Heart Failure

Cardiac Dysfunction and Noncardiac Dysfunction as Precursors of Heart Failure With Reduced and Preserved Ejection Fraction in the Community

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Background—Heart failure (HF) is a clinical syndrome characterized by signs and symptoms involving multiple organ systems. Longitudinal data demonstrating that asymptomatic cardiac dysfunction precedes overt HF are scarce, and the contribution of noncardiac dysfunction to HF progression is unclear. We hypothesized that subclinical cardiac and noncardiac organ dysfunction would accelerate the manifestation of HF.

Methods and Results—We studied 1038 participants of the Framingham Heart Study original cohort (mean age, 76±5 years; 39% men) with routine assessment of left ventricular systolic and diastolic function. Major noncardiac organ systems were assessed with the use of serum creatinine (renal), serum albumin (hepatic), ratio of forced expiratory volume in 1 second to forced vital capacity (FEV1:FVC ratio; pulmonary), hemoglobin concentration (hematologic/oxygen-carrying capacity), and white blood cell count (systemic inflammation). On follow-up (mean, 11 years), there were 248 incident HF events (146 in women). After adjustment for established HF risk factors, antecedent left ventricular systolic dysfunction (hazard ratio, 2.33; 95% confidence interval, 1.43 to 3.78) and diastolic dysfunction (hazard ratio, 1.32; 95% confidence interval, 1.01 to 1.71) were associated with increased HF risk. After adjustment for cardiac dysfunction, higher serum creatinine, lower FEV1:FVC ratios, and lower hemoglobin concentrations were associated with increased HF risk (all P<0.05); serum albumin and white blood cell count were not. Subclinical dysfunction in each noncardiac organ system was associated with a 30% increased risk of HF (P=0.013).

Conclusions—Antecedent cardiac dysfunction and noncardiac organ dysfunction are associated with increased incidence of HF, supporting the notion that HF is a progressive syndrome and underscoring the importance of noncardiac factors in its occurrence. (Circulation. 2011;124:24-30.)

Key Words: echocardiography ■ epidemiology ■ heart failure ■ risk factors

Heart failure (HF) is a clinical syndrome characterized by a constellation of signs and symptoms involving multiple organ systems such as the heart (classic pump failure), lungs (dyspnea), kidneys (salt and water retention), and liver (congestion). Current HF guidelines emphasize the importance of asymptomatic cardiac dysfunction as a preceding stage in the progression to clinically overt HF. Cross-sectional studies have demonstrated the presence of asymptomatic systolic or diastolic left ventricular (LV) dysfunction in the community in individuals at risk of, but without HF, and an even higher prevalence of these abnormalities in patients with overt HF. However, to demonstrate a prospective association between these structural precursors and future HF, longitudinal studies are needed.

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Importantly, the current HF staging system does not specifically acknowledge the potential association of noncardiac dysfunction with the occurrence of HF. Because the

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syndrome of HF involves multiple organ systems, even mild functional derangement of a noncardiac organ system may accelerate the manifestation of overt HF, particularly when other organ systems are also involved. Indeed, emerging evidence suggests that subclinical renal impairment,3 hypoalbuminemia,6,7 decline in pulmonary function,8,9 anemia,10 and systemic inflammation11 may all contribute to HF progression. Of note, the prevalence of noncardiac comorbidities is high among patients with overt HF, and these comorbidities are major determinants of mortality after the onset of HF.12,13 The relations of antecedent cardiac and noncardiac dysfunction (ie, present before the onset of overt HF) to the incidence of HF have not been studied comprehensively in the community. In a previous report,14 we described the prevalence and prognosis of asymptomatic LV systolic dysfunction in the community, but that investigation did not examine the association of LV diastolic dysfunction or noncardiac major organ system dysfunction with the risk of HF. Accordingly, we aimed to prospectively determine the association of cardiac and noncardiac dysfunction with the incidence of HF among older adults without HF in the community. To achieve this, we harnessed the unique availability of the longitudinal data and routine surveillance in the Framingham Heart Study. We hypothesized that subclinical dysfunction in both cardiac and noncardiac organ systems would accelerate the manifestation of HF. Further recognizing potential mechanistic differences between HF with reduced ejection fraction (HFREF) and HF with preserved ejection fraction (HFPEF), we also hypothesized that the types of antecedent subclinical organ system dysfunction may differ according to the type of incident HF (HFREF versus HFPEF).

Methods

Participants

The Framingham Heart Study is a longitudinal community-based cohort study that began in 1948.15 The original cohort has been under continuous surveillance, and participants are examined at the Framingham Heart Study clinic every 2 years. In the present investigation, we included participants attending the 20th biennial examination with routine assessment by Doppler echocardiography but without prevalent HF (Figure I in the online-only Data Supplement). Our focus was on subclinical organ dysfunction, so we excluded participants with overt organ dysfunction such as those with overt renal failure (defined as a serum creatinine \( \geq 2 \) mg/dL [176.8 \( \mu \)mol/L]; \( n = 12 \)). All participants provided written informed consent, and the study protocol was approved by the Institutional Review Board of the Boston University Medical Center.

Definition of Cardiac Dysfunction

Established HF risk factors modeled as covariates included age, sex, body mass index, systolic blood pressure, hypertension treatment, cholesterol, diabetes mellitus, prior myocardial infarction, and valvular heart disease. Left ventricular systolic dysfunction was assessed by echocardiographic EF estimated visually.14 Left ventricular diastolic dysfunction was defined on the basis of LV filling pattern as any abnormal relaxation, pseudonormal filling, or restrictive filling. Abnormal relaxation (mitral E/A <0.5, deceleration time \( >280 \) milliseconds) or restrictive filling (mitral E/A >2.0, deceleration time \( <120 \) milliseconds) was classified on the basis of mitral inflow patterns.16 In the absence of tissue Doppler imaging, pseudonormal LV filling was distinguished from normal LV diastolic function by the presence of any of the following: left atrial size at or above the sex-specific 80th percentile, LV mass at or above the sex-specific 80th percentile, or any atrial fibrillation. These criteria closely parallel recommendations from the European Society of Cardiology for the diagnosis of HFPEF17 and use the upper sex-specific quintiles of left atrial size and LV mass to characterize atrial enlargement and LV hypertrophy,18 respectively, in our elderly cohort. Both LV systolic dysfunction and diastolic dysfunction were modeled as binary variables (presence versus absence).

Definition of Noncardiac Major Organ System Dysfunction

We evaluated noncardiac major organ systems that could accelerate the manifestations of HF (dyspnea, fluid retention/ pedal edema, and exertional fatigue). Participants underwent routine spirometry and plethymography. Measurement variables used to define noncardiac function included the following8,7,10,11: (1) renal system, serum creatinine; (2) hepatic system, serum albumin concentration; (3) pulmonary system, ratio of forced expiratory volume in 1 second (FEV\(_1\)) to forced vital capacity (FVC) expressed as percent predicted for age and sex; (4) hematologic system/oxygen-carrying capacity, hemoglobin concentration; and (5) systemic inflammation, white blood cell count. These noncardiac function variables were modeled as both continuous and binary variables (see below). The sample size for analysis of noncardiac dysfunction variables was smaller (\( n = 676 \)) than the overall sample with available echocardiographic measures of LV systolic and diastolic function (\( n = 1038 \); Figure I in the online-only Data Supplement).

Outcome

Participants have been under ongoing, routine surveillance for incident HF since the baseline examination in 1987 to 1990. Heart failure was defined as satisfying the previously published Framingham criteria19 (presence of 2 major or 1 major plus 2 minor criteria) and adjudicated by a panel of 3 experienced investigators. The EF closest to the date of the HF event was used to categorize HF into HFPEF (EF \( >45\% \)) or HFREF (EF \( \leq 45\% \)).20 Measurements of EF performed at HF onset, during HF hospitalization, or within 1 year of HF onset in the absence of intervening myocardial infarction were eligible.20

Statistical Analyses

We used Cox proportional hazards regression models to assess the relationship of cardiac and noncardiac dysfunction variables to the incidence of HF after confirming that the assumption of proportionality of hazards was met. Covariates eligible for the multivariable model included LV systolic and diastolic dysfunction, continuous measures of noncardiac function (defined above), and established HF risk factors (defined above).

