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Peripheral Edema Due to Heart Disease: Diagnosis and Outcome

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Summary

Background: The purpose of this study was to determine whether baseline physical examination and history are useful in identifying patients with cardiac edema as defined by echocardiography, and to compare survival for patients with cardiac and noncardiac causes of edema.

Hypothesis: Physical examination and history data can help to identify patients with edema who have significant cardiac disease.

Methods: We reviewed the medical records of 278 consecutive patients undergoing echocardiography for evaluation of peripheral edema. We classified cardiac edema as the presence of any of the following: left ventricular ejection fraction < 45%, systolic pulmonary artery pressure > 45 mmHg, reduced right ventricular function, enlarged right ventricle, and a dilated inferior vena cava.

Results: The mean age of the 243 included patients was 67 ± 12 years and 92% were male. A cardiac cause of edema was found in 56 (23%). Independent predictors of a cardiac cause of edema included chronic obstructive pulmonary disease (COPD, odds ratio [OR] 1.74, 95% confidence interval [CI] 1.14–2.60) and crackles (OR 1.98, 95% CI 1.26–3.10). The specificity for a cardiac cause of edema was high (91% for COPD, 93% for crackles); however, the sensitivity was quite low (27% for COPD, for 24% crackles). Compared with patients without a cardiac cause of edema, those with a cardiac cause had increased mortality (25 vs. 8% at 2 years, $p < 0.01$), even after adjustment for other characteristics (hazard ratio 1.55, 95% CI 1.08–2.24).

Conclusions: A cardiac cause of edema is difficult to predict based on history and examination and is associated with high mortality.

Key words: edema, echocardiography, physical examination, heart disease, crackles, chronic obstructive pulmonary disease

Introduction

Peripheral edema is a common physical finding with numerous etiologies, including venous insufficiency, adverse reaction to medication, and elevated central venous pressure.[1] Echocardiography is often used for detecting conditions leading to elevated central venous pressure such as left ventricular (LV) systolic dysfunction, severe valvular disease, and pulmonary hypertension. Knowledge of cardiopulmonary disease is valuable for guiding treatment (e.g. angiotensin-converting enzyme inhibitors for LV dysfunction) and further work-up (e.g., to determine the etiology of pulmonary hypertension).[1]

However, echocardiography is expensive, and use in all patients is unlikely to be cost effective if the vast majority have a benign etiology of peripheral edema. An algorithm based on patient data available at the time of a clinic visit would be helpful for guiding the clinician in the use of echocardiography.

The purpose of this study was to determine whether patient characteristics can be used to predict which patients with pedal edema have significant cardiac disease. Furthermore, we sought to document the impact of cardiac abnormalities on outcome for patients with pedal edema.

Methods

Patients

Outpatients undergoing echocardiography at one of three echocardiography laboratories in the VA Palo Alto Health Care System were eligible if the reason for referral was evaluation of peripheral edema. Consecutive patients (n = 278) were enrolled between October 1998 and August 2002. Patients were excluded if they had a prior diagnosis of heart failure (n = 35) or were < 18 years of age (n = 0). The remaining 243 patients comprised the study cohort. The study was approved

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by the Institutional Review Board at the Stanford University School of Medicine.

Information from Chart Abstraction

We reviewed the chart of each patient to determine age, gender, history of chronic obstructive pulmonary disease, coronary artery disease, heart failure, complaints of shortness of breath, or dyspnea on exertion. We also recorded weight, jugular venous pressure (considered elevated if > 10 cm or described as elevated), crackles (rales), wheezing, S3, severity of edema (grade 1–4), bilateral edema (yes, no), and medication use. There were a mean 1.9 subjects per provider.

