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CLINICAL RESEARCH
Heart failure/cardiomyopathy

Haemodynamically irrelevant pericardial effusion is associated with increased mortality in patients with chronic heart failure

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Aims Pericardial effusion (PE) is a common finding in cardiac patients with chronic heart failure. The prognostic relevance of a small, haemodynamically non-compromising PE in such patients, however, remains to be determined.

Methods and results All patients referred to our heart failure clinic and having a baseline echocardiography and follow-up clinical visits were included. Patients with a haemodynamically relevant PE, acute myo-/pericarditis, systemic sclerosis, rheumatoid arthritis, heart transplantation, heart surgery within the last 6 months or malignancies within the last 3 years were excluded. Patients with or without a haemodynamically irrelevant PE were compared regarding all-cause mortality as the primary and cardiovascular death or need for heart transplantation as secondary outcomes. A total of 897 patients (824 patients in the control vs. 73 patients in the PE group) were included. In the PE group, left ventricular ejection fraction (LVEF) was lower [31%, interquartile range (IQR): 18.0–45.0] than in controls (34%, IQR: 25.0–47.0; $P = 0.04$), while the end-systolic diameters of the left ventricle and the left atrium were larger ($P = 0.01$ and $P = 0.001$, respectively). Similarly, in patients with PE, the right ventricle (RV) systolic function was lower ($P < 0.005$ for both the fractional area change and the tricuspid annulus movement), the dimensions of RV and right atrium (RA) were larger ($P < 0.05$ for RV and $P < 0.01$ for RA), and the degree of tricuspid regurgitation was higher ($P < 0.0001$). Furthermore, in the PE group, the heart rate was higher ($P < 0.001$) and the leukocyte count as well as CRP values were increased ($P = 0.004$ and $P < 0.0001$, respectively); beta-blocker use was less frequent ($P = 0.04$), while spironolactone use was more frequent ($P = 0.03$). The overall survival was reduced in the PE group compared with controls ($P = 0.02$). Patients with PE were more likely to suffer cardiovascular death (1-year estimated event-free survival: 86 ± 5 vs. 95 ± 1%; $P = 0.01$) and to require heart transplantation (1-year estimated event-free survival: 88 ± 4 vs. 95 ± 1%; $P = 0.009$). A multivariate Cox proportional hazard model revealed the following independent predictors of mortality: (a) PE ($P = 0.04$, hazard ratio (HR): 1.95, 95% confidence interval (CI): 1.0–3.7), (b) age ($P = 0.04$, HR: 1.02, 95% CI: 1.0–1.04) and (c) LVEF <35% ($P = 0.03$, HR: 1.7, 95% CI: 1.1–2.8).

Conclusion In chronic heart failure, even minor PEs are associated with an increased risk of all-cause mortality, cardiac death, and need for transplantation.

Keywords Pericardial effusion • Heart failure • Mortality

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Introduction

In patients with chronic heart failure, haemodynamically irrelevant PE is a common (12–20%) finding during routine echocardiography examinations.[1–3] Usually, such findings do not influence clinical decision-making as long as the PE is not considered haemodynamically compromising. While in some patients, pericardial fluid accumulation can be attributed to an underlying systemic or local inflammatory process[4] such as cancer[5] or myo-/pericarditis[6] or might occur after surgery,[7] the mechanism of PE and its prognostic value in heart failure remain elusive. Importantly, in patients with severe pulmonary hypertension, several studies have revealed a strong association of a small PE with adverse outcome.[8,9] The mechanism of increased pericardial fluid production is incompletely understood in that patient population.[10]

Thus, it was the aim of the present study to evaluate the prognostic relevance of haemodynamically insignificant PE in a heart failure population and to identify potential mechanisms for pericardial fluid accumulation in these patients.

Methods

Patient population and baseline characteristics

We searched our echo-laboratory and heart failure clinic database and identified all the patients who had undergone a baseline echocardiography from 1990 until 2010 and had a baseline and at least one follow-up visit in our heart failure clinic. The exclusion criteria were heart or lung transplantation before the baseline echocardiography, cardiac surgery within 6 months prior to baseline, myocardial infarction or suspected acute peri-/myocarditis within the last 3 months, rheumatoid arthritis, systemic sclerosis, systemic lupus, patients receiving chemotherapy due to cancer within the last 6 months, or patients with known metastatic cancer. Patients presenting with a haemodynamically relevant PE at baseline echocardiography were excluded as well.

Data on age, gender, body mass index, underlying heart rhythm, underlying heart disease (ischaemic vs. non-ischaemic), O_2 uptake during exercise, New York Heart Failure (NYHA) functional class, ICD/cardiac resynchronization therapy (CRT) implantation, and medication were retrieved from database and patient records.

Study groups and outcome measures

Patients presenting with a haemodynamically irrelevant PE on echocardiography were allocated to the PE group and the date of this echocardiogram represented the baseline. Patients with no signs of PE were included in the control group and the first available echocardiography represented the baseline. The primary outcome measure was all-cause mortality. Secondary outcome measures were cardiovascular mortality and need for heart transplantation. Inflammatory markers (leukocyte count and C reactive protein) and the right ventricular function were evaluated as well.

Echocardiography

All echocardiograms were analysed by two experienced physicians. Echocardiographic parameters (grading of mitral and tricuspid regurgitation, tricuspid annulus movement (TAM), left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), atrial and right ventricular dimensions) were analysed according to current guidelines of the European Society of Cardiology.[11–15] A PE was considered haemodynamically relevant if at least one of the following criteria was present: (i) paradoxical movement of the interventricular septum with respiration, (ii) presence of a collapsing right ventricle during diastole, and (iii) typical ventricular E-wave velocity changes with inspiration.[16]

Haemodynamic parameters

Patients with a PE who underwent left and right heart catheterization at baseline were matched to patients in the control group with data available on left and right heart catheterization. Patients were matched 1:1 with regard to age, gender, NYHA functional class, ischaemic vs. non-ischaemic cardiomyopathy, diuretic, angiotensin converting enzyme (ACE) inhibitor and beta-blocker treatment, and LVEF.

