Invited review

Hypertensive heart disease: left ventricular hypertrophy

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Abstract

Left ventricular (LV) hypertrophy (LVH) is target-organ-damage, a form of preclinical disease induced by volume and pressure overload, genetic factors and other stimuli. Over the last 20 years it has become clear that it is possible to assess LVH with increasing accuracy with echocardiographic and magnetic resonance methods. Both LVH per se but also the geometry has been shown to be important in understanding the basic pathology of the organ-damage as well predictive value regarding cardiovascular morbidity and mortality. In addition, systematic antihypertensive treatment does in fact reduce LVH, in fact 1 year of antihypertensive treatment resulted in 15 g/m^2 reduction in LV mass index. Furthermore, it has been shown that the resultant reduction in LV mass translates into reduction into cardiovascular morbidity and mortality which is statistical independent of the blood pressure per se. One standard deviation reduction in LV mass (25.3 g/m^2) resulted in 38% reduction of cardiovascular mortality. Left ventricular functional parameters are also affected by hypertensive disease. Left ventricular systolic function measured at the endocardial level appears supranormal when in fact it the myocardial contractility can be reduced. Antihypertensive treatment does reverse LV systolic function significantly even in patients preserved ejection fraction. In addition, improving LV systolic function does have prognostic significance. Left ventricular diastolic function is also very commonly affected in hypertensive disease. Even though we report significant improvement in transmitral flow parameters as bioassays for LV diastolic function this does in our cohorts translate into improvement in cardiovascular morbidity and mortality. This might be due to low power. Thus, clinicians should focus on blood pressure reduction, finding LVH, reducing LVH and improving LV systolic function even in conditions with preserved LV ejection fraction as these factors contribute to increased cardiovascular morbidity and mortality. Improvement of these factors results in significant improvement in outcome.

Key words: left ventricular hypertrophy, hypertensive heart disease, mortality, antihypertensive treatment.

Introduction

Left ventricular (LV) hypertrophy is a form of preclinical cardiac disease that may be induced by either pressure or volume myocardial overload as well as genetic factors and a variety of other stimuli. Pressure overload as exemplified by aortic stenosis and volume overload as exemplified by regurgitant valve disease or chronic anemia, initiates growth of cardiac myocytes and increase in connective tissue without notable derangements in the interstitial architecture. As a result, myocyte shortening may translate into efficient ventricular contraction with preserved diastolic properties. In hypertensive patients, there is often a combination of pressure and volume overload resulting in a mixture of myocyte

elongation, needed to accommodate a higher ventricular chamber volume and myocyte thickening, stimulated by the greater afterload [1, 2].

Left ventricular hypertrophy is a cardinal manifestation of preclinical cardiovascular disease [3] that strongly predicts myocardial infarction, stroke and cardiovascular death in patients with hypertension [4], in members of the general population [5] and in patients with or without angiographic coronary artery disease [6]. The risk of death or non-fatal complications is increased 2- to 4-fold in the presence of LV hypertrophy, independently of age, gender and other risk factors [4-6]. Further risk stratification may be obtained by characterization of LV geometric patterns [4]. Longitudinal studies in hypertensive patients [7-9] and the general population [10] have reported that individuals in whom LV hypertrophy regressed had lower rates of subsequent morbidity/mortality than those in whom LV mass increased. As a result, prevention or reversal of hypertensive LV hypertrophy has been widely accepted as a desirable goal. However, until recently available studies relating change in LV mass or electrocardiographic (ECG) indices thereof to prognosis have suffered from relatively small sample size, incomplete knowledge of blood pressure and treatment during follow-up and variably incomplete analyses [11]. Furthermore, it was uncertain how best to reverse hypertensive LV hypertrophy because most published studies have been relatively small and have commonly been of short duration, lacked comparative agents, had unblinded reading of echocardiograms or were performed in non-representative populations [12].

Larger trials had not been definitive because of confounding effects of concomitant non-drug therapy, high subject drop-out or absence of LV hypertrophy before therapy [13, 14]. More recently, the Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial enrolled hypertensive patients with ECG LV hypertrophy in a prospective, double-blind, randomized study large enough (n = 9,193) to determine whether greater reduction in morbid events is achieved by either use of losartan as opposed to the comparative agent (atenolol) or by regression as opposed to persistence or progression of ECG LV hypertrophy [15-17].