Echocardiographic Data

Each patient underwent echocardiography using standardized views using Hewlett Packard (Palo Alto, Calif., USA) ultrasound systems (HP 1500, HP 2500, HP 5500). We recorded rhythm (sinus, other), inferior vena cava size, (< 2 cm, ≥ 2cm), right ventricular (RV) size, RV systolic function, LV size, and LV systolic function. Right ventricular size and function were graded visually by experienced echocardiographers. A right ventricle that was more than 2/3 of the left ventricle was considered enlarged.[2] We defined RV systolic dysfunction as (1) any RV wall motion abnormalities or (2) descent of the base < 2.0 cm.[3] Left ventricular function was also graded visually using traced ejection fraction and fractional shortening as a guide. Left ventricular hypertrophy was defined as a diastolic septal wall thickness of ≥ 14 mm or a diastolic posterior wall thickness of ≥ 13 mm. We graded tricuspid valvular regurgitation using the Framingham Heart Study criteria.[4] Systolic pulmonary artery pressure was calculated by adding the estimated right atrial pressure (5 mmHg if the inferior vena cava was ≤ 2 cm in diameter, 15 mmHg if the inferior vena cava diameter was > 2 cm) to the peak gradient across the tricuspid valve. We defined pulmonary hypertension as a systolic pulmonary artery pressure > 45 mmHg.

Cardiac Edema

In defining cardiac edema, our goal was to include the common cardiac abnormalities that cause, or are markers of, elevated central venous pressure. Thus, cardiac edema was defined a priori as edema in the presence of a dilated inferior vena cava (≥ 2 cm), abnormal RV size or function, moderate or greater tricuspid regurgitation, LV systolic dysfunction (ejection fraction < 45%), or a pulmonary artery systolic pressure > 45 mmHg.

Follow-Up

The outpatient chart was reviewed for clinic visits occurring between 3 and 9 months (closest to 6 months) following echocardiography for the persistence of peripheral edema. We used the Social Security Death Index to determine survival following echocardiography.

Statistics

We used *t*-tests to compare continuous variables and chi-square tests for categorical variables and generated Kaplan-Meier curves to display survival for patients with cardiac and noncardiac edema. We used logistic regression to determine baseline factors associated with a cardiac cause of edema and to determine predictors of edema resolution at 6 months. We assessed differences in survival using the log-rank test and evaluated the effect of cardiac edema on survival after adjustment for other patient characteristics using proportional hazards analysis. Visual inspection indicated that the proportional hazards assumption was intact. All analyses were performed using JMP version 5.0 (SAS Institute, Cary, N.C., USA). All significance tests were two-sided. We assumed a p value of < 0.05 was statistically significant.

Results

Of 243 patients, 56 (23%) had echocardiographic evidence of a cardiac etiology for peripheral edema. Baseline characteristics of patients with and without cardiac edema are displayed in Table I. Compared with patients with noncardiac edema, those with cardiac edema were more likely to have shortness of breath, crackles, and wheezing on physical examination, a history of chronic obstructive pulmonary disease, and in a rhythm other than sinus. Severity (grade) or location (bilateral vs. unilateral) of edema was not associated with a cardiac etiology.

Among 56 patients with cardiac edema, the most common echocardiographic abnormality was an abnormal right ventricle (enlarged or hypokinetic) in 36 (63%), followed by elevated pulmonary pressure (> 45 mmHg systolic) in 20 of 33 with measurable tricuspid regurgitation (61%), reduced LV ejection fraction (< 45%) in 15 (26%), moderate or greater tricuspid regurgitation in 13 (25%), and a dilated inferior vena cava in 13 patients (25%). The majority of patients with cardiac edema (61%) had only one echocardiographic defining diagnosis, and > 80% had two or less echocardiographic diagnoses.

Clinical Predictors of Cardiac Edema

We used multivariate logistic regression to determine the history and physical examination findings associated with a cardiac cause of edema. Only a history of chronic obstructive pulmonary disease (odds ratio [OR] 1.74, 95% confidence interval [CI] 1.14–2.60) and crackles on physical examination (OR 1.98, 95% CI 1.26–3.10) were independently associated with cardiac edema in a model that examined age, history, the results of physical examination, and medication variables. Sensitivity for a cardiac abnormality was < 30% for both of these findings (Table II). The sensitivity increased to 41% if either chronic obstructive pulmonary disease or crackles were considered a positive screening test; however, the positive predictive value was < 50%.