The left ventricular end-diastolic pressure, right ventricular end-diastolic pressure, wedge pressure as well as the mean pulmonary arterial pressure were investigated. The transpulmonary gradient was calculated as mean pulmonary artery pressure − mean wedge pressure.

Laboratory parameters

Blood samples were taken at baseline. The leucocyte count was recorded. C-reactive protein and NT-proBNP levels were analysed using the cobas® analyzer (Roche Diagnostics, Basel, Switzerland) at the Institute of Clinical Chemistry of the University Hospital Zurich.

Follow-up examination

All patients had at least one follow-up visit in the heart failure clinic. Usually, patients were examined every 6 months by a heart failure specialist with a physical examination, and laboratory analysis including blood count, CRP, proBNP, and creatinine. Patients with a recently detected cancer were identified. If a patient died during follow-up, the results of an autopsy or the latest medical reports were analysed to identify the cause of death.

In patients with PE at baseline, all follow-up echocardiograms were analysed to document the evolution of the PE, and the time to resolution of the PE from a baseline was determined. In patients with PE at baseline, chest X-rays at baseline were examined for concomitant pleural effusions and noted as uni- or bilateral.

Statistics

All statistical analyses were performed using SPSS 20.0 (IBM Corporation, 1 New Orchard Road Armonk, New York 10504-1722, USA). Continuous variables are presented as the median and interquartile range (IQR) (25–75 percentile). The χ^2 and Mann–Whitney U test were used as appropriate. For survival analysis, a Kaplan–Meier curve was computed and a log rank *P*-value was calculated. A Cox proportional hazard model was applied for the primary outcome measure, corrected for age, gender, heart rate, heart rhythm, LVEF $<35\%$, body mass index, underlying heart disease, beta-blocker, and spironolactone therapy.

A sensitivity analysis with a Cox proportional hazard model was performed for mortality, also adjusting for NT-proBNP and CRP values (NT-proBNP and CRP were both obtained in 181 patients only).

A two-sided *P*-value of <0.05 was considered significant.

Table 1 Baseline characteristics

	No pericardial effusion (n = 824)	Pericardial effusion (n = 73)	P-value
Age (years)	55.5 (45.9–64.5)	53.4 (34.4–62.7)	0.05
Male (n, %)	675 (82)	53 (73)	0.06
BMI (kg/m^2)	25.8 (23.4–29.2)	24.7 (21.1–27.0)	0.004
Heart rate (b.p.m.)	76.0 (65.0–89.0)	87.0 (76.0–98.0)	<0.0001
VO_{2max} (ml/kg/min)	19.0 (15.0–25.0)	15.0 (13.0–21.5)	0.15
Rhythm (n, %)			0.03
Sinus rhythm	601 (81)	41 (66)	
Atrial fibrillation	95 (13)	14 (23)	
Pacemaker	46 (6)	7 (11)	
NYHA class (n, %)			0.01
I	49 (9)	2 (4)	
II	239 (42)	12 (24)	
III	241 (43)	29 (57)	
IV	37 (7)	8 (16)	
Cardiomyopathy (n, %)			
Dilatative/hypertrophic	311 (38)	45 (62)	
Non-compaction	16 (2)	0	
Dilatative cardiomyopathy/history of myocarditis	0	2 (3)	
Amyloid	2 (0)	0	
Ischaemic	287 (35)	14 (19)	
Valvular	53 (6)	4 (6)	
Congenital	32 (4)	2 (3)	
Other/unknown	123 (15)	6 (8)	
Leucocyte count (103/mL)	7.7 (6.1–9.1)	8.4 (7.0–11.3)	0.004
C-reactive protein (mg/L)	3.0 (1.0–12.0)	15.0 (4.2–40.3)	<0.0001
Platelets (103/μL)	223 (185–272)	223 (182–293)	0.47
NT-proBNP (ng/L)	1214 (411–2596)	2240 (1085–5379)	0.01
Sodium (mmol/L)	140 (137–141)	139 (137–141)	0.27
Haemoglobin (g/dL)	13.8 (12.8–14.9)	13.1 (11.5–14.7)	0.008
Creatinine (μmol/L)	103 (89–124)	101 (86.8–121)	0.68
Diuretics (n, %)	543 (66)	52 (71)	0.44
Calciumantagonist (n, %)	58 (7)	10 (14)	0.06
Digoxin (n, %)	165 (20)	15 (21)	0.88
ACE inhibitor (n, %)	447 (54)	43 (59)	0.46
ATII blocker (n, %)	88 (11)	7 (10)	0.77
Spironolactone (n, %)	100 (12)	16 (22)	0.03
Statin (n, %)	159 (19)	10 (14)	0.28
Beta-blocker (n, %)	479 (58)	33 (45)	0.04
ICD (n, %)	53 (6)	6 (8)	0.47
CRT (n, %)	28 (3)	2 (3)	0.76
Inclusion before 2001 (n, %)	306 (37)	22 (30)	0.26

Continuous variables are presented as median and interquartile range in brackets and nominal variables are presented as number and percentage in brackets.

