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Combined right ventricular systolic and diastolic dysfunction represents a strong determinant of poor prognosis in patients with symptomatic heart failure

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Abstract

Background: The presence of right ventricular systolic dysfunction is known to significantly worsen prognosis of patients with heart failure. However, the prognostic impact of right ventricular diastolic dysfunction and of its combination with right ventricular systolic dysfunction and with other prognostic markers has not yet been systematically studied. The aim of this study was to assess the prognostic impact of combined right ventricular systolic and diastolic dysfunction in patients with symptomatic heart failure due to ischemic or idiopathic dilated cardiomyopathy.

Methods: The study included 177 consecutive patients with symptomatic heart failure (mean left ventricular ejection fraction of 23%). All patients underwent clinical and laboratory examination, standard echocardiography completed by Doppler tissue imaging of the tricuspid annular motion, and right-sided heart catheterization. They were followed up for a mean period of 16 months (range, 1–48 months).

Results: During the follow-up, there were 28 cardiac-related deaths and 35 non-fatal cardiac events (31 hospitalizations for heart failure decompensation and 4 hospitalizations for malignant arrhythmias requiring the implantation of a cardioverter–defibrillator). The multivariate stepwise Cox regression modeling revealed the right ventricular systolic (represented by the peak systolic tricuspid annular velocity—Sa) and diastolic (represented by the peak early diastolic tricuspid annular velocity—Ea) function to be the independent predictors of event-free survival or survival ($p<0.01$). The Sa separated better between patients with and without the risk of cardiac events ($p<0.05$), while the Ea appeared to further distinguish patients with increased risk (those at risk of late event from those at risk of early non-fatal event and early death). The strongest predictive information was obtained by the combination of Sa and Ea creating the Sa/Ea categories. The Sa/Ea I category of patients (Sa$\geq$10.8 cm s^{-1} and Ea$\geq$8.9 cm s^{-1}) had excellent prognosis. On the other hand, the Sa/Ea IV category (Sa<10.8 cm s^{-1} and Ea<8.9 cm s^{-1}) was found to be at a very high risk of cardiac events ($p<0.001$ vs. Sa/Ea I). Imbalanced categories of patients (Sa/Ea II and III) with only one component (Sa or Ea) pathologically decreased were at medium risk when assessing event-free survival. However, a significantly better survival ($p<0.05$) was found in patients with Ea$\geq$8.9 cm s^{-1} (Sa/Ea I and III categories) as compared with those having Ea<8.9 cm s^{-1} (Sa/Ea II and IV categories). Thus, in contrast to event-free survival, the survival pattern was determined mainly by the Ea value with only little additional contribution of Sa.

Conclusions: The assessment of right ventricular systolic and diastolic function provides complementary information with a very high power to stratify prognosis of patients with heart failure. The combination of right ventricular systolic and diastolic dysfunction identifies those with a very poor prognosis.

Keywords: Prognosis; Heart failure; Right ventricular function

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1. Introduction

The prognosis of patients with symptomatic heart failure is poor [1–3]. The identification of variables with the ability to predict a high risk of cardiac events may result in a more aggressive medical or surgical therapy leading to the improvement of patient survival. It is now well established that the right ventricular systolic performance is a powerful predictor of mortality and morbidity in patients with heart failure secondary to ischemic or idiopathic dilated cardiomyopathy [4–6]. However, little is known about the prognostic importance of the right ventricular diastolic function which probably affects the morbidity, but the impact on mortality has not been proven [7]. Previous reports studying the prognostic power of left ventricular function convincingly demonstrated that the combination of significant systolic and diastolic dysfunction provides better prognostic information than does the left ventricular systolic dysfunction alone [7,8]. A similar additive prognostic impact of systolic and diastolic dysfunction can be expected analogically for the right ventricle. The Doppler tissue imaging of the tricuspid annular motion represents a unique opportunity to determine very quickly and simultaneously both the right ventricular systolic and diastolic function by measuring the annular velocities. In our previous report we described the independent prognostic power of the peak systolic tricuspid annular velocity in patients with heart failure [4]. However, its combination with parameters defining the right ventricular diastolic function (the peak early and late diastolic tricuspid annular velocities or their ratio) may provide even more powerful prognostic information. Thus, the purpose of this study was to assess the prognostic power of combined right ventricular systolic and diastolic dysfunction identified by Doppler tissue imaging of the tricuspid annular motion.