For each noncardiac function variable (including those found to be not significant), we initially examined generalized additive models with penalized splines to assess the potential nonlinearity of the association.21 None of the associations was found to be nonlinear. Therefore, we proceeded to model linear associations in Cox models. In the absence of any nonlinearity of the associations, we also used a priori cut points based on the lower 25th or upper 75th percentile of each continuous variable to create binary variables defining organ dysfunction for incorporation into a risk score. The risk score for noncardiac dysfunction was then calculated for each participant by allocating 1 point for each affected noncardiac organ system that was significantly associated with the risk of HF. This scoring system approach assumes that the hazards posed by dysfunction in each of the noncardiac systems are similar (weighted the same) and offers a simple, practical score that may be meaningfully applied in clinical settings. The association of the noncardiac risk score with incident HF was then plotted through the use of Kaplan-Meier curves and assessed with Cox proportional hazards modeling with adjustment for established HF risk factors (noted above) and cardiac dysfunction variables.

Finally, analyses were repeated separately for incident HFREF as the outcome (and censoring cases of HFPEF at the time of that event) or incident HFPEF as the outcome (and censoring cases of HFREF
Cardiac Dysfunction as a Risk Factor for Incident Heart Failure

Over a mean follow-up of 11 years, there were 248 incident first HF events (146 in women; 119 HFREF, 101 HFPEF, and unavailable EF for 28 HF events). In multivariable models adjusted for established HF risk factors (age, sex, body mass index, systolic blood pressure, hypertension treatment, cholesterol, diabetes mellitus, prior myocardial infarction, and valvular heart disease), both LV systolic dysfunction and LV diastolic dysfunction were associated with increased risk of incident HF (Table 2).

Noncardiac Risk Factors and Major Organ System Dysfunction Risk Score for Incident Heart Failure

Participants (n=676; mean age, 75±5 years; 42% men) without missing noncardiac risk factor variables had baseline characteristics (body mass index, systolic blood pressure, diabetes mellitus) similar to those with missing variables (all P>0.05). With adjustment for established HF risk factors and the presence of cardiac systolic and diastolic dysfunction, higher serum creatinine, lower FEV₁:FVC ratios, and lower hemoglobin concentrations were associated with increased risk of new-onset HF (Table 3). There was no association between serum albumin concentration (P=0.306) or white blood cell count (P=0.685) and incident HF. Individual Cox proportional hazards models with penalized splines for serum creatinine, FEV₁:FVC ratio, and hemoglobin did not reveal nonlinearity for the association with HF risk (Figure 1). Therefore, a risk score for noncardiac dysfunction was calculated using predetermined cut points (based on the 25th or 75th percentiles of the variables in the sample, as defined above) and awarding 1 point for each affected organ system (range, 0 to 3); regression coefficients for these variables were comparable in the multivariable models, further justifying their similar weighting in the score (Table 3). Of note, the cut points used to define organ “dysfunction” were within the ranges frequently observed in ambulatory elderly individuals in the general population. Increasing noncardiac risk score at baseline was positively associated with risk of HF (Figure 2).

In secondary analyses, results were similar when estimated glomerular filtration rate (by the Modification of Diet in Renal Disease equation) was used instead of serum creatinine (hazard ratio for each 1-SD decrease in estimated glomerular filtration rate, 1.24; 95% confidence interval, 1.03 to 1.50; P=0.026 with adjustment for established HF risk factors and the presence of cardiac dysfunction). Other biomarkers of noncardiac dysfunction (blood urea nitrogen, total bilirubin,
transaminases, hematocrit, C-reactive protein measured by traditional assays [high-sensitivity assays were unavailable], uric acid) were also tested for their associations with incident HF in secondary analyses, and results are shown in Table I in the online-only Data Supplement. These secondary analyses supported the original selection of creatinine, albumin, FEV₁:FVC ratio, and hemoglobin as simple, convenient, and widely available biomarkers to include in the final risk score. We also performed sensitivity analyses using different percentile cut points to define the risk score (tertiles instead of quartiles) and found similar results (data not shown).

Multivariable Risk Factors for All Incident Heart Failure, Heart Failure With Reduced Ejection Fraction, and Heart Failure With Preserved Ejection Fraction

In multivariable modeling for all incident HF, LV systolic dysfunction, LV diastolic dysfunction, and the noncardiac risk score were each associated with incident HF after adjustment for established HF risk factors (Table 4). There was no significant interaction between noncardiac risk score and the presence of LV systolic or diastolic dysfunction (P = 0.78 and P = 0.84, respectively). In multivariable modeling for HREF and HFPEF separately, antecedent LV systolic dysfunction, greater serum creatinine, and lower hemoglobin concentration were associated with incident HREF, whereas antecedent LV diastolic dysfunction and lower

Table 3. Noncardiac Risk Factors and Risk Score for Incident Heart Failure

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard Ratio (95% Confidence Interval)*</th>
<th>P*</th>
<th>Cutoff Percentile</th>
<th>Cutoff Value</th>
<th>Points Awarded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine</td>
<td>1.21 (1.01–1.45)</td>
<td>0.036</td>
<td>&gt;75th</td>
<td>&gt;1.05 mg/dL (&gt;92.8 μmol/L)</td>
<td>1</td>
</tr>
<tr>
<td>FEV₁:FVC ratio</td>
<td>1.21 (1.02–1.43)</td>
<td>0.029</td>
<td>&lt;25th</td>
<td>&lt;91% predicted</td>
<td>1</td>
</tr>
<tr>
<td>Hemoglobin concentration</td>
<td>1.24 (1.09–1.40)</td>
<td>&lt;0.001</td>
<td>&lt;25th</td>
<td>&lt;13 g/dL</td>
<td>1</td>
</tr>
</tbody>
</table>

FEV₁:FVC indicates ratio of forced expiratory volume in 1 second to forced vital capacity.

*Hazard ratios are for a 1-SD increase in serum creatinine, 1-SD decrease in FEV₁:FVC ratio, and 1-unit decrease in hemoglobin concentration after adjustment for age, sex, body mass index, systolic blood pressure, hypertension treatment, cholesterol, diabetes mellitus, prior myocardial infarction, valvular heart disease, and left ventricular systolic and diastolic function in 676 participants without any missing variables (170 heart failure events).

Figure 1. Association of measures of major noncardiac organ system function with risk of incident heart failure. Generalized additive models with penalized splines were used to assess the association of multivariable-adjusted hazards ratio for heart failure with (A) serum creatinine concentration, (B) ratio of forced expiratory volume in 1 second to forced vital capacity (FEV₁:FVC ratio), and (C) hemoglobin concentration. Lines indicate means (solid) and 95% confidence intervals (dotted). The y axes represent multivariable-adjusted Ln[hazards ratio]. (To obtain serum creatinine concentration in μmol/L, multiply values in mg/dL by 88.4.)

Figure 2. Cumulative incidence of incident heart failure according to noncardiac major organ system dysfunction risk score. The noncardiac organ system dysfunction risk score awarded 1 point for the presence of each of the following (range, 0 to 3): serum creatinine >1.05 mg/dL (92.8 μmol/L), ratio of forced expiratory volume in 1 second to forced expiratory volume <91% predicted, and hemoglobin concentration <13 g/dL. Increasing noncardiac risk score at baseline was associated with increasing risk of incident heart failure in our community-based sample (log rank P = 0.013).
Table 4. Association of Cardiac and Noncardiac Dysfunction With Incident Heart Failure

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Hazards Ratio (95% Confidence Interval)*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All incident HF</td>
<td></td>
<td></td>
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<tr>
<td>LV systolic dysfunction</td>
<td>1.97 (1.05–3.68)</td>
<td>0.034</td>
</tr>
<tr>
<td>LV diastolic dysfunction</td>
<td>1.40 (1.02–1.93)</td>
<td>0.039</td>
</tr>
<tr>
<td>Noncardiac risk score† per 1-unit increase</td>
<td>1.30 (1.06–1.60)</td>
<td>0.013</td>
</tr>
<tr>
<td>Incident HFREF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV systolic dysfunction</td>
<td>3.93 (1.86–8.30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum creatinine per 1-SD increase</td>
<td>1.32 (1.04–1.69)</td>
<td>0.025</td>
</tr>
<tr>
<td>Hemoglobin concentration per 1-unit decrease</td>
<td>1.31 (1.10–1.55)</td>
<td>0.002</td>
</tr>
<tr>
<td>Incident HFPEF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV diastolic dysfunction</td>
<td>1.88 (1.13–3.13)</td>
<td>0.016</td>
</tr>
<tr>
<td>FEV₁:FVC ratio per 1-SD decrease</td>
<td>1.38 (1.04–1.83)</td>
<td>0.024</td>
</tr>
</tbody>
</table>

HF indicates heart failure; LV, left ventricular; HFREF, heart failure with reduced ejection fraction; HFPEF, heart failure with preserved ejection fraction; and FEV₁:FVC, ratio of forced expiratory volume in 1 second to forced vital capacity.

