Role of Right Ventricular Systolic Function on Long-Term Outcome in Patients With Newly Diagnosed Systolic Heart Failure

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Background: Right ventricular (RV) systolic function has been recognized as a prognostic factor in endstage heart failure (HF) patients and in the present study we evaluated the effect of this dysfunction on prognosis in patients with newly-diagnosed systolic HF.

Methods and Results: We enrolled 180 consecutive patients with newly diagnosed systolic HF (ischemic or dilated cardiomyopathy). Echocardiographic evaluation was performed to assess biventricular function. Pulse-wave tissue Doppler imaging (TDI) readings were obtained from the lateral tricuspid annulus and the peak systolic annular velocity (Stv) was recorded. Patients were followed for a 2-year period and events (death or HF hospitalization) were recorded. During the follow-up, 79 patients (44%) had an adverse event. An inverse relationship was observed between the height of Stv and the probability of an event (odds ratio (OR) 0.716, 95% confidence interval (CI) 0.583–0.880, P=0.001), after controlling for potential confounders. Furthermore, creatinine clearance (CrCl) was inversely associated with the outcome: a 1-unit increase in CrCl was associated with a 0.98-times lower likelihood of having an event. When the analysis was stratified by CrCl <60 ml/min or ≥60 ml/min, Stv predicted adverse events in both groups (CrCl <60 ml/min: OR 0.62, 95%CI 0.39–0.98, P=0.04; CrCl ≥60 ml/min: OR 0.78, 95%CI 0.61–1.01, P=0.06).

Conclusions: Pulse-wave TDI readings of peak systolic velocity at the lateral tricuspid annulus, reflecting RV systolic function, has prognostic significance in newly-diagnosed systolic HF patients. (Circ J 2011; 75: 2176–2181)

Key Words: Echocardiography; Heart failure; Prognosis; Renal function; Right ventricle
by Stv, on clinical outcome after a 2-year follow-up in patients with newly diagnosed systolic HF, was studied.

### Methods

#### Patients

During a 36-month period, a total of 180 consecutive patients (17% females, mean age 63±14 years) hospitalized with newly diagnosed systolic HF and LVEF <40% were enrolled in the study. Patients with atrial fibrillation, severe valvular disease and prosthetic valves were excluded from the enrolment. New onset of acute HF, without previously known cardiac dysfunction, was diagnosed on the basis of the European Society of Cardiology criteria. Among the study patients, 146 (81%) were diagnosed as having ischemic cardiomyopathy and the rest (n=34, 19%) were diagnosed as having dilated cardiomyopathy.

#### Measurements

A complete medical history, as well as detailed information regarding medications, was recorded for all participants. Blood pressure (BP) was measured and patients with average BP ≥140/90 mmHg or receiving antihypertensive medication were classified as hypertensive. Participants with fasting blood sugar >7 mmol/L (125 mg/dl) or treatment with antidiabetic medication were classified as diabetic. Following the clinical investigation, patients were asked to provide information regarding their age, and smoking habits. Body mass index was calculated as the ratio of body weight divided by (height)². All other clinical variables (ie, etiology of cardiomyopathy, New York Heart Association (NYHA) functional class, medications) were registered at the time of discharge from hospital. The specific type of cardiomyopathy (ie, ischemic or dilated) was diagnosed from the medical history and coronary catheterization results. Renal function was estimated using creatinine clearance (CrCl) as calculated by the Cockcroft-Gault formula. Patients underwent a detailed echocardiographic assessment before hospital discharge, using a Hewlett Packard 5500 Sonos with a multifrequency transducer (2.5–4 MHz), equipped with TDI technology; images were taken while patients were in the left lateral decubitus position. TDI uses a modified wall filter and reduced gain to display myocardial velocity while avoiding blood flow detection. From the apical 4-chamber view, a 10-mm sample volume was placed at the lateral mitral annulus, and spectral TDI was recorded, with the mitral annulus motion parallel to the TDI cursor. Pulse-wave TDI is characterized by the myocardial systolic (Smv, Stv) and 2 diastolic waves (Emv, Etv and Amv, Atv), expressed in cm/s. Heart rate was recorded as beats/min. Mitral inflow velocities were recorded by standard pulse-wave Doppler at the tip of the mitral valve (E and A). Left atrial maximal (LAmx) and minimal (LArm) volumes, were also recorded. The LA EF was calculated as described by Dardas et al. Furthermore, flow propagation was calculated as reported by Garcia et al. VTILVOT is the velocity–time integral of the LV outflow tract, as detected by pulse Doppler, from the apical 5-chamber long-axis view. This parameter was used as a surrogate of LV stroke volume. EF was calculated using the biplane Simpson’s method. Only patients with LV systolic dysfunction (LVEF <40% by Simpson’s method) were enrolled. All values were averaged on 3–5 cycles obtained during end-expiration, at a sweep speed of 50 mm/s.

