CLINICAL/ORIGINAL PAPERS

Value of left ventricular filling parameters to predict mortality and functional class in patients with heart disease from the community

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Abstract
Surprisingly few studies described the value of Doppler parameters in patients from the community.

Aim
The aim was to determine the prevalence of prolonged IVRT (\(>0.105\) s) or a prolonged EDT (\(>0.280\) s) with a reduced \(E/A\) (<0.5) in heart patients from the community without valvular, systolic or rhythmic dysfunction. The associations of these parameters to all cause mortality and NYHA functional class were examined as well.

Methods
Seventy-two volunteer stable patients with a history of heart disease were identified from general practice. Patients with LVEF below 0.45, valvular abnormalities, atrial fibrillation, and pacemaker were excluded. Routine blood tests, echocardiography, chest X-ray, physical examination and mortality were evaluated.

Results
Patient findings: male 33\%, mean age of 68 years, hypertension 82\%, ischaemic heart disease 43\%, and NYHA class I + II + III in 50 + 39 + 11\%. Abnormal EDT occurred in 4\% (95\% CI from 0 to 9\%), IVRT in 18\% (9–27\%), \(E/A\) in 0\%. None had a restrictive pattern. EDT was longer in NYHA III than in NYHA I–II patients (median 0.25 vs. 0.19 s, \(p = 0.0006\)). \(E/A\) and IVRT were not associated with NYHA class or mortality. After 7.4 years 16 of 72 patients died. EDT predicted mortality in univariate analysis but not in a multivariate analysis where NYHA class and gender were the only significant predictors.

Conclusion
Prolonged EDT was weakly associated to NYHA class and mortality while IVRT and \(E/A\) were not. Prolonged IVRT was a frequent finding, but

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Introduction

One third to half of patients with congestive heart failure (CHF) have normal left ventricular (LV) systolic function depending on the criteria used.\(^1\-^5\) The rest may have diastolic dysfunction\(^6\) or no CHF at all. The definition of diastolic dysfunction is complex and measurements of diastolic function are influenced by age, gender, heart rate, and load conditions of the left ventricle. The interpretation of left ventricular filling parameters furthermore depends on the type of cardiac disease.\(^7\) The Rochester Epidemiology project used a rigorous algorithm to diagnose diastolic dysfunction. Prevalence of mild diastolic dysfunction was 20.8%. Moderate and severe diastolic dysfunctions were significantly related to mortality after adjusting for gender, age and left ventricular ejection fraction (LVEF).\(^8\)

The European Study Group on Diastolic Heart Failure has recommended cut-off values for abnormal E to A ratio (E/A), E-wave deceleration time (EDT) and isovolumetric relaxation time (IVRT) by Doppler echocardiography.\(^9\) Recent studies examined the prognostic value of these criteria and found that E/A \(> 1.5\) and to a lesser degree E/A \(< 0.6\) was correlated to surplus mortality and incident CHF.\(^10^-^12\) An E/A ratio \(< 1.0\) was associated with increased risk of cardiovascular event in hypertensive patients.\(^11\) EDT and IVRT are longer in men than in women,\(^13\) and an abnormal EDT and IVRT occurred in about 40% of patients referred for heart failure with normal systolic function.\(^14\)

A clinical problem arises when symptomatic patients have no obvious systolic and valvular dysfunction. In such patients, there are few data to support if the left ventricular filling parameters explain the reduced functional class and mortality. In clinical practice some cardiologists use the Doppler parameters to diagnose diastolic dysfunction in a broad range of patients. However, the scientific community is more reluctant about using these criteria because of the many potential pitfalls. Surprisingly few studies have been published to support the view that Doppler parameters are of any clinical value in patients from the community. One study found that E/A ratio was not helpful in explaining symptoms in referred heart patients.\(^15\)

Methodological bias may have been introduced in previous studies where patients with normal and abnormal cardiac function were examined together, but analysis should be targeted at different disease states instead.\(^7\)

The aim of this study was to determine the prevalence of abnormal EDT, E/A ratio and IVRT Doppler parameters in community patients with a history of heart disease without valvular heart disease, systolic dysfunction, or significant arrhythmia. Secondly, we analysed the associations of these parameters to clinical variables and mortality.

