

Restrictive left ventricular filling pattern and increase in antero-posterior left atrial diameter: two reliable predictors of clinical deterioration in chronic heart failure II NYHA class patients

Restriktif sol ventrikül doluş örneği ile birlikte sol atriyum ön-arka çaptaki artış: Kronik kalp yetersizliği NYKD sınıf II hastalarda klinik kötüleşmenin gerçek iki belirleyicisi

Renato De Vecchis, Carmela Cioppa, Anna Giasi, Armando Pucciarelli¹, Salvatore Cantatrione

Cardiology Unit, Presidio Sanitario Intermedio "Elena d' Aosta", Naples
¹Department of Cardiology, Postgraduate Medical School, Federico II University, Naples, Italy

ABSTRACT

Objective: To identify the Doppler echocardiographic criteria able to predict clinical deterioration of mild-to-moderate chronic heart failure (CHF) as well as, whenever possible, to evaluate the features of chronological relation of cavitory remodelling in left chambers during follow-up (FU).

Methods: A retrospective, case-controlled study, including a number of CHF II NYHA class patients, was carried out, to evaluate, by means of univariate and multivariable logistic regression analyses, the role as predictor of CHF worsening of some Doppler echocardiographic parameters, listed as follows: left ventricular mass index, analyzed both as continuous and as dichotomous ($>130 \text{ g/m}^2$) variable; left ventricular end-systolic volume (LVESV) $>57 \text{ ml}$; left ventricular ejection fraction (LVEF), divided into 2 classes: a) LVEF $>45\%$, i.e. normal or mildly impaired LVEF, and 2) reduced (45%-30%) LVEF; restrictive left ventricular filling pattern (RFP); antero-posterior left atrial diameter (LADi) $>50 \text{ mm}$; ratio of early mitral inflow to early myocardial velocity >8 .

Results: Of 173 patients enrolled, 60 patients (15 cases of transition to III NYHA class and 45 controls) were included in retrospective analysis. At univariate analysis, RFP and LADi $>50 \text{ mm}$ were shown to be associated with worsening of CHF. At multivariate analysis, the role of prognostic indicator of poor outcome was maintained by RFP (OR=17.0, 95%CI: 2.5-116.5) as well as by LADi $>50 \text{ mm}$ (OR=7.95, 95%CI: 1.27-49.6). On the other hand, in the subset of CHF with LVEF $>45\%$, increased LADi was not associated with occurrence of increase in LVESV or left ventricular progressive dilation during the subsequent follow-up.

Conclusions: In mild-to-moderate CHF, RFP and LADi $>50 \text{ mm}$ are predictors of adverse outcome, independently of the presence or severity of left ventricular systolic dysfunction. (*Anadolu Kardiyol Derg 2009; 9: 364-70*)

Key words: Heart failure, diastolic function, echocardiography, prognosis, predictive models

Özet

Amaç: Hafif-orta kronik kalp yetersizliği (KKY) klinik kötüleşmesinin belirlenmesi için Doppler ekokardiyografik kriterlerin saptanması. Ayrıca, mümkün olduğunca da takip süresinde sol odacıkların kavite remodelling'inin zamanla görünümünün değerlendirilmesi.

Yöntemler: Retrospektif, olgu-kontrol çalışmasında KKY NYKD sınıf II hastalar alınarak incelendi ve Doppler ekokardiyografik kriterlerinin KKY klinik kötüleşmesinin öngörme değerleri tek-yönlü ve çok-yönlü lojistik regresyon analizleri ile değerlendirildi. Aşağıda listesi verilen bazı Doppler ekokardiyografik parametreler KKY'nin kötüleşme parametreleri olarak analiz edildi; sol ventrikül sistol sonu volümü (SVSSV) $>57 \text{ ml}$; sol ventrikül ejeksiyon fraksiyonu (SVEF), iki sınıfa ayrılarak: a) SVEF $>45\%$ (normal ya da hafif bozuk SVEF) ve b) azalmış ($45\%-30\%$) SVEF; restriktif sol ventrikül doluş örneği (RDÖ); ön-arka sol atriyum çapı (SAÇ) $>50 \text{ mm}$; erken mitral doluşunun erken miyokard velositesine oranı >8 .

Bulgular: Yüz yetmiş üç hasta alındı, bunların 60'ı (15 olgu NYKD sınıf III'e geçti ve 45 kontrol) retrospektif analize dahil edildi. Tek-yönlü analizde, RDÖ ve SAÇ $>50 \text{ mm}$ KKY kötüleşmesi ile birlikte görüldü. Çok-yönlü analizde (RDÖ) (OR=17.0, %95 CI:12.5-116.5), ayrıca da SAÇ $>50 \text{ mm}$ (OR=7.95, %95 CI:1.27-49.6) kötü sonuçların prognostik belirlemede de rolü olduğu anlaşıldı. Diğer taraftan, takip sırasında sol ventrikül ilerleyici dilatasyonu ya da SVSSV'unda artmasında SVEF $>45\%$ ve SAÇ'ın belirleyici rolü tespit edilmedi.

