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Evaluation of a new quantitative echocardiographic estimate of elevated left ventricular filling pressure in clinical practice

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Background

Heart failure (HF) is associated with significant mortality and high-level of health-care costs [1], and prevalence is increasing with an ageing population [2]. Currently, the incidence of HF in Europe is about 3/1000 person-years (all age-groups) or about 5/1000 person-years in adults [3,4] The prevalence of HF is estimated to be 1-2% of adults [5]. Most commonly, HF is due to myocardial dysfunction: either systolic, diastolic, or both [6]. HF is hemodynamically characterized by decreased cardiac output and/or increased left ventricular (LV) filling pressures at rest or during exercise [7]. Elevated left ventricular filling pressures (LVFP) is an integral part of heart failure (HF) pathophysiology and diagnosis [3]. Increased left ventricular (LV) filling pressures give rise to elevated left atrial (LA) pressures, which in turn may result in pulmonary edema [8]. Accurate methods to detect, and quantify, elevated LV filling pressures are essential in the management of patients with HF [9].

Although, LV filling pressures can be accurately estimated using right or left cardiac catheterization by measuring either the pulmonary arterial wedge pressure (PAWP) or the LV end-diastolic pressure, such methods are both invasive and inaccessible [10]. Instead, echocardiographic methods are used in daily practice, but the diagnosis of elevated LV filling pressures is often challenging [9]. The diagnostic algorithms, currently recommended to be used in clinical practice are limited [11,12]. First of all, their binary outputs, i.e. concluding either presence or absence of elevated LV filling pressures based on discrete cutoff values, do not fully embrace the spectrum of disease from very low LV filling pressures, to low, or from moderately elevated to severely elevated, etc. Secondly, current algorithms are limited by a large proportion of inconclusive results [13-15]. Instead, a quantitative measure has greater potential to describe the full spectrum of the hemodynamic status, and better describe the effect of treatment, or the progression of disease. Recently, through studies combining echocardiographic and invasive studies, using LA volume, E-wave and S-wave velocities, a fully quantitative, accurate estimate of LV filling pressures, (ePAWP) was described, which in large-registry data, also showed to be associated with increased risk of cardiovascular death [16]. However, ePAWP was derived and validated in highly selected populations undergoing right heart catherization. Before being used in clinical practice, its diagnostic accuracy and feasibility in patients with clinically suspected HF needs to be described and compared to currently used diagnostic algorithms.

Research questions

1. What is the diagnostic accuracy of ePAWP in patients with suspected HF with a clinical referral for echocardiography?
2. Is there a difference in ePAWP between different HF groups, i.e. HF with reduced ejection fraction (HFrEF), HF with mildly reduced ejection fraction (HFmrEF) and HF with preserved ejection fraction (HFpEF)?
3. What is the feasibility of ePAWP determination in patients with suspected HF with a clinical referral for echocardiography?
4. How does ePAWP correlate with NT-proBNP?

Aims of study

1. To assess the diagnostic accuracy of ePAWP in patients with suspected HF who have a clinical referral for echocardiography.
2. To compare ePAWP values across different HF subtypes, including HF with reduced ejection fraction (HFrEF), HF with mildly reduced ejection fraction (HFmrEF), and HF with preserved ejection fraction (HFpEF).
3. To evaluate the feasibility of determining ePAWP in patients with suspected HF who have a clinical referral for echocardiography.
4. To investigate the correlation between ePAWP and NT-proBNP levels.

Study design

Retrospective observational cohort study

Study population

Patients who have undergone a clinical echocardiography at the Department of Clinical Physiology, Växjö, Sweden, due to suspected HF will be included retrospectively from Jan 2024 to Dec 2024 in this cohort study. In 2024, patients with a clinical suspicion of new HF received a specific code in the administrative system in preparation of a national person-centered and coordinated care pathway for patients with new HF, and can therefore be easily identified.

Inclusion and exclusion criteria:

Inclusion criteria:

- Age ≥18 years
- Sinus rhythm
- Suspected HF diagnosis and echocardiography performed between Jan 2024 and Dec 2024 at the Department of Clinical Physiology, Växjö Central Hospital, Växjö, Sweden.