Results

Patient population and baseline characteristics

A total of 1213 patients were retrieved from the database. One hundred patients having undergone heart or lung transplantation before the baseline echocardiography as well as 147 patients after recent cardiac surgery were excluded. Furthermore, 49 patients having sustained a myocardial infarction within 3 months before the baseline echocardiography, 6 patients with acute peri-/myocarditis, and 11 patients with uncontrolled cancer were also excluded. Three patients had a haemodynamically significant

PE. Among the 897 patients finally included, 73 patients exhibited a haemodynamically irrelevant PE.

There was a borderline significant difference between the PE and the control group with regard to age [53.4 years (IQR: 34.4–62.7) vs. 55.5 years (IQR: 45.9–64.5); $P = 0.05$], but not with regard to male gender (53 patients (73%) vs. 675 patients (82%), $P = 0.06$). A body mass index was lower in the PE group [24.7 kg/m^2 (IQR: 21.1–27.0) vs. 25.8 kg/m^2 (IQR: 23.4–29.2), $P = 0.004$; *Table 1*].

The heart rate was higher in patients with PE (87/min, IQR: 76.0–98.0) than that in controls (76/min, IQR: 65.0–89.0, $P < 0.0001$), use of beta-blockers was lower in patients with PE (33 patients, 45%) than in controls (479 patients, 58%, $P = 0.04$) and the number of patients with non-ischaemic cardiomyopathy was higher in the PE group ($n = 57$, 78%) than in controls ($n = 502$, 61%).

Thirty-one (43%) patients with PE had a chest X-ray at baseline. In 20 (64%) patients, a concomitant pleural effusion was found and in most cases located bilaterally ($n = 11$; 55%).

Left ventricular and atrial parameters

The left ventricular ejection fraction was lower (31% (IQR: 18.0–45.0) vs. 34% (IQR: 25.0–47.0); $P = 0.04$) and LVESD was larger in the PE (5.6 cm, IQR: 4.0–6.7) than the control group (4.9 cm, IQR: 3.7–5.9; $P = 0.01$). The left atrial endsystolic diameter was larger in the PE (5.0 cm, IQR: 4.4–5.8) than the control group (4.6 cm, 4.0–5.2); $P = 0.001$). The severity of mitral regurgitation did not differ between the PE and the control group [Grade 2 (IQR: 1–3) vs. Grade 2 (IQR: 1–2); $P = 0.67$, *Table 2*].

Right ventricular and atrial parameters

The right ventricular diameter (four-chamber view, short axis) was increased [3.5 cm (IQR: 2.9–4.0) vs. 3.2 cm (IQR: 2.7–3.6); $P = 0.02$] and the right ventricular systolic function was decreased in patients with PE compared with the control group: RV-fac [median 33% (IQR: 19.0–42.0) vs. 39% (IQR: 33.0–49.0); $P = 0.002$], tricuspid annulus movement [median 14.5 mm (IQR: 11.8–20.0) vs. 18.0 mm (IQR: 15.0–21.0); $P = 0.003$; *Figure 1*]. The right atrial end-systolic diameter was larger in the PE than the control group ($P = 0.001$). Tricuspid regurgitation was more pronounced in the PE than the control group [Grade 2 (IQR: 1–2) vs. Grade 1 (IQR: 1–2); $P < 0.0001$; *Table 2*].

Haemodynamic parameters

In the patient population with PE, 29 patients (40%) had left and right heart catheterization at baseline. These patients were matched 1:1 to patients retrieved from the control group. No significant difference between the groups was detected with regard to age, gender, NYHA functional class, diuretic or ACE inhibitor or beta-blocker treatment, ischaemic vs. non-ischaemic cardiomyopathy, and LVEF.

Patients with PE had a higher right ventricular end-diastolic pressure [8.5 mmHg (IQR: 6.0–15.5) vs. 6.5 mmHg (IQR: 3.0–10.0); $P = 0.008$] and mean pulmonary arterial pressure [32.0 mmHg (IQR: 22.5–43). vs. 22.5 mmHg (IQR: 16.3–36); $P = 0.03$], whereas the left ventricular end-diastolic pressure [22.5 mmHg (IQR: 18.3–30.8) vs. 20 mmHg (IQR: 13.3–26.3); $P = 0.27$] and the wedge pressure [20 mmHg (IQR: 14.0–27.0) vs. 16 mmHg (IQR: 9.5–24.5); $P = 0.14$] did not differ between the study groups (*Figure 2*). The transpulmonary gradient was higher in the PE group 12.0 mmHg, IQR: 6.5–18.5; $P = 0.04$) compared with controls (7.0 mmHg, IQR: 4.0–12.0).

Table 2 Echocardiography baseline parameters

	No pericardial effusion ($n = 824$)	Pericardial effusion ($n = 73$)	*P*-value
LVEF	34.0 (25.0–47.0)	31.0 (18.0–45.0)	0.04
LVESD	4.9 (3.7–5.9)	5.6 (4.0–6.7)	0.01
LVEDD	6.2 (5.3–7.0)	6.4 (5.4–7.4)	0.16
Mitral regurgitation			0.59
Minor	200 (32)	15 (25)	
Moderate	296 (48)	28 (47)	
Severe	79 (13)	10 (18)	
Tricuspid regurgitation			<0.0001
Minor	347 (57)	19 (31)	
Moderate	202 (34)	27 (44)	
Severe	31 (5)	12 (19)	
Fac (%)	39.0 (33.0–49.0)	33.0 (19.0–42.0)	0.002
TAM (mm)	18.0 (15.0–21.0)	14.5 (11.8–20.0)	0.003
Right ventricular diameter (cm)	3.2 (2.7–3.6)	3.5 (2.9–4.0)	0.02
Right ventricular end-diastolic area (cm^2)	18.0 (14.7–22.0)	21.9 (16.0–28.0)	0.001
Right atrial diameter long axis (cm)	5.2 (4.7–5.9)	5.9 (4.9–6.5)	0.005
Right atrial diameter short axis (cm)	4.1 (3.6–4.6)	4.5 (3.9–5.5)	0.001
Left atrial endsystolic diameter (cm)	4.6 (4.0–5.2)	5.0 (4.4–5.8)	0.001
Pulmonary pressure elevated	199 (24)	33 (45)	0.03

Continuous variables are presented as median and interquartile range in brackets and nominal variables are presented as number and percentage in brackets.