Sonuç: Hafif-orta KKY'inde RDÖ ve SAÇ $>50 \text{ mm}$ sol ventrikül disfonksiyonunun varlığı ya da şiddetinden bağımsız kötü sonuçların belirleyicisidir. (*Anadolu Kardiyol Derg 2009; 9: 364-70*)

Anahtar kelimeler: Kalp yetersizliği, diyastolik fonksiyon, ekokardiyografi, prognoz, prediktif modeller

Address for Correspondence / Yazışma Adresi: Renato De Vecchis, MD, Cardiology Unit, Presidio Sanitario Intermedio "Elena d' Aosta", Naples, Italy
Phone: +39 081 7516932 E-mail: r.de.vecchis@alice.it

©Telif Hakkı 2009 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.
©Copyright 2009 by AVES Yayıncılık Ltd. - Available on-line at www.anakarder.com

Introduction

The chronic heart failure (CHF) can have very long course. Thus, the planning of observational cohort studies, aimed to recruit the patients in early stage of disease and employing the mortality as endpoint, should provide for pluriennial duration of follow-up, in order to allow the researcher to observe a large enough set of cases (1). This problem can be bypassed by adopting, instead of mortality, as deputy endpoint, the transition from II to III NYHA CHF class. On the other hand, in our experience, the CHF outpatients are shown to be affected, for the most part, by hypertensive or diabetic, or hypertensive-diabetic heart disease, or merely affected by reduction, old age-related, in cardiac performance (i.e., by structural and functional deterioration descending from variable and combined effect exercised by fibrosis, hypertrophy with fibrocellular disarray, hibernating myocardium, apoptosis, all separately or simultaneously operating in elderly heart). That can imply the occurrence of some echocardiographic findings which do not faithfully reproduce the clinical and ultrasonographic pattern usually found associated with the most widely studied CHF clinical models(2), as those related to coronary artery disease, idiopathic dilated cardiomyopathy and rheumatic valvular diseases.

Several studies have documented that left ventricular ejection fraction (LVEF), i.e. the echocardiographic criterion of left ventricular (LV) function (3) most frequently used for predict the outcome in CHF patients, does not reach a reliable predictive accuracy for either sudden arrhythmic death (4-6) or death due to progressive heart failure (7). There is an obvious need for other ultrasonographic risk markers of cardiac death and /or clinical deterioration of heart failure. Among the putative criteria able to predict a worse clinical outcome, the restrictive left ventricular filling pattern (RFP) (8-9) and increased antero-posterior left atrial diameter (10, 11) have been recently proposed as promising landmarks of prognostic assessment, especially able to identify a poor prognosis in the setting of "diastolic" CHF. However, whether the diastolic filling patterns or increase in left atrial antero-posterior diameter could predict worsening of NYHA class in heart failure patients is not well established.

Our purpose was to evaluate the predictive value with respect to cardiac death or clinical deterioration (transition to III NYHA class) exhibited by some echocardiographic parameters as well as to investigate their possible role as predictors of morpho-volumetric changes in cardiac chambers, as typically occurring in CHF-related structural remodeling of heart.

Methods

Between April 2000 and January 2001, all consecutive CHF II NYHA class outpatients, who had undergone a clinical assessment coupled to one at least Doppler echocardiogram at Division of Cardiology of our Institute, were included in our study (n=203 pts).

As prerequisite for inclusion in our study, the location of each patient in CHF II NYHA class was established. On the other hand, the following exclusion criteria were established: CHF

clinical onset dating from less than three months; hemodynamically significant mitral stenosis; pericardial diseases; significant extracardiac illness; age more than 80 years; echocardiographic finding of LVEF <30% and /or Doppler finding of pulmonary artery pressure (PAP) >70 mm Hg.

Follow-up

For our study, we chose a retrospective case-controlled study design. The sample population of both cases and controls was taken from the same cohort of II NYHA class outpatients prospectively followed up by our Center (so-called "nested" case-control study). Furthermore, we stated the study follow-up have to be prolonged until to a suitable number of cases of CHF clinical deterioration and/or cardiac death were collected.

A total of 173 patients from April 2000 to May 2007 were included in the study (median follow-up -72 months).

