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VIEWPOINT

Time to reconsider the perception and management of hypertensive heart disease

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Heart failure burden of hypertensive heart disease

Heart failure (HF) is a global pandemic. Its prevalence is increasing with the aging of the population, with improved treatment of ischemic heart disease (IHD) and the availability of effective evidence-based therapies that prolong survival of patients with HF. Despite the age-standardized stable worldwide prevalence of systemic arterial hypertension, but considering that the rates of hypertension control with treatment have worsened in recent years, hypertension remains one of the main causes of HF with a global impact. In the last two decades, the presence of hypertension has increased in incident cases of HF either with reduced (HFrEF) or with preserved ejection fraction (HFpEF).[1] Additionally, the lifetime risk of HF is higher in people with hypertension than in those with normal blood pressure (BP), especially in women and the elderly.[1] On the other hand, the incidence of de novo HF in 23 hypertension trials involving 193 424 patients was 28.9% ($n = 7171$) of the all major cardiovascular events reported.[2] Therefore, HF continues to represent a major concern in hypertension management.

Hypertensive heart disease (HHD) can be defined as the cardiomyopathy that results from the response of the myocardium to the biomechanical stress imposed on the left ventricle by progressively increasing BP. HHD encompasses a broad spectrum including asymptomatic left ventricular hypertrophy (LVH) (either a concentric or an eccentric pattern) and clinical HF (either HFpEF or HFrEF). Epidemiological evidence supports that HHD is a major factor responsible for the increased risk of HF in the overall population. First, the global age-standardized prevalence rate of HHD has increased over the last 30 years, especially in women and older people.[3] Second, at the global population level, HHD represents the second cause of prevalent HF after IHD, but in adults aged 25 to 69 years, it accounts for the largest share of all causes of HF.[4] While the population-attributable risk of IHD-related HF was higher in high-income geographic areas, the HHD-related risk was higher in low- and middle-income areas.[3,4] Third, after 2011, age-adjusted mortality rate for HF and HHD increased at a faster rate than for HF attributable to other subtypes of heart disease.[5]

Challenging the current pathophysiological view of HHD

HHD can no longer be considered as the simple result of the hypertrophy of cardiomyocytes in response to pressure overload leading to the development of LVH, responsible for subsequent cardiac dysfunction and HF. Indeed, a review of 30 echocardiographic studies including 37 700 treated and untreated hypertensive patients showed that LVH was absent in approximately two-thirds of untreated patients despite having chronic high BP.[6] Furthermore, in a meta-regression analysis of 14 studies including 12 809 hypertensive patients, treatment-induced regression of LVH was found not to prevent new-onset HF.[7]

Therefore, the opinion has emerged that in patients with HHD changes in myocardial tissue that lead to its histological remodeling may result in alterations in cardiac function, perfusion and electrical activity contributing to increased risk of HF (*Table 1*).[8] Both decreased energetic efficiency and mechanical force of hypertrophic cardiomyocytes and increased apoptosis with reduced numbers of viable cardiomyocytes impair systolic function in the human hypertensive heart. In addition, diffuse reactive interstitial fibrosis (often accompanied by low-grade perivascular inflammation) increases the passive stiffness of the extracellular matrix, contributing to increased left ventricular (LV) pressure and impaired filling during diastole, and restricts stretching of cardiomyocytes in diastole, reducing their length-dependent force generation in systole. In this sense, increases in cardiomyocyte apoptosis[9] and interstitial deposition of type I collagen fibres[10] are observed in endomyocardial biopsies from patients with HHD and HF compared to patients with HHD without HF. The associations of increased apoptosis and fibrosis with adverse LV remodeling in

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Table 1 Main myocardial microscopic lesions found in hypertensive heart disease and their major cellular and molecular determinants

Compartment	Main lesions	Other lesions
Cardiomyocyte	Increased cell size	Increased death
	Parallel addition of new sarcomeres predominates over serial addition	Apoptosis predominates over autophagy and necrosis
Interstitium	Diffuse fibrosis	Perivascular inflammation
	Deposition of stiff type I collagen fibers predominates over deposition of non-stiff type III collagen fibers	CCR2+ infiltrating monocyte- derived macrophages predominate over CCR2- resident macrophages
Microcirculation		
Blood	Arteriolar wall thickening	Reduced capillary density
	VSMC hyperplasia and hypertrophy predominate over VSMC misalignment	Rarefaction predominates over insufficient vascular growth
Lymphatic	Insufficient lymphangiogenesis	Structural alterations
	Responses to antilymphoangiogenic factor (VEGF-A) predominate over responses to prolymphoangiogenic factors (VEGF-C and VEGF-D)	Altered lymphatic anchoring filaments and cell junctions predominate over normal filaments and junctions