Laboratory markers of cardiac function and inflammation

NT-proBNP, CRP, and leukocyte values at baseline were available in 232, 344, and 589 patients, respectively. The NT-proBNP value was significantly increased in the PE group compared with controls [2240 ng/L (IQR: 1085–5379) vs. 1214 ng/L (IQR: 411–2596); $P = 0.01$].

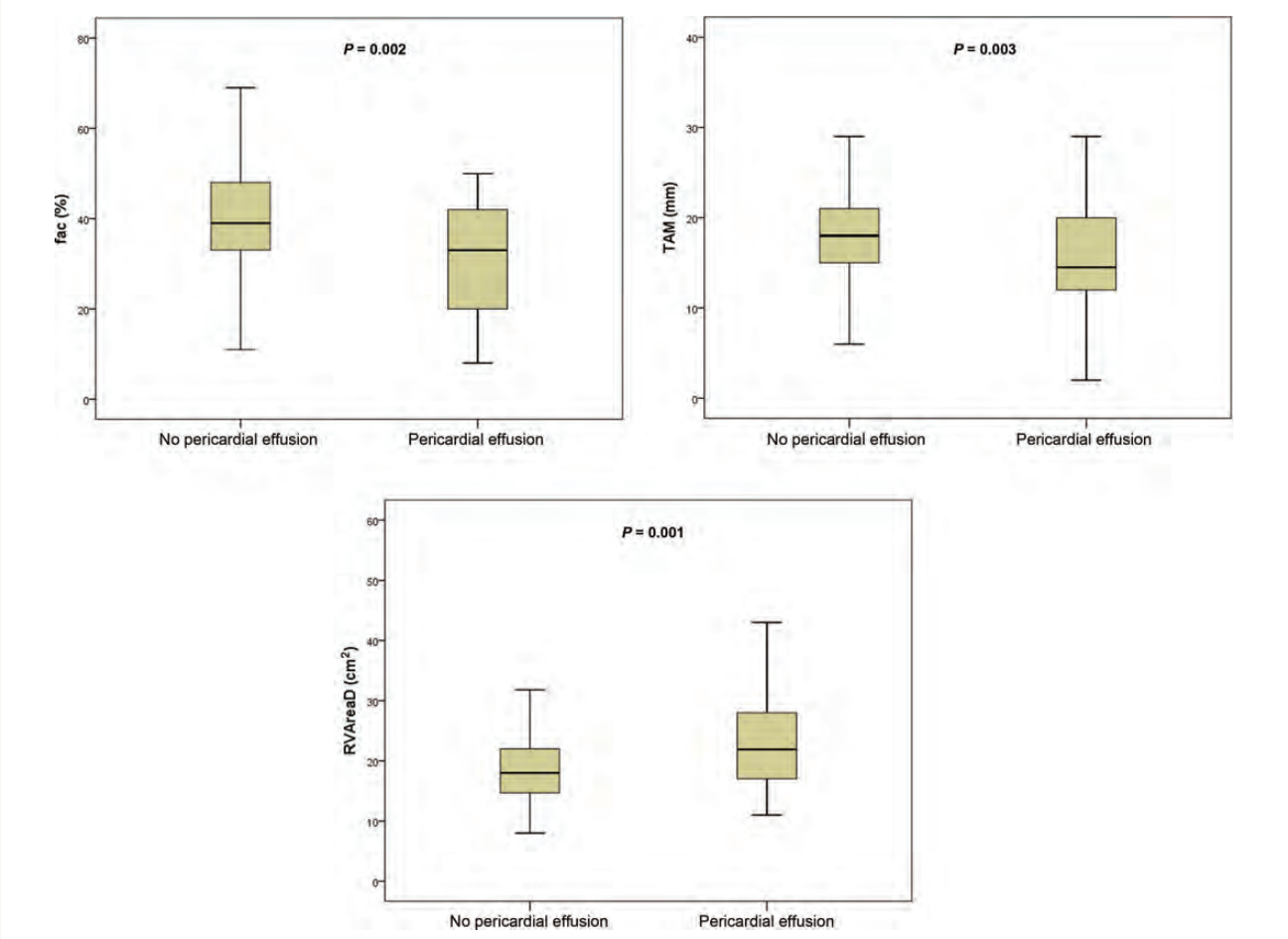

Figure 1 Parameters of the right ventricular function and dimension.

Laboratory markers of inflammation were significantly increased in the PE group compared with controls, i.e. the leucocyte count was higher [8.4 × 10^3/μL (IQR: 7.0–11.3) vs. 7.7 × 10^3/μL (IQR: 6.1–9.1); $P = 0.004$] as were the plasma levels of C-reactive protein [15.0 mg/L (IQR: 4.2–40.3) vs. 3.0 mg/L (IQR: 1.0–12.0); $P < 0.0001$); *Figure 3*].