Methods

Subjects

Patients were recruited from a cross-sectional study that examined the prevalence of heart disease and CHF in three general practices (GP) in Copenhagen during 1994–1996. The methods used for screening and case identification were described previously.\(^4\,^16\) We screened all subjects \(> 50\) years from all three general practices (n = 1755) and all subjects aged 40–49 years from one of the practices (n = 403). Screening was based on case record reviews and questionnaires. The questionnaire was sent to all subjects (n = 2000) outside nursing homes. It asked about previous symptoms, treatment, and hospitalisation for heart problems.

A total of 357 patients had a history of heart disease and 210 patients were excluded prior to examination for the following reasons: 38 lived in nursing homes, 36 did not respond to the questionnaire, 88 responded to the questionnaire but refused invitation to participate in further examinations, 37 were unable to attend due to non-cardiac medical or psychosocial conditions, 10 had severe CHF, and 1 patient died. We excluded patients with a recent admission for definite CHF or myocardial infarction (\(< 3\) months), and patients who were unable to use taxi or public transportation to attend a 2-day examination program at the hospital-based clinic.

A total of 147 patients were potential candidates, 126 accepted invitation for a cardiac examination, 108 had acceptable Doppler recordings.
and 72 patients were included after exclusion of 36 patients with structural heart disease. A history of heart disease means that the general practitioners had diagnosed and treated a patient for heart disease on the basis of an abnormal echocardiography, electrocardiogram, cardiac catheterisation, stress test, cardiac scintigram, hospital admission for myocardial infarction, typical angina pectoris in the Rose Questionnaire, atrial fibrillation, and or clinical signs of CHF.

Structural heart disease leading to exclusion was LVEF below 0.45 (9 men and 6 women), moderate—severe valvular abnormalities (4 men and 10 women), atrial fibrillation (4 men and 1 woman), and pacemaker-rhythm (1 man and 1 woman).

The study was approved by the local ethical committee (appraisal No: 01-086/95), and all examined patients gave informed consent.

**Physical examination and morbidity**

Patients underwent physical examination, chest X-ray, echocardiography, supine 12-lead electrocardiogram, and blood pressure measurements. Reduced functional class was defined as NYHA functional class II and III. Patients reporting chest pain underwent an exercise test. A final diagnosis was decided in each case after panel discussion (OWN and JFH).

Pulmonary disorder was based on a history of typical symptoms for chronic obstructive pulmonary disease or asthma.

**Echocardiography**

M-mode, two-dimensional and Doppler images including LV diastolic filling parameters were recorded and analysed later after blinding to other patient data. The following definitions were used.

LV systolic function was evaluated by the wall motion index score in the nine segment model for assessing wall motion inhomogeneity. In the absence of wall motion inhomogeneity the squared formula of fractional shortening was used to calculate LVEF. The intra-observer and inter-observer standard deviation of a single EF estimate were equal, 0.05 EF units (coefficient of variation, CV% = 8%). Systolic dysfunction was defined as an LVEF below 0.45, which is approximately equal to a fractional shortening of 0.26 and wall motion index score of 1.5.

LV mass was calculated by the formula of Devereaux and LV hypertrophy means an LV mass > 134 g/m² for men and 110 g/m² for women. Valvular disease was defined as ≥ grade 2 (of 3) regurgitation of the aortic or mitral ostium based on Doppler color flow or a peak aortic gradient ≥ 20 mmHg. An additional criterion was dilatation of LV (> 60 mm), left atrium (> 50 mm) or LV hypertrophy, as these are morphological indicators of significant valvulopathy.

**Diastolic dysfunction**: impaired relaxation was defined according to the European Study Group of Diastolic Heart Failure as an isolated prolonged IVRT (≥ 0.105 s) or a prolonged EDT (≥ 0.280 s) with a reduced E/A (≤ 0.5)9; since specific cut-off values for restrictive filling (low EDT and high E/A ratio) were not given, we applied age- and gender-specific 2.5% percentile for normality of EDT and 97.5% percentiles for normality of E/A ratio, according to ‘The Tromsø Study’23 defined as EDT ≤ 0.130 s with an E/A > 1.5. The coefficients of variation for EDT, IVRT, and E/A were 13.4%, 14.3% and 8.1%, respectively.

**Mortality**: all cause mortality data were obtained from the Danish Central Person Registry March 8th, 2001. Patients were observed up to 7.4 years with a median time of 4.8 years.