As part of the LIFE trial, over 10% of study participants were enrolled in the LIFE echocardiography substudy in which echocardiograms were performed at study baseline and yearly thereafter [18]. The echocardiography population was representative of the main LIFE study in age, blood pressure and prevalences of cardiovascular diseases and diabetes at baseline but differed from the remaining LIFE participants in being disproportionately male, due predominately to participation in the echocardiographic substudy of several Veterans' Administration Hospitals in the USA and a center in Norway that recruited participants from the all-male Oslo Heart Study. Height and heart rate were higher and body mass index lower in echocardiography substudy participants. A higher population of blacks were enrolled in the echocardiography substudy compared to the overall LIFE population to assess possible ethnic differences in LV geometry and the performance of ECG indices of LV hypertrophy [18].

Assessment of left ventricular hypertrophy

Because of the importance of assessing LV hypertrophy as a marker of cardiac risk, several methods have been developed to estimate LV mass. Although electrocardiography carries independent prognostic information echocardiography is more sensitive for assessing LV hypertrophy [19, 20]. Furthermore, echocardiography remains to date the only modality that has been anatomically validated in humans for estimation of LV mass [21]. Use of a standardized protocol and training of sonographers are needed to limit variability of echocardiographic measurements. Data from the PRESERVE study document excellent interstudy variability and show the ability to detect small changes of LV mass in modest-sized populations [22]. Palmieri et al. reported that the short-term between study variability had high interclass correlation (RHO = 0.93), an estimator of variability between replicate measurements, resulting in LV mass ±34 g or ±18 g in a single patient had ≥90 or ≥80% likelihood to be true changes, repectively [22].

Lately, both 3-dimentional echocardiography [23] and cardiac magnetic resonance imaging [24] has been shown to have lower variability than 2-dimensional echocardiography and magnetic resonance imaging has now been used in population-based studies [25]. However, there are still no human necropsy-comparison data to validate magnetic resonance imaging.

This has lead to controversy regarding image modality for detection of LV hypertrophy [26, 27] The current data suggest that 41 patients are needed per treatment arm to provide statistical power of 90%, at an error level of 1% to detect a between-group difference of at least 10 g/m^2. Similar, 3-dimensional echocardiography needs 15 patients per arm and magnetic resonance imaging 14 patients per arm. Thus, echocardiographic LV mass remains an excellent bioassay for clinical studies of LV hypertrophy that require moderate or large population sizes to obtain sufficient clinical endpoints or to encompass participants with varied characteristics [22, 23].

Left ventricular mass index and left ventricular geometry

Echocardiographic partition values for LV hypertrophy/body surface area were suggested by Hammond et al. [28] to be 134 g/m^2 for men and 110 g/m^2 for women. However, more recent data, PRESERVE derived using newer echo-cardiographs in reference populations that met more stringent criteria of normality [29, 30] suggest partition values of 116 g/m^2 for men and 104 g/m^2 for women. A comparison of LIFE Echocardiography study participants to apparently normal adults showed that indexation of LV mass for height [2, 7, 32] avoided the underestimation of the preva-lence of LV hypertrophy in overweight and obese patients that occurs with indexation of LV mass by body surface area. In view of increasing obesity worldwide, indexation by the allometric power of height becomes increasingly important.

The combination of LV mass index (LVMI) and relative wall thickness has been used to identify three different abnormal LV geometric patterns [4, 31]. Termed concentric remodeling (normal LVMI with increased relative wall thickness), eccentric (increased LVMI and normal relative wall thickness) and concentric hypertrophy (increased LVMI and increased relative wall thickness). Relative wall thickness has been calculated either as the ratio of 2 × posterior wall thickness/LV internal diameter [32] or as the ratio of (interventricular septal + posterior wall thickness)/LV internal diameter [33, 34]. Analyses of data from a working population from New York suggests partition value of relative wall thickness to be 0.43 [30, 35].