2. Materials and methods

2.1. Study population

The study included 177 consecutive patients with symptomatic heart failure (classes II–IV according to the New York Heart Association), who were admitted to our clinic as potential candidates for orthotopic heart transplantation for pre-transplant investigation from May 1999 to May 2003. There were the following inclusion criteria: (a) sinus rhythm on electrocardiography, (b) a good quality of echocardiographic imaging of the tricuspid annular motion, (c) absence of acute coronary event or coronary revascularization within the last 3 months, (d) absence of malignancy, advanced liver, renal, and lung disease, (e) no need for myocardial revascularization or urgent heart transplantation. Fourteen patients not stabilized on hospital admission (resting dyspnea, need for parenteral diuretics or catecholamine support, ankle edema, rales on lung auscultation) were investigated and included in the study after cardiac compensation. We excluded 5 patients with bad quality of echocardiographic imaging of the tricuspid annular motion, and 4 patients with valvular disease. The etiology of heart failure was ischemic cardiomyopathy (≥70% angiographically verified luminal diameter narrowing of at least one major coronary artery or documented myocardial infarction—98 patients) or idiopathic dilated cardiomyopathy (79 patients). The diagnosis of idiopathic cardiomyopathy was made on the basis of echocardiography, electrocardiography (no Q waves) and clinical criteria; in 30 patients above 40 years of age with risk factors for coronary artery disease, the absence of coronary artery disease was confirmed by coronary angiography. Of patients with ischemic cardiomyopathy, 21 had a history of coronary artery bypass surgery. The clinical characteristics of the patient population are listed in Table 1. Medical therapy was optimized before entering the study. One hundred and sixty-six (94%) patients were taking angiotensin-converting enzyme inhibitors, 126 (71%) digitalis, 176 (99%) furosemide, 129 (73%) spironolactone, and 132 (75%) beta blockers. In spite of this intensive therapy, the majority of patients were in the New York Heart Association classes III (132, 75%) or IV (6, 3%). Only 39 patients (22%) were in class II. In 45 patients (25%), elective orthotopic heart transplantation was indicated following the initial investigation. On entering the study, the patients underwent physical examination, routine blood chemistry and hematologic measurement, 12-lead electrocardiography, chest radiography, standard echocardiography, Doppler tissue imaging of the tricuspid annular motion, and right-sided heart catheterization. All the patients gave their written consent to the investigation. The study complies with the 1975 Declaration of Helsinki and was approved by the institutional ethics committee.

2.2. Echocardiography

Standard echocardiography and pulsed Doppler tissue imaging of the tricuspid annular motion were obtained in all the patients. We used a SONOS 5500 (Hewlett Packard, Andover, MA, USA) equipment with a phased array transducer of 2.5 MHz, and with a system equipped with Doppler tissue imaging technology. A detailed concept and the technical aspects of Doppler tissue imaging were described previously [9,10]. Doppler tissue measurements were performed with patients in the left lateral decubitus position during shallow respiration or end-expiratory apnea. Guided by the two-dimensional four-chamber view, a sample volume was placed on the tricuspid annulus at the place of attachment of the anterior leaflet of the tricuspid valve. Care was taken to obtain an ultrasound beam parallel to the direction of the tricuspid annular motion. Peak systolic (Sa), peak early (Ea) and late (Aa)

Table 1
Baseline patient characteristics

Parameter	Whole population	Patients without event	Patients with event
Sample size	177	115	62
Range of follow-up (months)[a]	6–45 (28)	8–48 (28)	5–43 (25)
Etiology of heart failure: dilated cardiomyopathy[b]	79 (44.6%)	43 (37.4%)*	36 (58.1%)*
Age (year)[c]	52 (51; 53)	53 (51; 55)	51 (49; 53)
Male sex[b]	147 (83.1%)	97 (84.4%)	50 (80.7%)
Clinical history[b]			
Diabetes mellitus	42 (23.7%)	28 (24.4%)	14 (22.6%)
Systemic hypertension	63 (35.6%)	43 (37.4%)	20 (32.3%)
Hypercholesterolemia	104 (58.8%)	69 (60.0%)	35 (56.5%)
NYHA class			
II	39 (22.0%)	27 (23.5%)	12 (19.4%)
III	132 (74.6%)	86 (74.8%)	46 (74.2%)
IV	6 (3.4%)	2 (1.7%)	4 (6.5%)
Clinical characteristics[c]			
Heart rate (beats min^{-1})	74 (72; 76)	73 (70; 76)	76 (73; 79)
Systolic BP (mm Hg)	118 (116; 120)	119 (117; 121)	116 (113; 119)
Right heart catheterization variables[c]			
PAP (mm Hg)	28 (26; 30)	25 (23; 27)*	34 (31; 37)*
Cardiac index (l min^{-1}/m^2)	2.1 (2.0; 2.2)	2.2 (2.1; 2.3)	2.0 (1.9; 2.1)
RAP (mm Hg)	7 (6; 8)	6 (5; 7)	7 (6; 8)
PCWP (mm Hg)	19 (17; 21)	17 (15; 19)*	24 (21; 27)*
Echocardiographic variables[c]			
Sa (cm s^{-1})	10.7 (10.3; 11.1)	11.3 (10.8; 11.8)*	9.9 (9.3; 10.5)*
Ea (cm s^{-1})	10.3 (9.9; 10.7)	10.6 (10.2; 11.0)	9.8 (9.2; 10.4)
Aa (cm s^{-1})	14.2 (13.5; 14.9)	14.4 (13.6; 15.2)	13.9 (12.6; 15.2)
Ea/Aa	0.81 (0.76; 0.86)	0.81 (0.74; 0.88)	0.81 (0.71; 0.91)
LVEF (%)	23 (22; 24)	24 (23; 25)	23 (21; 25)
LVEDV (ml)	246 (233; 259)	243 (227; 259)	251 (234; 269)
LVESV (ml)	189 (179; 199)	187 (173; 201)	194 (181; 208)
LVEDD (mm)	69 (67; 71)	68 (66; 70)*	72 (70; 74)*
LVESD (mm)	59 (57; 61)	58 (56; 60)*	61 (59; 63)*
RVEDD (mm)	33 (32; 34)	32 (30; 34)*	36 (34; 38)*