A Cox proportional hazard model (analysing $n = 181$ patients) confirmed an independent association of PE ($p = 0.03$; HR 3.2, 95% CI 1.1–9.4) and NT-proBNP (per 100 ng/L: $P < 0.0001$, hazard ratio (HR): 1.01, 95% CI: 1.007–1.02), but not CRP (per mg/L: $P = 0.47$, HR: 1.005, 95% CI: 0.99–1.02) with mortality.

Echocardiographic follow-up

Fifty-three (73%) patients in the PE group had an echocardiographic follow-up. The median follow-up period was 4.4 months (IQR: 1.8–14). Thirteen (25%) patients had persisting PE. Four patients (31%) with persisting PE died, while only 6 patients (15%) died in the group with resolved PE (1-year estimated event-free survival: 63.5 ± 15% vs. 96.7 ± 3%; $P = 0.007$).

Clinical follow-up

The median follow-up time was 1.8 years (IQR: 0.3–5.5) in the PE group and 3.4 years (IQR: 1.1–7.1) in the control group. A total of 209 patients (23%) died with 159 patients (18%) dying from a cardiac cause, 11 patients (1%) from infection, and 14 patients (2%) from cancer. In 15 patients (2%) the cause of death remained unknown (*Table 3*). In 38 patients (4%) a malignancy was diagnosed during the follow-up period.

The overall survival was significantly reduced in patients with PE as compared with controls (*Figure 4*; *P*-value = 0.02). A Cox proportional hazard model revealed an independent association of PE with death (*Table 4*; $P = 0.04$). Patients in the PE group were more likely to die from a cardiac cause as compared with the control group (1-year estimated event-free survival: 86 ± 5 vs. 95 ± 1%; $P = 0.01$; *Table 3*). Heart transplantation was necessary in 77 (9%) patients. Patients with a PE were more likely to require transplantation when compared with the control group (1-year estimated event-free survival: 88 ± 4% vs. 95 ± 1%; $P = 0.009$; *Table 3*).

Discussion

This study demonstrates that in a chronic heart failure population the presence of a haemodynamically irrelevant PE is independently associated with a nearly two-fold hazard of death. Of note, a persistent PE at echocardiographic follow-up was associated with unfavourable outcome when compared with patients with resolved

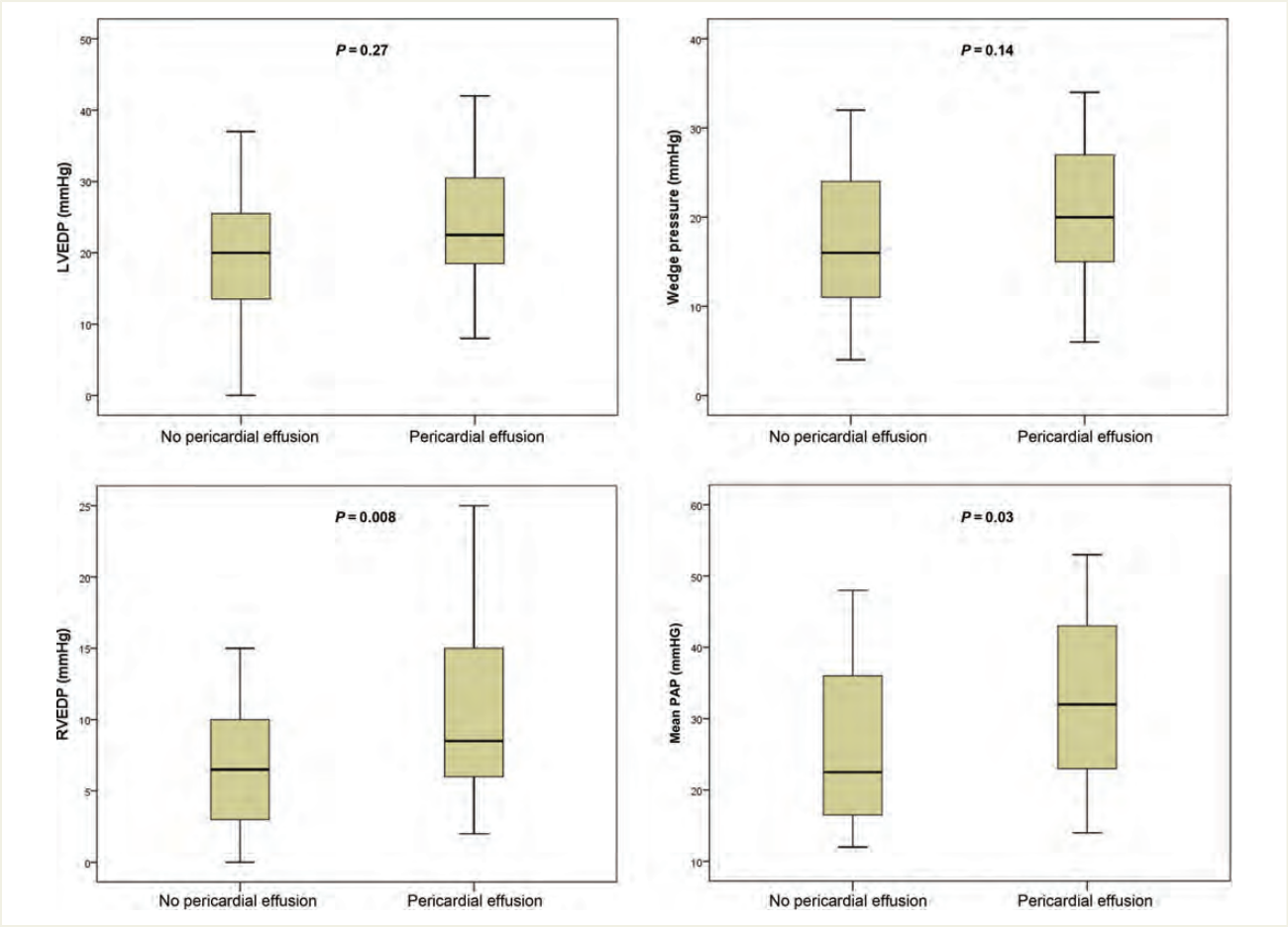

Figure 2 Left and right ventricular filling pressures at baseline.