CCR2, C-C chemokine receptor type 2; VSMC, vascular smooth muscle cell; VEGF, vascular endothelial growth factor.

these studies support a potential role for these lesions in the transition from subclinical HHD to clinically manifest HF.[9,10]

More recently, attention has focused on changes in the coronary blood and lymphatic microcirculations in the hypertensive heart that may have a deleterious impact on cardiac function. In addition to functional changes (e.g., vasomotor dysregulation and proinflammatory-profibrogenic activation of the endothelium), anatomic changes (e.g., increased medial thickness-to-lumen ratio and decreased maximum cross-sectional area of pre-arterioles and arterioles, and decreased vascular density due to capillary rarefaction) have been described in patients with HHD.[8] These changes make the myocardium a permanently ischemic tissue that facilitates the death of cardiomyocytes and reparative fibrosis and, consequently, HF. Supporting this possibility, Brown et al.[11] demonstrated in hypertensive patients with HFrEF and without coronary artery disease who underwent positron emission tomography (PET) myocardial perfusion imaging that a low LV myocardial blood flow-to-mass ratio (indicative of a supply/demand mismatch) was associated with greater LV mass, worse LV systolic function, and elevated levels of circulating cardiac troponins T and I. Interestingly, a lower LV blood flow-to-mass ratio was independently associated with hospitalization for incident HF, among other adverse clinical outcomes.[11] On the other hand, insufficient cardiac lymphangiogenesis and lymphatic dysfunction may facilitate myocardial edema and contribute to inflammation and fibrosis in the hypertensive heart.[8]

Importantly, HHD is characterized by myocardial remodeling, namely interstitial fibrosis, not only in the left ventricle but also the left atrium.[8] Left atrial remodeling may culminate in atrial fibrillation and atrial contractile dysfunction, thus contributing to the development of HF. Finally, right heart myocardial remodeling may develop in HHD independently of the influence of lung disease or pulmonary hypertension and may affect right ventricular and right atrial function. Therefore, it is increasingly apparent that HHD encompasses a range of cardiac alterations beyond macroscopic LVH, characterized by microscopic myocardial lesions and subsequent functional changes that affect the heart as a whole. In the origin of these alterations must be also implicated mechanisms typical of hypertension as a systemic process that affects target organs other than the heart (e.g., ventricular–arterial uncoupling due to stiffness of the aorta and large arteries).

Innovative diagnostic and therapeutic approaches to HHD

The growing HF burden of HHD represents an unmet medical need. Therefore, HHD requires an innovative diagnostic approach based on phenotyping of myocardial tissue remodeling to identify high-risk HF patients and personalize treatment to regress remodeling and prevent the transition to HF (*Figure 1*). As myocardial remodeling cannot be routinely evaluated through endomyocardial biopsies, it is necessary to investigate the clinical utility of combining biomarkers. On the one hand, circulating biomarkers that identify the molecular and histological signatures of the remodeled myocardium (e.g., proteins, non-coding RNAs, metabolites and/or epigenetic modifications).[12] On the other hand, advanced imaging-derived biomarkers that characterize myocardial tissue (e.g., parameters assessed with LV strain, cardiovascular magnetic resonance [CMR] imaging, computed tomography or PET of myocardial perfusion).[13]

Two recent studies focused on imaging and circulating biomarkers of myocardial interstitial fibrosis may support this novel approach. In asymptomatic hypertensive patients, myocardial interstitial fibrosis on CMR imaging with non-ischemic late gadolinium