NYHA=New York Heart Association; BP=blood pressure; PAP=pulmonary artery pressure; RAP=right atrial pressure; PCWP=pulmonary capillary wedge pressure; Sa=peak systolic tricuspid annular velocity; Ea=peak early diastolic tricuspid annular velocity; Aa=peak late diastolic tricuspid annular velocity; LV=left ventricular; EF=ejection fraction; EDV=end-diastolic volume; ESV=end-systolic volume; EDD=end-diastolic diameter; ESD=end-systolic diameter; RVEDD=right ventricular end-diastolic diameter.

[a] Follow-up: range of 10–90% percentiles with median follow-up time (parentheses).

[b] Binary/categoric variables: numbers (in parentheses % of cases).

[c] Continuous variables: mean supplied with 95% confidence limits.

* Mark for statistically significant difference ($p<0.05$) between patients with or without event.

diastolic tricuspid annular velocities, along with simultaneous electrocardiography, were recorded on videotape at a speed of 50 mm s^{-1} for subsequent analysis. When evaluating peak systolic velocity, the initial peak that occurs during isometric contraction was ignored. All pulsed Doppler tissue imaging parameters were measured on 3–6 consecutive heart cycles and mean value was calculated. The same methodology was applied in our previous study demonstrating a good accuracy and reproducibility of pulsed Doppler tissue imaging of tricuspid annular motion for the non-invasive detection of right ventricular systolic function [11]. In addition to pulsed Doppler tissue imaging, conventional echocardiography was performed, including M-mode, two-dimensional, pulsed and color Doppler echocardiography. Left ventricular ejection fraction was calculated according to the modified Simpson's rule [12].

2.3. Right heart catheterization

One hundred and seventy-one patients underwent right heart catheterization within 24 h of echocardiography. In 6 patients, catheterization was not performed for technical reasons. The investigations were performed via the right subclavian vein or the right jugular vein. A 7F thermodilution catheter (model 131HF7, Baxter Healthcare, Irvine, CA, USA) was inserted through the right heart cavities into the pulmonary capillary wedge position. Measurements of mean right atrial pressure, mean pulmonary artery pressure, and mean pulmonary capillary wedge pressure were obtained with patients in supine position using a mechanoelectrical transducer (model P23XL, Ohmeda Medical Devices Division, Oxnard, CA, USA). Cardiac output was measured by the thermodilution technique. The thermodilution curve was recorded and calculated using a thermodilution module of

the above-mentioned monitor. The cardiac index was calculated as follows: cardiac index (l min^{-1}/m^2)=cardiac output ($l \cdot$min^{-1})/body surface area (m^2).

2.4. Follow-up

The patients were followed up for cardiac mortality and non-fatal cardiac events relating to heart failure such as hospitalization for worsening of heart failure and the need for implantation of a cardioverter–defibrillator due to malignant ventricular arrhythmias. Cardiac death was defined as death due to congestive heart failure, myocardial infarction, malignant arrhythmias or cardiac arrest. In patients who died out of hospital and in whom autopsy was not performed, a sudden unexpected death (within 1 hour of the onset of symptoms) was attributed to a cardiac cause. In the case of patient's death or admission to hospital, the admitting departments or referring physicians were contacted to elucidate the exact reason for hospitalization or cause of death. Only one event was considered in each patient in the following hierarchy: death>need for cardioverter–defibrillator>hospitalization for heart failure. Survival was defined as freedom from cardiac-related death, event-free survival was defined as freedom from combined end-point (cardiac-related death, need for implantation of a cardioverter–defibrillator, hospitalization for heart failure). Since all the patients were referred to our clinic as potential candidates for heart transplantation and echocardiographic results influenced the indication for heart transplantation, this procedure was not considered a cardiac event, and the follow-up of 40 patients who underwent heart transplantation ended with the date of this procedure. The follow-up data were available from all patients and the mean follow-up period was 16 months (range, 1–48 months).