PE. Cardiovascular events were the main cause of death in these patients with as well as in those without PE; however, at 1 year, patients with PE had an increased risk to die from a cardiac cause compared with those without it, and they were more likely to require heart transplantation. In addition, patients with PE had a higher NT-proBNP level identifying a higher risk population for major adverse events.[17,18] Consistent with these observations, patients with PE had a lower left and right ventricular ejection fraction, larger left and right atrial dimensions, and a worse NYHA functional class.

While the exact underlying mechanisms, by which the PE might be associated with adverse outcome remains to be determined,[19,20] the results of the present study suggest that congestion of venous blood or lymphatic fluid return to the right heart might have an impact on the evolution of PE of non-inflammatory origin. Furthermore, pulmonary pressure *per se* and/or regulatory mechanisms operative under these conditions seem to be of importance. Nevertheless, the mechanisms by which PE might be associated with adverse outcome remain speculative. In patients with severe pulmonary hypertension, an impaired right ventricular function and/or a PE are detected in 22 and 25%, respectively, and both are independently associated with a poor prognosis.[21] Intriguingly, it has been shown previously that NT-proBNP reflects the right ventricular structure and function in patients with pulmonary hypertension.[22] In line with this interpretation, in the present study, patients with a PE exhibited a worse right ventricular function, larger right ventricular and right atrial dimensions, more pronounced tricuspid regurgitation as well as a higher prevalence of pulmonary hypertension and elevated NT-proBNP, when compared with controls. In the subgroup of patients with left and right heart catheterization at baseline, patients with PE did indeed exhibit significantly elevated right ventricular filling pressures and an increased mean arterial pulmonary pressure, whereas the left ventricular filling pressure and wedge pressure did not differ between the PE and the control group. These data provide evidence for an important role of the right ventricular function in the development of PE in heart failure patients. The transpulmonary gradient was increased in the PE group suggesting that a reactive component on top of the left ventricular dysfunction might contribute to pulmonary hypertension.[23]

The right ventricular and haemodynamic data support and extend the findings of a recent study identifying the right ventricular function, right ventricular dimension, and pulmonary hypertension as major determinants of functional tricuspid regurgitation,[24] but