Different studies have shown quite different prevalences of LV hypertrophy depending on the population studied and methods used for calculation of LVMI as well as relative wall thickness. Studies have used a variety of partition values for LV mass and relative wall thickness to identify LV hypertrophy and geometric remodeling and hence also come to very different prevalences of abnormal geometry [35]. Concentricity, i.e. increased relative wall thickness is associated with low weight [36], older age [37] and black ethnicity [25, 38] independent of body composition. However, it remains controversial whether higher relative wall thickness is a genetic variation or a reflection of the composite influence of greater pressure- than volume-load as well as a response to offset increased wall stress [34]. The relation between LVMI and relative wall thickness seems to be important as several studies have shown that stratification by different geometric patterns gives valuable information concerning morbidity and mortality [4, 39-43]. In some studies, subjects with concentric hypertrophy (i.e. increased LVMI and relative wall thickness) had the highest incidence of cardiovascular events and death, those with eccentric hypertrophy or concentric remodeling had intermediate rates, and those with normal LV geometry had the least complications [4, 39-43].

Although it has been suggested that treatment of LV geometry would be beneficial, previous studies did not find independent prognostic information of LV geometry when taking LV mass at baseline into account at baseline [40, 41, 43].

Treating left ventricular hypertrophy and geometry

Systematic antihypertensive treatment is effective in reducing LV mass and relative wall thickness. In the LIFE trial, one year of antihypertensive treatment that reduced blood pressures by 23/11 mm Hg resulted in a reduction in LVMI by 15 g/m^2 or more than 12% [44]. Similarly, relative wall thickness was reduced an absolute 4% or proportionately by almost 10%. Left ventricular geometry improved significantly as normal geometry increased from less than 20% at baseline to more than 50% after one year of treatment. Concentric LV geometry was especially reduced with concentric hypertrophy prevalence reduced from 25 to only 6%. As a consequence only 1 in 6 patients with either concentric remodeling or hypertrophy at baseline had the same geometric pattern after one year of treatment. Greater early reduction in LV mass was associated with female gender and reduction in body mass index, systolic and pulse pressure and Doppler stroke volume. Reduction in relative wall thickness was associated with lower diastolic blood pressure, lower LV ejection fraction and also increased stroke volume [44]. Data from the LIFE echocardiographic study additionally showed that further reduction of LV mass and relative wall thickness occurred during the second year of systematic antihypertensive therapy, during a period where blood pressures decreased only slightly with even further increase in the prevalence of normal geometry [45]. The clinical implication is that treatment of LV hypertrophy should have at least two year duration to achieve maximum benefit even if there is no further reduction in blood pressure.

Prognostic significance of treating left ventricular hypertrophy

Despite benefits from blood pressure reduction per se, Devereux et al. demonstrated a substantial associated benefit with regard to cardiovascular morbidity and mortality from reduction in echocardiographic LV mass [46]. During 4.8 years of systematic antihypertensive treatment, in-treatment reduction of LVMI by 25.3 g/m^2 (1 SD)

was associated with 22% reduction in composite endpoints, 38% reduction in cardiovascular mortality and 24% reduction in fatal and non-fatal stroke independent of the effect of blood pressure lowering and randomized treatment regimen in the LIFE study. Similar time-varying Cox analyses showed that in-treatment absence of LV hypertrophy, treated as a yes-no diagnosis, was associated with a 42% reduction in composite endpoints, 66% reduction in cardiovascular mortality and 52% reduction in fatal and non-fatal myocardial infarction, also adjusted for the effect of blood pressure lowering. This report and a parallel one showing independent association of lower ECG indices of LV hypertrophy with reduced rates of cardiovascular events in the entire LIFE population [47] provided the first demonstration of a blood pressure-independent effect of LV mass reduction on prognosis. These findings support the concept of reducing cardiac target organ damage as a goal of antihypertensive treatment. In other analysis from the LIFE study, losartan was more effective than atenolol in reducing echocardiographic LV mass [48] or electrocardiographic indices thereof [49]. Further analyses of the LIFE echocardiographic data showed that even though LV geometry changed significantly during treatment, time-varying LV geometry predicted higher risk of composite endpoints [HR 2.99 (1.16-7.71) for concentric remodeling, HR 1.79 (1.17-2.73) for eccentric hypertrophy, and HR 2.71 (1.13-6.45) for concentric hypertrophy when adjusting for randomized treatment, Framingham risk score, race, as well as time-varying systolic blood pressure] [50]. This suggests that concentric LV geometry carries the most risk, extending an observational study by Muiesan et al. in a group of 436 hypertensive patients in which persistent or new development of concentric LV geometry was associated with higher risk of cardiovascular morbidity and mortality during prospective follow-up [51].

