Despite significant progress in the treatment of heart failure, its incidence and prevalence are rising in the United States. In order to further heart failure prevention efforts, the American Heart Association and the American College of Cardiology proposed a classification scheme for heart failure to include stage A patients (those who do not have structural heart disease but are at risk for heart failure) and stage B patients (those with asymptomatic cardiac structural or functional abnormalities). Measures implemented to prevent progression of patients at risk for heart failure rely on our ability to predict accurately who will most likely benefit from early interventions. Because heart failure eventually leads to multiorgan involvement, even mild dysfunction of a noncardiac organ may trigger clinical manifestations of heart failure. In addition, preexisting asymptomatic ventricular dysfunction may interact with a dysfunctional noncardiac organ and accelerate the progression to overt heart failure. To date, there is little information available to describe the contribution of asymptomatic systolic and diastolic dysfunction or that of noncardiac organ dysfunction to the occurrence of heart failure, and the article by Lam et al in the present issue of Circulation is bringing forth important data in that regard.

One thousand thirty eight participants from the Framingham Heart Study who were free of heart failure or overt renal failure at enrollment (1987–1990) were followed up for an average of 11 years. Detailed echocardiographic assessment was performed at baseline, and participants with an ejection fraction ≤45% were considered to have asymptomatic systolic dysfunction, whereas those with an ejection fraction >45% and with abnormal relaxation or pseudonormal or restrictive filling were considered to have asymptomatic diastolic dysfunction. In line with their hypothesis that major noncardiac organ dysfunction may accelerate the progression to heart failure, the investigators also examined several organ systems: renal (serum creatinine), hepatic (albumin), pulmonary (forced expiratory volume in 1 second [FEV1], forced vital capacity [FVC]), hematological (hemoglobin), and systemic inflammation/oxidative stress (white cell count). Cut points based on the lower 25th or upper 75th percentile of each of the above continuous variables were used in order to define noncardiac organ dysfunction. The cohort was older (average age 76 years), with most participants being women and having a history of hypertension; very few had diabetes mellitus or coronary artery disease. The noncardiac organ system assessment yielded unremarkable results, with those participants labeled as showing noncardiac organ dysfunction having values that most clinicians will consider fairly ordinary (eg, serum creatinine >1.05 mg/dL, hemoglobin <13 g/dL, or FEV1/FVC ratio <91% predicted).

After adjustment for traditional risk factors, asymptomatic systolic dysfunction (present at baseline in 5% of the participants) doubled the overall risk for developing symptomatic heart failure, whereas the risk for developing systolic heart failure was increased 4-fold. Similarly, asymptomatic diastolic dysfunction (present in a third of participants at baseline) was associated with a 30% increased overall risk for developing heart failure and with a doubling of the risk for developing diastolic heart failure.

When the impact of noncardiac organs on incident heart failure was tested, only the renal, pulmonary, and hematopoietic systems showed significant effects. Each of the above organ dysfunctions was associated with a 30% increased overall risk for developing heart failure, and the risk increased proportionally if ≥1 organ was involved. There was no significant interaction between noncardiac organ system dysfunction and the presence of left ventricular systolic or diastolic dysfunction at baseline, indicating that these represent distinct pathways to progression to clinical heart failure. Interestingly, whereas higher serum creatinine and lower hemoglobin were associated with incident systolic heart failure, a lower FEV1/FVC ratio was associated with development of diastolic heart failure, indicating likely separate pathophysiology of the heart failure syndrome.

