International Journal of Cardiology 228 (2017) 422–426

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Modes of death in patients with heart failure and preserved ejection fraction

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ARTICLE INFO

Article history:
Received 24 August 2016
Accepted 6 November 2016
Available online xxxx

Keywords:
Right heart failure
Heart failure with preserved ejection fraction
Modes of death

ABSTRACT

Background: Recent studies suggest that reduced right ventricular function is an important predictor of outcome in patients with heart failure and preserved ejection fraction (HFpEF). Because affected patients suffer from a broad spectrum of non-cardiac co-morbidities, it remains unclear, whether they actually die from right heart failure (RHF) or as a consequence of other conditions.

Methods: Consecutive patients with a confirmed diagnosis of HFpEF were enrolled in this prospective registry. Local and external medical records, as well as telephone interviews with relatives were used to ascertain modes of death. RHF was accepted as a mode of death, if the following criteria were met: 1. right ventricular dysfunction assessed by transthoracic echocardiography, and 2. clinical signs of right heart decompensation at the time of death.

Results: Out of 230 patients with complete follow-up, 16.5% ($n = 38$) died after a mean of 30 ± 17 months. 60.5% deaths were classified as cardiovascular and 34.2% as non-cardiovascular. In 5.3% patients, the reason for death remained unknown. Of the cardiovascular cases ($n = 23$), 91.4% of deaths were attributed to RHF, 4.3% died from stroke and 4.3% from sudden cardiac death. Of the non-cardiovascular deaths ($n = 13$), 46.2% of deaths were attributed to major infections and 38.4% deaths were related to cancer. Other reasons for death included ileus (7.7%) and major bleeding (7.7%).

Conclusion: In our well-characterised HFpEF cohort, more than half of all deaths could directly be attributed to RHF. The right ventricle seems to be a meaningful therapeutic target in a subset of patients.

1. Background

Nearly one half of all patients who present with a clinical syndrome of heart failure are found to have a preserved left ventricular ejection fraction (HFpEF). Despite unremarkable findings regarding left ventricular systolic function, affected patients face a dismal prognosis with high mortality rates [1]. Recent evidence from our group [2,3] and others [4,5] suggests that it is primarily the function of the right ventricle that determines the clinical course of affected patients. In fact, impaired right ventricular function as visualized by transthoracic echocardiography or cardiac magnetic resonance imaging has been related to recurrent hospitalizations and death in various HFpEF cohorts [2–5].

These observations are in some disagreement with the broadly accepted notion that most HFpEF patients die from non-cardiac comorbid conditions [6]. In those who pass away from cardiac reasons, sudden cardiac death has been suggested as the primary cause of death [7].

The aim of the present study was to shed light on the actual modes of death in patients with HFpEF. To that end we studied a unique HFpEF cohort, in whom significant coronary artery disease, a frequent companion in this condition, has been ruled out at enrolment.

2. Materials and methods

2.1. Study population

This prospective, observational cohort study was performed at the Division of Cardiology of the Medical University of Vienna, a tertiary referral center for HFpEF. The study protocol adheres to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Medical University of Vienna (EK #796/2010). Written informed consent was collected in all patients before study enrolment.

Eligible patients were prospectively followed in intervals of six months (or shorter) in our outpatient clinic. Telephone calls replaced visits in cases of immobility. The primary study endpoint was death from any cause.

2.2. Clinical definitions

HFpEF was diagnosed according to the current consensus statement of the European Society of Cardiology [8] and the guidelines of the American College of Cardiology Foundation/American Heart Association [9]. The following criteria had to be fulfilled: 1. Signs or symptoms of heart failure, 2. left ventricular ejection fraction ≥ 50%, 3. N-terminal brain natriuretic peptide (NT-proBNP) > 220 pg/mL, 4. Evidence of left ventricular diastolic

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http://dx.doi.org/10.1016/j.ijcard.2016.11.154
0167-5273/

dysfunction by transthoracic echocardiography. Right heart catheterization was performed and HFpEF confirmed, if pulmonary artery wedge pressure exceeded 12 mm Hg.

