Heart Failure

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

Carolyn S.P. Lam, MBBS, MRCP; Asya Lyass, PhD; Elisabeth Kraigher-Krainer, MD;
Joseph M. Massaro, PhD; Douglas S. Lee, MD, PhD; Jennifer E. Ho, MD; Daniel Levy, MD;
Margaret M. Redfield, MD; Burkert M. Pieske, MD, PhD;
Emelia J. Benjamin, MD, ScM; Ramachandran S. Vasan, MD

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 (FEV_1: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[1,2] 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,[3]

and an even higher prevalence of these abnormalities in patients with overt HF.[4] However, to demonstrate a prospective association between these structural precursors and future HF, longitudinal studies are needed.

Editorial see p 4
Clinical Perspective on p 30

Importantly, the current HF staging system[1] 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,[5] hypoalbuminemia,[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. 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 HFPEF[17] 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 function included the following[5–7,10,11]: (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 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 Framingham criteria[19] (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 ≤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

Table 1.   Baseline Characteristics

Characteristics	
n	1038
Age, y	76±5
Men, n (%)	409 (39)
Cardiovascular risk factors	
Body mass index, kg/m²	26.6±4.5
Systolic blood pressure, mm Hg	147±22
Hypertension, n (%)	799 (77)
Hypertension treatment, n (%)	551 (53)
Ratio of total to HDL cholesterol	4.85±1.65
Diabetes mellitus, n (%)	104 (10)
Myocardial infarction, n (%)	96 (9)
Valve disease, n (%)	41 (4)
Cardiac function	
LV systolic dysfunction, n (%)	57 (5)
LV diastolic dysfunction, n (%)*	372 (36)
Noncardiac function	
Serum creatinine, mg/dL	0.93±0.23
Serum albumin, g/dL	4.23±0.36
FEV₁:FVC ratio, % predicted	96.9±10.9
Hemoglobin concentration, g/dL	14.0±1.5
Blood cell count, ×10⁹/L	6.8±2.3

HDL indicates high-density lipoprotein; LV, left ventricular; and FEV_1: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,[17] 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.[3] The distributions of measures of noncardiac function were within the ranges expected for elderly individuals in the general population.[5]

Table 2.   Cardiac Dysfunction as a Risk Factor for Incident Heart Failure

Characteristic	Hazard Ratio (95% Confidence Interval)	P*
LV systolic dysfunction	2.33 (1.43–3.78)	<0.001
LV diastolic dysfunction	1.32 (1.01–1.71)	0.039

LV indicates left ventricular.

*Adjusted for 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

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 FEV_1: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, FEV_1: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.[5] 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,

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

Characteristic	Hazard Ratio (95% Confidence Interval)*	P*	Cutoff Percentile	Cutoff Value	Points Awarded
Serum creatinine	1.21 (1.01–1.45)	0.036	>75th	>1.05 mg/dL (>92.8 μmol/L)	1
FEV$_1$:FVC ratio	1.21 (1.02–1.43)	0.029	<25th	<91% predicted	1
Hemoglobin concentration	1.24 (1.09–1.40)	<0.001	<25th	<13 g/dL	1

FEV$_1$: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).