2.5. Statistical analysis

All statistical tests were performed on an intention-to-treat principle and no case was excluded prior to the analyses. A p value<0.05 was taken as a universal indicative limit for statistical significance in all univariate and multivariate analyses. Standard descriptive statistics were used to express the differences among subgroups of cases (mean supplied with 95% confidence limits or relative frequencies). Standard univariate statistical techniques were used to test the differences between the chosen subgroups of patients: Fisher's exact test in binary outcomes, chi-square test for ordinal categoric variables, unpaired Student's t-test for normally distributed continuous variables, and Mann-Whitney test for non–normally distributed continuous variables [13]. Correlation analysis between Sa and other variables was based on a quantitative Pearson's correlation coefficient. Both univariate and multivariate analytic strategy was applied to quantify the predictive power of examined variables to the predefined study end-points: 1, cardiac-related death, 2, combined end-point [14]. The best maximum likelihood estimates of the cut-off values for parameters of interest were obtained by a receiver operating characteristic (ROC) curve analysis [15]. The stratified Kaplan–Meier product-limit method was applied to discriminate the survival rates between two or more subgroups given by potential predictors. The standard Peto-Prentice generalized log-rank test was used as a comparative statistical test. A stepwise multivariate Cox proportional hazard analysis was used as a final model identifying significant predictors of survival or event-free survival. The hazard ratio was estimated within its 95% confidence limits and supported by the significance level. The final set of independent prognostic factors was identified by a backward stepwise selection algorithm.

3. Results

3.1. Clinical, echocardiographic, and right heart catheterization variables

Table 1 demonstrates the clinical, echocardiographic, and right heart catheterization variables in the whole patient population and in patients with or without cardiac events. In patients with cardiac events, the etiology of heart failure was more frequently idiopathic dilated cardiomyopathy. These patients exhibited a higher pulmonary artery pressure and pulmonary capillary wedge pressure on catheterization as well as larger end-diastolic and end-systolic ventricular diameters on standard echocardiography. Doppler tissue imaging of tricuspid annular motion revealed a significantly lower Sa and a tendency of Ea to decrease in patients with cardiac events. The Ea/Aa ratio and Aa values exhibited only negligible differences between patients with and without events. Although there was a significant association between the occurrence of dilated cardiomyopathy and the risk of cardiac events, no diagnostically related differences in Sa, Ea, and Aa values were found, as demonstrated in Table 2. Principally investigated Doppler tissue variables are therefore independent of the etiology of heart failure and could be processed simultaneously without any risk of intrinsic bias due to diagnostic differences.

Table 2
Principally investigated echocardiographic variables as related to the diagnosis

Parameter[a]	Ischemic heart disease	Dilated cardiomyopathy
Sample size	98	79
Sa (cm s^{-1})	10.7 (10.2; 11.2)	10.7 (10.1; 11.3)
Ea (cm s^{-1})	10.0 (9.5; 10.5)	10.6 (10.1; 11.1)
Aa (cm s^{-1})	13.8 (13.0; 14.6)	14.6 (13.6; 15.6)
Ea/Aa	0.82 (0.74; 0.90)	0.79 (0.73; 0.85)

Abbreviations as in Table 1.
[a] Continuous variables: mean supplied with 95% confidence limits.

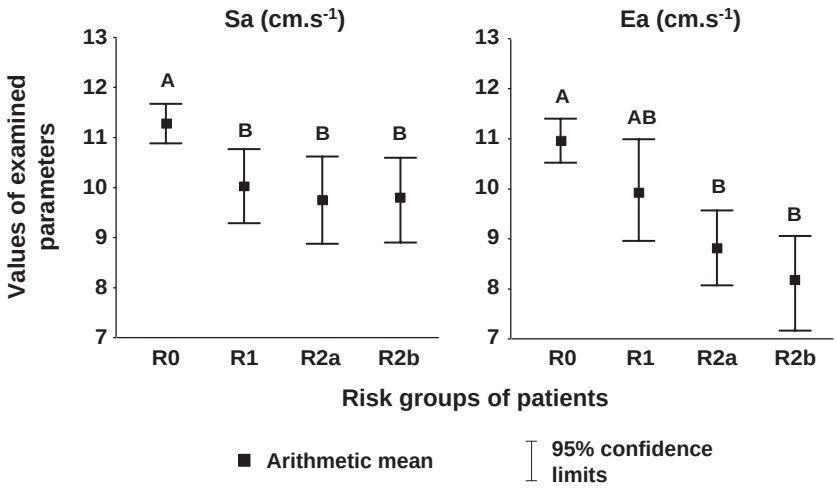

Fig. 1. The values of the peak systolic tricuspid annular velocity (Sa) and of the peak early diastolic tricuspid annular velocity (Ea) in individual risk groups R0–R2. R0—patients without any event, R1—patients with any event occurred after 6 months of follow-up, R2a—patients with early non-fatal event occurred within the first 6 months of follow-up, R2b—patients with early death occurred within the first 6 months of follow-up. A–B: marks for mutual statistical comparison of risk categories R. Variants marked by the same letter are not significantly different ($p<0.05$).

3.2. Follow-up data

Of 177 patients studied, 63 (36%) suffered a cardiac event. There were 28 cardiac-related deaths; 15 patients died from progressive heart failure, 13 died suddenly. Thirty-five patients suffered a non-fatal cardiac event; 31 were hospitalized for heart failure decompensation, 4 because of need for implantation of a cardioverter–defibrillator. No patient underwent myocardial revascularization during the follow-up.