The current study builds on prior evidence that systolic and diastolic dysfunctions exist in the community and extends these findings to prove that they are strongly associated with the development of clinical heart failure. Although data from the Cardiovascular Health Study showed that systolic and diastolic dysfunction can lead to heart failure, they did not clearly identify the individual specific contributions. In contrast, Lam et al demonstrate that left ventricular systolic dysfunction predicts future systolic heart failure, and diastolic dysfunction portends diastolic heart failure. These findings are important and fill the knowledge gap linking stage B to stage C in the American College of Cardiology/ American Heart Association classification scheme, whether
referring to systolic or diastolic heart failure. Moreover, as mounting evidence shows that the proportion of community patients at risk (stage A) or with impaired ventricular function (stage B) is quite high (22% and 34%, respectively), the current study emphasizes the need for continuous prevention in order to stop the inexorable progression to clinical heart failure.

The true novelty of the current research consists in identifying the role of noncardiac organ systems in the early stages of heart failure. Although advanced heart failure triggers extracardiac manifestations (poor perfusion and worsening congestion leading to cardio-renal syndrome6 and restrictive lung physiology), no prior studies have shown that even minor preexisting dysfunction can accelerate the progression to heart failure.

In the current study, renal dysfunction conferred a 30% increased risk for developing systolic heart failure. The kidney regulates the extracellular fluid volume, and minor abnormalities in kidney function can impair its capacity to maintain this volume within the normal range. Expansion of the extracellular fluid volume increases the preload and leads to left ventricular dilation and remodeling that may increase the oxygen demand and create a situation of relative myocardial ischemia. In addition, myocardial remodeling may cause functional mitral insufficiency, which may contribute to pulmonary hypertension and can impair the left and right ventricular function. If perpetuated, the volume overload and increased preload can increase transmural myocardial pressure and left ventricular mass leading to left ventricular hypertrophy, a major risk factor for systolic dysfunction. In addition, in the case of preexistent systolic dysfunction (even asymptomatic), the beneficial atrial-renal reflexes and the decrease in renal sympathetic tone are abolished, and the renin-angiotensin-aldosterone system gets activated, leading to further myocardial remodeling, impaired salt and water excretion, and eventually clinical heart failure.

Even a mild decrease in hemoglobin levels with resultant decrease in oxygen carrying capacity can lead to decreased renal perfusion, and subsequent renal failure may lead to decreased endogenous erythropoietin levels that ultimately worsen anemia, leading to an increased cardiac workload, completing the vicious circle of cardio-renal-anemia syndrome. Indeed, in the present study both renal and hematopoietic system dysfunction had the same hazard ratio (1.31) for incident systolic heart failure, and their additive effect doubled the risk.2

Airflow obstruction has been associated with smaller left ventricular end-diastolic volumes and reductions in stroke volume and cardiac output despite a preserved ejection fraction, translating into higher filling pressures. Impaired left ventricular filling in this case is due to the alveolar hypoxia and related pulmonary vascular changes (vasoconstriction and vascular remodeling), pulmonary hyperinflation (with decreased venous return), and ventricular interdependence (impairing ventricular filling). If perpetuated, these changes will lead to structural alveolar remodeling causing an increased resistance to gas transfer across the alveolar-capillary membrane and triggering dysnea as a manifestation of diastolic heart failure. Not surprisingly, in keeping up with recent studies, the current investigation also found that abnormal lung function confers a 40% increased risk of incident diastolic heart failure.

The data presented by Lam et al are important and provocative, opening new avenues for understanding the complexity of the heart failure syndrome. The traditional view of myocardial infarction or hypertension alone causing heart failure no longer applies. It is clear that dysfunctions in multiple organs interact with a structurally or functionally abnormal myocardium to hasten the progression to heart failure (the Figure). Further research should focus on sex and racial interaction (eg, women are more likely to have anemia and lower lung volumes; blacks are more likely to have renal dysfunction), as well as on the effects of early therapeutic interventions that target stage A and B patients (eg, angiotensin-converting enzyme inhibitors can delay the progression of ventricular systolic dysfunction and that of renal insufficiency). Until then, clinicians beware, because all roads lead to heart failure!

Disclosures

None.
References


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Omnis Viae Romam Ducunt: Asymptomatic Cardiac and Noncardiac Organ System Dysfunction Leads to Heart Failure
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