TABLE I Characteristics of patients with cardiac and noncardiac edema

Characteristic	Cardiac edema (n = 56)	Noncardiac edema (n = 187)	p Value
Age (mean ± SD)	68 ± 11	68 ± 12	0.78
Male (%)	54 (96)	169 (90)	0.16
Past medical history			
Shortness of breath (%)	23 (40)	39 (21)	0.003
Coronary artery disease (%)	17 (33)	42 (23)	0.16
Chronic obstructive pulmonary disease (%)	14 (27)	17 (9)	0.001
Physical examination			
JVP > 10 cm (%) [a]	3 (11)	4 (4)	0.18
S3 (%)	0	0	1.0
Wheezing (%)	5 (10)	4 (2)	0.01
Crackles (%)	12 (24)	12 (7)	0.0005
Bilateral edema (%)	44 (89)	147 (86)	0.48
Edema grade (mean ± SD)	1.83 ± 0.8	1.66 ± 0.7	0.25
Medications			
Furosemide (%)	24 (45)	73 (40)	0.52
Beta blocker (%)	17 (32)	48 (27)	0.43
Calcium-channel blocker (%)	15 (28)	49 (27)	0.88
ACE inhibitor (%)	17 (32)	68 (38)	0.46
Laboratory values (in 209)			
Creatinine > 1.5 mg/dl (%)	12 (27)	27 (16)	0.10
BUN > 25 mg/dl (%)	12 (27)	43 (26)	0.93
Echocardiogram findings			
Sinus rhythm (%)	45 (79)	173 (93)	0.002
Pericardial effusion (%)	1 (2)	6 (3)	0.56
Mild or greater left ventricular hypertrophy (%)	16 (28)	61 (33)	0.50
Ejection fraction < 45 (%)	15 (26)	0 [b]	[a]
Pulmonary artery pressure > 45 mmHg (%)	20 (61)	0 [b]	[a]
Moderate or greater tricuspid regurgitation (%)	13 (25)	0 [b]	[a]
Dilated inferior vena cava (%)	13 (25)	0 [b]	[a]
Abnormal right ventricle (%)	36 (63)	0 [b]	[a]

[a] Data were available for echocardiographic findings in all patients; history of chronic obstructive pulmonary disease, coronary disease, and medications in 234 (96%); physical examination in 220 (91%) including assessment of JVP in 127 (52%); and laboratory data in 209 (86%). There was no difference in the prevalence of missing data between those with and without cardiac edema. Pulmonary pressure could be estimated in 122 patients.
[b] These echocardiographic findings define cardiac edema.
Abbreviations: SD = standard deviation, JVP = jugular venous pressure, ACE = angiotensin-converting enzyme, BUN = blood urea nitrogen.

TABLE II Test characteristics for crackles and chronic obstructive pulmonary disease for the diagnosis of cardiac edema [a]

Characteristic	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Crackles, (%)	24 (12/49)	93 (159/171)	50 (12/24)	81 (159/196)
COPD, (%)	27 (14/52)	91 (165/182)	45 (14/31)	81 (165/203)
Crackles or COPD, (%)	41 (20/49)	84 (143/171)	42 (20/48)	83 (143/172)

[a] Cardiac edema is defined as edema in the presence of one of the following: dilated inferior vena cava (≥ 2 cm), moderate or greater tricuspid regurgitation, decreased right ventricular function, enlarged right ventricle, pulmonary systolic blood pressure > 45 mmHg, or left ventricular ejection fraction < 45%. Data from 220 patients with physical examination data and 234 with past medical history data.
Abbreviation: COPD = chronic obstructive pulmonary disease.

