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SHORT COMMUNICATION

Relative contribution of risk factors/co-morbidities to heart failure pathogenesis: interaction with ejection fraction

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Abstract

Aims The relative impact of each individual coexisting morbidity on the pathogenesis of heart failure (HF) is incompletely understood. This study aimed to evaluate the prevalence of individual cardiac and non-cardiac coexisting morbidities both in the overall HF population and in the subgroup of HF patients with a single coexisting morbidity, stratified by left ventricular ejection fraction (LVEF) categories, as a measure of the relative contribution of each co-morbidity to the pathogenesis of HF.
Methods and results This is a prospective, observational study, in which unselected ambulatory patients with chronic HF visiting the HF clinic of a tertiary university hospital from January 2016 to January 2019 were classified according to baseline LVEF into three groups: (i) LVEF $<$ 40%, (ii) LVEF = 40–49%, and (iii) LVEF $\geq$ 50% and then evaluated for various coexisting morbidities. Overall, 1064 patients (age 73.4 ± 12.1 years, male gender 57.7%, LVEF 43.6 ± 13.9, N-terminal pro-brain natriuretic peptide 2187 ± 710 ng/L, and estimated glomerular filtration rate 67.2 ± 25 mL/min/1.73 m^2) were recruited in this study. Of these, 361 (33.9%) had an LVEF $<$ 40%, 247 (23.2%) an LVEF = 40–49%, and 456 (42.9%) an LVEF $\geq$ 50%. There were 90 (8.5%) HF patients with a single coexisting morbidity, 33 (36.7%) with LVEF $\geq$ 50%, 27 (30.0%) with LVEF = 40–49%, and 30 (33.3%) with LVEF $<$ 40%. Among these patients, those with LVEF $\geq$ 50% suffered mostly from hypertension (85.7%), whereas the second most common coexisting morbidity was atrial fibrillation (AF) (9.5%). HF patients with LVEF = 40–49% usually suffered from hypertension (35.7%), AF (28.6%), or myocardial infarction (MI) (21.4%). Finally, HF patients with LVEF $<$ 40% usually suffered from MI (30.8%), AF (30.8%), or hypertension (15.4%).
Conclusions Hypertension is strongly associated with the development of HF with low, intermediate, or near-normal/normal LVEF whereas a history of MI or AF with HF with a low or an intermediate LVEF.

Keywords Heart Failure; Morbidity; Co-morbidity; Coexisting disease; Hypertension; Myocardial infarction; Atrial fibrillation; Ejection fraction

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Background

Many cardiac and non-cardiac coexisting morbidities are frequently prevalent in patients with heart failure (HF).[1] In most patients, the anatomical, physiological, and clinical features of HF, regardless of the left ventricular ejection fraction (LVEF), are determined by complex interactions between coexisting morbidities themselves as well as between coexisting morbidities and HF. It is widely accepted that the burden of coexisting morbidities, usually expressed by their prevalence, adversely affects HF outcomes.[2] However, this may not always be the case. In the BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF), the highest prevalence of coexisting morbidities was seen in HF

patients with LVEF ≥ 50%.[3] Overall, coexisting morbidities were associated with a lower quality of life, but this was more pronounced in HF patients with LVEF < 40%. Moreover, most coexisting morbidities were associated with higher mortality risk, although the associations with diabetes mellitus (DM) were only present in HF patients with LVEF < 40%. The relative impact of each individual coexisting morbidity to HF pathogenesis is incompletely understood.

Aims

This study aimed to evaluate the prevalence of individual cardiac and non-cardiac coexisting morbidities both in the overall HF population and in the subgroup of HF patients with a single coexisting morbidity, stratified by LVEF categories, as a measure of the relative contribution of each co-morbidity to the pathogenesis of HF.