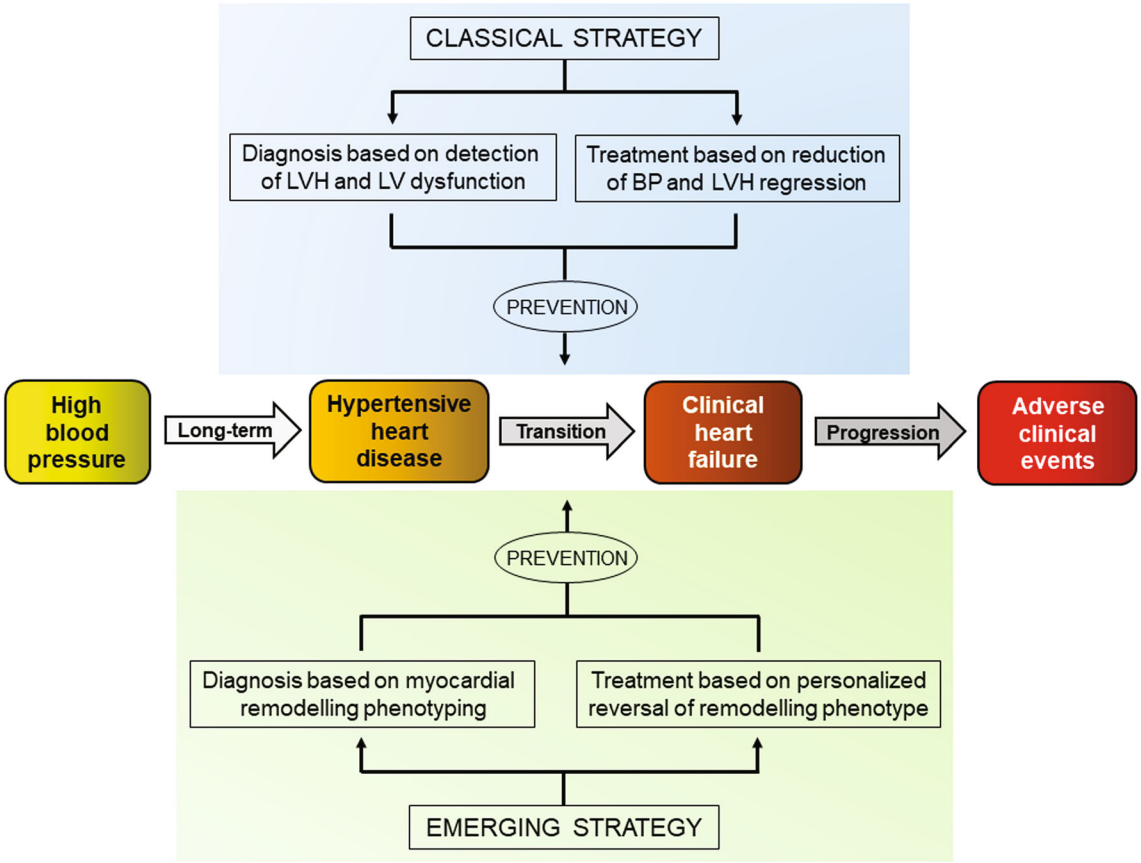

Figure 1 Classic and emerging adjunctive diagnostic and therapeutic strategies to prevent the transition from hypertensive heart disease to clinically overt heart failure. BP, blood pressure; LV, left ventricular; LVH, left ventricular hypertrophy.

enhancement (LGE) was associated with greater LV mass, worse function, and elevated circulating levels of N-terminal pro-B type natriuretic peptide (NT-proBNP).[14] Importantly, non-ischemic LGE was also associated with adverse outcomes, including first hospitalization for HF.[14] On the other hand, in individuals at risk for HF (including over 78% with chronic arterial hypertension), a circulating biomarker of myocardial interstitial fibrosis (i.e., serum C-terminal type I collagen propeptide [PICP]) was associated with greater LV mass, worse LV diastolic function, and elevated levels of circulating NT-proBNP.[15] Of note, a decrease in serum PICP with spironolactone treatment was associated with improvements in LV diastolic dysfunction (e.g., reduction in diastolic mitral inflow velocity to early diastolic mitral annulus velocity [E/e' ratio]).[15]

Presumably, using a multimodal approach supplemented with machine learning and artificial intelligence applications, distinct myocardial remodeling phenotypes with heterogeneous pathophysiology and consequently variable HF risk and therapeutic requirements will be identified in patients with HHD. To this aim, multinational collaborative efforts are needed to provide large independent cohorts with the simultaneous assessment of the panels of biomarkers and develop and validate algorithms to support clinical decision-making.

Changing science and health policy in HHD

HF attributable to chronic hypertension is one of the greatest threats to the society today, and will become even more so in the future, especially in certain geographic areas of the world and for some population groups. Our collective understanding of HHD remains incomplete, which helps fuel the risk for HF. Therefore, translational research is urgently necessary to learn more about the mechanisms leading to changes at cellular and tissue levels that induce myocardial remodeling in patients with HHD. In addition, personalized multiple biomarker-guided therapeutic strategies based on stratification of HHD patients according to their remodeling phenotype should be designed and evaluated in future clinical trials to prevent HF in these patients. Physicians, basic scientists, public health systems, insurance companies, pharmaceutical companies, patients, and regulatory bodies, need to be involved in this paradigm shift.

