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Advances in the Epidemiology of Heart Failure and Left Ventricular Remodeling

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Heart failure (HF) continues to impose a major public health burden.[1] Whereas considerable improvements in HF treatment have resulted from clinical trials, epidemiologic investigations complement clinical trials by enhancing our ability to identify individuals at risk and, in turn, facilitate the development of interventions aimed at the primary prevention of HF. Accordingly, there have been several noteworthy advances to date in the epidemiology of heart failure and subclinical myocardial disease, which are summarized below.

Dynamic Left Ventricular Remodeling Over the Life Course

Adverse left ventricular (LV) remodeling is considered an intermediate phenotype of HF, given the high incidence of HF events observed among individuals with subclinical abnormalities LV structure or function (also known as 'stage B heart failure').[2] Recent investigations have harnessed longitudinal data from large epidemiologic cohorts to examine how the heart remodels over the adult life course, and to characterize the factors that contribute to this remodeling. The most common form of adverse LV remodeling is increased LV mass, which has long been associated with incident HF; this association was originally demonstrated using electrocardiography, followed by echocardiography, and then recently confirmed using cardiac magnetic resonance imaging studies.[3,4] Longitudinal data have now validated the results of prior cross-sectional studies indicating that LV mass progressively increases over the life course, and particularly in the presence of risk factors such as obesity, hypertension, and diabetes.[5] However, increased LV mass can result from a variety of different remodeling patterns, including concentric or eccentric changes in geometry.[6,7] The most common remodeling pattern observed in 'normally aging' individuals over the life course is a concentric remodeling pattern, in which LV wall thickness progressively increases and LV cavity dimensions progressively decrease in the setting of preserved and increasing ejection fraction.[3,8] Interestingly, the rate of increase in relative wall thickness is more pronounced in women compared to men across all ages, and especially so in later life. This finding may be related to intriguing histologic evidence of less cardiomyocyte dropout and slightly higher cardiomyocyte turnover observed in aging women compared to men.[9,10] These gender differences may also account for the higher

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prevalence of concomitantly increased ventricular and vascular stiffness observed in older women versus men living in the community.[11]

However, the extent to which the concentric remodeling pattern of 'normal' aging contributes to the lifetime risk of HF[12] is far from clear. The presence of conventional risk factors for HF actually serves to modify this typical remodeling pattern. For instance, in the setting of obesity, hypertension, and diabetes, LV wall thickness remains increased but cavity dimensions do not decrease proportionately with age.[8] This likely reflects an impaired compensatory response to increased wall stress, which is evidenced by a less robust increase in ejection fraction over time. That said, absolute values of LV ejection fraction remain invariably in the normal range, indicating that morphologic changes in cardiac structure can be accompanied by subclinical changes in cardiac performance that are not reflected by major changes in EF.[13,14] Indeed, concentric as well as eccentric cardiac phenotypes are known to include sub-phenotypes characterized by better or worse function.[7] And, concordant with evidence of progressive age-associated increases in left atrial size,[15] conventional measures of diastolic dysfunction are highly prevalent among middle-aged and older adults in the community[16,17] and have been shown to increase risk for HF.[17,18] Thus, further work is needed to clarify the functional changes that occur as LV geometry evolves over time, with and without exposure to traditional risk factors, and how these changes contribute to HF risk.

The impact of novel risk factors on LV remodeling also warrants further study. In addition to traditional risk factors, recent data have associated dyslipidemia,[19] physical inactivity/abdominal obesity,[20,21] and sleep apnea[22] with increased risk for HF in the community. Other recent investigations have demonstrated a familial aggregation of LV geometric phenotypes, particularly concentric LV hypertrophy.[23] Family history of HF has also been associated with a greater odds of eccentric LV geometry in offspring free of HF.[23] Thus, future studies should consider the genetic influences of LV remodeling, in parallel with the study of non-genetic determinants.