Exclusion criteria were significant valvular or congenital heart disease, significant coronary artery disease requiring percutaneous coronary intervention or aorto-coronary bypass surgery, and severe congenital abnormalities of the lungs, thorax or diaphragm as previously described [10]. Additionally, patients with cardiac amyloidosis were excluded. Screening for cardiac amyloidosis was done according to current recommendations [11,12] and included cardiac magnetic resonance imaging, transthoracic echocardiography, ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy and if necessary, endomyocardial biopsy.

2.3. Ascertainment of death

Local and external medical records, as well as telephone interviews with relatives were used to ascertain the mode of death. A detailed report was created for every death that was reviewed by two independent physicians (D.B, S.A).

A diagnosis of terminal right heart failure (RHF) was established, if the following criteria were met: 1. right ventricular dysfunction (RVD) assessed by echocardiography, 2. clinical signs of right heart decompensation at the time of death including dyspnoea, ascites, liver enzyme elevation, peripheral oedema, fluid accumulation and jugular distension. Terminal bradycardia related to HF led to a 'heart failure death' judgement.

Sudden cardiac death was defined as either a documented arrhythmogenic death in the absence of pre-existing circulatory failure or the out-of-hospital occurrence of an unexpected presumed pulseless condition together with the absence of an obvious non-cardiac explanation.

2.4. Imaging modalities

All patients underwent conventional transthoracic echocardiography (Vivid 5 and 7, General Electric Inc.) according to the guidelines of the American Society of Echocardiography [13]. Two independent observers blinded to clinical data assessed right ventricular function. An additional board-certified senior physician was consulted in case of disagreement.

Tricuspid annular plane systolic excursion (TAPSE) and two dimensional right ventricular fractional area change (RV-FAC) were measured according to recommended guidelines [14]. A TAPSE below 16 mm and/or a RV-FAC below 35% defined RVD [14].

End-diastolic and end-systolic volumes were used to calculate the ejection fraction using the Simpson's biplane method on the apical four- and two-chamber views [13].

Furthermore, all patients without contraindications underwent a cardiac magnetic resonance imaging study on a 1.5-Tesla scanner (Avanto, Siemens Medical Solutions, Erlangen, Germany). Studies consisted of functional and late gadolinium enhancement imaging, according to standard protocols [15].

2.5. Cardiac catheterization

For hemodynamic confirmation of HFpEF, a 7F Swan-Ganz catheter (Baxter, Healthcare Corp, Munich, Germany) was inserted via a femoral approach. CathCorLX (Siemens AG, Erlangen, Germany) was used to measure pressures, which were recorded as average of eight measurements over eight recorded heart cycles. Cardiac output was assessed by thermodilution and by Fick's method. Pulmonary pulse pressure was calculated as the difference between systolic pulmonary artery pressure and diastolic pulmonary

Table 1
Baseline characteristics of survivors versus non-survivors.