The following risk factors were investigated:

- left ventricular ejection fraction (LVEF), expressed as continuous and categorical variable; for use of LVEF as categorical variable, we stated the following two classes should be employed: 1) normal or mildly impaired - LVEF>45% and 2) reduced LVEF, i.e., in our case record, LVEF ranging from 45 to 30%
- left ventricular end systolic volume (LVESV)>57 ml
- left ventricular mass index (LVMI), expressed as continuous and dichotomous (LVMI>130 g/m²) variable
- antero-posterior left atrial diameter (LADi)>50 mm
- deceleration time (DT) of early Doppler mitral valve flow velocity <120 msec and ratio of early (E) to late (A) transmitral flow velocity (E/A ratio) >2-this combined finding being qualified as "restrictive LV filling pattern"(RFP)
- ratio of E flow velocity divided by early (E') LV basal longitudinal myocardial lengthening velocity (E/E' ratio) >8 - as deduced by combined use of transmitral conventional Doppler echocardiography (E) and tissue Doppler imaging (E').

Echocardiography

The Doppler echocardiographic 2-dimensional images were obtained by using commercially available equipment(Vivid 7, General Electrical Medical Systems, Horten, Norway) and using a 3-MHz phased array probe. Gray scale images were acquired at a frame rate between 50 and 70 per second, and the digital loops were subsequently stored up by employing an optical disc for offline analysis (EchoPac 6.0, General Electric Medical Systems). End-systolic and end-diastolic LV volumes were calculated from the apical 4- and 2-chamber views, and EF was calculated using the method of discs approach- Simpson's biplane rule (3). Frame-by-frame tracking of speckles throughout the LV wall over the cardiac cycle was employed to calculate the waveforms of segmental strain and strain rate and to derive the early (E') LV basal longitudinal myocardial lengthening velocity, as needed for measurement of E/E' ratio.

Study design

The kind of our study was a retrospective case-controlled study. The dependent variable was represented by exitus and/or

worsening of CHF (the latter namely lying in transition to clinical pattern of III NYHA class, characterized by dyspnea and/or palpitations due to minimal physical efforts, with regression (disappearance) of symptoms induced by rest in the bed or sitting in armchair).

We stated for every case of death or transition to III NYHA class a suitable number of controls should be enrolled, the draw being derived from the same population of CHF II NYHA class patients followed up at our Center (so-called "nested" case-control study). The controls were matched for age, sex and tobacco smoking use. Moreover, the controls had to be characterized by follow-up as long as cases.

Statistical analysis

Statistical analysis was performed using EPI INFO (version 3.3 for Windows, from Center for Disease Control and Prevention, Atlanta, USA) software. Data were reported as mean \pm SD and ratios. The comparison of categorical variables was accomplished using Chi-square test and continuous variables were compared using unpaired t test.

Sample size

In our study, whenever a case of clinical deterioration had been signaled and a shift into III NYHA class had been documented, a number of controls (from one to three) were recruited. In addition, we stated that for admission to final statistic analysis, every control should have maintained a II NYHA class stable condition for a period as long as that needed to be spent before the diagnosis of transition to III NYHA class was made in matched corresponding case. By using a confidence interval of 95% (i.e. $\alpha=0.05$) and by assuming, on the basis of epidemiologic literature data (12-13), a frequency of exposure to risk factors equal to 20% in controls and 75% in cases (expected odds ratio=12), we considered 3 controls for each case and 10 cases at least should be recruited, in order to allow the study to attain the statistic power of 80%. On the whole, we calculated 40 patients at least (10 cases and 30 controls) should be entered in statistical analysis. A higher value (1:2 or 1:1) of case: control ratio was thought as plausible only if sample of cases included more than 20 units.

Logistic regression analysis

In our study, univariate and multivariate not conditional logistic regression analyses were performed. For the prediction of dependent variables, represented by: 1) worsening of CHF and/or 2) cardiac death, independent variables entered into the model were LVEF, LVEF>45%, LVEF ranging from 45% to 30%, LVESV>57 ml, LVMI, LVMI>130g/m², LADi>50 mm, RFP, and E/E'>8. The effects of the factors investigated are given as odds ratios with 95% confidence intervals.

For analysis, some variables were evaluated as dichotomous variables (LVESV>57 ml, LADi>50 mm, RFP, E/E'>8), whereas LVEF and LVMI were evaluated as continuous (LVEF, LVMI) and as categorical (LVEF>45%, LVEF ranging from 45% to 30%, LVMI>130g/m²) variables.

In addition to risk analysis in the total study population, pre-defined subgroup analysis was carried out separately for patients

with LVEF>45% and for those with LVEF \leq 45%. The cut-off points for risk variables were pre-defined on the basis of cut-off points used in previous studies. By means of these cut-off values, we derived a number of 2X2 contingency tables, aimed to identify the respective levels of sensitivity, specificity, positive and negative predictive value, as well as the respective values of positive and negative likelihood ratio and diagnostic odds ratio.