**Statistical analysis**

Reported measures represent mean of 5 measurements, and within subject variation was calculated as the coefficient of variation of 5 repeated measurements. Relations between dichotomous Doppler mitral inflow parameters and other dichotomous factors were evaluated by the chi-squared test using the Yates’ continuity correction. The differences in median EDT, IVRT and E/A between groups were evaluated by the Mann–Whitney test.

A linear regression model evaluated E/A, EDT and IVRT as continuous response variables against the factors that were significant in univariate analysis. Since no patients had a strict restrictive filling pattern all Doppler parameters were entered as continuous variables meaning that the models only examined aspects of slow relaxation. P-values < 0.05 indicated statistical significance.

Differences in mortality between groups were evaluated by the log rank test. Tertiles and quintiles of EDT and E/A were examined in the Kaplan–Meier plot for proportional hazard, and groups with equal mortality were lumped together. A Cox model tested the effect of Doppler parameters on survival. Based on 10–20 endpoints the model was powered to examine 1 or 2 variables simultaneously.

For explorative reasons we also examined whether EDT would be pushed out of the model.
by more conventional variables. Apart from age and gender variables we included NYHA class and LVEF because they are so important for evaluation of the prognosis in patients with CHF.

The computer package "Statistica" (Statsoft, USA) was used for all calculations.

Results

Baseline characteristics

Baseline characteristics of the 72 included patients are presented in Table 1, drug treatment in Table 2, and echocardiographic findings in Tables 3 and 4. Age covered values from 50 to 85 years, the vast majority (82%) had hypertension, and one half were asymptomatic (NYHA class I).

<table>
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<th>Table 1 Baseline characteristics</th>
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<td>Death after 5 years</td>
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<td>Smoker, previous</td>
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<td>Smoker, current</td>
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<td>Pulmonary disease</td>
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<td>Pulmonary disorder</td>
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Nineteen subjects (26%) had previously received treatment for CHF, more than half took a diuretic while 14 did not receive any of these drugs.

The mean heart rate (range 46–93), EF (range 0.45–0.87) and M-mode parameters were normal for age. Few patients had severe LV hypertrophy as indicated by the reported mean plus 2 standard deviations of posterior wall and septum thickness that was less than 1.3 cm.

Table 4 shows that 18% would have diastolic dysfunction according to the predefined criteria, because of an IVRT \( \geq 0.105 \) s. Just 3 patients had an EDT \( \geq 0.28 \) s and 5 had EDT \( \leq 0.13 \) s, but no patients had the restrictive pattern with both low EDT and a high \( E/A \) ratio.

Association of LV filling parameters to baseline characteristics

EDT, IVRT and \( E/A \) were examined in several univariate analyses against age (continuous variable...
as well as >1/70 years), gender, NYHA class, history of hypertension, previous myocardial infarction, diabetes, angina, obstructive pulmonary disease, BMI, ischaemia in the ECG, previous treatment for CHF, and cardiovascular treatment. Among all comparisons the following statistical significant associations were found:

**EDT was longer in NYHA class III as compared with class I–II patients (median 0.25 vs. 0.19 s, p = 0.0006), and longer in men as compared with women (0.21 vs. 0.19, p = 0.02).**

The E/A ratio was smaller in patients taking diuretic treatment than without (median 0.73 vs. 0.80, p = 0.02).

A prolonged IVRT was not associated to any of the clinical factors, neither as a continuous nor dichotomous variable.

**Multivariate associates of LV filling parameters**

The association between continuous Doppler indices and the aforementioned clinical features was examined as well, and the following statistical significant associations were found.

**EDT (ms) was positively associated with NYHA class (I, II, III), diastolic blood pressure (mmHg) and age (years) (R = 0.42).**

**E/A was inversely associated with diastolic blood pressure (mmHg), age (years) and positively to diuretic treatment (R = 0.40).**

**IVRT (ms) was only associated with systolic blood pressure (mmHg) (R = 0.23).**

**Association between LV filling parameters and mortality**

Sixteen deaths were observed among the 72 patients. The mortality of the present cohort was significantly lower (p < 0.05, log rank test) than the mortality of patients excluded because of valvular and LV systolic dysfunctions (16 deaths among 29 patients).