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, FEV$_1$: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
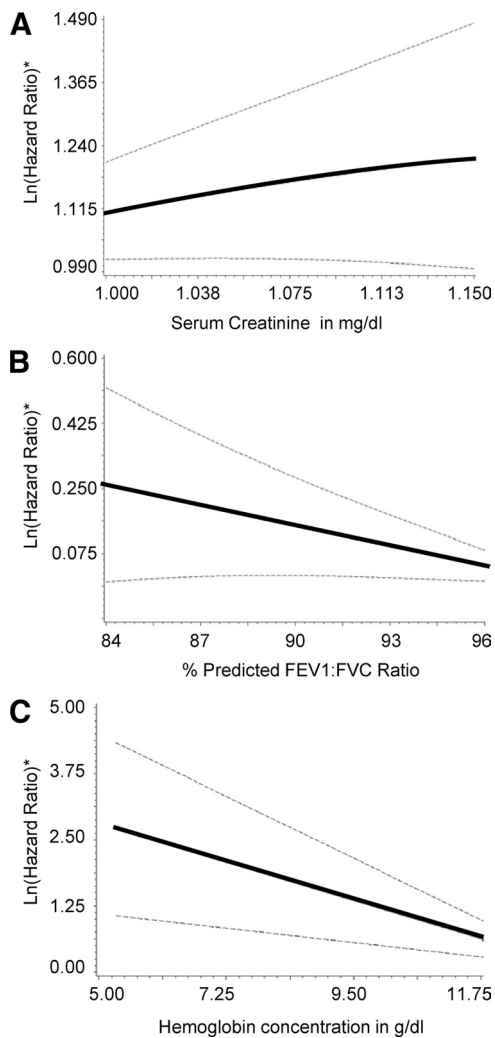
Figure 1. Association of measures of major noncardiac organ system function with risk of incident heart failure. Generalized additive models with penalized splines were used to assess the association of multivariable-adjusted hazards ratio for heart failure with (**A**) serum creatinine concentration, (**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.)
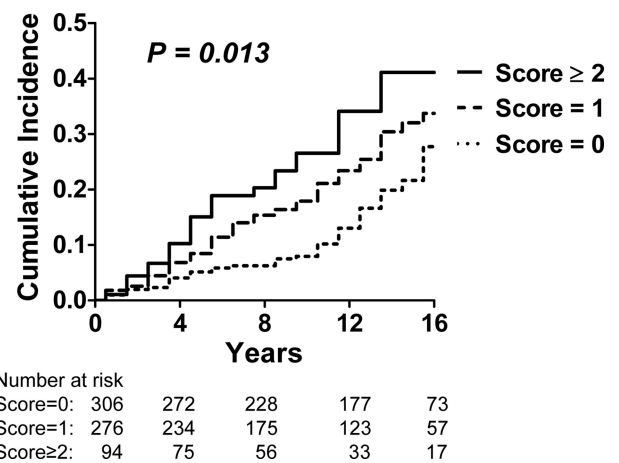
Figure 2. Cumulative incidence of incident heart failure according to noncardiac major organ system dysfunction risk score. The noncardiac organ system dysfunction risk score awarded 1 point for the presence of each of the following (range, 0 to 3): serum creatinine >1.05 mg/dL (92.8 μmol/L), ratio of 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

Characteristics	Hazards Ratio (95% Confidence Interval)*	P*
All incident HF		
LV systolic dysfunction	1.97 (1.05–3.68)	0.034
LV diastolic dysfunction	1.40 (1.02–1.93)	0.039
Noncardiac risk score† per 1-unit increase	1.30 (1.06–1.60)	0.013
Incident HFREF		
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
FEV_1: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 FEV_1: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.

FEV_1: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 (FEV_1: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 dia-

stolic 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),[3,22] as well as increased prevalence and severity of LV dysfunction in patients with clinical HF (stage C HF).[3,4] 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,[23] 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.[24] 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.[5] 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,[8] whereas even mild airflow obstruction is associated with abnormal LV diastolic filling.[9] Anemia affects the oxygen-carrying capacity of the blood and is an adverse marker in overt HF.[10] 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.[25] In contrast, we did not find a significant association with hypoalbuminemia; 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.[10] 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,[26,27] the frequent coexistence of HF in patients with chronic obstructive lung disease,[28] and a recent study in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort demonstrating an association between airflow obstruction and abnormal LV filling.[9] Although this also raises the question of potential misdiagnosis of HFPEF, it is unlikely, given the high specificity of the Framingham criteria for HF,[29] 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,[20] pathophysiological,[30] molecular,[31] and outcome[32] 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[19] 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.[3,24] 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.