Results

The duration of follow-up was prolonged until May 2007 (median follow-up-72 months). Thirty patients were censored, as being lost at follow-up; therefore, among 173 patients followed up at our Center until the end of study follow-up, we could document one case of cardiac death (sudden) plus 14 cases of irreversible transition to III NYHA class. By considering the need of three controls for every case of death or transition to more severe NYHA class, we restricted final analysis to 15 ascertained cases on the whole, plus corresponding controls, the latter being matched with the former for age, sex, tobacco smoking use and duration (months) of follow-up. Thus, the final analysis included a sample of 60 patients (15 cases and 45 controls), of whom 28 were females. The mean age was 75 \pm 12 years (Table 1).

The odds ratios analyzed in the study are listed in Table 2. At univariable analysis, RFP (OR=19.5 95%CI 4.40-86.26 p=0.0001) and LADi>50 mm (OR=11.40 95%CI 2.83-45.84 p=0.0006) were shown to be associated with worsening CHF.

At multivariate analysis, the role of prognostic indicator of poor outcome was maintained by RFP (OR=17 95%CI: 2.49-116.57 p=0.0038) as well as by LADi>50 mm (OR=7.95 95%CI: 1.275-45.59, p=0.0264). By using the 2X2 contingency table, the 6 patients with RFP, which not have developed LADi>50 mm, were shown to have a large odds of adverse outcome, compared to patients free from RFP and LADi>50 mm (OR=36).

Moreover, among the remaining 8 patients with RFP joined with LADi>50 mm, 6 were absolutely falling into III NYHA class (odds of adverse outcome=6/2=3); whereas, among the remaining 6 patients with left atrial enlargement but free from RFP, the transition to III NYHA class was found in 3/6 cases (odds of adverse outcome=3/3=1), thus the combined finding of RFP plus LADi >50 mm being demonstrated to multiply by 3 the strength of association between LA marked dilation and clinical worsening, although it did not attain a significant p-value (OR=3.0, p=0.342). The adjusted OR (by Mantel -Haenszel method) was calculated to be equal to 8.77, the crude OR value being estimated to be equal to 19.50. Consequently, as crude OR was exceeding Mantel Haenszel adjusted OR by more than 10%, we qualified the variable LADi>50 mm as confounding variable. We used in this case the definition of positive confounding, because the confounding effect was inducing an overestimation of the magnitude of the association between the other two variables (RFP and adverse outcome), i.e. the crude OR estimate was further away from 1.0 than it would be if confounding were not present.

A further logistic regression analysis, separately performed in normal and depressed LVEF subsets, confirmed again the role

Table 1. Clinical characteristics of patients

Variables	Worsening CHF or death (n=15)	Neither worsening CHF nor death (n=45)	Total (n=60)	*p
Male, n	7	23	30	0.99
Age, years	78±4	77±5	77±6	0.485
Main Disease				
Hyp, n	5	16	21	0.876
CHD, n	2	8	10	0.30
Diabetes, n	3	8	11	0.28
Previous AMI, n	2	7	9	0.322
DCM, n	1	4	5	0.409
HCM, n	1	2	3	0.434
AoSt, n	1	0	1	0.25
Therapy				
Beta-blockers, n	10	32	42	0.99
ACE-inhibitors, n	13	37	50	0.30
Loop diuretics, n	10	11	21	0.0078
Nitrates, n	5	6	11	0.178
Digitalis, n	2	8	10	0.30
Calcium channel blockers, n	1	5	6	0.366
Data are represented as proportions and mean±SD				
*Chi- square and unpaired t tests				
AMI-acute myocardial infarction, AoSt- aortic valve degenerative calcific stenosis, CHD - coronary heart disease, DCM - idiopathic dilated cardiomyopathy, HCM - hypertrophic cardiomyopathy, Hyp -hypertensive heart disease				

of both RFP and LADi as markers of increased risk of worsening CHF, irrespective of normal or abnormal LVEF values.

A very high level of sensitivity (86.6%), able to predict the transition to III NYHA class, was achieved by $E/E' > 8$, which was coupled, however, with inadmissibly low (20.9%) level of specificity, thereby resulting in diagnostic odds ratio (DOR) calculated equal to 1.72 (Table 3). The parameters, which were shown to have a high predictive value, were $LADi > 50$ mm and RFP. The former exhibited sensitivity and specificity values respectively equal to 66 and 88.3%, both concurring to generate a positive likelihood ratio of 5.17 coupled with DOR estimated equal to 11.4 ($p = 0.0005$ as desumed from Fisher exact test). The RFP predictive performance was characterized in turn by sensitivity of 66.6% joined with specificity of 90.6%, which both contributed to obtain a positive likelihood ratio of 7.16, thereby producing a DOR value estimated equal to 19.5 ($p < 0.0003$, Fisher exact test).

Discussion

In our study, adverse outcome (=functional decline with "worsening CHF) in mild-to-moderate CHF patients is predicted by manifest disturbances of Doppler velocimetric mitral pattern (RFP) as well as by left atrial structural changes ($LADi$ diameter > 50 mm), i.e. by echocardiographic parameters usually employed as indicators of apparent "isolated" or prevailing

diastolic dysfunction, if even repeated measurements have documented normal or only mildly decreased LVEF values.