3.3. The relation of tricuspid annular velocities and cardiac events

Based on the occurrence of cardiac events, 4 groups of patients were defined: R0—patients without any event, R1—patients with any event occurred after 6 months of follow-up, R2a—patients with early non-fatal event occurred within the first 6 months of follow-up, and R2b—patients with early death occurred within the first 6 months of follow-up. Fig. 1 demonstrates the Sa and Ea values in the individual risk groups. Unambiguous and significant differences in the values of Sa were found between R0 and the other groups. However, the Sa did not distinguish among the risk categories of R1–R2. In contrast, the Ea did not reveal such clear separation of patients with and without risk of cardiac events as did the Sa, but it appeared to contribute to further discrimination among patients with different risk levels. To define the optimal cut-off values of Sa and Ea discriminating the different risk groups of patients, the ROC analysis was performed. The Sa<10.8 cm s^{-1} indicated any risk value of patients, the Ea<8.9 cm s^{-1} separated effectively only risk groups of patients with early event. In both cases the values of sensitivity and specificity exceeded 72% and cut-off values were found to be statistically significant ($p<0.05$). No further discrimination between groups R2a and R2b was confirmed in ROC analyses, although there was a decreasing trend in Ea values between these groups. The values of Aa and Ea/Aa had a negligible discriminating potential (data

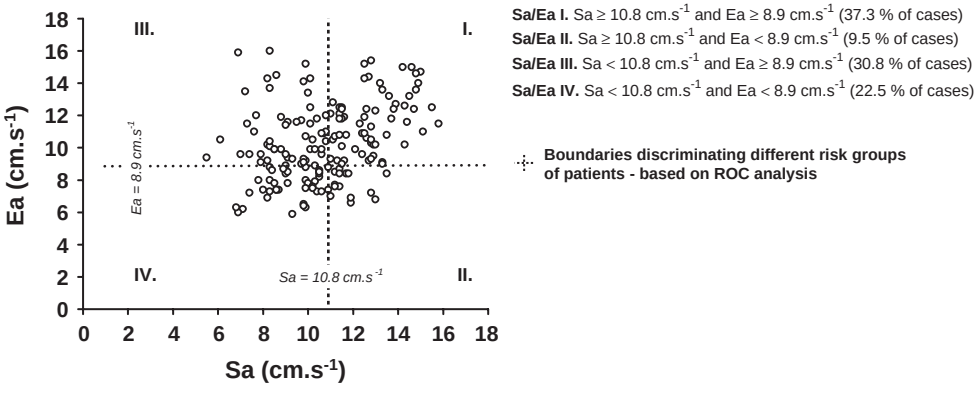

Fig. 2. The distribution of Sa and Ea values and the definition of Sa/Ea categories. Sa—peak systolic tricuspid annular velocity, Ea—peak early diastolic tricuspid annular velocity.

Table 3
Predictive potential of examined variables in univariate Cox regression models

Parameter[a]	Predefined end-points[a]					
	Event-free survival			Survival		
	Relative risk (95% CI)	p value	Survivors/ Non-survivors[b]	Relative risk (95% CI)	p value	Survivors/ Non-survivors[b]
Principally examined echocardiographic variables[c]						
Sa (cm s^{-1})	0.80 (0.72; 0.89)	<0.001	11.3/9.9	0.88 (0.75; 0.98)	0.047	10.9/10.0
Ea (cm s^{-1})	0.87 (0.78; 0.98)	0.021	10.6/9.8	0.78 (0.65; 0.94)	0.005	10.5/9.3
Balanced categories Sa/Ea (cm s^{-1})[c]						
Sa/Ea I. Sa≥10.8 and Ea≥8.9	0.26 (0.13; 0.50)	<0.001	48.6/16.7	0.44 (0.28; 0.91)	0.042	40.1/22.2
Sa/Ea II. Sa≥10.8 and Ea<8.9	1.09 (0.47; 2.54)	0.853	9.2/10.0	1.80 (0.62; 3.21)	0.313	8.5/14.8
Sa/Ea III. Sa<10.8 and Ea≥8.9	1.51 (0.89; 2.53)	0.132	26.6/38.3	0.73 (0.31; 1.72)	0.457	31.8/25.9
Sa/Ea IV. Sa<10.8 and Ea<8.9	2.48 (1.46; 4.24)	<0.001	15.6/35.0	2.46 (1.13; 5.40)	0.031	19.7/37.0
Etiology of heart failure: dilated cardiomyopathy)[d]	2.01 (1.21; 3.33)	0.006	37.4/58.1	1.69 (0.80; 3.57)	0.167	42.3/57.1
Right heart catheterization variables[c]						
PAP (mm Hg)	1.05 (1.03; 1.07)	<0.001	25/34	1.03 (1.01; 1.08)	0.028	27/33
PCWP (mm Hg)	1.06 (1.02; 1.09)	<0.001	17/24	1.04 (1.01; 1.08)	0.024	19/24
Cardiac index (l min^{-1}/m^2)	0.43 (0.23; 0.76)	0.003	2.2/ 2.0	0.53 (0.22; 1.26)	0.139	2.1/2.0
RAP (mm Hg)	1.05 (1.00; 1.11)	0.044	6/7	1.05 (0.97; 1.12)	0.241	7/8
Echocardiographic variables[c]						
LVESD (mm)	1.04 (1.01; 1.08)	0.008	58/61	1.03 (0.98; 1.08)	0.128	59/61
RVEDD (mm)	1.05 (1.01; 1.09)	0.009	32/36	1.03 (0.98; 1.09)	0.223	33/34
LVEDD (mm)	1.05 (1.02; 1.08)	0.021	68/72	1.04 (0.99; 1.08)	0.109	69/71
LVEF (%)	0.96 (0.91; 0.99)	0.042	24/23	0.97 (0.91; 1.04)	0.393	24/23