Left ventricular systolic function in patients with left ventricular hypertrophy

Assessment of LV systolic performance by the ratio of observed LV endocardial fractional shortening to the value predicted by the level of end-systolic stress in normal individuals [52, 53] may appear to identify LV function as "supranormal" in hypertensive patients compared with normal controls, even in the absence of LV hypertrophy [52, 54, 55]. LH V midwall shortening, in relation to stress, provides a different impression of the integrity of systolic performance; midwall shortening may be impaired in hypertensive patients with normal or supranormal LV ejection fraction. Wachtell et al. confirmed that LV endocardial fractional shortening or midwall shortening were lower with higher LV mass and relative wall thickness either alone or in combination. In the subgroup with concentric LV hypertrophy we found that over 40% had overt LV systolic dysfunction, manifested by endocardial fractional shortening or midwall shortening below the 2.5th percentile of normal values. Even in the subgroup with normal LV geometry we found impaired LV systolic performance in 10% of cases, 5 times more commonly than in the reference population [30, 56]. It was further found that hypertensive patients with normal geometry or with eccentric LV hypertrophy had high end-systolic stress compared to normal adults. This result, previously reported in mildly hypertensive adults [57], also reflects the Laplace relationship, which indicates that high relative wall thickness tends to normalize wall stress. Moreover, impaired endocardial fractional shortening was most prevalent in eccentric LV hypertrophy while impaired midwall shortening was most prevalent with concentric remodeling or, especially concentric hypertrophy.

The clinical significance of impaired LV systolic performance in hypertensive patients is not yet fully clarified, however, there are numerous reports of patients with heart failure and "normal" LV systolic chamber function [58]. In the Framingham Heart Study in participants aged 40 to 89 years and free of chronic heart failure, Levy et al. [59] found that hypertension antedated the development of heart failure. After adjusting for age and heart failure risk factors in proportional hazards regression models, the hazard of developing heart failure in hypertensive compared with normotensive subjects was about 2-fold higher in men and 3-fold higher in women. Multivariate analyses revealed that hypertension had a high population-attributable risk for chronic heart failure, accounting for 39% of cases in men and 59% in women. Survival following the onset of hypertensive heart failure was bleak; only 24% of men and 31% of women survived 5 years. Furthermore, recent reports support a relationship between depressed systolic midwall mechanics and abnormal diastolic LV filling in patients with high LV mass [60, 61].

Changes in left ventricular systolic function during antihypertensive treatment

Systematic antihypertensive treatment can change systolic performance substantially. Blood pressure lowering by 27/13 mm Hg in the LIFE echo study resulted in slight reduction in endocardial fractional shortening while midwall shortening increased from 15.4 to 16.8% and stress-corrected midwall shortening, a measure of myocardial contractility, increased from 97 to 105%.

Multivariate analyses confirmed that these improvements were related to changes in LV mass and relative wall thickness as well as in stroke volume [62]. These findings indicate that partial normalization of blood pressure and LV mass can result in reversal of both supranormal LV chamber function and the low function of average myocardial fibers at the LV midwall that often is impaired in hypertensive heart disease. Furthermore, Gerdts et al. reported that hypertensive women in the LIFE echocardiography study retained higher LV ejection fraction and stress-corrected midwall shortening compared to men despite of less hypertrophy regression during long-term antihypertensive treatment [63].

The clinical significance is that LV systolic function can be improved by systematic antihypertensive treatment even in patients with preserved LV ejection fraction.