The search for echocardiographic predictors of adverse outcome continuously develops in the scenario of novel knowledge arising from routine use in clinical practice of more and more complex technologies and diagnostic algorithms. On the one hand, in mild-to-moderate chronic heart failure our study shows the poor predictive value of LVEF ranging from 45 to 30% as marker of clinical deterioration (particularly, the poor correlation of this parameter with seriousness of clinical picture and cardiopulmonary functional impairment seems to be documented); on the other hand, the study highlights the good predictive value of adverse outcome seen associated with RFP and/or left atrial enlargement (i.e. antero-posterior diameter longer than 50 mm). These results may be due to particular composition of case-record as characterized by high percentage of hypertensive and diabetic heart disease. Actually, in the further (14-17) as well as in the latter (18-23) condition, the pattern of left ventricular morphological and ultrastructural changes includes mostly a decrease in longitudinal fibers systolic contraction, with almost unchanged or preserved function of radial and circumferential myocardial fibers. Thus, in the set of hypertensive and/or diabetic heart disease, an important distortion and longitudinal oversizing of ventricular chamber (straining along the craniocaudal axis of left ventricle) may occur, together with an increase in left ventricular volumes,

Table 2. Univariate and multivariate Doppler echocardiographic predictors of worsening of CHF: logistic regression analysis

Univariate logistic regression analysis			
	OR	95% CI	p
LVEF, %	1.042	0.958-1.133	0.3319
LVEF>0.45	1.812	0.546-6.007	0.3307
LVEF 45-30%	1.373	0.352-5.351	0.6472
LVESV>57 ml	0.648	0.140-2.999	0.5795
LVMI	1.017	0.989-1.047	0.2262
LVMI>130g/m ²	1.633	0.495-5.382	0.4201
LADi>50mm	11.40	2.835-45.840	0.0006
RFP	19.50	4.408-86.257	0.0001
E/E'>8	1.72	0.327-9.047	0.5216
Multivariable logistic regression analysis			
Variables	OR	95% CI	p
LVEF, %	1.162	0.973-1.387	0.0964
LVEF>0,45	1.934	0.042-87.26	0.7343
LVEF45-30%	25.04	0.70-891.68	0.0773
LVESV>57 ml	0.323	0.026-3.93	0.3757
LVMI	1.017	0.934-1.107	0.6949
LVMI>130g/m ²	1.137	0.026-48.80	0.9466
LADi>50mm	7.952	1.275-45.59	0.0264
RFP	17.041	2.49-116.57	0.0038
E/E' > 8	2.411	0.201-28.81	0.4869

E - peak early mitral valve flow velocity, E'- early LV basal (annular) longitudinal myocardial lengthening velocity, LADi - left atrial antero-posterior diameter, LVEF - left ventricular ejection fraction, LVESV - left ventricular end-systolic volume, LVMI - left ventricular mass index, RFP - restrictive left ventricular filling pattern,

although a reduction in LVEF has not been produced yet, as detectable by means of Simpson's method (3, 24-26), i.e. the most frequently used echocardiographic technique to measure LV global systolic function (the LV volumes being calculated by tracing, from one or two orthogonal apical views, the LV endocardial surface).

In hypertensive and/or diabetic heart disease (27-32) as well as in hypertrophic cardiomyopathy and other diseases causing increase of left ventricular mass (33-34), the involvement of left atrium is early and it descends from propagation of high levels of LV end-diastolic pressure (35-37), which are faithfully reproduced by Doppler velocimetric pattern found in these cases, characterized by E/A ratio >2 and deceleration time(DT)<120 msec, so-called "restrictive left ventricular filling pattern" or RFP (38). The occurrence of RFP has been associated with LV end-diastolic pressure of 20 mm Hg or more (39-41); thus, it should be believed as a consequence and a marker of difficult LA diastolic emptying (35-37); likewise, RFP can be thought to prove the unfavorable remodeling in left atrium has already begun and is ongoing, even if overt LA dilation, defined by antero-posterior dimension of left atrium (LADi) > 50 mm, cannot be detected yet. The combined finding of RFP plus LA enlargement can be assumed as unfavorable result, due to hemodynamic as

well as structural deterioration, induced in CHF patients by left ventricular end-diastolic pressure steadily located at levels of 20 mm Hg or more (42-43).

In the set of patients who exhibits this pattern (hindered LV diastolic emptying plus LA enlargement), the sequence of morphovolumetric changes in left chambers may differ from that seen in dilated cardiomyopathy (ischemic or idiopathic) (39-41).