Mortality

Survival was significantly worse for patients with cardiac than for those with noncardiac edema (Fig. 1). At 2 years, mortality for those with a cardiac cause of edema was 25 ± 13%, compared with 8 ± 4% for those without a cardiac cause. In a multivariate proportional hazards model of survival that examined age, history, and physical examination variables, only a

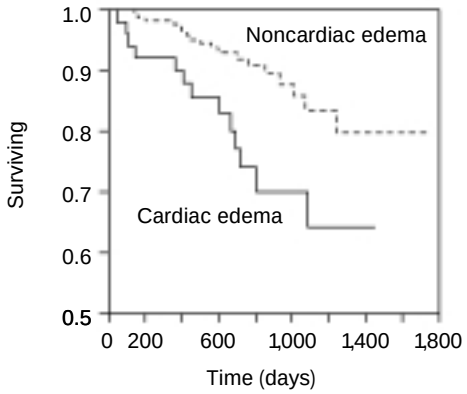

FIG. 1 Survival for patients with and without cardiac peripheral edema. Survival is significantly worse for patients with a cardiac cause of edema (p = 0.007).

cardiac cause of edema (hazard ratio 1.55, 95% CI 1.08– 2.24) and age (hazard ratio 1.63 per 10 year increase, 95% CI 1.15–2.41) were significantly associated with worse survival.

Clinical Predictors of Ejection Fraction < 45%

Patients with crackles (11% of all patients) were more likely than those without crackles to have a depressed ejection fraction (Fig. 2). The sensitivity of crackles for detecting an ejection fraction < 45% was 46% (6/13) with a specificity of 91% (189/207). The positive predictive value was 25% (6/24) and the negative predictive value was 96% (189/196).

Edema Persistence

Follow-up physical examination was recorded in 177 patients (73%) between 3 and 9 months following echocardiography. Of these, 110 (62%) had persistent edema at 6 months. Patients with cardiac edema were more likely to have persistent edema (74%, 31/42) than were those with noncardiac edema (59%, 79/135 p = 0.07). Multivariate logistic modeling found that the presence of cardiac disease increased the risk of persistent edema at 6 months (OR 1.52, 95% CI 1.03–2.25) after controlling for age. Other variables (history, physical examination, and medication use) were not associated with persistent peripheral edema.

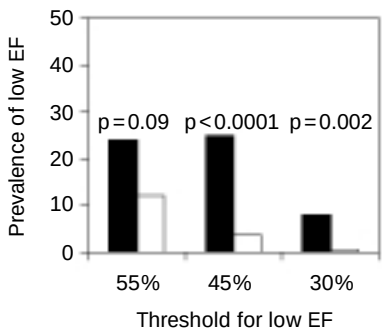

FIG. 2 Prevalence of depressed left ventricular ejection fraction (EF) for patients with and without crackles. ■ = Crackles, □ = no crackles.

Discussion

This study found that, among patients referred for echocardiography to determine the etiology of peripheral edema, a history of chronic obstructive pulmonary disease and the presence of crackles were specific but not sensitive for detecting a cardiac abnormality. Cardiac edema was more likely than noncardiac edema to persist for 6 months, but other edema characteristics such as severity and bilateral location did not distinguish between a cardiac and noncardiac cause. A potential cardiac cause of edema was found in more than one out of every five patients, including reduced LV ejection fraction, reduced RV function or increased size, pulmonary hypertension, moderate or greater tricuspid regurgitation, or a dilated inferior vena cava indicating elevated right atrial pressure. Moreover, those with one of these cardiac abnormalities were more likely to die.

One goal of our study was to identify a low-risk group of patients with unexplained peripheral edema who would not need further evaluation with echocardiography but in whom information from the history and physical examination would be used. We were unable to identify such a low-risk group, as those without the two identified risk factors (chronic obstructive pulmonary disease and crackles on examination) still had a 17% probability of cardiac disease.