Abbreviations as in Table 1.
[a] Only models leading to statistically significant relationship (p<0.05) were included in the table. *Event-free survival* combines all risk events including death, *survival* means only death event.
[b] Mean values (continuous variables) or percentage (binary variables) that discriminate between survivors and non-survivors.
[c] Continuous variable.
[d] Binary or categoric variable.

not shown). Fig. 2 demonstrates the distribution of Sa and Ea values and the definition of 4 Sa/Ea categories. It documents that Sa and Ea values can be reasonably combined without the risk of redundancy, because their correlation was weak (correlation coefficient r=0.296). Fig. 2 further shows that all possible combinations are applicable including the contrasting situation with one parameter at high and the other at low values.

3.4. Predictors of cardiac events

The investigated variables (listed in Table 1) were examined as potential predictors of survival study end-points in univariate Cox regression models. Table 3 shows those which contributed significantly (p<0.05) to the time-related predictions of event-free survival or survival. The analysis confirmed the predictive potential of Sa and Ea

Table 4
Survival endpoints in the multivariate stepwise Cox regression modeling[a]

End-point parameters included[b]	Coefficient (SE)	Model Log-likelihood	Log-likelihood ratio test	Relative risk[c] (95% conf. limits)
Model for event-free survival				
Null model		−289.1		
Step 1. Category Sa/Ea I.	−1.224 (0.318)	−276.8	<0.001	0.30 (0.16; 0.54)
Step 2. +PCWP	0.053 (0.012)	−255.8	<0.001	1.05 (1.02; 1.08)
Step 3. +Etiology of heart failure	0.896 (0.202)	−248.2	<0.001	2.45 (1.65; 3.64)
Step 4. +Category Sa/Ea IV.	0.613 (0.197)	−244.9	<0.001	1.85 (1.26; 2.73)
Model for survival				
Null model		−130.9		
Step 1. Category Sa/Ea IV.	0.791 (0.328)	−123.1	0.031	2.21 (1.16; 4.21)
Step 2. +PCWP	0.041 (0.013)	−116.8	0.013	1.04 (1.01; 1.08)

Abbreviations as in Table 1.
[a] Multivariate stepwise procedure was driven only by statistical measures (Log-likelihood function). All models worked with Sa/Ea balanced categories coded as separated binary variables (see also Fig. 2 and Table 3).
[b] Dilated cardiomyopathy is coded as the risk value.
[c] Relative risk associated with variables entered in multivariate models as independent predictors.

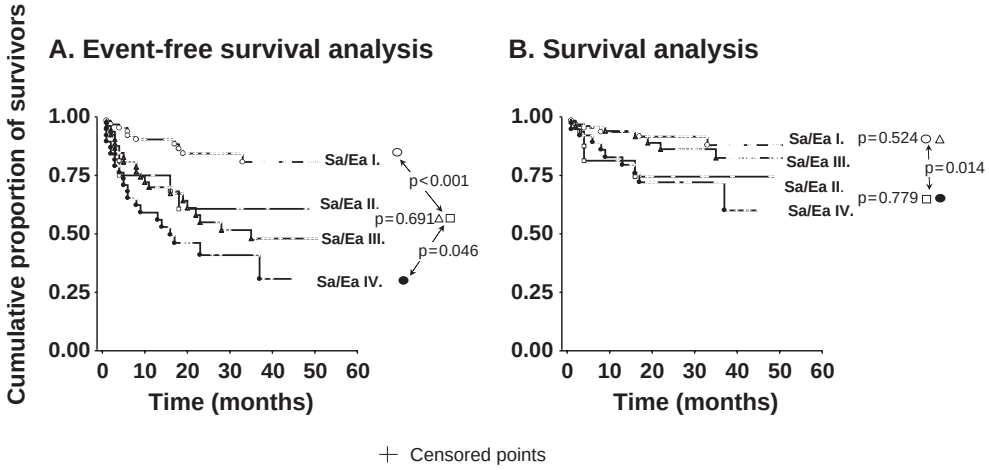

Fig. 3. Event-free survival and survival stratified according to the Sa/Ea categories. Abbreviations as in Figs. 1 and 2.

values and also very important risk-related predictions based on Sa/Ea categories. It is apparent that Ea is more related to cardiac death (i.e. survival) than Sa, while the opposite situation occurs in the case of event-free survival. To define the contribution of single parameters to the final predictions in simultaneous application, the multivariate stepwise Cox regression models were performed. The values of Sa and/or Ea were found to be important independent predictors of event-free survival and survival in all final models. However, the strongest predictive information was found with models using Sa/Ea categories (Table 4).