*Adjusted for age, sex, body mass index, systolic blood pressure, hypertension treatment, cholesterol, diabetes mellitus, prior myocardial infarction, and valvular heart disease (valvular heart disease excluded for HFPEF) in 676 participants without any missing variables (170 total HF events: 82 HFREF, 66 HFPEF, 22 EF unavailable).

†Components of the noncardiac risk score are described and their individual hazards ratios are shown in Table 3.

FEV₁:FVC ratio were associated with incident HFPEF after adjustment for established HF risk factors (Table 4).

In further analyses adjusted for smoking and excluding participants with overt pulmonary dysfunction (FEV₁:FVC <60%; n=3), hypoalbuminemia (albumin <2.5 g/dL; n=0 [no participant had hypoalbuminemia]), or anemia (hemoglobin <10.5 g/dL; n=7), results were essentially unchanged (data not shown). Using an EF cut point of 50% (instead of 45%) to distinguish HFPEF from HFREF revealed similar results (Table II in the online-only Data Supplement).

Discussion

Principal Findings

In our prospective study of a large, community-based sample, antecedent subclinical cardiac and noncardiac major organ system dysfunction was associated with risk of future HF. The presence of asymptomatic LV systolic and diastolic dysfunction preceded and increased the risk of incident HF by >2-fold and >30%, respectively. These findings support the emphasis in current HF guidelines regarding the progressive nature of HF and the importance of recognizing preceding asymptomatic cardiac dysfunction. Our data also extend the previous HF staging system by providing evidence for the association of noncardiac dysfunction with progression to clinical HF. After adjustment for cardiac dysfunction, the presence of subclinical renal impairment, airflow limitation, or anemia was each associated with 30% increased risk of incident HF. Finally, antecedent LV systolic dysfunction was associated with future HFREF, whereas antecedent LV diastolic dysfunction was associated with future HFPEF. Furthermore, subclinical renal impairment and lower hemoglobin concentrations were associated with a higher incidence of HFREF, whereas baseline airflow obstruction was related positively to the risk of future HFPEF. The implications of these findings for the early identification of individuals at risk of HF and potential strategies to prevent the progression to overt HF deserve further study.

Left Ventricular Systolic and Diastolic Dysfunction and Risk of Heart Failure

Previous cross-sectional studies have provided evidence for the existence of asymptomatic LV dysfunction in the general community (stage B HF in the American College of Cardiology/American Heart Association classification system), as well as increased prevalence and severity of LV dysfunction in patients with clinical HF (stage C HF). Although these cross-sectional data supported the proposed stages of the HF, prior studies were limited by potential reverse causality because the assessment of LV function was performed at the same point in time as the diagnosis of clinical HF. Furthermore, cross-sectional studies may be criticized for scientific circularity of reasoning in that the presence of LV systolic or diastolic dysfunction is used to make the diagnosis HFREF or HFPEF, respectively. Prospective data are needed to resolve these issues. In the Cardiovascular Health Study, LV systolic and diastolic dysfunction predicted incident HF over a mean follow-up of 5.2 years. However, the relationships between the type of LV dysfunction (systolic versus diastolic) and the type of HF (HFREF versus HFPEF) were not assessed. More recently, researchers from the Mayo Clinic reported a 2-year HF incidence rate of 1.9% in a selected sample of 82 patients with preclinical diastolic dysfunction. Patients with systolic dysfunction were not studied. Our current data are consistent with these prior data and extend previous knowledge by demonstrating that LV systolic dysfunction predicts future HFREF, whereas LV diastolic dysfunction portends HFPEF. Therefore, the present data help to fill the knowledge gap linking stage B to stage C in the American College of Cardiology/American Heart Association classification scheme, whether referring to HFREF or HFPEF.

Noncardiac Dysfunction and Risk of Heart Failure

Heart failure is a clinical syndrome characterized by a constellation of signs and symptoms involving multiple organ systems besides the heart. Thus, even mild functional derangement of a noncardiac organ system, which in itself is not severe enough to produce symptoms, may accelerate the manifestation of overt HF, particularly when other organ systems are also involved. A decline in renal function affects sodium handling and fluid homeostasis, thus increasing the propensity to manifest fluid overload. Pulmonary function has a direct impact on the manifestation of dyspnea. Subclinical chronic pulmonary disease is characterized by low-grade inflammation and may contribute to progression of atherosclerosis and myocardial dysfunction, whereas even mild airflow obstruction is associated with abnormal LV diastolic filling. Anemia affects the oxygen-carrying capacity of the blood and is an adverse marker in overt HF. The availability...
of systematic, multisystem measurements during routine surveillance in the Framingham Heart Study enabled comprehensive assessment of these varied noncardiac organ systems in relation to incident HF in the community. Our findings regarding the association with renal impairment are consistent with the Health ABC Heart Failure Model for incident HF in the elderly. In contrast, we did not find a significant association with hypalbuminemia; this may be due to differences in study samples (larger proportion of blacks and lower baseline serum albumin in the Health ABC Study).

In aggregate, these results suggest that the manifestation of clinically overt HF may be hastened by subclinical dysfunction in multiple organ systems. This is likely to particularly affect elderly individuals who have age-related decline in multiorgan function or multiple noncardiac comorbidities. Recognizing the contribution of noncardiac dysfunction to HF progression may carry important clinical implications for preventing and managing HF. Further studies are warranted to validate these findings in other populations, to evaluate for potential effect modification by covariates such as sex, and to assess the potential impact of treatment of these risk factors on the risk of future HF.

**Association of Noncardiac Dysfunction With Heart Failure With Reduced Ejection Fraction Versus Heart Failure With Preserved Ejection Fraction**

The distinction between factors associated with incident HFREF versus HFPEF deserves comment. The association of renal dysfunction and anemia with the risk of HFREF is consistent with classic studies of the cardiorenal syndrome and the known prognostic impact of anemia in overt HFREF. Interestingly, the most prominent noncardiac predictor of incident HFPEF was airflow obstruction. This observation is supported by large epidemiological studies showing a high prevalence of pulmonary disease in patients with HFPEF, the frequent coexistence of HF in patients with chronic obstructive lung disease, and a recent study in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort demonstrating an association between airflow obstruction and abnormal LV filling. Although this also raises the question of potential misdiagnosis of HFPEF, it is unlikely, given the high specificity of the Framingham criteria for HF, the reliability of the diagnosis as demonstrated by consistent application of the same criteria over decades and stringent adjudication of end points in the Framingham Heart Study, and the lack of an alternative explanation for the clinical presentation (because the extent of pulmonary impairment was not severe enough to explain symptoms). Overall, the different predictors of HFREF versus HFPEF are consistent with prior epidemiological, pathophysiological, molecular, and outcome data supporting the notion that HFREF and HFPEF may represent separate entities. These observations may guide future clinical trial design, particularly in HFPEF, for which trials have so far been disappointing.

**Strengths and Limitations**

The strengths of our study include the large community-based sample, uniform measurements of function of multiple organ systems, and longitudinal follow-up with continuous surveillance for and careful validation of HF outcomes. Furthermore, the use of purely clinical criteria for the diagnosis of HF independently of LVEF is particularly advantageous in this setting. Limitations include the lack of tissue Doppler characterization of diastolic dysfunction and the inherent pitfalls in using echocardiographic indexes of diastolic filling as indicators of diastolic dysfunction. Nonetheless, mitral Doppler indexes are widely available, and our results are consistent with previous studies using more comprehensive assessment of diastolic dysfunction. We acknowledge the observational nature of our study, which precludes conclusions regarding causality, as well as the modest effect sizes for noncardiac organ system variables and the potential for residual confounding or effect modification by other factors. We did not use time-varying covariates, but we speculate that organ dysfunction would worsen with aging in most individuals, leading to even stronger associations with incident HF. Our uniformly white sample limits the generalizability of our findings to other ethnicities, and independent validation in other cohorts is warranted.