Variable	Survivors ($n = 192$)	Non-survivors ($n = 38$)	All patients ($n = 230$)	*P*-value
Baseline characteristics				
Age, years	71.1 ± 8.5	72.8 ± 8.2	71.4 ± 8.5	0.243
Male sex, n [%]	58 [30.2]	12 [31.6]	70.0 [30.4]	0.868
Body mass index, kg/m^2	30.5 ± 6.5	31.0 ± 8.0	30.6 ± 6.7	0.665
Diabetes mellitus, n [%]	68 [35.6]	19 [50.0]	87.0 [38.0]	0.096
Significant coronary artery disease, n [%]	43 [22.6]	9 [23.7]	52.0 [22.8]	0.888
Arterial hypertension, n [%]	181 [95.3]	38 [100]	219.0 [96.1]	0.171
COPD, n [%]	80 [41.5]	16 [41.5]	96 [41.6]	0.963
History of atrial fibrillation, n [%]	110 [57.9]	26 [68.4]	136.0 [59.7]	0.277
Heart rate, beats/min	72.2 ± 14.5	72.6 ± 12.4	72.4 ± 13.4	0.704
NYHA functional class				<0.001
II, n [%]	70.0 [37.8]	2.0 [5.3]	36.0 [21.6]	
III, n [%]	103.0 [55.7]	29.0 [76.3]	66.0 [66.0]	
IV, n [%]	12.0 [6.5]	7.0 [18.4]	9.5 [12.5]	
6-min walk distance, meters	331 ± 117	241 ± 112	316 ± 121	<0.001
GFR, mL/min/1.73 m^2	61.4 ± 20.2	49.6 ± 16.4	59.4 ± 20.1	0.001
NT-pro BNP, pg/mL	1552 ± 1976	3522 ± 4706	1875 ± 2709	<0.001
Conventional echocardiography				*P*-value
Right ventricular fractional area change, %	40.9 ± 11.1	31.0 ± 3.6	39.8 ± 11.0	0.002
TAPSE, mm	19.6 ± 5.2	13.4 ± 2.1	19.3 ± 5.4	<0.001
Lung function test				*P*-value
PaO_2, mm Hg	72.3 ± 12.5	68.2 ± 12.6	71.6 ± 12.6	0.097
$PaCO_2$, mm Hg	38.0 ± 5.9	38.3 ± 6.3	38.1 ± 5.9	0.802
DLCO, % predicted	62.4 ± 17.8	55.6 ± 17.1	61.2 ± 17.8	0.111
Vital capacity, % predicted	85.1 ± 27.0	80.7 ± 4.2	84.4 ± 26.5	0.386
FEV1, % predicted	74.3 ± 26.9	69.1 ± 23.9	73.4 ± 26.5	0.309
Invasive hemodynamic parameters				*P*-value
PAP mean, mm Hg	33.7 ± 9.9	38.9 ± 10.2	34.6 ± 10.1	0.010
PAP systolic, mm Hg	52.4 ± 17.5	60.7 ± 16.0	53.9 ± 17.5	0.003
PAP diastolic, mm Hg	21.8 ± 6.9	25.8 ± 9.3	22.5 ± 7.5	0.055
PAWP, mm Hg	19.8 ± 5.2	22.1 ± 5.6	20.2 ± 5.3	0.033
Diastolic pressure gradient, mm Hg	1.8 ± 4.3	3.7 ± 6.6	2.2 ± 4.9	0.134
Transpulmonary gradient, mm Hg	13.8 ± 7.0	16.8 ± 5.4	14.4 ± 7.1	0.019
Right atrial pressure, mm Hg	12.4 ± 5.4	14.8 ± 6.9	12.8 ± 5.8	0.109
Pulse pressure, mm Hg	30.5 ± 13.2	35.0 ± 10.6	31.3 ± 12.9	0.011
LV-end diastolic pressure, mm Hg	20.2 ± 6.3	22.6 ± 6.8	20.5 ± 6.4	0.125
Pulmonary vascular resistance, dynes · s · cm^{-5}	221 ± 122	281 ± 156	232.1 ± 130.4	0.024
Pulmonary arterial compliance, mL/mm Hg	2.8 ± 1.4	2.2 ± 0.8	2.7 ± 1.4	0.003
Cardiac output, L/min	2.7 ± 0.6	2.7 ± 0.8	2.7 ± 0.7	0.538

Data are presented as mean ± standard deviations or n [%]; NYHA: New York Heart Association, GFR: glomerular filtration rate, NT-pro BNP: N-terminal brain natriuretic peptide, TAPSE: tricuspid annular plane systolic excursion, PaO_2: partial arterial pressure of oxygen, $PaCO_2$: partial arterial pressure of carbon dioxide, DLCO: capacity of the lung for carbon monoxide, FEV1: forced vital capacity in 1 s; PAP: pulmonary artery pressure, PAWP: pulmonary arterial wedge pressure; LV: left ventricle.