Methods

This is a prospective, observational study, in which unselected ambulatory patients with chronic HF visiting the HF clinic of a tertiary university hospital from January 2016 to January 2019 were included. Patients were classified according to baseline LVEF into three groups: (i) LVEF < 40%, (ii) LVEF = 40–49%, and (iii) LVEF ≥ 50%.[4] Three major cardiac coexisting morbidities [hypertension, previous myocardial infarction (MI), and atrial fibrillation (AF)] and six frequent non-cardiac coexisting morbidities [obesity, dyslipidaemia, DM, chronic kidney disease (CKD), anaemia, and chronic obstructive pulmonary disease (COPD)] were recorded at baseline. Coexisting morbidity definitions were as follows: (i) hypertension was defined as reported hypertension in the electronic patient records (EPRs) within the past 3 years; (ii) obesity: body mass index ≥30 kg/m^2 anytime within the past 3 years; (iii) dyslipidaemia: reported dyslipidaemia in the EPRs within the past 3 years plus prescription of at least one hypolipidaemic drug; (iv) DM: reported DM in EPRs within the past 3 years plus prescription of at least one hypoglycaemic drug; (v) CKD: reported CKD stage ≥IIIa in EPRs within the past 3 years or an estimated glomerular filtration rate of <60 mL/min/1.73 m^2 at registration (Kidney Disease Improving Global Outcomes 2012 Clinical Practice Guideline), calculated according to the formula of the CKD Epidemiology Collaboration; (vi) anaemia: anaemia in EPRs within the past 3 years or haemoglobin <130 g/L for men and <120 g/L for women at registration; and (vii) COPD: COPD reported in EPRs within the past 3 years.

Categorical variables are reported as count (percentage) and continuous variables as mean ± standard deviation. Intergroup comparisons of continuous variables were performed using analysis of variance whereas intergroup comparisons of categorical variables using cross-tabulation and the χ^2 test. A P value <0.05 was considered statistically significant. All statistical analyses were performed using WINKS SDA 7.0.5 statistical package (TexaSoft, Austin, TX).

Results

Overall, 1064 patients (age 73.4 ± 12.1 years, male gender 57.7%, LVEF 43.6 ± 13.9, N-terminal pro-brain natriuretic peptide 2187 ± 710 ng/L, and estimated glomerular filtration rate 67.2 ± 25 mL/min/1.73 m^2) were recruited in this study. Of these, 361 (33.9%) had an LVEF < 40%, 247 (23.2%) an LVEF = 40–49%, and 456 (42.9%) an LVEF ≥ 50%. The baseline characteristics of the study population are depicted in *Table 1*. In comparison with patients with LVEF = 40–49% and LVEF ≥ 50%, patients with LVEF < 40% were more likely to be male, to be current smokers, to have experienced a prior MI, dyslipidaemia, anaemia, and CKD, but less likely to have hypertension or obesity. The two most frequent coexisting morbidities by LVEF category were as follows: (i) LVEF ≥ 50%: hypertension (95.4%) and obesity (61.0%), (ii) LVEF = 40–49%: hypertension (66.8%) and prior MI (55.1%), and (iii) LVEF < 40%: prior MI (80.1%) and hypertension (58.7%).

There were 90 (8.5%) HF patients with a single coexisting morbidity, 33 (36.7%) with LVEF ≥ 50%, 27 (30.0%) with LVEF = 40–49%, and 30 (33.3%) with LVEF < 40%. In this subgroup, those with LVEF ≥ 50% suffered mostly from hypertension (85.7%), whereas the second most common coexisting morbidity was AF (9.5%). HF patients with LVEF = 40–49% usually suffered from hypertension (35.7%), AF (28.6%), or MI (21.4%), whereas HF patients with LVEF < 40% usually suffered from MI (30.8%), AF (30.8%), or hypertension (15.4%) (*Figure 1*).

Discussion

From the prevalence of co-morbidities in the overall HF population and especially in the subgroup with a single coexisting morbidity of the present study, the following conclusions can be drawn: (i) hypertension is the most common coexisting morbidity in HF, and it may be the cause of HF in all groups; (ii) MI is one of the main causes of HF with LVEF < 40%, but it may also cause HF with LVEF = 40–49%; and (iii) AF is present in all groups of HF. However, in contrast to hypertension and MI, which exhibit an antecedent–consequent or complicating association with HF, AF exhibits a reciprocal ('chicken and egg') association.[5]

Arterial hypertension is often associated with left ventricular (LV) remodelling/hypertrophy,[6] and although increased