**Conclusions**

Our prospective observations in a large, community-based sample demonstrate that antecedent subclinical cardiac and noncardiac major organ system dysfunction is associated with increased risk of clinical HF. These findings contribute to the understanding of HF as a progressive disease syndrome and underscore the potential importance of noncardiac risk factors in predisposing to the manifestation of overt HF.

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**Disclosures**

None.

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CLINICAL PERSPECTIVE
In our prospective study of a large, community-based sample, antecedent subclinical cardiac and noncardiac major organ system dysfunction was associated with risk of future heart failure. The presence of asymptomatic left ventricular systolic and diastolic dysfunction preceded and increased the risk of incident heart failure by >2-fold and >30%, respectively. With adjustment for cardiac dysfunction, the presence of subclinical renal impairment, airflow limitation, or anemia was each associated with 30% increased risk of incident heart failure. Notably, the significant risk factors differed according to the type of incident heart failure (preserved versus reduced ejection fraction). Antecedent left ventricular systolic dysfunction, subclinical renal impairment, and lower hemoglobin concentrations were associated with a higher incidence of heart failure with reduced ejection fraction, whereas antecedent diastolic dysfunction and baseline airflow obstruction were related positively to the risk of future heart failure with preserved ejection fraction. This study provides longitudinal evidence for the progressive nature of heart failure as emphasized in current heart failure guidelines and underscores the potential importance of noncardiac risk factors in predisposing to the manifestation of overt heart failure. The implications for the early identification of individuals at risk of heart failure and potential strategies to prevent progression to overt heart failure deserve further study.

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In the article by Lam et al, “Cardiac Dysfunction and Noncardiac Dysfunction as Precursors of Heart Failure With Reduced and Preserved Ejection Fraction in the Community,” which was published in the July 5, 2011 issue of the journal (Circulation. 2011;124:24–30), an error occurred in the affiliation for Elisabeth Kraigher-Krainer, MD and Burkert M. Pieske, MD, PhD.

The author affiliations should appear as follows:

“… Department of Cardiology, Medical University of Graz, Graz, Austria (E.K.-K., B.P.); …”

The online version of the article has been updated. The authors regret the error.

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SUPPLEMENTAL MATERIAL

Supplementary Table 1. Association of other biomarkers of non-cardiac dysfunction and incident heart failure

<table>
<thead>
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<th>Organ system</th>
<th>Continuous variable</th>
<th>Hazards ratio</th>
<th>P value</th>
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<tbody>
<tr>
<td>1. Renal</td>
<td>BUN per 1 unit increase</td>
<td>1.02 (0.99-1.05)</td>
<td>0.291</td>
</tr>
<tr>
<td></td>
<td>eGFR per 1 unit decrease</td>
<td>1.24 (1.03-1.50)</td>
<td>0.026</td>
</tr>
<tr>
<td>2. Hepatic</td>
<td>Total bilirubin per 1 unit increase</td>
<td>1.42 (0.79-2.56)</td>
<td>0.244</td>
</tr>
<tr>
<td></td>
<td>ALT per 1 unit increase</td>
<td>1.00 (0.99-1.01)</td>
<td>0.642</td>
</tr>
<tr>
<td></td>
<td>AST per 1 unit increase</td>
<td>1.00 (0.99-1.02)</td>
<td>0.762</td>
</tr>
<tr>
<td>3. Pulmonary</td>
<td>FEV1 per 1 unit decrease</td>
<td>1.02 (0.70-1.47)</td>
<td>0.932</td>
</tr>
<tr>
<td></td>
<td>FVC per 1 unit decrease</td>
<td>1.05 (0.81-1.36)</td>
<td>0.734</td>
</tr>
<tr>
<td>4. Hematologic</td>
<td>Hct per 1 unit decrease</td>
<td>1.03 (0.87-1.22)</td>
<td>0.761</td>
</tr>
<tr>
<td>5. Systemic inflammation/</td>
<td>CRP* per 1 unit increase</td>
<td>1.01 (0.98-1.04)</td>
<td>0.538</td>
</tr>
<tr>
<td>oxidative stress</td>
<td>Uric acid per 1 unit increase</td>
<td>1.07 (0.94-1.22)</td>
<td>0.286</td>
</tr>
</tbody>
</table>

BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate by MDRD equation; ALT, alanine transaminase; AST, aspartate aminotransferase; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; Hb, hemoglobin; Hct, hematocrit; WBC, white blood cell count; CRP, C-reactive protein

*Traditional CRP assay (high-sensitivity CRP assay not available)
Supplementary Table 2. Results comparing an ejection fraction cutpoint of 50% versus 45% for defining left ventricular systolic dysfunction

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Using EF 45% as cutpoint</th>
<th>Using EF 50% as cutpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incident HFREF</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV systolic dysfunction</td>
<td>3.93 (1.86 – 8.30)</td>
<td>3.99 (1.89 - 8.42)</td>
</tr>
<tr>
<td>Serum creatinine per 1SD increase</td>
<td>1.32 (1.04 – 1.69)</td>
<td>1.32 (1.03 – 1.67)</td>
</tr>
<tr>
<td>Hemoglobin concentration per 1 unit decrease</td>
<td>1.31 (1.10 – 1.55)</td>
<td>1.49 (1.15 – 1.92)</td>
</tr>
<tr>
<td><strong>Incident HFPEF</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV diastolic dysfunction</td>
<td>1.88 (1.13 – 3.13)</td>
<td>1.95 (1.15 – 3.30)</td>
</tr>
<tr>
<td>FEV1:FVC ratio per 1SD decrease</td>
<td>1.38 (1.04 – 1.83)</td>
<td>1.30 (0.97 – 1.75)</td>
</tr>
</tbody>
</table>

HFREF, heart failure with reduced ejection fraction; HFPEF, heart failure with preserved ejection fraction; LV, left ventricular; FEV1:FVC, ratio of forced expiratory volume in 1 second to forced vital capacity

*Adjusted for age, sex, body mass index, systolic blood pressure, hypertension treatment, cholesterol, diabetes mellitus, prior myocardial infarction, and valvular heart disease (valvular heart disease excluded for HFPEF) in 676 participants without any missing variables (170 total HF events: 82 HFREF, 66 HFPEF, 22 EF unavailable).
Supplementary Figure 1.

Framingham Heart Study
Original cohort participants attending the 20th biennial examination (N=1,401)

Excluded prevalent heart failure (N=68), overt renal failure (N=12), missing echo (N=283)

Doppler echocardiography for cardiac systolic and diastolic function (N=1,038)

Incident heart failure (N=248)

Analysis for association of cardiac risk factors with incident heart failure

Pulmonary function and blood tests for non-cardiac risk factors (N=676)

Incident heart failure (N=170)

EF unknown (N=22)

HFREF (N=82)

HFPEF (N=66)

Analysis for association of cardiac and non-cardiac risk factors with HFREF vs HFPEF
Figure Legends

Supplementary Figure 1. Flowchart of participants

Eligible participants were those of the Framingham Heart Study Original cohort attending the 20th biennial examination with routine assessment by Doppler echocardiography, but without prevalent HF or overt renal failure (defined as a serum creatinine>2 mg/dL [176.8 μmol/l]) (N=1,038). There were a total of 248 new heart failure events during a mean follow up of 11 years. In a subset of 676 participants in whom there were no missing echocardiographic or non-cardiac organ function variables, 170 new heart failure events occurred (82 heart failure with reduced ejection fraction [HFREF], 66 heart failure with preserved ejection fraction [HFPEF], 22 ejection fraction unavailable).
일반인에서 심장 및 주요 장기의 기능저하는 심부전 발생의 위험인자다

최동주 교수 분당서울대학교병원 순환기내과

Summary

배경
심부전은 다기관을 동시에 포함하는 증상과 징후를 특징으로 하는 임상증후군이다. 시간의 흐름에 따른 종적 연구의 데이터에 의하면, 놀랍게도 무증상의 심장 기능 저하도 심부전의 원인이 될 수 있는 것으로 알려져 있으나, 심장 외의 다른 장기들의 기능부전도 심부전 발생에 기여할지에 대해서는 밝혀져 있지 않다. 이 연구의 목적은 심장과 심장 외의 다른 장기의 기능저하가 심부전 발생을 가속화할지를 알아보는 데 있다.