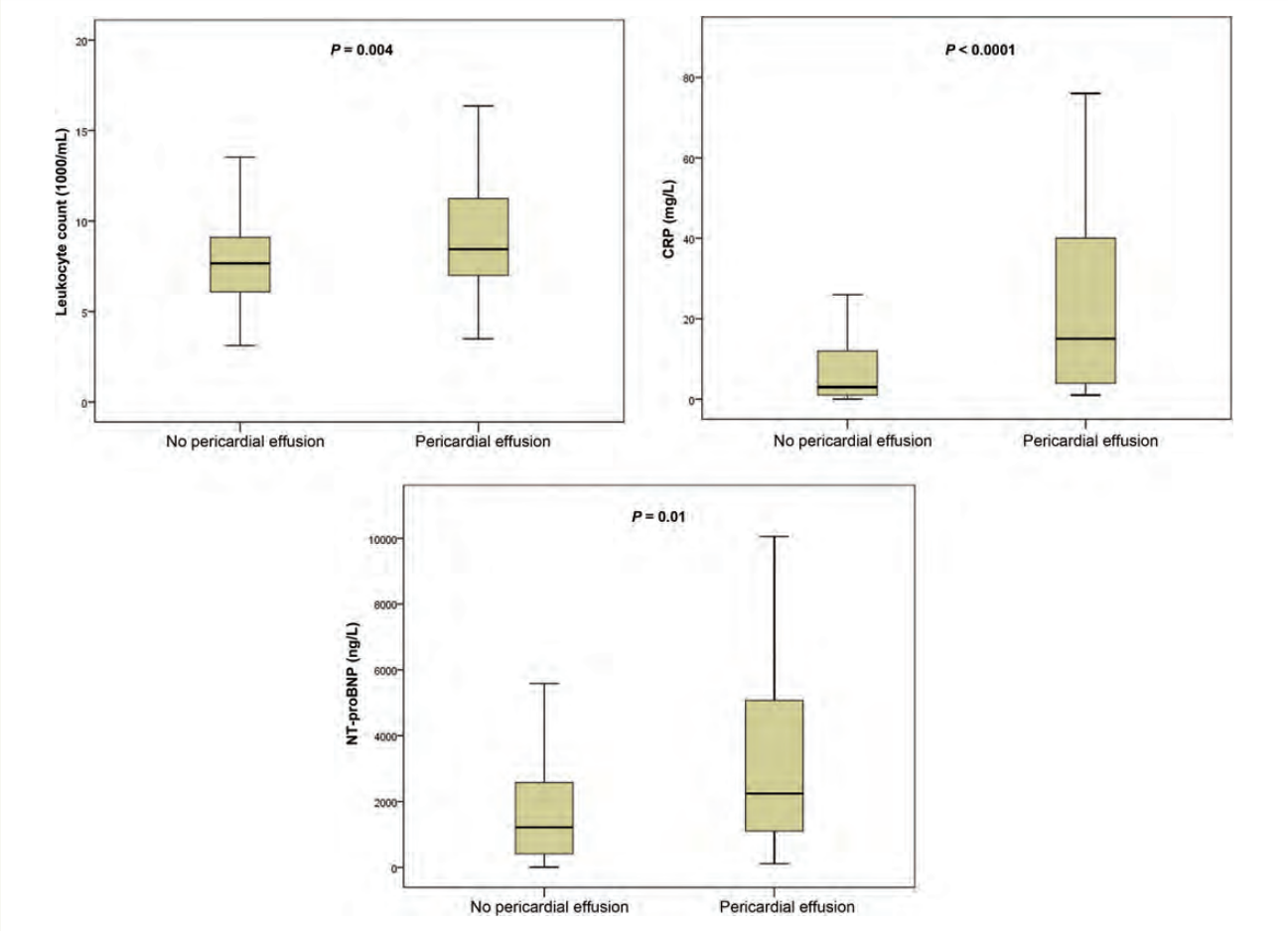

Figure 3 Inflammatory parameters and NT-proBNP.

Table 3 Follow-up in the study groups

	No pericardial effusion ($n = 824$)	Pericardial effusion ($n = 73$)	*P*-value
Follow-up (years)	3.4 (1.1–7.1)	1.8 (0.3–5.5)	0.03
Death	186 (23)	23 (32)	
Cardiac death	142 (17)	17 (23)	
Infection	10 (1)	1 (1)	
Unknown	13 (2)	2 (3)	
Cancer	12 (2)	2 (3)	
Other	9 (1)	1 (1)	
Cancer	33 (4)	5 (7)	
Cardiac death: 1-year estimator of event-free survival	95 ± 1	86 ± 5	0.01
Heart transplantation	66 (8)	11 (15)	
Heart transplantation: 1-year estimator of event-free survival	95 ± 1	88 ± 4	0.009

Continuous variables are presented as median and interquartile range in brackets and nominal variables are presented as number and percentage in brackets.

further demonstrate an association of such changes with PE. Similar data were demonstrated in patients with predominantly preserved LVEF.[25] However, the latter study was limited by the inclusion of all patients with PE; moreover, detailed echocardiographic data on right ventricular function and haemodynamics were not presented. In contrast, a recently published study failed to show a prognostic

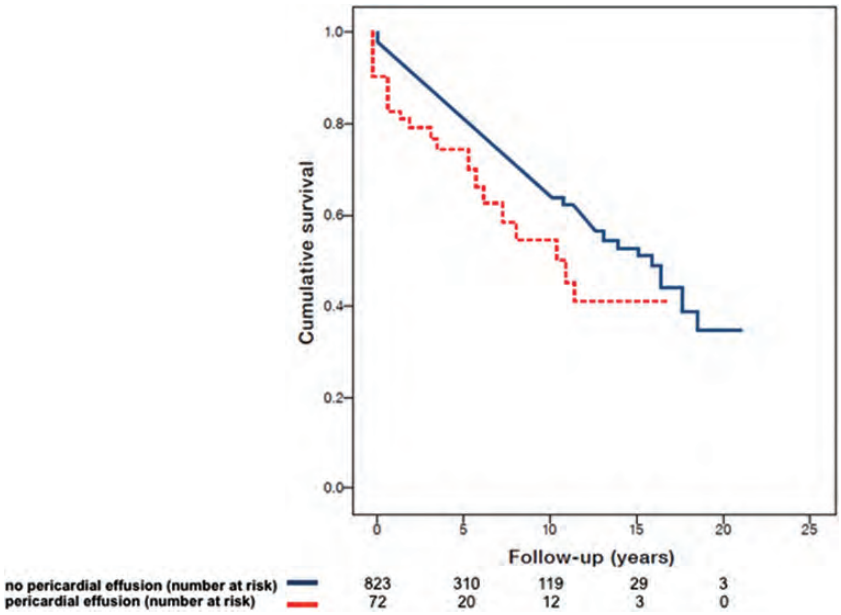

Figure 4 Kaplan–Meier survival analysis of heart failure patients with pericardial effusion compared with those without ($p = 0.02$).

Table 4 Cox proportional hazard model

Variable	Hazard ratio	95% confidence intervals	*P*-value
Left ventricular ejection fraction <35%	1.70	1.1–2.8	0.03
Pericardial effusion	1.95	1.0–3.7	0.04
Age (per year)	1.02	1.0–1.04	0.04
Heart rate (per b.p.m.)	1.01	1.0–1.03	0.051
Male gender	0.67	0.37–1.2	0.14
Sinus rhythm vs. atrial fibrillation	0.74	0.35–1.5	0.41
Ischaemic vs. non-ischaemic cardiomyopathy	0.77	0.49–1.2	0.24
Spironolactone treatment	0.85	0.43–1.3	0.64
Beta-blocker treatment	0.84	0.54–1.3	0.43
Body mass index (kg/m^2)	1.01	0.97–1.1	0.66

impact of PE in patients with chronic heart failure.[26] Unfortunately, only half of the baseline population could finally be included in that study. Moreover, the selection of the patients enrolled remained unclear, and may explain that in a multivariate analysis PE was not an independent predictor of mortality. Consistent with the findings of our study, however, the same authors demonstrated that right atrial and right ventricular diameters were increased, ejection fraction was lower, and mortality was higher in the PE group.

In a subgroup analysis, patients with a resolved PE had a more favourable outcome compared with patients with persisting PE indicating improved heart failure treatment and recompensation in patients with resolved PE. In contrast, a persistent PE caused by the chronic volume overload may identify a patient population at particularly increased risk.