Actually, in dilated cardiomyopathy, LA enlargement occurs simultaneously or just after LV dilation, whereas, in the set of hypertensive heart disease or diabetic cardiomyopathy, the LA enlargement can be frequently demonstrated, even if distortion and straining along the radial, short axis of left ventricle have not happen yet, and impaired long axis shortening and lengthening only can be detected, by means of tissue Doppler imaging, in the presence of normal values of LVEF (2, 16-23, 30, 43-45).

After the LA has been dilated, the usual outcome is represented by pulmonary bed venous-capillary congestion, which can be not associated with simultaneous occurrence of progressive dilation of left ventricle. Actually, in our experience, derived from prolonged follow-up, the shift towards overt III NYHA class condition didn't be joined with simultaneous finding of depressed LVEF in most cases; moreover, in the cases which not had exhibited a marked depression in LVEF, even if involved by clinical deterioration attaining the features of III NYHA class, LVEF, as measured during the subsequent follow up, was documented to steady at normal or only mildly impaired values, as those found before the transition to III NYHA class.

Thus, we can affirm in chronic heart failure with normal or only mildly reduced LVEF, RFP and/or LADi > 50 mm are able to indicate increased risk of clinic and hemodynamic deterioration (transition to III NYHA class), but not are predictors of succeeding increase in LV volumes or decrease in LVEF during subsequent follow-up.

Study limitations

The observational nature of the study design may produce an endpoint bias and not allow definite conclusions to be reached about the clinical utility of the ultrasonographic variables tested as specific predictors of worsening CHF. It is still possible that small size of sample could have biased the relevance of the results.

Conclusions

On the basis of our data, the following conclusions can be drawn:

1) The search for a reduced LV systolic function, which is solely or mainly effected by measuring the LVEF by means of Simpson's method, can generate erroneous conclusions, as the exclusion of systolic function impairment in the cases of mild-to-moderate CHF in which the LVEF, repeatedly measured, has been shown to be normal or only mildly decreased ($\geq 45\%$);

2) In our experience, RFP and LA antero-posterior dimension (LADi) >50 mm have been demonstrated to predict a worse clinical outcome;

Table 3. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio(LR+), negative likelihood ratio (LR-), and diagnostic odds ratio (DOR) of several variables indicating risk of worsening of CHF

Variables	Sensitivity, %	Specificity, %	PPV, %	NPV, %	LR+	LR-	DOR
LVEF>0.45	46.6	67.4	33.3	78.3	1.43	0.79	1.81
LVEF 45-30%	53.3	32.6	21.6	66.6	0.79	1.43	0.55
LVESV>57 ml	80	13.9	24.5	66.6	0.93	1.43	0.648
LVMI>130 g/m ²	46.6	65.1	31.8	77.7	1.339	0.82	1.633
LADi>50 mm	60	88.3	64.2	86.3	5.17	0.453	11.4
RFP	66.6	90.6	71.4	88.6	7.16	0.367	19.5
E/E'>8	86.6	20.9	27.6	81.81	1.096	0.636	1.72

E - peak early mitral valve flow velocity, E' - early LV basal (annular) longitudinal myocardial lengthening velocity, LADi - left atrial antero-posterior diameter, LVEF - left ventricular ejection fraction, LVESV - left ventricular end-systolic volume, LVMI - left ventricular mass index, RFP - restrictive left ventricular filling pattern,

3) In mild-to-moderate CHF, adverse outcome (functional decline with “worsening CHF”) can be predicted by manifest disturbances of Doppler velocimetric mitral pattern (RFP) or by left atrial structural changes (LADi>50 mm), i.e. by echocardiographic parameters usually employed as indicators of apparent “isolated” or prevailing diastolic dysfunction, if even repeated LVEF measurements have documented normal or only mildly decreased values.