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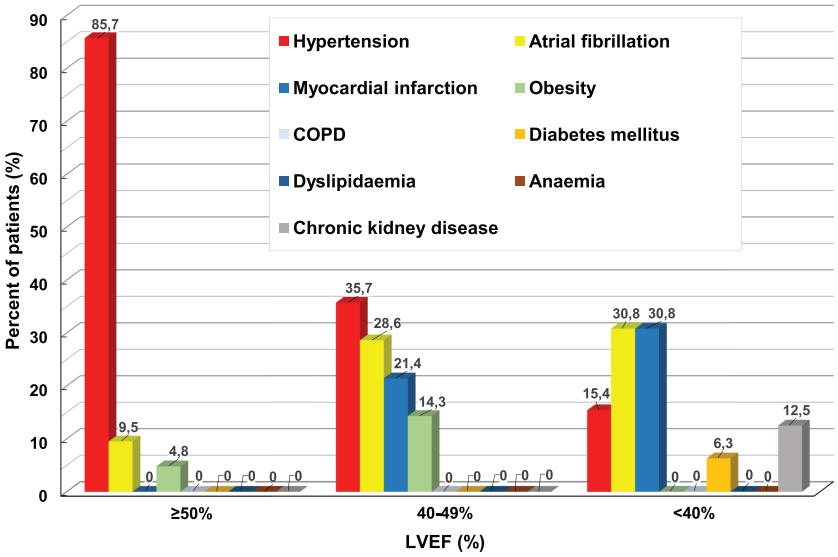
Table 1 Baseline characteristics of the heart failure population stratified by LVEF

Parameter	Total $n = 1064$	LVEF ≥ 50% $n = 456$	LVEF = 40–49% $n = 247$	LVEF < 40% $n = 361$	*P* value
Age (years ± SD)	73.4 ± 12.1	73.1 ± 11.6	72.8 ± 14.3	74.1 ± 11.3	0.353
Male gender, *n* (%)	614 (57.7)	211 (46.3)	147 (59.5)	256 (70.9)	<0.0001
LVEF (% ± SD)	43.6 ± 13.9	56.5 ± 4.7	44.5 ± 2.1	26.7 ± 6.8	<0.0001
Current smoking, *n* (%)	460 (43.2)	139 (30.5)	117 (47.4)	204 (56.5)	<0.0001
Weight (kg ± SD)	79.8 ± 13.3	83.7 ± 13.6	76.3 ± 11.5	77.4 ± 12.9	<0.0001
Height (m ± SD)	1.67 ± 0.09	1.65 ± 0.09	1.67 ± 0.10	1.69 ± 0.08	<0.0001
BMI (±SD)	28.63 ± 4.34	30.66 ± 4.42	27.19 ± 3.27	27.04 ± 3.78	<0.0001
NT-proBNP (ng/L ± SD)	2187 ± 710	1414 ± 498	1961 ± 565	3319 ± 918	<0.0001
eGFR (mL/min/1.73 m^2 ± SD)	67.2 ± 25	68.3 ± 24	67.1 ± 22	65.8 ± 23	<0.0001
Risk factor/co-morbidity					
Obesity, *n* (%)	402 (37.8)	278 (61.0)	54 (21.9)	70 (19.4)	<0.0001
Hypertension, *n* (%)	812 (76.3)	435 (95.4)	165 (66.8)	212 (58.7)	<0.0001
Myocardial infarction, *n* (%)	468 (44.0)	43 (9.4)	136 (55.1)	289 (80.1)	<0.0001
COPD, *n* (%)	155 (14.6)	59 (12.9)	32 (13.0)	64 (17.7)	0.118
Diabetes mellitus, *n* (%)	256 (24.1)	98 (21.5)	53 (21.5)	105 (29.1)	0.025
Atrial fibrillation, *n* (%)	331 (31.1)	147 (32.2)	72 (29.1)	112 (31.0)	0.698
Dyslipidaemia, *n* (%)	448 (42.1)	154 (33.8)	112 (45.3)	182 (50.4)	<0.0001
Anaemia, *n* (%)	328 (30.8)	120 (26.3)	76 (30.8)	132 (36.6)	0.007
Chronic kidney disease, *n* (%)	298 (28.0)	93 (20.4)	71 (28.7)	134 (37.1)	<0.0001
Number of coexisting morbidities					
None, *n* (%)	26 (2.4)	4 (0.9)	10 (4.1)	12 (3.3)	0.017
One, *n* (%)	90 (8.5)	33 (7.2)	27 (10.9)	30 (8.3)	0.306
Two, *n* (%)	246 (23.1)	134 (29.4)	54 (21.9)	58 (16.1)	0.002
Three, *n* (%)	254 (23.9)	123 (27.0)	60 (24.3)	71 (19.7)	0.158
Four, *n* (%)	216 (20.3)	93 (20.4)	47 (19.0)	76 (21.1)	0.882
Five, *n* (%)	136 (12.8)	37 (8.1)	34 (13.8)	65 (18.0)	0.001
Six, *n* (%)	67 (6.3)	26 (5.7)	8 (3.2)	33 (9.1)	0.018
Seven, *n* (%)	21 (2.0)	4 (0.9)	3 (1.2)	14 (3.9)	0.007
Eight, *n* (%)	8 (0.8)	2 (0.4)	4 (1.6)	2 (0.6)	0.201
Nine, *n* (%)	—	—	—	—	—