방법 및 결과
Framingham Heart Study에 처음 등록하며, 좌심실 수축기와 확장기 기능이 검사된 1,038명(평균 연령, 76±5세; 남성, 39%)을 대상으로 하였다. 심장 외의 장기 기능은 혈장 creatinine(신장), 혈중 알부민(간), FEV1/FVC 비율(폐), 헤모글로빈(혈액/산소운반능), 백혈구 수(전신 염증)을 통해 평가하였다. 추적기간(평균 11년) 중 248명(여성, 146명)에서 심부전이 발생하였다. 기존의 심부전 발생 위험인자로 보정한 후, 선행했던 좌심실 수축기능 부전(HR, 2.33; 95% CI, 1.43-3.78)과 확장기능부전(HR, 1.32; 95% CI, 1.01-1.71)은 심부전 발생의 위험인자로 작용하였다. 심장 기능부전을 보정한 후 혈장 creatinine의 증가, FEV1/FVC 비율 감소, 혈모글로빈 농도 감소 등이 심부전 발생을 증가시킨 반면(모두 P<0.05), 혈장 알부민과 백혈구 수는 연관성이 없었다. 증상이 없는 심장 외 각각의 장기 기능부전은 심부전 발생의 위험을 30% 증가시켰다(P=0.013).

결론
심장과 심장 외 장기의 무증상 기능부전은 향후 심부전 발생을 증가시키며, 심부전은 점진 진행하는 증후군이다. 심부전 진행에서 심장 외의 요인들도 중요한 역할을 한다.
심부전의 특징 중 하나는 여러 장기의 기능저하를 동반하는 중후군이라는 것이다. 심장은 물론 폐, 신장, 간 등의 다른 장기의 이상을 동반한다. 최근 심부전 지침은 중상이 나타나기 전 단계의 심장 기능저하도 B단계 심부전으로 규정하여 심부전으로 진행할 수 있는 전 단계이므로 적극적으로 치료할 것을 권장하고 있다. 단면적 연구들에 의하면 일반인 중에서 심부전이 없어도 고위험군에서 수축기 혹은 이완기 심장 기능저하를 보이는 경우가 많으며, 심부전이 동반되는 경우는 더 많다고 보고되고 있다. 그러나 이러한 해부학적, 구조적 이상이 심부전으로 이행될 것인지에 대한 전향적, 종합 연구는 없었다. 특히, 지금의 심부전 병기(staging)는 심장이 아닌 다른 장기와 심부전과의 관계에 대한 언급은 없다.

본 연구는 대규모, 전향적, 지역주민을 대상으로 한 연구로 선행하는 무증상의 심장 기능부전과 심장 외 장기의 기능부전 모두가 미래의 심부전 발생 위험을 높임을 밝혔다. 무증상 심장 기능부전은 위험도를 2배 증가시키고, 심장 외 장기의 기능부전은 위험도를 30% 증가시켰다. 심장 기능저하를 보정한 후에도 신 기능저하, 폐 기능저하 및 반혈은 심부전 발생을 30% 증가시켰다. 특히, 중요한 위험인자는 심부전이 수축기 심부전인지 확장기 심부전인지, 그 종류에 따라서 달랐다. 심장 기능저하, 신 기능저하와 반혈은 수축기 심부전 발생에 연관되는 반면, 폐 기능저하는 확장기 심부전과 관련되었다.

이 연구에서 정의한 장기 기능부전의 정의는 수축기능부전은 EF(ejection fraction) 45% 이하, 이완기능부전은 abnormal relaxation[mitrail E/A <0.5, DT(deceleration time) <280msec] 혹은 restrictive filling(mitrail E/A >2.0, DT <120msec)으로 하였고, 도플러가 없는 경우는 좌심방 크기, 좌심실 질량 및 심방세동 유무로 정상과 비정상 좌심실증만(pseudonormal left ventricular filling)을 구별하였는데, 좌심실 이완기능부전에 관한 이중적 기준이 이 연구의 주요 제한점이다. 심장외 장기의 기능부전은 신장은 혈청 creatinine, 간은 혈청 albumin 농도, 폐는 FEV1/FVC 비율, 혈액의 산소운반능은 혈모글로빈 농도, 전신 염증반응은 백혈구 수로 정의하였다.

본 연구는 최근 심부전 치료지침이 강조하는 것처럼, 심부전은 진행하는 질환임을 제자 확인하였고, 심장이 아닌 다른 장기의 기능 감소도 심부전 진행에 영향을 미칠 수 있음을 밝혔다. 특히, 일반 주민을 대상으로 밝힌 장기간의 종합 연구라는 데 의미가 더 크다.

본 연구 결과에 따르면 심부전이 발생할 수 있는 위험군을 조기에 찾아내는 것이 중요하다. 그런 위험군은 심장 기능 저하는 물론 타 장기의 기능부전에도 주의를 요한다. 이들을 조기에 치료하여 심부전으로 진행하는 것을 미연에 예방할 수 있을지에 대해서는 더 많은 전향적 연구가 필요하다.
Heart Failure (HF) is a clinical syndrome characterized by a constellation of signs and symptoms involving multiple organ systems such as the heart (classic pump failure), lungs (dyspnea), kidneys (salt and water retention), and liver (congestion). Current HF guidelines emphasize the importance of asymptomatic cardiac dysfunction as a preceding stage in the progression to clinically overt HF. Cross-sectional studies have demonstrated the presence of asymptomatic systolic or diastolic left ventricular (LV) dysfunction in the community in individuals at risk of, but without HF, and an even higher prevalence of these abnormalities in patients with overt HF. However, to demonstrate a prospective association between these structural precursors and future HF, longitudinal studies are needed.

Clinical Perspective on p 152

Importantly, the current HF staging system does not specifically acknowledge the potential association of noncardiac dysfunction with the occurrence of HF. Because the...
syndrome of HF involves multiple organ systems, even mild functional derangement of a noncardiac organ system may accelerate the manifestation of overt HF, particularly when other organ systems are also involved. Indeed, emerging evidence suggests that subclinical renal impairment,^6^ hypoa-
buminemia,^6,^7 decline in pulmonary function,^8,^9 anemia,^10^ and systemic inflammation^11^ may all contribute to HF progression. Of note, the prevalence of noncardiac comorbidities is high among patients with overt HF, and these comorbidities are major determinants of mortality after the onset of HF.12,13

The relations of antecedent cardiac and noncardiac dysfunction (ie, present before the onset of overt HF) to the incidence of HF have not been studied comprehensively in the community. In a previous report,14 we described the prevalence and prognosis of asymptomatic LV systolic dysfunction in the community, but that investigation did not examine the association of LV diastolic dysfunction or noncardiac major organ system dysfunction with the risk of HF. Accordingly, we aimed to prospectively determine the association of cardiac and noncardiac dysfunction with the incidence of HF among older adults without HF in the community. To achieve this, we harnessed the unique availability of the longitudinal data and routine surveillance in the Framingham Heart Study. We hypothesized that subclinical dysfunction in both cardiac and noncardiac organ systems would accelerate the manifestation of HF. Further recognizing potential mechanistic differences between HF with reduced ejection fraction (HFREF) and HF with preserved ejection fraction (HFPEF), we also hypothesized that the types of antecedent subclinical organ system dysfunction may differ according to the type of incident HF (HFREF versus HFPEF).

### Methods

#### Participants

The Framingham Heart Study is a longitudinal community-based cohort study that began in 1948.15 The original cohort has been under continuous surveillance, and participants are examined at the Framingham Heart Study clinic every 2 years. In the present investigation, we included participants attending the 20th biennial examination with routine assessment by Doppler echocardiography but without prevalent HF (Figure I in the online-only Data Supplement). Our focus was on subclinical organ dysfunction, so we excluded participants with overt organ dysfunction such as those with overt renal failure (defined as a serum creatinine $>2$ mg/dL [176.8 µmol/L]; $n=12$). All participants provided written informed consent, and the study protocol was approved by the Institutional Review Board of the Boston University Medical Center.