Although our study cohort was referred for echocardiography, our findings are consistent with a report of 45 patients with bilateral leg edema from a general medical practice.[5] In that study, 42% had either pulmonary hypertension (systolic > 40 mmHg), or LV or RV dysfunction. An ejection fraction < 50% was observed in 18% (8/45), compared with 11% (26/243) in our study. Pulmonary hypertension (> 40 mmHg) was noted in 20% (9/44) compared with 28% of the 144 patients in our study who had a measurable pulmonary pressure. The similar rates of cardiac disease between this study and ours suggest that our results may be comparable with values for patients with unexplained peripheral edema in the community. The actual prevalence of cardiac edema among all patients with edema is likely to be lower, given that patients with edema that is believed to be due to a noncardiac cause were unlikely to be referred. Thus, our findings are most applicable to patients with edema of unknown cause.

The sensitivity and specificity of patient characteristics for predicting a cardiac cause are also affected by our use of a referral population. Patients may have been more likely to be referred because they had crackles or chronic obstructive pulmonary disease. This referral bias will increase artificially the sensitivity of those findings and decrease the specificity.[6] Even with this bias, we found that sensitivity of physical examination and history findings for detecting a cardiac cause of ede-

ma was never above 50%, suggesting that the sensitivity of crackles or chronic obstructive pulmonary disease for detecting cardiac disease in the community will be quite low.

Clinical Implications

There are several clinical implications of this study. First, in patients with unexplained peripheral edema and chronic obstructive pulmonary disease or crackles, a cardiac abnormality is likely to be present in near 40% of patients indicating a need for further evaluation. In patients without chronic obstructive pulmonary disease or crackles, further evaluation in those with unexplained edema is still reasonable given that 17% will have a potential cardiac cause of edema.

A diagnostic test to determine the etiology of peripheral edema should only be performed if it will lead to improved patient outcome. There are several potential benefits of echocardiography. Patients found to have a reduced ejection fraction will benefit from angiotensin-converting enzyme (ACE) inhibitors and beta blockers.[7] Those with elevated right-sided pressures or RV dysfunction may be found to have treatable pulmonary conditions (e.g., recurrent thromboembolism, sleep apnea). Whether the cost of echocardiography can be justified by these potential benefits requires further study.

The inability to detect a low-risk group based on history and physical examination suggests that laboratory markers such as B-type natriuretic peptide may be useful in patients with peripheral edema.[8] Those with peripheral edema and normal B-type natriuretic peptide levels may not need further evaluation.

With the exception of crackles, physical examination as recorded by the patient's primary provider was not helpful in distinguishing a cardiac from a noncardiac cause. Edema grade and extent (bilateral vs. unilateral) were not significantly different between those with and without cardiac edema. The lack of reporting the jugular venous pressure suggests that primary care providers of patients in our sample had no confidence in their ability to accurately measure the central venous pressure on physical examination. Additional studies are needed to determine the ability of providers to use this inexpensive method of detecting heart failure.

Limitations

In addition to the limitations of a referral sample discussed above, our study included few women (8% of participants). If the relationship between physical examination, medical history, and cause of peripheral edema differs between men and women, our findings will only apply to male patients. In addition, our study could not determine the prevalence of peripheral edema in the community. Because of the retrospective nature of our study, we could not standardize the physical examination. A more detailed examination than that documented by the clinicians in our study may have been more helpful in detecting cardiac disease.

Conclusion

Our study found that physical examination and history findings were insensitive for detecting a cardiac cause of peripheral edema. Of patients with a history of chronic obstructive pulmonary disease or crackles on examination, 40% had a cardiac cause of edema. However, a group at low risk for cardiac edema could not be identified. Given the inaccuracy of the history and physical examination, the high mortality in patients with peripheral edema due to heart disease, and the potential for treatment of cardiopulmonary abnormalities, an echocardiogram is an appropriate evaluation for patients with unexplained peripheral edema.

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