References

- Bowers D, House A, Owens D. Come leggere e capire uno studio clinico. Del Corno F, Cotti F, Villa L, translators. Italy: Raffaello Cortina editore; 2004. [authorized translation by from original English language edition Bowers D, House A, Owens D. Understanding clinical papers. John Wiley & Sons Ltd: 2001.]. Italian.
- El-Menyar AA, Galzerano D, Asaad N, Al-Mulla A, Arafa SEO, Al Suwaidi J. Detection of myocardial dysfunction in the presence of normal ejection fraction. *J Cardiovasc Med* 2007; 8: 923-33.
- Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005; 18: 1440-63.
- Huikuri HV, Mäkikallio TH, Raatikainen MJ, Perkiömäki J, Castellanos A, Myerburg RJ. Prediction of sudden cardiac death: appraisal of the studies and methods assessing the risk of sudden arrhythmic death. *Circulation* 2003; 108: 110-5.
- Ezekowitz JA, Armstrong PW, McAlister FA. Implantable cardioverter defibrillators in primary and secondary prevention: a systematic review of randomized, controlled trials. *Ann Intern Med* 2003; 138: 445-52.
- Buxton AE. The clinical use of implantable cardioverter defibrillators: Where are we now? Where should we go? *Ann Intern Med* 2003; 138: 512-4.
- Kearney MT, Fox KA, Lee AJ, Prescott RJ, Shah AM, Batin PD et al: Predicting death due to progressive heart failure in patients with mild-to-moderate chronic heart failure. *J Am Coll Cardiol*. 2002; 40: 1801-8.
- Somarathne JB, Whalley GA, Poppe KK, Gamble GD, Doughty RN. Pseudonormal mitral filling is associated with similarly poor prognosis as restrictive filling in patients with heart failure and coronary heart disease: a systematic review and meta-analysis of prospective studies. *J Am Soc Echocardiogr*. 2009 Mar 21. [Epub ahead of print]
- Meta-analysis Research Group in Echocardiography (MeRGE) Heart Failure Collaborators. Collaborators (140): Doughty RN, Gamble GD, Poppe KK, Somaratne JB, Whalley GA, Doughty RN, et al. Independence of restrictive filling pattern and LV ejection fraction with mortality in heart failure: an individual patient meta-analysis. *Eur J Heart Fail* 2008; 10: 786-92.
- Kizer JR, Bella JN, Palmieri V, Liu JE, Best LG, Lee ET et al. Left atrial diameter as an independent predictor of first clinical cardiovascular events in middle-aged and elderly adults: The Strong Heart Study (SHS). *Am Heart J* 2006; 151: 412-8.
- Danzmann LC, Bodanese LC, Köhler I, Torres MR: Left atrioventricular remodeling in the assessment of the left ventricle diastolic function in patients with heart failure: a review of the currently studied echocardiographic variables. *Cardiovasc Ultrasound* 2008;6: 56.
- Dean AG, Arner TG, Sangam S, Sunki GG, Friedman R, Lantinga M, et al. Programmi complementary. In: *Manuale di EpiInfo* edizione italiana. Epi Edizioni (Italy): 2005. p. 185-95. [authorized translation from EpiInfo tm user’s manual , version 3.3 for Windows Atlanta: Centers for Disease Control; 2002]. Italian.
- Feinstein AF. *Clinical biostatistics*. St Louis: Mosby; 1977.
- Wang M, Yip GW, Wang AY, Zhang Y, Ho PY, Tse MK et al. Tissue Doppler imaging provides prognostic value in patients with systemic hypertension and left ventricular hypertrophy. *J Hypertens* 2005; 23: 183-91.
- Waggoner AD, Bierig SM. Tissue Doppler imaging: a useful echocardiographic method for the cardiac sonographer to assess systolic and diastolic ventricular function. *J Am Soc Echocardiogr* 2001; 14: 1143-52.
- Vinereanu D, Nicolaidis E, Tweddel AC, Fraser AG. ‘Pure’ diastolic dysfunction is associated with long-axis systolic dysfunction. Implications for the diagnosis and classification of heart failure. *Eur J Heart Fail* 2005; 7: 820-8.
- Poulsen SH, Andersen NH, Ivarsen PI, Mogensen CE, Egeblad H. Doppler tissue imaging reveals systolic dysfunction in patients with hypertension and apparent “isolated” diastolic dysfunction. *J Am Soc Echocardiogr* 2003; 16: 724-31.