Disclosures

None.

References

1. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 Focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation*. 2009;119:e391–e479.

2. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, Tavazzi L, Smiseth OA, Gavazzi A, Haverich A, Hoes A, Jaarsma T, Korewicki J, Levy S, Linde C, Lopez-Sendon JL, Nieminen MS, Pierard L, Remme WJ. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): the Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. *Eur Heart J*. 2005;26:1115–1140.

3. Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA*. 2003;289:194–202.

4. Lam CS, Roger VL, Rodeheffer RJ, Bursi F, Borlaug BA, Ommen SR, Kass DA, Redfield MM. Cardiac structure and ventricular-vascular function in persons with heart failure and preserved ejection fraction from Olmsted County, Minnesota. *Circulation*. 2007;115:1982–1990.

5. Smith GL, Shlipak MG, Havranek EP, Foody JM, Masoudi FA, Rathore SS, Krumholz HM. Serum urea nitrogen, creatinine, and estimators of

renal function: mortality in older patients with cardiovascular disease. *Arch Intern Med.* 2006;166:1134–1142.

6. Horwich TB, Kalantar-Zadeh K, MacLellan RW, Fonarow GC. Albumin levels predict survival in patients with systolic heart failure. *Am Heart J.* 2008;155:883–889.

7. Arques S, Ambrosi P, Gelisse R, Luccioni R, Habib G. Hypoalbuminemia in elderly patients with acute diastolic heart failure. *J Am Coll Cardiol.* 2003;42:712–716.

8. Hawkins NM, Petrie MC, Jhund PS, Chalmers GW, Dunn FG, McMurray JJ. Heart failure and chronic obstructive pulmonary disease: diagnostic pitfalls and epidemiology. *Eur J Heart Fail.* 2009;11:130–139.

9. Barr RG, Bluemke DA, Ahmed FS, Carr JJ, Enright PL, Hoffman EA, Jiang R, Kawut SM, Kronmal RA, Lima JA, Shahar E, Smith LJ, Watson KE. Percent emphysema, airflow obstruction, and impaired left ventricular filling. *N Engl J Med.* 362:217–227.

10. Groenveld HF, Januzzi JL, Damman K, van Wijngaarden J, Hillege HL, van Veldhuisen DJ, van der Meer P. Anemia and mortality in heart failure patients a systematic review and meta-analysis. *J Am Coll Cardiol.* 2008;52:818–827.

11. Ernst E, Hammerschmidt DE, Bagge U, Matrai A, Dormandy JA. Leukocytes and the risk of ischemic diseases. *JAMA.* 1987;257:2318–2324.

12. Shah SJ, Gheorghiade M. Heart failure with preserved ejection fraction: treat now by treating comorbidities. *JAMA.* 2008;300:431–433.

13. Henkel DM, Redfield MM, Weston SA, Gerber Y, Roger VL. Death in heart failure: a community perspective. *Circ Heart Fail.* 2008;1:91–97.

14. Wang TJ, Evans JC, Benjamin EJ, Levy D, LeRoy EC, Vasan RS. Natural history of asymptomatic left ventricular systolic dysfunction in the community. *Circulation.* 2003;108:977–982.

15. Dawber TR, Meadors GF, Moore FE Jr. Epidemiological approaches to heart disease: the Framingham study. *Am J Public Health Nations Health.* 1951;41:279–281.

16. Sagie A, Benjamin EJ, Galderisi M, Larson MG, Evans JC, Fuller DL, Lehman B, Levy D. Reference values for Doppler indexes of left ventricular diastolic filling in the elderly. *J Am Soc Echocardiogr.* 1993;6:570–576.

17. Paulus WJ, Tschope C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, Marino P, Smiseth OA, De Keulenaer G, Leite-Moreira AF, Borbely A, Edes I, Handoko ML, Heymans S, Pezzali N, Pieske B, Dickstein K, Fraser AG, Brutsaert DL. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J.* 2007;28:2539–2550.

