Regression of target organ damage

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Increased left-ventricular mass (left-ventricular hypertrophy) and albuminuria are measures of target organ damage central to assessing risk of future cardiovascular morbidity and mortality in patients with hypertensive and other cardiovascular disease [1,2]. However, beyond the value of markers of target organ damage for prediction of risk is whether there is available treatment for reversal of target organ damage and whether this improvement also leads to less risk of subsequent cardiovascular morbidity or mortality.

Left-ventricular mass is strongly related to blood pressure, body size, left-ventricular work load and, after puberty, sex. In patients with hypertension, lowering blood pressure reduces cardiovascular risk and can reduce left-ventricular mass. However, lowering blood pressure into the normal range does not necessarily normalize cardiovascular risk in patients with hypertension. Findings from the Losartan Intervention For Endpoint reduction (LIFE) study demonstrated that reductions in left-ventricular mass are associated with significant decreases in cardiovascular risk independent of the risk reduction from the blood pressure lowering *per se*, suggesting that failure to reduce left-ventricular mass during antihypertensive treatment may explain, in part, residual risk, despite normalization of blood pressure [3].

Albuminuria is a measure of target organ damage of the vasculature and a marker of total atherosclerotic burden. There is a significant correlation between the rate of albumin excretion into the urine, and the degree of lipid deposition into arterial walls and the extent of atherosclerosis [4]. Among hypertensive patients, there is a continuous relationship between the level of baseline albuminuria and cardiovascular morbidity and mortality [5], and decreases in albuminuria during antihypertensive treatment are associated with reduction in cardiovascular morbidity and mortality that is independent of risk reduction achieved by the reduction in blood pressure [6].

Thus, it would not be surprising if simultaneous improvement of target organ damage in two or more 'organs' lead to additive risk reductions in cardiovascular morbidity and mortality, especially if the two 'organ' damage represents different parts of the pathophysiological pathway leading to myocardial infarction, stroke and cardiovascular mortality. Supporting this hypothesis, data from the LIFE study showed that reductions of in-treatment albuminuria and electrocardiographic left-ventricular hypertrophy were associated with decreased risk of cardiovascular events, independently of each other, after adjustment for baseline albuminuria, left-ventricular hypertrophy and traditional cardiovascular risk factors [7], indicating that both a reduction in albuminuria and regression of left-ventricular hypertrophy may improve prognosis. This supports the idea that albuminuria and left-ventricular hypertrophy are to some degree markers of different aspects of cardiovascular damage [7].

Notwithstanding, there is significant overlap in the impact of hypertension on different measures of cardiovascular target organ damage. Previous study by our group has shown that hypertensive patients with electrocardiographic left-ventricular hypertrophy and the strain pattern of repolarization, an additional strong cardiovascular risk marker, also have higher levels of urine albumin/creatinine ratio [8]. Particularly relevant to the current study, reduction in urine albumin/creatinine ratio during treatment correlated to reduction in left-ventricular hypertrophy, independently of reduction in blood pressure, suggesting that a relationship between left-ventricular hypertrophy and glomerular albumin leakage that is not just due to parallel blood pressure-induced changes [9]. Reasons for this remain unclear, but may be due to longer duration of disease and/or genetic factors.

In the current issue of *Journal of Hypertension,* Rodilla *et al.* [10] builds upon this previous study on target organ damage in hypertensive patients, demonstrating that regression of echocardiographic left-ventricular hypertrophy is dependent on the degree of albuminuria. In their group of patients with untreated hypertension and left-ventricular hypertrophy, reduction of blood pressure burden was the main driving factor associated with left-ventricular hypertrophy regression, but significant reduction of urine albumin/creatinine ratio was also related to left-ventricular hypertrophy regression. Patients with microalbuminuria at baseline and significant reduction in albuminuria during treatment had similar probabilities of left-ventricular hypertrophy regression as patients who were normoalbuminuric at baseline. In contrast, patients with baseline microalbuminuria with less reduction of their

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albuminuria were significantly less likely to regress their left-ventricular hypertrophy. Importantly, these associations were independent of the degree of blood pressure reduction. These findings suggest that the degree of vascular disease burden, as manifested by albuminuria, is an independent predictor of the magnitude of left-ventricular hypertrophy, and that persistence or development of albuminuria during antihypertensive treatment may well be indicative of a lower likelihood of regression of hypertrophy in response to blood pressure lowering. In addition, there may be a genetic explanation for this observation. Recent studies suggest that microRNAs (miRs), a class of noncoding RNAs that negatively regulate gene expression, are involved in the phenotypic expression of target organ damage [11]. Although it still remains unclear which or how many of the miRs are involved, both miR-1 and miR-133a seem to be likely candidates for expression of cardiac and vascular hypertrophy as well as kidney disease [12–14].

Future studies should be designed to more definitely address whether monitoring of albuminuria can be used as a marker of the efficacy of antihypertensive treatment to reduce left-ventricular mass in addition to its value as a marker of cardiovascular risk.

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Conflicts of interest

There are no conflicts of interest.

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