#### Definition of Cardiac Dysfunction

Established HF risk factors modeled as covariates included age, sex, body mass index, systolic blood pressure, hypertension treatment, cholesterol, diabetes mellitus, prior myocardial infarction, and valvular heart disease. Left ventricular systolic dysfunction was assessed by echocardiographic EF estimated visually.14 Left ventricular diastolic dysfunction was defined on the basis of LV filling pattern as any abnormal relaxation, pseudonormal filling, or restrictive filling. A bimodal relaxation (mitral E/A $<0.5$, deceleration time $>280$ milliseconds) or restrictive filling (mitral E/A $>2.0$, deceleration time $<120$ milliseconds) was classified on the basis of mitral inflow patterns.16 In the absence of tissue Doppler imaging, pseudonormal LV filling was distinguished from normal LV diastolic function by the presence of any of the following: left atrial size at or above the sex-specific 80th percentile, LV mass at or above the sex-specific 80th percentile, or any atrial fibrillation. These criteria closely parallel recommendations from the European Society of Cardiology for the diagnosis of HFPEF17 and use the upper sex-specific quintiles of left atrial size and LV mass to characterize atrial enlargement and LV hypertrophy,18 respectively, in our elderly cohort. Both LV systolic dysfunction and diastolic dysfunction were modeled as binary variables (presence versus absence).

#### Definition of Noncardiac Major Organ System Dysfunction

We evaluated noncardiac major organ systems that could accelerate the manifestations of HF (dyspnea, fluid retention/pedal edema, and exertional fatigue). Participants underwent routine spirometry and phlebotomy. Measurement variables used to define noncardiac dysfunction included the following9,10,11: (1) renal system, serum creatinine; (2) hepatic system, serum albumin concentration; (3) pulmonary system, ratio of forced expiratory volume in 1 second (FEV$_1$) to forced vital capacity (FVC) expressed as percent predicted for age and sex; (4) hematologic system/oxygen-carrying capacity, hemoglobin concentration; and (5) systemic inflammation, white blood cell count.

These noncardiac dysfunction variables were modeled as both continuous and binary variables (see below). The sample size for analyses of noncardiac dysfunction variables was smaller ($n=676$) than the overall sample with available echocardiographic measures of LV systolic and diastolic function ($n=1038$; Figure I in the online-only Data Supplement).

#### Outcome

Participants have been under ongoing, routine surveillance for incident HF since the baseline examination in 1987 to 1990. Heart failure was defined as satisfying the previously published Framing-
ham criteria19 (presence of 2 major or 1 major plus 2 minor criteria) and adjudicated by a panel of 3 experienced investigators. The EF closest to the date of the HF event was used to categorize HF into HFPEF (EF $>45\%$) or HFREF (EF $\leq45\%$).20 Measurements of EF performed at HF onset, during HF hospitalization, or within 1 year of HF onset in the absence of intervening myocardial infarction were eligible.

#### Statistical Analyses

We used Cox proportional hazards regression models to assess the relationship of cardiac and noncardiac dysfunction variables to the incidence of HF after confirming that the assumption of proportionality of hazards was met. Covariates eligible for the multivariable model included LV systolic and diastolic dysfunction, continuous measures of noncardiac function (defined above), and established HF risk factors (defined above).

For each noncardiac function variable (including those found to be not significant), we initially examined generalized additive models with penalized splines to assess the potential nonlinearity of the association.21 None of the associations was found to be nonlinear. Therefore, we proceeded to model linear associations in Cox models. In the absence of any nonlinearity of the associations, we also used an a priori cut points based on the lower 25th or upper 75th percentile of each continuous variable to create binary variables defining organ dysfunction for incorporation into a risk score. The risk score for noncardiac dysfunction was then calculated for each participant by allocating 1 point for each affected noncardiac organ system that was significantly associated with the risk of HF. This scoring system approach assumes that the hazards posed by dysfunction in each of the noncardiac systems are similar (weighted the same) and offers a simple, practical score that may be meaningfully applied in clinical settings. The association of the noncardiac risk score with incident HF was then plotted through the use of Kaplan-Meier curves and assessed with Cox proportional hazards modeling with adjustment for established HF risk factors (noted above) and cardiac dysfunction variables.

Finally, analyses were repeated separately for incident HFREF as the outcome (and censoring cases of HFPEF at the time of that event) or incident HFPEF as the outcome (and censoring cases of HFREF
Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>76 ± 5</td>
<td></td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>409 (39)%</td>
<td></td>
</tr>
</tbody>
</table>

Cardiovascular risk factors

<table>
<thead>
<tr>
<th>Body mass index, kg/m²</th>
<th>26.6 ± 4.5</th>
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<tbody>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>147 ± 22</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>799 (77)</td>
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<tr>
<td>Hypertension treatment, n (%)</td>
<td>551 (53)</td>
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<tr>
<td>Ratio of total to HDL cholesterol</td>
<td>4.85 ± 1.65</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>104 (10)</td>
</tr>
<tr>
<td>Myocardial infarction, n (%)</td>
<td>96 (9)</td>
</tr>
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<td>Valve disease, n (%)</td>
<td>41 (4)</td>
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</table>

Cardiac function

<table>
<thead>
<tr>
<th>LV systolic dysfunction, n (%)</th>
<th>57 (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV diastolic dysfunction, n (%)</td>
<td>372 (36)</td>
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</table>

Noncardiac function

<table>
<thead>
<tr>
<th>Serum creatinine, mg/dL</th>
<th>0.93 ± 0.23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum albumin, g/dL</td>
<td>4.23 ± 0.36</td>
</tr>
<tr>
<td>FEV₁/FVC ratio, % predicted</td>
<td>96.9 ± 10.9</td>
</tr>
<tr>
<td>Hemoglobin concentration, g/dL</td>
<td>14.0 ± 1.5</td>
</tr>
<tr>
<td>Blood cell count, ×10^12/L</td>
<td>6.8 ± 2.3</td>
</tr>
</tbody>
</table>

HDL indicates high-density lipoprotein; LV, left ventricular; and FEV₁/FVC, ratio of forced expiratory volume in 1 second to forced vital capacity expressed as percent predicted for age and sex. Values are mean ± SD unless otherwise stated. Serum creatinine concentration can be converted to μmol/L by multiplying the value in mg/dL by 88.4.

*Diastolic dysfunction included any abnormal relaxation (mitral E/A < 0.5, deceleration time > 280 milliseconds), pseudonormal LV filling (distinguished from normal LV diastolic function by the presence of any of the following: left atrial size at or above the sex-specific 80th percentile [4.8 cm in men, 4.4 cm in women], LV mass at or above the sex-specific 80th percentile [158.4 g/m² in men, 141.9 g/m² in women], or any atrial fibrillation), or restrictive filling (mitral E/A > 2.0, deceleration time < 120 milliseconds).

at the time of that event). Cox proportional hazards regression was used in which variables entered into the model included LV systolic and diastolic dysfunction, measures of noncardiac function, and the established HF risk factors noted above. Valvular heart disease was excluded in the analysis for HFPEF, consistent with current diagnostic criteria, and included as a covariate in the analysis for HFREF.

All analyses were performed with SAS, and a 2-sided value of P < 0.05 was used to indicate statistical significance. All authors had full access to and take full responsibility for the integrity of the data.

Results

Baseline Characteristics

The study sample consisted of 1038 elderly participants (Table 1). More than three quarters of the sample were hypertensive, and about half were on antihypertensive treatment. The prevalence of asymptomatic LV systolic and diastolic dysfunction was 5% and 36%, respectively, consistent with other community-based studies. The distributions of measures of noncardiac function were within the ranges expected for elderly individuals in the general population.

Cardiac Dysfunction as a Risk Factor for Incident Heart Failure

Over a mean follow-up of 11 years, there were 248 incident first HF events (146 in women; 119 HFREF, 101 HFPEF, and unavailable EF for 28 HF events). In multivariable models adjusted for established HF risk factors (age, sex, body mass index, systolic blood pressure, hypertension treatment, cholesterol, diabetes mellitus, prior myocardial infarction, and valvular heart disease) in 1038 participants (248 heart failure events).