On univariate analysis EDT was associated with mortality, while IVRT and E/A were not. **Fig. 1 shows a higher cumulative survival in patients with shorter versus longer EDT (p < 0.02, log rank test).** A total of 33% (24/72) patients had EDT > 0.21 s. This cut-off point was arbitrarily defined as the value that best separated poor and good prognosis after observing the mortality in relation to quintiles of EDT: first (EDT < 0.16 s, deaths/n = 2/11), second (EDT from 0.16 to 0.17 ms, deaths/n = 1/10), third (EDT from 0.18 to 0.20 ms, deaths/n = 1/21), fourth (EDT from 0.21 to 0.23 s, deaths/n = 7/15), and fifth (EDT > 0.24 s, deaths/n = 5/15). The hazard ratio of EDT was 1.01 per ms (95% CI from 1.003 to 1.025, p = 0.02).

For explorative reasons we examined whether EDT would be pushed out of the model by any of the clinical factors.
the traditional CHF variables such as age, gender, LVEF and NYHA class. Then the only significant predictors were NYHA class (hazard ratio = 1.7 per I, II, III, 95% CI from 1.2 to 2.5, \( p = 0.007 \)) and gender (hazard ratio = 3.0 for men, 95% CI from 1.1 to 8.2, \( p = 0.031 \)). EDT thus became insignificant in multivariate analysis.

Discussion

Main finding

The major new finding of this study is the description of the mortality in relation to abnormal LV filling parameters in a sample of community patients with a history of heart disease and no significant LV hypertrophy, arrhythmic, valvular or systolic dysfunction on echocardiography. In these low risk patients no patients had a restrictive pattern. There was a high prevalence of a raised IVRT (18%) but IVRT and E/A were poor markers of functional class and mortality. However there was a trend that a prolonged EDT was related to NYHA class and mortality but the clinical value needs further examination in other studies.

We suggest so far that the term diastolic dysfunction be avoided when based on an echocardiogram showing a moderately prolonged IVRT, EDT or a low E/A or any combination hereof in this kind of patients.

Other studies

Surprisingly few studies were published with a similar focus. Also very few studies have examined the clinical value of these parameters in subjects with heart disease after exclusion of those with structural abnormalities. We excluded those with arrhythmic, valvular and systolic dysfunctions to explore if there would be any independent clinical value the Doppler parameters to explain symptoms or mortality. That was not the case.

The present study differs from others in one important aspect. We included unselected patients with a history of heart disease from general practice instead of patients who had been referred because of worsening symptoms.

Previous studies have used different criteria for the definition and inclusion of patients. Hospital-based studies of patients with CHF used a diagnosis of diastolic dysfunction based on exclusion rather than explicit criteria. Despite the differences in the studied populations, many aspects of our study are consistent with the previous studies.

In agreement with MacFadyens study we found no subjects with a restrictive filling pattern. That study also found that EDT was, but that E/A ratio was not, related to clinical symptoms. A prolonged EDT was also significant in other studies regarding the association to an increased mortality, blood pressure, and age.

Strengths and limitations

The present study sought to examine some of the earliest used parameters of diastolic function, because such data do not exist. These parameters introduced after phase I and II studies had showed abnormal LV filling in severe CHF patients, but they were never examined in unselected clinical settings before new measures of LV filling were suggested based on color-M mode and tissue Doppler.

The case of pseudonormalised Doppler parameters was not considered in this study, and we believe it was a minor problem because we examined those without severe hypertrophy or dysfunction of the left ventricle and valves.

The study population selected was small. This may carry a risk of type II errors with regard to not identifying statistical significant associations between the study variables and endpoints if the clinical significance is small. No more than 1–2 significant markers could be identified in a Cox regression model with only 16 endpoints. Nonetheless, in this low risk population we have shown that gender and NYHA class were more powerful predictors of mortality than EDT and certainly than E/A and IVRT.

Perspective

The present study reflects the clinical setting where an echocardiogram is performed in community patients with hypertension and/or suspected heart disease. When LV systolic dysfunction, valvar disease and atrial fibrillation have been excluded there is little value of mild to moderate abnormal IVRT or E/A to predict mortality or a poor NYHA functional class. EDT was related to NYHA class and mortality in univariate analysis and may thus merit further analysis.

References

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