Conflict of interest: J.D. is consultant to AstraZeneca, Bayer, Vifor Pharma and Glaxo, Smith and Kline. J.B. is consultant to Abbott, Adrenomed, Amgen, Applied Therapeutics, Array, AstraZeneca, Bayer, Boehringer Ingelheim, CVRx, G3 Pharma, Impulse Dynamics, Innolife,

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References

1. Rapsomaniki E, Timmis A, George J, Pujades-Rodriguez M, Shah AD, Denaxas S, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. *Lancet*. 2014;**383**:1899–911.
2. Tocci G, Sciarretta S, Volpe M. Development of heart failure in recent hypertension trials. *J Hypertens*. 2008;**26**:1477–86.
3. Dai H, Bragazzi NL, Younis A, Zhong W, Liu X, Wu J, et al. Worldwide trends in prevalence, mortality, and disability-adjusted life years for hypertensive heart disease from 1990 to 2017. *Hypertension*. 2021;**77**:1223–33.
4. Bragazzi NL, Zhong W, Shu J, Much AA, Lotan D, Grupper A, et al. Burden of heart failure and underlying causes in 195 countries and territories from 1990 to 2017. *Eur J Prev Cardiol*. 2021;**28**:1682–90.
5. Shah NS, Molsberry R, Rana JS, Sidney S, Capewell S, O'Flaherty M, et al. Heterogeneous trends in burden of heart disease mortality by subtypes in the United States, 1999-2018: observational analysis of vital statistics. *BMJ*. 2020;**370**: m2688.
6. Cuspidi C, Sala C, Negri F, Mancia G, Morganti A; Italian Society of Hypertension. Prevalence of left-ventricular hypertrophy in hypertension: an updated review of echocardiographic studies. *J Hum Hypertens*. 2012;**26**:343–9.
7. Costanzo P, Savarese G, Rosano G, Musella F, Casaretti L, Vassallo E, et al. Left ventricular hypertrophy reduction and clinical events. A meta-regression analysis of 14 studies in 12,809 hypertensive patients. *Int J Cardiol*. 2013;**167**:2757–64.
8. González A, Ravassa S, López B, Moreno MU, Beaumont J, San José G, et al. Myocardial remodeling in hypertension. *Hypertension*. 2018;**72**:549–58.
9. Ravassa S, González A, López B, Beaumont J, Querejeta R, Larman M, et al. Upregulation of myocardial Annexin A5 in hypertensive heart disease: association with systolic dysfunction. *Eur Heart J*. 2007;**28**:2785–91.
10. Querejeta R, López B, González A, Sánchez E, Larman M, Martínez Ubago JL, et al. Increased collagen type I synthesis in patients with heart failure of hypertensive origin: relation to myocardial fibrosis. *Circulation*. 2004;**110**: 1263–8.
11. Brown JM, Zhou W, Weber B, Divakaran S, Barrett L, Bibbo CF, et al. Low coronary flow relative to myocardial mass predicts heart failure in symptomatic hypertensive patient with no obstructive coronary artery disease. *Eur Heart J*. 2022;**43**:3323–31.
12. González A, Richards AM, de Boer RA, Thum T, Arfsten H, Hülsmann M, et al. Cardiac remodelling - part 1: from cells and tissues to circulating biomarkers. A review from the Study Group on Biomarkers of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2022;**24**: 927–43.
13. Tadic M, Cuspidi C, Marwick TH. Phenotyping the hypertensive heart. *Eur Heart J*. 2022;**43**:3794–810.
14. Iyer NR, Le T-T, Kui MSL, Tang H-C, Chin C-T, Phua S-K, et al. Markers of focal and diffuse nonischemic myocardial fibrosis are associated with adverse cardiac remodeling and prognosis in patients with hypertension: the REMODEL Study. *Hypertension*. 2022;**79**:1804–13.
15. Kobayashi M, Girerd N, Ferreira JP, Kevin D, Huttin O, González A, et al.; on behalf of the HOMAGE Trial Committees and Investigators. The association between markers of type I collagen synthesis and echocardiographic response to spironolactone in patients at risk of heart failure: findings from the HOMAGE trial. *Eur J Heart Fail*. 2022;**24**:1559–68.