Cardiac Dysfunction as a Risk Factor for Incident Heart Failure

Noncardiac Risk Factors and Major Organ System Dysfunction Risk Score for Incident Heart Failure

Participants (n = 676; mean age, 75 ± 5 years; 42% men) without missing noncardiac risk factor variables had baseline characteristics (body mass index, systolic blood pressure, diabetes mellitus) similar to those with missing variables (all P > 0.05). With adjustment for established HF risk factors and the presence of cardiac systolic and diastolic dysfunction, higher serum creatinine, lower FEV₁/FVC ratios, and lower hemoglobin concentrations were associated with increased risk of new-onset HF (Table 3). There was no association between serum albumin concentration (P = 0.306) or white blood cell count (P = 0.685) and incident HF. Individual Cox proportional hazards models with penalized splines for serum creatinine, FEV₁/FVC ratio, and hemoglobin did not reveal nonlinearity for the association with HF risk (Figure 1). Therefore, a risk score for noncardiac dysfunction was calculated using predetermined cut points (based on the 25th or 75th percentiles of the variables in the sample, as defined above) and awarding 1 point for each affected organ system (range, 0 to 3); regression coefficients for these variables were comparable in the multivariable models, further justifying their similar weighting in the score (Table 3). Of note, the cut points used to define organ “dysfunction” were within the ranges frequently observed in ambulatory elderly individuals in the general population. Increasing noncardiac risk score at baseline was positively associated with risk of HF (Figure 2).

In secondary analyses, results were similar when estimated glomerular filtration rate (by the Modification of Diet in Renal Disease equation) was used instead of serum creatinine (hazard ratio for each 1-SD decrease in estimated glomerular filtration rate, 1.24; 95% confidence interval, 1.03 to 1.50; P = 0.026 with adjustment for established HF risk factors and the presence of cardiac dysfunction). Other biomarkers of noncardiac dysfunction (blood urea nitrogen, total bilirubin,
transaminases, hematocrit, C-reactive protein measured by traditional assays [high-sensitivity assays were unavailable], uric acid) were also tested for their associations with incident HF in secondary analyses, and results are shown in Table I in the online-only Data Supplement. These secondary analyses supported the original selection of creatinine, albumin, FEV1:FVC ratio, and hemoglobin as simple, convenient, and widely available biomarkers to include in the final risk score. We also performed sensitivity analyses using different percentile cut points to define the risk score (tertiles instead of quartiles) and found similar results (data not shown).

### Multivariable Risk Factors for All Incident Heart Failure, Heart Failure With Reduced Ejection Fraction, and Heart Failure With Preserved Ejection Fraction

In multivariable modeling for all incident HF, LV systolic dysfunction, LV diastolic dysfunction, and the noncardiac risk score were each associated with incident HF after adjustment for established HF risk factors (Table 4). There was no significant interaction between noncardiac risk score and the presence of LV systolic or diastolic dysfunction (P=0.78 and P=0.84, respectively). In multivariable modeling for HFREF and HFPEF separately, antecedent LV systolic dysfunction, greater serum creatinine, and lower hemoglobin concentration were associated with incident HFREF, whereas antecedent LV diastolic dysfunction and lower...

### Table 3. Noncardiac Risk Factors and Risk Score for Incident Heart Failure

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard Ratio (95% Confidence Interval)*</th>
<th>P*</th>
<th>Cutoff Percentile</th>
<th>Cutoff Value</th>
<th>Points Awarded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine</td>
<td>1.21 (1.01–1.45)</td>
<td>0.036</td>
<td>&gt;75th</td>
<td>&gt;1.05 mg/dL (~92.8 μmol/L)</td>
<td>1</td>
</tr>
<tr>
<td>FEV1:FVC ratio</td>
<td>1.21 (1.02–1.43)</td>
<td>0.029</td>
<td>&lt;25th</td>
<td>&lt;91% predicted</td>
<td>1</td>
</tr>
<tr>
<td>Hemoglobin concentration</td>
<td>1.24 (1.09–1.40)</td>
<td>&lt;0.001</td>
<td>&lt;25th</td>
<td>&lt;13 g/dL</td>
<td>1</td>
</tr>
</tbody>
</table>

FEV1:FVC indicates ratio of forced expiratory volume in 1 second to forced vital capacity.

*Hazard ratios are for a 1-SD increase in serum creatinine, 1-SD decrease in FEV1:FVC ratio, and 1-unit decrease in hemoglobin concentration after adjustment for age, sex, body mass index, systolic blood pressure, hypertension treatment, cholesterol, diabetes mellitus, prior myocardial infarction, valvular heart disease, and left ventricular systolic and diastolic function in 676 participants without any missing variables (170 heart failure events).

**Figure 1.** Association of measures of major noncardiac organ system function with risk of incident heart failure. Generalized additive models with penalized splines were used to assess the association of multivariable-adjusted hazards ratio for heart failure with (A) serum creatinine concentration, (B) ratio of forced expiratory volume in 1 second to forced vital capacity (FEV1:FVC ratio), and (C) hemoglobin concentration. Lines indicate means (solid) and 95% confidence intervals (dotted). The y axes represent multivariable-adjusted Ln(hazards ratio). (To obtain serum creatinine concentration in μmol/L, multiply values in mg/dL by 88.4.)

**Figure 2.** Cumulative incidence of incident heart failure according to noncardiac major organ system dysfunction risk score. The noncardiac organ system dysfunction risk score awarded 1 point for the presence of each of the following (range, 0 to 3): serum creatinine >1.05 mg/dL (92.8 μmol/L), ratio of forced expiratory volume in 1 second to forced expiratory volume <91% predicted, and hemoglobin concentration <13 g/dL. Increasing noncardiac risk score at baseline was associated with increasing risk of incident heart failure in our community-based sample (log rank P=0.013).
Participations with overt pulmonary dysfunction (FEV1:FVC adjustment for established HF risk factors (Table 4). Results (Table II in the online-only Data Supplement). 45%) to distinguish HFPEF from HFREF revealed similar (data not shown). Using an EF cut point of 50% (instead of \( \langle \text{no participant had hypoalbuminemia} \)), or anemia (hemoglobin concentration per 1-unit decrease). Incident HFPEF LV systolic dysfunction 3.93 (1.86–8.30) <0.001 Serum creatinine per 1-SD increase 1.32 (1.04–1.69) 0.025 Hemoglobin concentration per 1-unit decrease 1.31 (1.10–1.55) 0.002 Incident HFPEF LV diastolic dysfunction 1.88 (1.13–3.13) 0.016 FEV1:FVC ratio per 1-SD decrease 1.38 (1.04–1.83) 0.024

HF indicates heart failure; LV, left ventricular; HFREF, heart failure with reduced ejection fraction; HFPEF, heart failure with preserved ejection fraction; and FEV1:FVC, ratio of forced expiratory volume in 1 second to forced vital capacity.

*Adjusted for age, sex, body mass index, systolic blood pressure, hypertension treatment, cholesterol, diabetes mellitus, prior myocardial infarction, and valvular heart disease (valvular heart disease excluded for HFPEF) in 676 participants without any missing variables (170 total HF events: 82 HFREF, 66 HFPEF, 22 EF unavailable).

†Components of the noncardiac risk score are described and their individual hazards ratios are shown in Table 3.

FEV1:FVC ratio were associated with incident HFPEF after adjustment for established HF risk factors (Table 4).

In further analyses adjusted for smoking and excluding participants with overt pulmonary dysfunction (FEV1:FVC <60%; n=3), hypoalbuminemia (albumin <2.5 g/dL; n=0 [no participant had hypoalbuminemia]), or anemia (hemoglobin <10.5 g/dL; n=7), results were essentially unchanged (data not shown). Using an EF cut point of 50% (instead of 45%) to distinguish HFPEF from HFREF revealed similar results (Table II in the online-only Data Supplement).

