Symptoms in heart failure correlate poorly with objective haemodynamic parameters

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Introduction
Heart failure (HF) is a common condition with high morbidity and mortality increasing in prevalence throughout the civilised world (1). Although great advancements have been made in the understanding of pathophysiology and treatment of this condition, surprisingly little is known regarding correlation between patient’s symptoms and objective data. For years, it has been known that patients most frequently report dyspnoea, oedema and fatigue for several hours to days before presenting to the hospital for heart failure (2). Studies in the past have shown the types of symptoms patient may present with and how these symptoms correlate with age and gender (3). However, it is still poorly understood whether symptoms of dyspnoea, orthopnoea, fatigue and abdominal discomfort, which are the main reason of hospitalisation in HF, correspond to objective clinical findings. The purpose of this study was to investigate the haemodynamic, echocardiographic and laboratory correlations to various HF symptoms.

Methods
This study is a retrospective analysis of the limited access dataset from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial provided by the National Heart, Lung and Blood Institute (NHLBI).
According to the NHLBI policy, datasets from major clinical trials funded by NHLBI can be released to investigators not participating in the original trial 5 years after the publication of the trial results. These datasets include the protocol and all collected variables with their descriptions and definitions. All personal identifiers are removed.

Documentation for limited access datasets is comprehensive and sufficiently clear to enable investigators who are not familiar with a specific dataset to use it. The documentation includes a brief description of the study, including a general orientation to the study and its components; study examination and assessment time points; data collection forms; study protocol/procedures; descriptions of variable recoding performed; and a list of major study publications.

The original study was a multicentre trial that compared therapy guided by pulmonary artery catheters with therapy guided by clinical assessment in hospitalised patients with acute decompensated HF. Patients were admitted for New York Heart Association (NYHA) class IV symptoms. They also had to have at least one prior admission for exacerbation of HF within 6 months before randomisation and left ventricular ejection fraction < 30% using contrast ventriculography, radionuclide ventriculography, or quantitative echocardiography within 1 year before randomisation. For patients randomised to the Swan-Ganz guided therapy arm, following haemodynamic parameters were recorded: right atrial pressure, pulmonary artery systolic, diastolic and mean pressure, pulmonary capillary wedge pressure, systemic vascular resistance, mixed venous oxygen saturation and arterial blood pressure. Three sets of haemodynamic measures were recorded daily at 8 am and at 4 pm while the catheter was in place. Same person was obtaining all the measurements at a given centre. The lowest pulmonary capillary wedge pressure achieved each day and all haemodynamic variables associated with this pulmonary capillary wedge pressure were entered into the study database. In addition, two sets of haemodynamic measures were recorded 1 h before removal of Swan-Ganz catheter (4).

Echocardiographic parameters analysed included left atrial size, left ventricular wall thickness, end-systolic and end-diastolic volume, ejection fraction, velocities of early and late mitral filling, right ventricular fractional area change, velocity of mitral and tricuspid regurgitation and severity of mitral regurgitation. Laboratory tests were available for serum sodium, potassium, creatinine, liver function tests, albumin, platelets, haemoglobin and haematocrit.

We analysed a limited access dataset from the ESCAPE Trial, provided by the NHLBI. Symptoms including dyspnoea, orthopnoea, fatigue and gastrointestinal (GI) discomfort were graded by their severity from minimal (0) to maximal (3) on admission for decompensated HF, at discharge, at 3 months and at 6 months from the admission. Results of Minnesota Living with Heart Failure (MLHF) score and assigned NYHA functional class were available at the same time points. Half of the patients (those who were randomised to the Swan-Ganz arm in the original trial) had haemodynamic parameters recorded using a Swan-Ganz catheter as well. Echocardiographic and laboratory data were collected both in the hospital and at follow-up. As symptoms were not normally distributed, the data were analysed using Spearman’s correlation coefficient and linear regression analysis (SPSS).

**Results**

A total of 433 patients with decompensated HF and decreased systolic function (ejection fraction < 30%) were included in this trial. The baseline characteristics of the patients are listed in Table 1. Orthopnoea, dyspnoea, fatigue and abdominal discomfort were evaluated to determine if a correlation existed between these symptoms and various haemodynamic, echocardiographic and laboratory data. These same clinical variables used to determine correlation to symptoms were also applied to determine if positive correlation existed between NYHA classification and MLHF questionnaire for quality of life.

The dataset was very complete. Table 2 provides the total number of patients seen on admission, on 3-month follow-up, and on 6-month follow-up and also the count and percentage of various diagnostic tests done. Data on severity of symptoms were collected in 430 out of 433 individuals at baseline, and almost in everybody at both follow-up points. Physical findings, such as heart rate and blood pressure, were collected in all participants. Echocardiography and laboratory test were carried out in majority of patients (Table 2).

Using the trial design, patients were randomised into Swan-Ganz guided management or to a standard clinical management. Therefore, parameters of invasive haemodynamics, including right atrial pressure, pulmonary artery systolic and diastolic pressure, cardiac index and cardiac output, pulmonary capillary wedge pressure and systemic vascular resistance were available in roughly half of the patients.

Both on admission and on discharge, orthopnoea and dyspnoea at baseline correlated positively,
although very weakly, with haemodynamic measurements of pulmonary artery pressures during systole and diastole. Both symptoms were also inversely related to systemic systolic and diastolic pressures. In addition, orthopnoea was inversely related to echocardiographic findings of mitral inflow deceleration time. Interestingly, both symptoms correlated inversely with right and left atrial size. Laboratory findings for serum creatinine albumin, sodium, total bilirubin, haemoglobin and haematocrit were all inversely related to dyspnoea at baseline, discharge and 3-month follow-up. Orthopnoea was similarly related to fewer variables (Table 3).