Exclusion criteria:

- Inadequate image quality
- Non-sinus rhythm

Methods:

Patients who have undergone a clinical echocardiography at the Department of Clinical Physiology, Växjö, Sweden, will be included retrospectively from Jan 2024 to Dec 2024 and estimate of LV filling pressures (ePAWP) is measured. ePAWP will be calculated for all patients using the formula: $0.179 \times \text{LAVi (ml/m}^2\text{)} + 2.672 \times \text{mitral E/PVs} + 2.7$ [16]. The final diagnosis of HF, and the subtype (HFrEF, HFmrEF, HFpEF) will be adjudicated from information in the echocardiographic report and patient charts. The diagnostic accuracy of ePAWP will be described for all patients, and for patients with reduced or preserved ejection fraction (EF) separately and described by sensitivity, specificity, positive and negative predictive value. For comparison, the diagnostic accuracy of ASE/EACVI algorithm, E/e' and left atrial strain will also be described.

Baseline data will also be obtained from patient charts including prevalent cardiovascular diagnoses (hypertension, angina pectoris, myocardial infarction, diabetes, hypercholesterolemia, chronic kidney disease, pulmonary disease (asthma, chronic obstructive pulmonary disease, interstitial lung disease), smoking status, creatinine, hemoglobin, NT-proBNP, and medications at the time of examination.

Statistical analysis plan

Baseline characteristics will be summarized using mean ± standarddeviation or median (interquartile range), depending on the distribution of the data. Comparisons of means between

different HF groups will be performed using one-way ANOVA, with post-hoc tests for pairwise comparisons as appropriate using the Student t-test. For comparisons of medians, the Kruskal-Wallis test, or pairwise Wilcoxon rank-sum tests, will be used. Diagnostic accuracy will be evaluated for ePAWP, and other echocardiographic measures of LV filling pressure, for the diagnosis of HF, and described using receiver operating curve (ROC) analysis described with area under the curve with 95% confidence intervals, and sensitivity, specificity, positive and negative predictive values based on optimal cutoffs determined by the Youden Index. Correlation will be assessed using either Pearson's r or Spearmans rho depending on the distribution of the data.
Feasilibilty will be described with number and % of completed ePAWP estimations.

Sample size estimation

To determine the diagnostic accuracy of ePAWP, and other echocardiographic measures, among patients with suspected heart failure in terms of sensitivity and specificity, 257 subjects are needed for an expected sensitivity and specificity at 80±10% with an α at 0.05 and allowing for 20% dropout [21], e.g. due to atrial fibrillation or poor image quality.

Ethics

The implementation of the study has been approved by the Ethical Review Authority (Dnr 2024-07591-01). The diary number has been obtained and the application to establish a register of the participants will be sent to the PUL representative in the region and the application for the diary number is completed. The study is retrospective and is based entirely on medical records. A potential ethical problem regarding the patients' integrity is handled by pseudonymization of data. The results are presented at group level.

Project implications

Determination of LV filling pressures is important in HF diagnostics and management. ePAWP has been validated invasively, and its prognostic value has been documented [16]. However, ePAWP was derived and validated in highly selected populations undergoing right heart catherization, thus with access to the reference standard for LV filling pressures (invasively measured pulmonary artery wedge pressure, PAWP). Before being used in clinical practice, its diagnostic accuracy in patients with clinically suspected HF needs to be described and compared to currently used diagnostic algorithms.

In parallel to this cohort study, two other cohort studies are planned. The first one aims to determine whether changes in ePAWP are reflective of changes in LV filling pressure which would strengthen the clinical use of the method. This is accomplished non-invasively by relying on existing data on changes in PAWP in postural changes and passive leg lift [17-21]. Further the second cohort study aims to study changes in ePAWP during hemodialysis in patients with renal failure. HF is common among patients with renal failure [22], both due to reciprocal interactions between renal and cardiac hemodynamics, and to concomitant cardiovascular disease [23]. Patients with advanced renal failure are commonly affected by venous congestion and high LV filling pressures, which can be relieved by hemodialysis. However, optimizing of fluid volumes is difficult, and the balance of reducing symptoms related to volume overload to those related to hypovolemia is delicate [20]. Consequently, patients with renal failure undergoing hemodialysis will not only serve as a reliable group undergoing an actual reduction in cardiac congestion (pre- vs. post-dialysis) but also offer insights into the feasibility of employing ePAWP in this context. If successful, this quantitative marker of LV filling pressure may furnish valuable information regarding the extent of volume reduction required.

Time plan

Application to Ethical Review Authority	November 2024
Ethical Review approval	November 2024
Data acquisition	2024 – 2026
Analysis of data	2025 – 2026
Presentation of results	2027

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