Prognostic significance of treating systolic function in left ventricular hypertrophy and preserved left ventricular systolic function

In a study of 294 hypertensive patients receiving varying treatment, de Simone et al. [64] showed that depressed midwall shortening predicted adverse outcomes, especially in the subgroup with LV hypertrophy, whereas endocardial fractional shortening did not. This was subsequently confirmed in other observational studies [65, 66]. Data from the LIFE echocardiographic study further expanded knowledge of treatment effects on LV systolic function. Analysis in hypertensive patients with preserved ejection fraction showed that higher in-treatment endocardial fractional shortening was associated with 28% fewer subsequent fatal and non-fatal myocardial infarctions, whereas in-treatment stress-corrected endocardial fractional shortening was not associated with any endpoints. In contrast, improved in-treatment midwall shortening was associated with an 18% reduction in the risk of the composite endpoint of stroke, myocardial infarction, and cardiovascular mortality as well as a 33% reduction in risk of the component fatal and non-fatal myocardial infarction. Improvement in stress-corrected midwall shortening was in addition to the composite endpoint (23% reduction) and myocardial infarction (31% reduction) also associated to a 29% reduction in the component fatal and non-fatal stroke when adjusting for time-varying systolic and diastolic blood pressure and time-varying LVMI and randomized treatment [67]. The clinical significance is that antihypertensive treatment and reduction in LV hypertrophy also improves LV systolic function, and even small improvements in LV systolic function, especially at the midwall, translates into less cardiovascular morbidity and mortality [67].

Left ventricular diastolic function in patients with left ventricular hypertrophy

It has been accepted ever since the early demonstration that ECG P wave abnormality preceded evidence of LV hypertrophy that the evolution of hypertensive LV hypertrophy is initiated by abnormalities of LV diastolic function, in presence of preserved LV systolic function. It is well established that LV relaxation is often abnormal in hypertensive patients with [68] or without [69] LV hypertrophy, suggesting that abnormal relaxation might be an early response to cardiac overload caused by hypertension [69, 70]. Increased cardiac myocyte volume, myocardial ischemia caused by hypertensive microvascular disease, and a mismatch between increased oxygen demand, and reduced coronary flow reserve may all contribute to the abnormal diastolic relaxation [71].

Data from the LIFE echocardiography study found very high prevalences (>80%) of abnormal diastolic LV filling patterns in hypertensive patients with electrocardiographic LV hypertrophy [60]. Most of these patients had a decreased E/A-ratio and prolonged deceleration time, readily-recognized manifestations of impaired early diastolic LV relaxation, but an appreciable minority had a "pseudonormal" LV filling pattern. Furthermore, isovolumic relaxation time, A-peak, atrial filling fraction and left atrial dimension, an indirect index of atrial overload due to abnormal diastolic function differed significantly among the four LV geometric patterns [60]. There was also a strong association between higher LV mass and worse LV early diastolic relaxation as manifested by prolonged isovolumic relaxation time (IVRT). This association remained significant in regression analyses that took into account other variables also associated with longer IVRT, including male gender, lower peak early LV filling velocity and higher deceleration time, briefer mitral valve opening time and lower pulse pressure/stroke volume ratio. Among the minority of LIFE patients with normal LV mass, isovolumic relaxation time (IVRT) was significantly longer in those with concentric LV remodeling characterized by high relative wall thickness, than in those with normal relative wall thickness (i.e. normal geometry). On the other hand, in the presence of LV hypertrophy, relative wall thickness was not a significant correlate of IVRT. This finding suggests that increased LV mass is a stronger stimulus to impaired LV relaxation than is a concentric LV geometric pattern. These observations also suggest that for antihypertensive therapy to be optimally beneficial for LV filling it would be desirable to normalize not only LV mass but also relative wall thickness.

This observation of a strong association between abnormal filling and concentric LV hypertrophy has been confirmed by de Simone *et al.* in data from the HyperGen study [72]. It has been speculated

that LV wall thickness and cavity dimension per se contribute to diastolic dysfunction [73] but this has not been confirmed in all studies [74].

Wachtell et al. reported from the LIFE echocardiography study a relationship between LV diastolic abnormality and abnormal LV systolic function [75]. Impaired LV early diastolic relaxation, as manifested by prolonged isovolumic relaxation time, was associated with lower LV systolic myocardial function independently of age and other relevant covariates. In addition, lower levels of stress-corrected LV midwall shortening and early diastolic relaxation were both related to higher LV mass, but the relation between prolonged isovolumic relaxation time and reduced LV systolic midwall function remained significant when LV mass was taken into account.