3.5. Event-free survival and survival stratified according to combined right ventricular functional parameters

Fig. 3 shows the Kaplan–Meier analysis of event-free survival and survival stratified according to Sa/Ea categories. Event-free survival was very significantly driven by categories Sa/Ea I (the lowest risk) and IV (the highest risk). Imbalanced categories with only one pathologically decreased component (Sa or Ea, categories Sa/Ea II and III) fell into the region of medium risk. A different situation occurred in the survival pattern. A significantly better prognosis was found in Sa/Ea I and III categories (both exhibiting Ea≥8.9 cm s^{-1}) as compared with Sa/Ea II and IV categories (both having Ea<8.9 cm s^{-1}, p=0.014). Thus, the survival pattern was determined mainly by the Ea value with only a little additional contribution of Sa.

4. Discussion

4.1. Evaluation of the right ventricular systolic and diastolic function using Doppler tissue imaging

The velocities of the tricuspid annular motion assessed by pulsed-wave tissue Doppler imaging have been repeatedly shown to reflect the right ventricular systolic and diastolic function. The peak systolic tricuspid annular velocity (Sa) reflects the right ventricular systolic function. It has been found to significantly correlate with right ventricular fractional area change (r=0.78, 16) and the right ventricular ejection fraction determined by the first-pass radionuclide ventriculography (r=0.65, 11). The Sa<11.5 cm s^{-1} predicts the right ventricular dysfunction (ejection fraction<45%) with a sensitivity of 90% and a specificity of 85% [11]. Recently, the myocardial acceleration during isovolumic contraction derived from the isovolumic contraction wave pattern has been recommended to assess the right ventricular systolic function because of its relative preload and afterload independence [17].

To assess the right ventricular diastolic function, the peak early diastolic tricuspid annular velocity (Ea) and the peak late tricuspid annular velocity (Aa) as well as their ratio Ea/Aa may be used. A significant decrease in Ea and Ea/Aa was found in many cardiologic diseases or syndromes including heart failure secondary to coronary artery disease or idiopathic dilated cardiomyopathy [11], systemic hypertension [18], Chagas' disease [19], arrhythmogenic right ventricular cardiomyopathy [20], etc. Despite the overt right ventricular diastolic dysfunction, the Aa did not differ significantly from healthy controls in the majority of these studies [11,18–20]. Thus, the Ea or Ea/Aa rather than Aa should be utilized to define the right ventricular diastolic dysfunction. The decrease in Ea and Ea/Aa ratio reflects a worsening of the right ventricular relaxation analogically as a decrease in the corresponding mitral diastolic annular velocities heralds a disturbance in left ventricular relaxation. The right ventricular Ea/Aa ratio was found to significantly correlate to the left ventricular Ea/Aa ratio [18]. The diastolic tricuspid annular velocities are age [21] and right ventricular systolic function [16] dependent. Nageh et al. [16] found a weak inverse relation of Ea and Aa to the right ventricular filling pressures. However, this finding was not confirmed by Sundereswaran et al. [22]. Irrespective of this discrepancy, both authors concordantly stressed the ability of the E/Ea ratio to estimate the mean right atrial pressure (E represents the peak right ventricular inflow velocity in early

diastole). Importantly, there is no "pseudonormalization" of Ea during progressive increase in right ventricular filling pressure [16] indicating that the parameters derived from annular motion are less preload dependent than those derived from transtricuspid flow. None of the diastolic velocities related significantly to heart rate or pulmonary artery pressure [16].

4.2. Prognostic importance of the right ventricular systolic and diastolic function

To date, many reports have clearly demonstrated the prognostic importance of the right ventricular systolic function in patients with heart failure of both ischemic and nonischemic etiology [4–6,23–28]. For the risk stratification of such patients, several echocardiographic right ventricular systolic parameters have been found to possess independent prognostic power [4–6]. Ghio et al. [6] measured the tricuspid annular plane systolic excursions (TAPSE) using the M-mode echocardiography and described a poor prognosis of patients with TAPSE≤14 mm. A similar result was obtained by Karatasakis et al. [5]. Meluzin et al. [4] used the peak systolic tricuspid annular velocity (Sa) derived from pulsed-wave Doppler tissue imaging and identified Sa<10.8 cm s^{-1} as an independent predictor of cardiac events. Concerning the right ventricular diastolic dysfunction, it is known to be a very common feature in patients with heart failure [11,29]. However, little is known on its prognostic impact. To quantify the right ventricular diastolic function, Yu and Sanderson [7] used the right ventricular Doppler filling parameters and defined the right ventricular diastolic dysfunction by a shortening of the tricuspid valve deceleration time of early filling *E* wave below 143 ms, and by a reversal in the tricuspid valve-peak *E*/peak atrial filling velocity (*E*/*A* ratio<1). In this study, the presence of right ventricular diastolic dysfunction significantly predicted cardiac morbidity but not cardiac mortality. Meluzin et al. [4], who tested the prognostic power of parameters derived from diastolic tricuspid annular velocities, did not find any independent prognostic impact of the diastolic variables tested (the peak rate of tricuspid annular motion in early and late diastole or their ratio). However, the combination of systolic and diastolic right ventricular functional parameters may be more efficient than the application of these parameters alone.