Beyond the Left Ventricle: Extra-Cardiac Predictors of Heart Failure Risk

Notwithstanding the centrality of subclinical LV disease in the development of HF, recent clinical investigations have shed light on the importance of extra-cardiac contributors to HF risk. It is well known that the LV functions in physiologic equilibrium with the right heart,[24] the pulmonary circuit,[25] and other major organ systems. Accordingly, adverse LV remodeling and dysfunction have been associated with pulmonary airflow obstruction[26] and decreased renal function[27] in cross-sectional studies; abnormalities in serum creatinine,[28,29] albumin,[28,29] and hemoglobin[30] have also been associated with HF risk and/or worse HF outcomes. Until recently, however, extra-cardiac contributions to subclinical LV disease and dysfunction had not been investigated comprehensively. In a large community-based sample, Lam and colleagues examined markers of subclinical dysfunction of several non-cardiac organ systems and reported that lower FEV1:FVC ratios and hemoglobin and higher serum creatinine were each associated with a 30% increased risk of incident HF after adjustment for conventional HF risk factors.[17] Interestingly, renal dysfunction and anemia were particularly associated with incident HF with reduced ejection fraction (HFREF) and pulmonary obstructive disease with incident HF with preserved ejection fraction (HFPEF). Still, the strongest predictors of incident HFREF and HFPEF were asymptomatic systolic and diastolic dysfunction, respectively. Thus, the extent to which subclinical cardiac dysfunction promotes subclinical non-cardiac dysfunction, or vice versa, remains unclear. However, these findings underscore the fact that progression to HF is likely a multi-organ, multi-systemic process.[31] Further research is needed to define the interdependent

hemodynamic, neurohormonal, paracrine, and/or other mechanisms that underlie the interactions between cardiac and non-cardiac organ systems.

Biomarkers of Left Ventricular Remodeling and Heart Failure

Biologic markers can be used to classify subclinical disease phenotypes as well as for prognostication.[7,32] Additionally, biomarkers can also be used to provide insight regarding the pathobiology of both LV remodeling and HF.[33,34] Although there have been few systematic investigations of multiple 'pathway markers', recently published studies have identified markers reflecting activity of select biological pathways that are associated with LV remodeling and with incident HF. Velagaleti and colleagues found that biomarkers of inflammation (C-reactive protein), hemostasis (fibrinogen and plasminogen activator inhihibitor-1[PAI-1), and activation of the renin-angiotensin-aldosterone system (aldosterone-to-renin ratio [ARR]) were each associated with LV geometry in separate models.[35] However, only ARR was associated with eccentric as well as concentric LV hypertrophy when all biomarkers were included in the same model. The same investigators applied a similar multimarker strategy to investigate predictors of incident HF and observed that only the B-type natriuretic peptide (BNP) and the urinary albumin-to-creatinine ratio (UACR) emerged as significant predictors of non-ischemic HF risk in analyses that also included C-reactive protein, PAI-1, homocysteine, and ARR.[36] These findings are consistent with prior literature suggesting that markers of RAAS activation are more strongly associated with LV remodeling parameters,[37] whereas BNP is more widely recognized as a risk predictor of overt HF.[38] Both of these pathways have been targeted for therapeutic interventions (e.g., pharmacologic modulation of the RAAS versus natriuretic peptide pathways).[39–43] Extending from this work, recent studies have identified alternate putative biomarkers of subclinical LV disease (e.g. adiponectin[44]) and HF risk (e.g. growth differentiation factor-15[45] and markers of fibrosis[46]). An additional area of intense research is the search for common genetic variants that may underlie LV remodeling,[47,48] incident HF,[49] and mortality after the onset of HF.[50,51] The potential role of these newer biomarkers as targets remains to be determined. It is conceivable that both genetic and circulating biomarkers could be combined with standard risk factors for predicting HF risk or for identifying individuals at risk of developing adverse LV remodeling and/or subclinical LV dysfunction. Important information will also accrue from ongoing experimental studies that are investigating alterations in myocardial gene expression patterns in cardiac hypertrophy and HF,[52] and have demonstrated reciprocal changes in metabolic and signaling pathways in the myocardium with increasing severity of HF.[53]

Conclusion

In summary, recent epidemiologic investigations have provided us with several key insights regarding LV remodeling and HF risk. First, the LV undergoes progressive morphologic changes over the adult life course, characterized by a concentric remodeling pattern that is modified in the setting of exposure to traditional and novel risk factors, on a background of genetic determinants that have yet to be fully identified. The extent to which the 'normal aging' pattern of LV remodeling leads to eventual LV dysfunction and the time course of such evolution remains unclear. Second, the subclinical abnormalities leading up to clinical HF are not limited to the LV, but include alterations involving the right heart and other key organ systems, highlighting that chronic non-cardiac processes are developing in concert with subclinical LV remodeling and dysfunction in the progression to clinical HF. Finally, biomarkers representing the activity of select biologic pathways appear associated with both LV remodeling and propensity for HF. These same pathways could also underlie the interdependent contributions of cardiac and non-cardiac dysfunction to HF risk. Ongoing genomic and gene expression studies are likely to augment investigations of these candidate

pathways as well highlight previously unidentified targets for further research. Taken together, recent developments in epidemiologic research have provided a wealth of additional insights into the precursors of HF and will, hopefully, continue to fuel ongoing discovery and development of preventive therapies.

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