18. Vasan RS, Benjamin EJ, Larson MG, Leip EP, Wang TJ, Wilson PW, Levy D. Plasma natriuretic peptides for community screening for left ventricular hypertrophy and systolic dysfunction: the Framingham Heart Study. *JAMA.* 2002;288:1252–1259.

19. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. *N Engl J Med.* 1971;285:1441–1446.

20. Lee DS, Gona P, Vasan RS, Larson MG, Benjamin EJ, Wang TJ, Tu JV, Levy D. Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: insights from the Framingham Heart Study of the National Heart, Lung, and Blood Institute. *Circulation.* 2009;119:3070–3077.

21. Desquilbet L, Mariotti F. Dose-response analyses using restricted cubic spline functions in public health research [published online ahead of print January 19, 2010]. *Stat Med.* doi: 10.1002/sim.3841.

22. Fischer M, Baessler A, Hense HW, Hengstenberg C, Muscholl M, Holmer S, Doring A, Broeckel U, Riegger G, Schunkert H. Prevalence of left ventricular diastolic dysfunction in the community: results from a Doppler echocardiographic-based survey of a population sample. *Eur Heart J.* 2003;24:320–328.

23. Aurigemma GP, Gottdiener JS, Shemanski L, Gardin J, Kitzman D. Predictive value of systolic and diastolic function for incident congestive heart failure in the elderly: the Cardiovascular Health Study. *J Am Coll Cardiol.* 2001;37:1042–1048.

24. Correa de Sa DD, Hodge DO, Slusser JP, Redfield MM, Simari RD, Burnett JC, Chen HH. Progression of preclinical diastolic dysfunction to the development of symptoms. *Heart.* 2010;96:528–532.

25. Butler J, Kalogeropoulos A, Georgiopoulou V, Belue R, Rodondi N, Garcia M, Bauer DC, Satterfield S, Smith AL, Vaccarino V, Newman AB, Harris TB, Wilson PW, Kritchevsky SB. Incident heart failure prediction in the elderly: the Health ABC Heart Failure score. *Circ Heart Fail.* 2008;1:125–133.

26. Bursi F, Weston SA, Redfield MM, Jacobsen SJ, Pakhomov S, Nkomo VT, Meverden RA, Roger VL. Systolic and diastolic heart failure in the community. *JAMA.* 2006;296:2209–2216.

27. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. *J Am Coll Cardiol.* 2006;47:76–84.

28. Rutten FH, Cramer MJ, Grobbee DE, Sachs AP, Kirkels JH, Lammers JW, Hoes AW. Unrecognized heart failure in elderly patients with stable chronic obstructive pulmonary disease. *Eur Heart J.* 2005;26:1887–1894.

29. Mosterd A, Deckers JW, Hoes AW, Nederpel A, Smeets A, Linker DT, Grobbee DE. Classification of heart failure in population based research: an assessment of six heart failure scores. *Eur J Epidemiol.* 1997;13:491–502.

30. van Heerebeek L, Borbely A, Niessen HW, Bronzwaer JG, van der Velden J, Stienen GJ, Linke WA, Laarman GJ, Paulus WJ. Myocardial structure and function differ in systolic and diastolic heart failure. *Circulation.* 2006;113:1966–1973.

31. Borbely A, Papp Z, Edes I, Paulus WJ. Molecular determinants of heart failure with normal left ventricular ejection fraction. *Pharmacol Rep.* 2009;61:139–145.

32. Somaratne JB, Berry C, McMurray JJ, Poppe KK, Doughty RN, Whalley GA. The prognostic significance of heart failure with preserved left ventricular ejection fraction: a literature-based meta-analysis. *Eur J Heart Fail.* 2009;11:855–862.

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.

Go to http://cme.ahajournals.org to take the CME quiz for this article.