BMI, body mass index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; SD, standard deviation.

blood pressure is considered the major determinant of LV structural alterations, several other factors (ethnicity, gender, salt intake, obesity, neurohumoral activation, genetics, early vs. late diagnosis, adequate vs. inadequate antihypertensive therapy, etc.) influence LV mass and geometry, promoting a spectrum of remodelling from concentric to eccentric.[7] As a

Figure 1 Distribution of single coexisting morbidity by left ventricular ejection fraction (LVEF) categories. COPD, chronic obstructive pulmonary disease.



result, although hypertension more often provokes concentric remodelling/hypertrophy and the development of HF with LVEF $\geq$ 50%, such as in our study and very similar to the findings of the recently published PARAGON-HF study where 95% of the patients included had hypertension and HF with LVEF $\geq$ 50%,[8] it may also cause eccentric hypertrophy either directly or through the development of MI.

History of a prior MI made the development of HF with an LVEF $<$ 50% more probable in our study. In general, coronary artery disease (CAD) may be present in 23–73% of patients with HF, with a higher prevalence among patients with low LVEF.[9] The prevalence of CAD/MI in HF with near-normal/normal LVEF has probably been overestimated as it is largely depending on the definition used. A prevalence of 21–59% has been reported in hospital cohorts and 23–50% in randomized controlled trials; however, the prevalence drops to $<$27% in community/outpatient cohorts,[10] such as in our study. MI is the primary clinical intermediate between CAD and HF. Following an MI, cardiomyocyte apoptosis and necrosis trigger a cascade of immunoinflammatory pathways and cellular activities that promote a unique pattern of LV remodelling that usually favours the development of a large LV with a low LVEF.[11]

Finally, the loss of atrial kick and especially the chronic rapid and irregular heart rhythm produced by variable atrioventricular conduction in patients with AF may result in a distinct, reversible type of HF called 'tachycardia-induced cardiomyopathy'.[12] Conversely, HF can increase the risk for the development of AF in several ways, including elevation of cardiac filling pressures, dysregulation of intracellular calcium, and autonomic and neuroendocrine dysfunction.[13]

Conclusions

Among various risk factors and co-morbidities, the presence of hypertension is strongly associated with the development of HF with low, intermediate, or near-normal/normal LVEF; a history of a previous MI strongly contributes to an incident HF with a low or an intermediate LVEF, depending on the degree of myocardial insult; and the presence of AF, before or after HF, is strongly associated with an HF with a low or an intermediate LVEF. Cardiologists and other physicians caring for patients with chronic HF need to be vigilant to coexisting morbidities that may be responsible for the development as well as the progression of the syndrome or may complicate the care of these patients. In this regard, it is of outmost importance to realize that some of the coexisting morbidities such as hypertension and MI always precede (risk factors), whereas others such as AF may either precede or follow (co-morbidities) HF development.

Conflict of interest

G.G. has received honoraria from Amgen, Bayer, Boehringer Ingelheim, Elpen, Genesis Pharma, Menarini, Novartis, Pfizer, Servier, Vianex, and WinMedica. A.X. has received honoraria from Novartis. M.P. has received honoraria from Elpen. J.S. has received honoraria from Astra, Bayer, Boehringer Ingelheim, Elpen, Lilly, Menarini, Novartis, Pfizer, Sanofi, Servier, Vianex, and WinMedica. F.T. has received research support and honoraria from Amgen, Bayer, Boehringer Ingelheim, Elpen, Genesis Pharma, Lilly, Menarini, Merck, Novartis, Sanofi, Servier, Vianex, and WinMedica.

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