Although the clinical significance of prolonged IVRT and other abnormalities of LV filling have not yet fully been clarified there are numerous reports of patients with heart failure and apparently normal systolic LV function [58]. Levy et al. concluded in a study from Framingham that hypertension was the most common risk factor for chronic heart failure, and it contributed to the pathogenesis of a large proportion of heart failure cases in a population-based sample [59]. There are several reports that hypertension and LV hypertrophy plays an important role in the development of heart failure. Available population-based studies document significant prediction of cardiovascular events by indices of LV diastolic dysfunction [76-78], but have not to date related them specifically to CHF among hypertensive adults.

However, it remains controversial whether heart failure patients with preserved LV systolic function by exclusion have LV diastolic heart failure [79-82].

Change in left ventricular diastolic function during antihypertensive treatment

In view of the strong relations between LV mass and relative wall thickness and transmitral flow variables, Wachtell et al. examined whether reduction in LV mass and relative wall thickness as well as blood pressure by systematic antihypertensive treatment over one year could improve diastolic transmitral flow variables [83]. Blood pressure lowering by 23/11 mm Hg resulted in more normal isovolumic relaxation time and E/A ratio while LV inflow deceleration time increased. The directionally opposite changes in isovolumic relaxation time and deceleration time indicate improvements in both active LV relaxation (manifested by the shortened IVRT) and passive chamber stiffness during early diastole [84]. Furthermore, the prevalences of normal transmitral filling increased while prevalences of abnormal relaxation and pseudonormal pattern decreased and restrictive filling pattern remained unchanged. Patients with LV mass reduction had significant improvement in left atrial diameter, isovolumic relaxation time, E/A-ratio and mitral valve deceleration time. However, patients without LV mass reduction had no change in their diastolic filling variables. Further multivariate analyses showed that IVRT shortening was independently associated with reduction in LV mass, increase in E/A-ratio was independently associated with reduction in diastolic blood pressure and increase in the deceleration time was independently associated with reduced end-systolic relative wall thickness. Although antihypertensive therapy resulted in LV mass or relative wall thickness regression and significant improvement of diastolic filling variables, abnormalities of diastolic LV filling remained common after 1 year of observation.

These results support the finding by Yalcin and co-workers [85] that 6 months antihypertensive treatment with perindopril in 24 patients led to reduction in LV mass and left atrial volume and increased E/A-ratio, but contrasts with a study by Cuspidi in a small population (n=39) in which 6 months of antihypertensive treatment had no significant effect on LV diastolic filling parameters [86].

The clinical implication is that regression of hypertensive LV hypertrophy and of concentric LV geometry is associated with partial normalization of several LV diastolic filling variables, including the IVRT, E/A-ratio and mitral valve deceleration time, independent of the reduction in blood pressure, indicating direct effects of normalization of LV geometry on diastolic filling parameters. The complexity of factors influencing LV diastolic filling is highlighted by the fact that the deceleration time of early diastolic filling passive inflow increased at the same time as the as the IVRT decreased. This implies that the deceleration time was effected in opposite directions, being lengthened by impaired relaxation and shortened by increased LV stiffness due to increased relative wall thickness and probable alterations in myocardial connective tissue. A strong relation between invasively-measured early diastolic chamber stiffness and shortened deceleration time was reported in an experimental study by Little et al. [84] and in a human study by Garcia et al. [87]. Treatment improved relaxation predominated in shortening the IVRT while reducing passive LV chamber stiffness predominated in prolonging the deceleration time of early diastolic transmitral flow. The improvement of diastolic dysfunction parameters may contribute to the ability of blood pressure reduction to prevent congestive heart failure and highlights the potential of normalization of LV geometry by antihypertensive therapy to prevent or treat congestive heart failure in hypertensive patients with LV hypertrophy an LV diastolic dysfunction, a condition for which no direct treatment yet exists [88].

Prognostic significance of treating diastolic function in left ventricular hypertrophy

Several studies indicate that abnormal E/A-ratio predicts poor outcome in patients with hypertension [89], dilated cardiomyopathy [90], myocardial infarction [91] and in samples of the general population [76, 77].