4.3. The combined left ventricular and right ventricular systolic and diastolic dysfunction in patient risk stratification

In patients with left ventricular systolic dysfunction and chronic heart failure, the presence of advanced left ventricular diastolic dysfunction dramatically increases mortality and the rate of non-fatal cardiac events [30,31]. This was very convincingly demonstrated in the study of Xie and co-workers [31], in which the presence of severe diastolic dysfunction (indicated by the restrictive left ventricular filling) increased the 2-year mortality by more than 40%. Rihal et al. [8] and Yu and Sanderson [7] very clearly documented and confirmed that the prognostic impact of the presence of severe systolic and diastolic dysfunction is additive. In the study of Rihal et al. [8] including a cohort of 102 patients with dilated cardiomyopathy, the subgroup of patients with an ejection fraction <25% and a deceleration time <130 ms (indicating the restrictive left ventricular filling pattern and severe left ventricular diastolic dysfunction) had a 2-year survival of only 35%. The subgroup with an ejection fraction <25% and a deceleration time>130 ms had an intermediate 2-year-survival of 72%, whereas patients with an ejection fraction≥25% had a 2-year survival≥95% regardless of deceleration time. Similar results were obtained by Yu and Sanderson [7]. Thus, there is no doubt that the combination of severe left ventricular systolic and diastolic dysfunction represents a marker of very poor prognosis, much worse than that defined by the presence of either left ventricular systolic or diastolic dysfunction alone. An analogical relation can be expected for the combination of the right ventricular systolic and diastolic function in assessing the patient risk. To date, however, no data are available on the prognostic impact of the presence of both right ventricular systolic and diastolic dysfunction in patients with heart failure and no combined prognostic markers have been determined. In the present study the information on right ventricular systolic and diastolic function was obtained simultaneously and very quickly by measuring peak tricuspid annulur velocities using pulsed-wave Doppler tissue imaging of the tricuspid annular motion. Our results clearly demonstrate the superiority of combining the right ventricular systolic and diastolic function over the assessment of either systolic or diastolic function alone for the patient risk stratification. The determination of only Sa clearly identified low and high risk patients, but it was not able to distinguish among the categories with increased risk (R1, R2a, R2b). In contrast, the Ea did not separate the patients with and without risk of cardiac events with an acceptable statistical power, though it enabled further stratification of high risk patients. A combination of Sa and Ea allowed the creation of 4 Sa/Ea categories dividing the patients into low, moderate, and high risk groups with a high statistical power. The low risk category is defined by a preserved or only mildly depressed right ventricular systolic and diastolic function (Sa≥10.8 cm s^{-1} and Ea≥8.9 cm s^{-1}). On the other hand, the presence of both significant right ventricular systolic and diastolic dysfunctions (Sa<10.8 cm s^{-1} and Ea<8.9 cm s^{-1}) represents a marker of very poor prognosis. Patients with only one abnormal component (Sa or Ea) are at moderate risk of cardiac events. However, the Ea<8.9 cm s^{-1} predicts a high risk of cardiac-related death irrespective of Sa. The normal values of Sa and Ea (mean±standard deviation) for age-matched healthy controls were found to reach 15.5±2.6 cm s^{-1} and 15.6±3.9 cm s^{-1}, respectively [11].

4.4. Study limitations

The main limitation of this study is the fact that our patient population is selected and does not represent the average cohort of patients with heart failure encountered in daily clinical practice. Since the patients were referred to our hospital as potential candidates for orthotopic heart transplantation, a significant proportion of patients above 60 years of age and those with serious co-morbidities were not included. We also excluded patients with atrial fibrillation or right ventricular pacing, because the accuracy of tricuspid annular velocities for the evaluation of right ventricular function has not yet been validated in such patients. In addition, not all of the parameters known to affect the prognosis of patients with heart failure (such as peak oxygen consumption, restrictive left ventricular filling, etc.) were systematically monitored and included into survival analysis. Irrespective of these limitations, the study provides a new, easily obtainable non-invasive combined right ventricular systolic and diastolic marker defining the high risk category of patients with symptomatic heart failure.

5. Conclusions

Our study clearly demonstrates the importance of the assessment of right ventricular systolic and diastolic function for the risk stratification of patients with symptomatic heart failure. The information on right ventricular systolic and diastolic function can be obtained by measuring peak tricuspid annular velocities using pulsed-wave Doppler tissue imaging. The measurement of the peak systolic tricuspid annular velocity (Sa) and the peak early diastolic tricuspid annular velocity (Ea) provides complementary information with a very high power to predict the adverse prognosis. The patients with Sa<10.8 cm s^{-1} and Ea<8.9 cm s^{-1} are at very high risk of cardiac events and should be intensively treated and carefully followed up.

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