Likewise, fatigue was positively related to pulmonary artery pressures on admission, and negatively to serum sodium, potassium, albumin and haemoglobin (Table 4). Abdominal discomfort did not appear to have measurable relationship with objective findings.
When we examined the relationship between haemodynamic, echocardiographic and laboratory data and NYHA class, we found again very low, although statistically significant inverse relationship with serum levels of sodium, potassium, albumin, haemoglobin and haematocrit at 3 months. Somewhat stronger dependence was found for MLHF scores (Table 5).

There was no correlation of symptoms, NYHA class, or MLHF scores with age, gender, peak VO₂ on cardiopulmonary stress test, body mass index, either right or left ventricular systolic function, B-type natriuretic peptide, cardiac output or cardiac index, troponin level, velocity of tricuspid regurgitation and multiple other factors predicting morbidity and mortality in HF.

Discussion

In this analysis of the limited access dataset from the ESCAPE trial, we examined the relationship between typical HF symptoms and objective findings in patients with advanced systolic HF. To our knowledge, correlation of symptoms of HF was never studied on such an extensive dataset with multiple functional, haemodynamic, echocardiographic and laboratory parameters recorded serially at different stages of natural history of advanced HF, from exacerbation on admission to subcompensation on discharge and stable condition at 3 months after discharge.

The most striking finding is extreme weakness of all found correlations. Most significant correlations, we found were related to congestion. Congestion is a syndrome of fluid retention and volume overload that unites elevated pulmonary arterial and pulmonary capillary pressure, mitral inflow deceleration time, elevated creatinine, low sodium and anaemia. However, the numeric magnitude of these relationships is very low, although statistically significant and quite consistent.

The findings of this study are interesting, because it is well known from clinical experience, small studies (2) and large registries (3,5), that patients with HF are admitted to the hospital with primary symptoms of dyspnoea and orthopnoea. It has also been well established that intracardiac pressure starts rising several days before hospital admission (6). Intuitively, correlation between symptoms and right sided pressures should be strong, but in fact, this correlation is barely noticeable.

Not many prior studies addressed the issue of symptoms and their correlation with measured parameters of haemodynamics. There were few studies evaluating dyspnoea and fatigue in relation to exertion and haemodynamic function, and they have shown little to no correlation of objective findings to perceived symptoms. Lipkin et al. (7) measured pulmonary capillary wedge pressure, arterial blood gases,
pH and lactate concentrations in HF patients walking on a treadmill until limiting fatigue and found no connection between exercise capacity and resting or exercise pulmonary capillary wedge pressure or the change in pulmonary capillary wedge pressure during exercise. Instead, they found higher lactate concentration and greater pH changes in individuals who exercised harder. They concluded that the sensation of breathlessness is not simply related to elevated intracardiac pressures, but may, in part, be caused by stimulation of peripheral chemoreceptors in response with metabolic acidosis.

All patients in the ESCAPE trial had left ventricular and right ventricular systolic function measured at three points in time. However, not a single symptom at any point correlated with any of these measurements. Admittedly, left ventricular ejection fraction was very low by inclusion criteria (< 30%), and therefore, the variability of ejection fraction was much less than in typical studies with much wider spectrum of systolic function. To the contrary, right ventricular systolic function varied widely, and there was still no correlation.

Previously, the analysis of controlled and observational studies that reported measures of either exercise time or oxygen uptake and haemodynamic variables in patients with HF also proved no association between left ventricular ejection fraction and exercise capacity (8). In another study, left ventricular ejection fraction was very low by inclusion criteria (< 30%), and therefore, the variability of ejection fraction was much less than in typical studies with much wider spectrum of systolic function. To the contrary, right ventricular systolic function varied widely, and there was still no correlation.

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| Table 5 | Correlation of MLHF score to haemodynamic, echocardiographic and laboratory data |
|---------|-----------------------------------------|
| MLHF score | N | Admission | 6 months |
| Beta | p-value | Beta | p-value |
| Echocardiographic variables | | | | |
| Right ventricular size, discharge | 119 | 9.98 | 0.02 |
| Left atrium, baseline | | | | |
| Left ventricular ejection fraction, discharge | 145 | | | |
| Tricuspid regurgitation velocity, 3 months | 94 | | | |
| Laboratory variables | | | | |
| Serum potassium, admission | 296 | | | |
| Creatinine, admission | 297 | | | |
| Creatinine, discharge | 280 | | | |
| Creatinine, 3 months | 192 | | | |
| Serum albumin, admission | 229 | | | |
| Total bilirubin, discharge | 135 | | | |

Conclusions

In summary, after having examined multiple objectively measured parameters in HF patients, including functional, haemodynamic, echocardiographic and laboratory parameters, we found almost no relationship with severity of dyspnoea, orthopnoea, fatigue...
and GI discomfort. Very few weak, but consistent correlations reveal some association of symptoms, NYHA functional class and Minnesota Living with Heart Failure score with indicators of volume overload and haemodilution, or congestion with secondary elevation of intracardiac pressures, hyponatraemia and renal dysfunctions. However, the magnitude of these relationships is so low that obviously some other factors, not measured or not measurable, determine the perception of symptoms.

**Limitations**

Cardiopulmonary stress test was performed in minority of patients, which is understandable because subjects enrolled in the trial were in acute heart failure on admission. Cardiopulmonary stress test is not routinely done in this subset of patients unless they are candidates for cardiac transplantation, and it also time and effort consuming.

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