy may have maladaptive features.

The prevailing paradigm of hypertensive heart disease is that it first leads to concentric ventricular hypertrophy, followed by the development of ventricular dilation and contractile impairment with systolic dysfunction and a reduced left ventricular ejection fraction.[85] An early hypothesis held that blood supply inadequate to meet the demands of the thickened myocardium results in microvascular ischaemia.[86] Other potential explanations include alteration of contractile proteins,[87] remodelling of the extracellular matrix with consequent fibrosis,[88] and changes in activation of the b-adrenergic pathway.[89]

Diastolic heart failure represents nearly 50% of the cases of congestive heart failure in the community, with hypertension being the most prevalent feature.[90] In this entity, although diastolic dysfunction with the addition of symptomatic status represents the dominant picture, subtle contractile abnormalities may also be present in many, if not most, patients. Furthermore, patients with diastolic heart failure commonly appear to have concentric left ventricular hypertrophy, in contrast to the eccentric left ventricular hypertrophy seen in systolic heart failure patients.[91] The importance of diastolic heart failure in hypertensive disease must also be underscored by the fact that the outcome and survival of heart failure patients with a preserved ejection fraction appears to be similar to that of patients with a reduced ejection fraction.[92]

Arrhythmias

Arrhythmias represent a common feature in hypertensive disease, with a wide spectrum ranging from supraventricular premature beats to atrial fibrillation and from ventricular premature complexes to ventricular tachycardia or sudden cardiac death.[93]

Atrial fibrillation is one of the most common supraventricular arrhythmias in hypertension, with a 1.5 and 1.4 fold increased risk of atrial fibrillation for hypertensive men and women, respectively.[94] Several studies have suggested that mean systolic diurnal and nocturnal blood pressures, left atrial dimension, left ventricular mass and evidence of diastolic dysfunction are associated with the appearance of atrial fibrillation in hypertensive patients.[95,96]

Ventricular arrhythmias are also commonly encountered in hypertensive patients, with left ventricular hypertrophy being an important parameter for their appearance.[97] A graded relationship between the frequency and complexity of ventricular arrhythmias and left ventricular hypertrophy has been reported.[98] The importance of ventricular arrhythmias in hypertension was underlined in the Framingham Study, which indicated that the presence of ventricular premature contractions increased the risk of sudden death by a factor of 2.9 in men and 1.6 in women.[99]

More complex ventricular arrhythmias, such as non-sustained ventricular tachycardia, have also been found to occur commonly in hypertensive patients with left ventricular hypertrophy, and evidence suggests that they may contribute to the higher incidence of sudden death in those patients.[97]

Subendocardial ischaemia, underperfused myocardium, decreased coronary reserve, irregular hypertrophy pattern and inhomogeneous propagation of the electric impulse, intrinsic changes in the myocyte, myo-

cardial fibrosis, mechanical stretching of the myocyte, and excessive activity of the sympathetic nervous system, are considered as possible mechanisms for arrhythmias in systemic hypertension.[100]

Summary

Hypertension should be regarded not as a simple elevation of blood pressure, but as a constellation of functional and structural abnormalities that create a phenotypic portrait of hypertensive disease. Recent research has expanded our knowledge related to hypertensive heart disease.[101-104] Future assessment of hypertensive patients' global risk should probably incorporate not only evaluation of the known traditional risk factors, such as hypercholesterolaemia, smoking, glucose levels and left ventricular hypertrophy, but also myocardial fibrosis, microvascular ischaemia, arterial stiffness, systemic inflammation, endothelial dysfunction and level of apoptosis.

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