Numerous systemic or local inflammatory conditions such as rheumatoid diseases,[27] myo-/pericarditis,[6] or cancer[28] may increase permeability and in turn lead to a capillary leak and the development of a PE.[29] Of note, severe heart failure goes along with systemic inflammation as well.[30,31] In the present study, leukocyte counts and C-reactive protein levels were increased in patients with PE when compared with those without it, suggesting, that the systemic inflammation occurring in severe heart failure might induce some capillary leakage thereby contributing to pericardial fluid accumulation. Since markers of inflammation are associated with a worse outcome also in patients with chronic heart failure,[32] it cannot be excluded that the presence of PE merely reflects the presence of such a systemic inflammatory reaction in these patients. Noteworthy, in the present study, 64% of patients with PE had a concomitant pleural effusion at baseline. It is well known that an elevation of the systemic venous pressure and inflammation may affect both pericardial and pleural effusions.[10]

Haemodynamically non-compromising PE carries a worse prognosis especially in patients with heart failure and persistent PE despite heart failure therapy according to current guidelines.[33] Our findings therefore suggest the need for an intensified surveillance of patients in whom PEs are detected. In how far an optimized heart failure treatment with, e.g. implanted devices, to improve fluid management will lead to a reduction in PE and an

improved outcome in these patients needs to be clarified in a prospective randomized trial.

Limitations

Observational studies are prone to confounding bias and missing values. Especially, biomarker data were available only in a small subset of patients. We have performed multivariate adjustments to reduce the confounding but we cannot be sure that there is no residual confounding, especially with regard to variables which were not included in the model. Moreover, in comparison to the overall study population, the subgroup with PE is relatively small which could limit the robustness of the results. A transient appearance of a PE between the follow-up visits in some of the patients cannot be excluded. We do report on a long recruitment and observation period ranging from 1990 to 2010, but a similar number of patients with PE was included before the year 2001 which renders major observational biases unlikely; therefore, a potential change in medication and daily clinical practice has probably not influenced the results obtained.

Conclusion

In summary, this study suggests that even haemodynamically irrelevant PEs, as detected by echocardiography, are associated with adverse outcome. Potential (but speculative) mechanisms are right ventricular failure and systemic inflammation due to severe heart failure. In how far an optimized heart failure treatment decreases pericardial fluid accumulation along with improving survival needs further consideration in a prospective trial.

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CARDIOVASCULAR FLASHLIGHT

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Pre- and post-operative assessment of valvular and aortic flow using 4D flow magnetic resonance imaging

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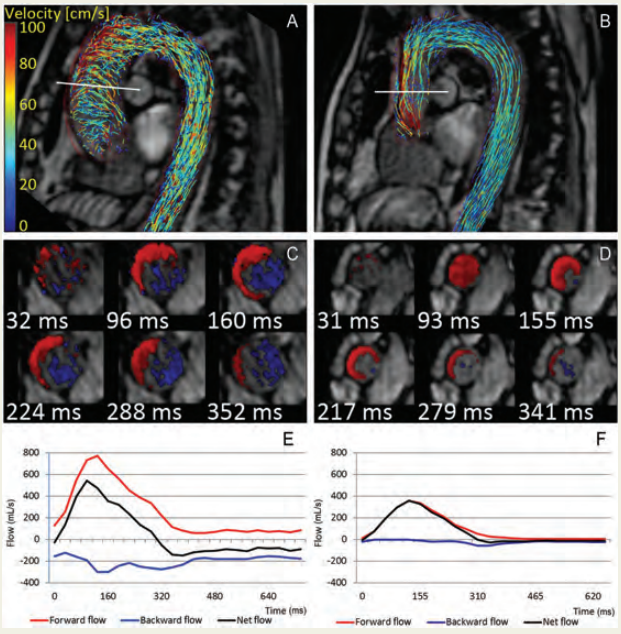

Findings in a 71-year-old male patient are reported who presented with an aneurysm of the ascending aorta and a heavily calcified bicuspid aortic valve with severe stenosis and mild regurgitation. Transthoracic echocardiography and invasive assessment showed normal left ventricular function, a severely reduced valve area of 0.77 cm^2, and a dilation of the ascending aorta of 52 mm. To further investigate the haemodynamic influence of the valvular and aortic pathology, a pre- and post-operative assessment using time-resolved three-dimensional phase-contrast magnetic resonance imaging (4D Flow MRI) was performed using a 1.5T MR scanner (Philips Achieva, Best, The Netherlands). Blood flow analysis was performed using a prototype software package (GTFlow, GyroTools, Zurich, Switzerland). After the pre-operative 4D Flow MRI exam, the patient underwent replacement of the aortic root with a biological aortic valve prosthesis (25 mm, Medtronic Freestyle®) and of the ascending aorta, using a collagen-impregnated woven prosthesis (28 mm, Hemashield Woven®). A post-operative 4D Flow MRI scan was obtained 85 days after the operation. *Panels 1A* and *B* compare pathlines pre- and post-operation. While helical flow patterns are observed in the ascending aorta pre-operation (*Panel 1A*, Supplementary material online, *Movie S1*), normal flow patterns are found after the operation (*Panel 1B*, Supplementary material online, *Movie S2*). The distinct systolic retrograde flow channel (*Panels 1C* and *E*) observed pre-operation disappeared entirely after the operation (*Panels 1D* and *F*), indicating increased efficiency of blood transport. Likewise, systolic peak flow was significantly reduced after the operation (*Panels 1E* and *F*). In summary, this example demonstrates the value of 4D Flow MRI in assessing patients with valvular and aortic disease. The method holds potential for advanced pre-operative patient assessment and follow-up monitoring with particular emphasis on quantifying haemodynamic implications of structural alterations in a non-invasive and comprehensive manner.

Supplementary material is available at *European Heart Journal* online.