Even though improvement of LV structure also improves LV diastolic function variables, a further question would be whether this improvement in diastolic function translates into a reduction in subsequent cardiovascular morbidity and mortality. Data from the LIFE echocardiography study showed that more than 4 years of systematic antihypertensive therapy resulted in an increase in the prevalence of normal transmitral flow pattern from 28 to 46% of patients [92]. However, even though antihypertensive treatment often resulted in a marked increase in the prevalence of normal mitral valve flow pattern, this "normalization" of diastolic function was not associated with reduced cardiovascular morbidity and mortality when adjusting for blood pressure, left atrial size, LV mass and treatment in time-varying Cox analyses. Although there is a possibility that this interpretation is a result of a type II error, it is also quite possible that maintenance of normal diastolic filling pattern at baseline or normalization of abnormal transmitral flow during treatment is of lesser importance compared to reduction of BP and of LV hypertrophy with regard to cardiovascular morbidity and mortality in treated hypertensive patients with target organ damage at baseline. It is also possible that maximum improvement in LV diastolic filling patterns requires several years of aggressive antihypertensive treatment, which may not have allowed enough time thereafter to show an impact on cardiovascular morbidity and mortality [92]. The strong relation between E/A-ratio and cardiovascular events in a prior study with 11 years of follow-up supports this interpretation [89].

Conclusions

Finding and treating cardiac target organ damage in hypertensive patients has been given more emphasis in the current European Society of Hypertension/Europeans Society of Cardiology Guidelines [93]. Definition of hypertension is dependent upon different levels of blood pressure and upon the presence of target organ damage and also coincides with the intensity of antihypertensive treatment.

One to two decades ago, data suggested that LV hypertrophy predicted cardiovascular morbidity and mortality. More recent studies have clarified the importance of indexation and utilization of correct partition values to identify LV hypertrophy. Furthermore, systematic treatment is very effective in reducing LV hypertrophy and normalizing LV geometry. Finally, reduction in LV mass, absence of LV hypertrophy and to a lesser degree normalization of relative wall thickness reduce cardiovascular morbidity and mortality quite significantly, independent of the blood pressure reduction *per se*, emphasizing the importance of choosing pharmacotherapy known to reverse LV mass effectively.

Recent trials have also clarified the high prevalence of abnormal myocardial function and contractility even when patients have preserved LV ejection fraction and shown that reduction in LV mass and relative wall thickness by systematic antihypertensive treatment is in turn associated with improvement in LV myocardial function. Furthermore, recent data suggest that the improvement of LV systolic myocardial function, in patients with preserved LV ejection fraction, is associated with a reduction in cardiovascular morbidity and mortality independently of the blood pressure and LV mass reduction per se, emphasizing the importance of choosing pharmacotherapy known to increase myocardial contractility effectively [67].

Finally, recent trials show high prevalences of LV diastolic abnormalities in hypertensive patients with LV hypertrophy. Data also document relations between LV systolic and diastolic abnormality, rendering completely isolated abnormal LV diastolic function uncommon in hypertensive patients with LV hypertrophy. Furthermore, recent data suggest that systematic antihypertensive treatment over almost 5 years partially normalizes transmitral flow variables and that this normalization is associated with LV mass regression. However, normalization of LV diastolic function was not, as is the case with LV systolic function, found to be associated with an improvement of cardiovascular morbidity and mortality in hypertensive patient with LV hypertrophy [92]. However, it is possible that it may take longer than 5 years for normalization of LV diastolic function to impact on cardiovascular morbidity and mortality.

Thus, in the short term (i.e. 5 years) clinicians should focus on blood pressure reduction, finding LV hypertrophy in hypertensive patients, reducing LV hypertrophy if present and improving LV systolic myocardial function, even when hypertensive patients have preserved LV ejection fraction, in order to reduce cardiovascular morbidity and mortality. Improvement of LV diastolic function that is achieved may result in improved exercise tolerance and also less heart failure but appears to be of lesser importance than blood pressure reduction, LV hypertrophy regression and

improvement of myocardial function for prevention of major cardiovascular events.

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