**Discussion**

Principal Findings

In our prospective study of a large, community-based sample, antecedent subclinical cardiac and noncardiac major organ system dysfunction was associated with risk of future HF. The presence of asymptomatic LV systolic and diastolic dysfunction preceded and increased the risk of incident HF by >2-fold and >30%, respectively. These findings support the emphasis in current HF guidelines regarding the progressive nature of HF and the importance of recognizing preceding asymptomatic cardiac dysfunction. Our data also extend the previous HF staging system by providing evidence for the association of noncardiac dysfunction with progression to clinical HF. After adjustment for cardiac dysfunction, the presence of subclinical renal impairment, airflow limitation, or anemia was each associated with 30% increased risk of incident HF. Finally, antecedent LV systolic dysfunction was associated with future HFREF, whereas antecedent LV diastolic dysfunction was associated with future HFPEF. Furthermore, subclinical renal impairment and lower hemoglobin concentrations were associated with a higher incidence of HFREF, whereas baseline airflow obstruction was related positively to the risk of future HFPEF. The implications of these findings for the early identification of individuals at risk of HF and potential strategies to prevent the progression to overt HF deserve further study.

Left Ventricular Systolic and Diastolic Dysfunction and Risk of Heart Failure

Previous cross-sectional studies have provided evidence for the existence of asymptomatic LV dysfunction in the general community (stage B HF in the American College of Cardiology/American Heart Association classification system), as well as increased prevalence and severity of LV dysfunction in patients with clinical HF (stage C HF). Although these cross-sectional data supported the proposed stages of the HF, prior studies were limited by potential reverse causality because the assessment of LV function was performed at the same point in time as the diagnosis of clinical HF. Furthermore, cross-sectional studies may be criticized for scientific circularity of reasoning in that the presence of LV systolic or diastolic dysfunction is used to make the diagnosis HFREF or HFPEF, respectively. Prospective data are needed to resolve these issues. In the Cardiovascular Health Study, LV systolic and diastolic dysfunction predicted incident HF over a mean follow-up of 5.2 years. However, the relationships between the type of LV dysfunction (systolic versus diastolic) and the type of HF (HFREF versus HFPEF) were not assessed. More recently, researchers from the Mayo Clinic reported a 2-year HF incidence rate of 1.9% in a selected sample of 82 patients with preclinical diastolic dysfunction. Patients with systolic dysfunction were not studied. Our current data are consistent with these prior data and extend previous knowledge by demonstrating that LV systolic dysfunction predicts future HFREF, whereas LV diastolic dysfunction portends HFPEF. Therefore, the present data help to fill the knowledge gap linking stage B to stage C in the American College of Cardiology/American Heart Association classification scheme, whether referring to HFREF or HFPEF.

Noncardiac Dysfunction and Risk of Heart Failure

Heart failure is a clinical syndrome characterized by a constellation of signs and symptoms involving multiple organ systems besides the heart. Thus, even mild functional derangement of a noncardiac organ system, which in itself is not severe enough to produce symptoms, may accelerate the manifestation of overt HF, particularly when other organ systems are also involved. A decline in renal function affects sodium handling and fluid homeostasis, thus increasing the propensity to manifest fluid overload. Pulmonary function has a direct impact on the manifestation of dyspnea. Subclinical chronic pulmonary disease is characterized by low-grade inflammation and may contribute to progression of atherosclerosis and myocardial dysfunction, whereas even mild airflow obstruction is associated with abnormal LV diastolic filling. Aemia affects the oxygen-carrying capacity of the blood and is an adverse marker in overt HF. The availability
of systematic, multisystem measurements during routine surveillance in the Framingham Heart Study enabled comprehensive assessment of these varied noncardiac organ systems in relation to incident HF in the community. Our findings regarding the association with renal impairment are consistent with the Health ABC Heart Failure Model for incident HF in the elderly. In contrast, we did not find a significant association with hypoalectinemia; this may be due to differences in study samples (larger proportion of blacks and lower baseline serum albumin in the Health ABC Study).

In aggregate, these results suggest that the manifestation of clinically overt HF may be hastened by subclinical dysfunction in multiple organ systems. This is likely to particularly affect elderly individuals who have age-related decline in multorgan function or multiple noncardiac comorbidities. Recognizing the contribution of noncardiac dysfunction to HF progression may carry important clinical implications for preventing and managing HF. Further studies are warranted to validate these findings in other populations, to evaluate for potential effect modification by covariates such as sex, and to assess the potential impact of treatment of these risk factors on the risk of future HF.

Association of Noncardiac Dysfunction With Heart Failure With Reduced Ejection Fraction Versus Heart Failure With Preserved Ejection Fraction

The distinction between factors associated with incident HFREF versus HFPEF deserves comment. The association of renal dysfunction and anemia with the risk of HFREF is consistent with classic studies of the cardiorenal syndrome and the known prognostic impact of anemia in overt HFREF. Interestingly, the most prominent noncardiac predictor of incident HFPEF was airflow obstruction. This observation is supported by large epidemiological studies showing a high prevalence of pulmonary disease in patients with HFPEF, the frequent coexistence of HF in patients with chronic obstructive lung disease, and a recent study in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort demonstrating an association between airflow obstruction and abnormal LV filling. Although this also raises the question of potential misdiagnosis of HFPEF, it is unlikely, given the high specificity of Framingham criteria for HF, the reliability of the diagnosis as demonstrated by consistent application of the same criteria over decades and stringent adjudication of end points in the Framingham Heart Study, and the lack of an alternative explanation for the clinical presentation (because the extent of pulmonary impairment was not severe enough to explain symptoms). Overall, the different predictors of HFREF versus HFPEF are consistent with prior epidemiological, pathophysiological, molecular, and outcome data supporting the notion that HFREF and HFPEF may represent separate entities. These observations may guide future clinical trial design, particularly in HFPEF, for which trials have so far been disappointing.

Strengths and Limitations

The strengths of our study include the large community-based sample, uniform measurements of function of multiple organ systems, and longitudinal follow-up with continuous surveillance for and careful validation of HF outcomes. Furthermore, the use of purely clinical criteria for the diagnosis of HF independently of LVEF is particularly advantageous in this setting. Limitations include the lack of tissue Doppler characterization of diastolic dysfunction and the inherent pitfalls in using echocardiographic indexes of diastolic filling as indicators of diastolic dysfunction. Nonetheless, mitral Doppler indexes are widely available, and our results are consistent with previous studies using more comprehensive assessment of diastolic dysfunction. We acknowledge the observational nature of our study, which precludes conclusions regarding causality, as well as the modest effect sizes for noncardiac organ system variables and the potential for residual confounding or effect modification by other factors. We did not use time-varying covariates, but we speculate that organ dysfunction would worsen with aging in most individuals, leading to even stronger associations with incident HF. Our uniformly white sample limits the generalizability of our findings to other ethnicities, and independent validation in other cohorts is warranted.

Conclusions

Our prospective observations in a large, community-based sample demonstrate that antecedent subclinical cardiac and noncardiac major organ system dysfunction is associated with increased risk of clinical HF. These findings contribute to the understanding of HF as a progressive disease syndrome and underscore the potential importance of noncardiac risk factors in predisposing to the manifestation of overt HF.

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Disclosures

None.

References

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**CLINICAL PERSPECTIVE**

In our prospective study of a large, community-based sample, antecedent subclinical cardiac and noncardiac major organ system dysfunction was associated with risk of future heart failure. The presence of asymptomatic left ventricular systolic and diastolic dysfunction preceded and increased the risk of incident heart failure by >2-fold and >30%, respectively. With adjustment for cardiac dysfunction, the presence of subclinical renal impairment, airflow limitation, or anemia was each associated with 30% increased risk of incident heart failure. Notably, the significant risk factors differed according to the type of incident heart failure (preserved versus reduced ejection fraction). A antecedent left ventricular systolic dysfunction, subclinical renal impairment, and lower hemoglobin concentrations were associated with a higher incidence of heart failure with reduced ejection fraction, whereas antecedent diastolic dysfunction and baseline airflow obstruction were related positively to the risk of future heart failure with preserved ejection fraction. This study provides longitudinal evidence for the progressive nature of heart failure as emphasized in current heart failure guidelines and underscores the potential importance of noncardiac risk factors in predisposing to the manifestation of overt heart failure. The implications for the early identification of individuals at risk of heart failure and potential strategies to prevent progression to overt heart failure deserve further study.