18. Marwick TH. Tissue Doppler imaging for evaluation of myocardial function in patients with diabetes mellitus. *Curr Opin Cardiol* 2004; 19: 442-6.
19. Hansen A, Johansson BL, Wahren J, von Bibra H. C-peptide exerts beneficial effects on myocardial blood flow and function in patients with type 1 diabetes. *Diabetes* 2002; 51: 3077-82.
20. Fang ZY, Yuda S, Anderson V, Short L, Case C, Marwick TH. Echocardiographic detection of early diabetic myocardial disease. *J Am Coll Cardiol* 2003; 41: 611-7.
21. Andersen NH, Poulsen SH, Eiskjaer H, Poulsen PL, Mogensen CE. Decreased left ventricular longitudinal contraction in normotensive and normoalbuminuric patients with type II diabetes mellitus: a Doppler tissue tracking and strain rate echocardiography study. *Clin Sci (Lond)* 2003; 105: 59-66.
22. Vinereanu D, Nicolaidis E, Tweddel AC, Madler CF, Holst B, Boden LE, et al. Subclinical left ventricular dysfunction in asymptomatic patients with type II diabetes mellitus, related to serum lipids and glycated hemoglobin. *Clin Sci (Lond)* 2003; 105: 591-9.
23. Fang ZY, Leano R, Marwick TH. Relationship between longitudinal and radial contractility in subclinical diabetic heart disease. *Clin Sci (Lond)* 2004; 106: 53-60.
24. Schiller NB, Shah P, Crawford M, De Maria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two dimensional echocardiography. American Society of Echocardiography. Committee on Standards, Subcommittee on Quantitation of two-dimensional echocardiograms. *J Am Soc Echocardiogr* 1989; 2: 358-67.
25. Nicolosi GL. Trattato di ecocardiografia clinica. Italy: Piccin Padova; 1999. Italian. 26) Quinones MA, Waggoner AD, Reduto LA, Nelson JG, Young JB, Winters WL Jr, et al. A new, simplified and accurate method for determining ejection fraction with two-dimensional echocardiography. *Circulation* 1981; 64: 744-53.
27. van Hoesen KH, Factor SM: A comparison of the pathological spectrum of hypertensive, diabetic, and hypertensive-diabetic heart disease. *Circulation* 1990; 82: 848-55.
28. Grossman E, Messerli FH. Diabetic and hypertensive heart disease. *Ann Intern Med* 1996; 125: 304-10.
29. Factor SM, Borczuk A, Charron MJ, Fein FS, van Hoesen KH, Sonnenblick EH. Myocardial alterations in diabetes and hypertension. *Diabetes Res Clin Pract* 1996; 31 Suppl: S133-42.
30. Marwick TH: Diabetic heart disease. *Heart* 2006; 92: 296-300.
31. Thomas L, Levett K, Boyd A, Leung DY, Schiller NB, Ross DL. Changes in left atrial function with aging: evaluation by Doppler tissue imaging. *Eur J Echocardiogr* 2003; 4: 92-100.
32. Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Roedeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA* 2003; 289: 194-202.
33. Pinamonti B, Di Lenarda A, Nucifora G, Gregori D, Perkan A, Sinagra G. Incremental prognostic value of restrictive filling pattern in hypertrophic cardiomyopathy: a Doppler echocardiographic study. *Eur J Echocardiogr* 2008; 9: 466-71.
34. de Simone G, Gottdiener JS, Chinali M, Maurer MS. Left ventricular mass predicts heart failure not related to previous myocardial infarction: the Cardiovascular Health Study. *Eur Heart J* 2008; 29: 741-7.
35. Prioli A, Marino P, Lanzoni L, Zardini P. Increasing degrees of left ventricular filling impairment modulate left atrial function in humans. *Am J Cardiol* 1998; 82: 756-61.
36. Dernelis JM, Stefanadis CI, Zachaurolis AA, Toutouzas PK. Left atrial mechanical adaptation to long standing hemodynamic loads based on pressure-volume relations. *Am J Cardiol* 1998; 81: 1138-43.
37. Rossi A, Zardini P, Marino P. Modulation of left atrial function by ventricular filling impairment. *Heart Fail Rev* 2000;5: 325-31.
38. Paulus WJ, Tschöpe C, Sanderson JE, Rusconi C, Flachskampf FA, Raademakers FE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J* 2007; 28: 2539-50.
39. Pinamonti B, Di Lenarda A, Sinagra G, Camerini F. Heart Muscle Disease Study Group: Restrictive left ventricular filling pattern in dilated cardiomyopathy assessed by Doppler echocardiography: clinical, echocardiographic and haemodynamic correlations and prognostic implications. *J Am Coll Cardiol* 1993; 22: 808-15.
40. Giannuzzi P, Imparato A, Temporelli PL, de Vito F, Silva PL, Scapellato F, et al. Doppler-derived mitral deceleration time as early filling as a strong predictor of pulmonary capillary wedge pressure in postinfarction patients with left ventricular systolic dysfunction. *J Am Coll Cardiol* 1994; 23: 1630-7.
41. Temporelli PL, Scapellato F, Corrà U, Eleuteri E, Imparato A, Giannuzzi P. Estimation of pulmonary wedge pressure from transmitral Doppler in patients with chronic heart failure and atrial fibrillation. *Am J Cardiol* 1999; 83: 724-7.
42. Revera M, Ghio S. Stima ecocardiografica della pressione di incuneamento polmonare. In: Ghio S, editor. *Ecocardiografia Nella Insufficienza Cardiaca*. Milano: Poletto Editore Gaggiano; 2005. p. 34-8. Italian.
43. Abhayaratna WP, Marwick TH, Smith WT, Becker NG. Characteristics of left ventricular diastolic dysfunction in the community: an echocardiographic survey. *Heart* 2006; 92: 1259-64.
44. Yu CM, Lin H, Yang H, Kong SL, Zhang Q, Lee SW. Progression of systolic abnormalities in patients with 'isolated' diastolic heart failure and diastolic dysfunction. *Circulation* 2002; 105: 1195-201.
45. Nikitin NP, Witte KK, Clark AL, Cleland JG. Color tissue Doppler-derived long-axis left ventricular function in heart failure with preserved global systolic function. *Am J Cardiol* 2002; 90: 1174-7.