#### Endpoint

The study’s endpoint was a clinical event (ie, cardiovascular death or hospitalization because of cardiovascular disease) during a 2-year period. The first event to occur was considered as the endpoint of the study. No secondary endpoints were used.

#### Bioethics

The study’s design complied with the Declaration of Helsinki.
and was approved by the local ethics committee; patients gave an informed written consent.

**Statistical Analysis**

Continuous variables are presented as mean values±standard deviation, and categorical variables are presented as frequencies. Associations between categorical variables were tested by Pearson’s chi-square test. Comparisons between mean values of normally distributed continuous variables between groups of patients were performed using independent samples t-test and 1-way analysis of variance (ANOVA), after testing for normality and equality of variances. Multiple logistic regression analysis was used to evaluate the association between systolic RV function and long-term (2 years) outcome (death or rehospitalisation), after adjustment for several confounders (creatinine clearance, Etv, Atv, E/A, VTI
LVOT, NYHA classification and existence of ischemic cardiomyopathy). All reported P-values are based on 2-sided tests and compared with a significance level of 5%. SPSS 18.0 software (SPSS Inc, Chicago, IL, USA) was used for all statistical calculations.

**Results**

**Follow-up Evaluation**

During the 2 years of follow-up after hospital discharge, 79 patients had an event (44% event rate; 25 were fatal, mortality rate=13.9%). Those who experienced an adverse event were older, had lower CrCl levels, advanced NYHA stage, higher prevalence of ischemic HF and lower values for Stv in the TDI evaluation, as compared with those without an event (Table 1).

**Predictors of 2-Year CVD Events**

Data analysis revealed that 1 cm/s higher value of Stv reduces the odds of adverse cardiovascular (CVD) events by 28% during the 2-year follow-up (odds ratio (OR) 0.72, 95% confidence interval (CI): 0.58–0.88, P=0.001), after controlling for CrCl.
Etv, Atv, E/A, VTI and NYHA and existence of ischemic cardiomyopathy. Furthermore, CrCl was inversely associated with the outcome; particularly, a 1-unit increase in the CrCl rate was associated with 0.98-times lower odds of having a CVD event (Table 3). When the analysis was stratified by CrCl <60 ml/min or CrCl ≥60 ml/min, Stv remained significant for the prediction of adverse CVD events in both groups (CrCl <60 ml/min: OR 0.62, 95%CI: 0.39–0.98, P=0.04; CrCl ≥60 ml/min: OR 0.78, 95%CI: 0.61–1.01, P=0.06), after the same adjustments were made.

**Discussion**

In the present study, patients with newly diagnosed systolic HF were followed for 2 years as we sought to determine the potential prognostic value of RV systolic dysfunction, as assessed by means of Stv in the lateral tricuspid annulus. The primary endpoint was death or hospitalization because of CVD. Data analysis revealed age, etiology of HF and Stv as independent prognostic factors of the outcome. Renal function showed a borderline effect on CVD events rate in the overall study sample (P<0.08); splitting the analysis according to CrCl, Stv remained significant even in patients with impaired renal function (CrCl <60 ml/min). LV systolic and diastolic functions were not associated with CVD outcome.

Reduced RVEF has been associated with overall survival more accurately than VO2max in both severe and moderate HF. The prevalence of RV dysfunction in patients with reduced LVEF reaches almost 73% when assessed by Stv. It has been suggested that Stv values <11.5 cm/s predict the presence of RV systolic dysfunction (EF<45% by radionuclide ventriculography) with a sensitivity of 90% and a specificity of 85%. Ghio et al showed that a normal RVEF in the presence of pulmonary hypertension (secondary to HF) results in better prognosis, similar to that of patients without pulmonary hypertension. Conversely, in patients without pulmonary hypertension, the presence of RV dysfunction does not adversely affect prognosis. Taken together, these data seem to suggest that it is the ability (or inability) of the RV to generate adequate pressure to ensure LV filling, rather than the filling pressures per se, that affects the clinical course of patients. Conceptually, as long as the RV functions sufficiently to overcome the increased filling pressures and provide the LV with an adequate preload, relatively stable LV function can be maintained. The finding of Ghio et al that in the absence of pulmonary hypertension RV function does not bear prognostic significance may be explained by the established knowledge that, when pulmonary circulation pressures are normal, LV preload can be maintained even in the absence of a RV. Additionally, in patients with dilated cardiomyopathy, an interaction between the LV and RV has been detected. In that case, the reduced RVEF can cause reduced LV stroke volume, even in the absence of increased RV preload.

In a study by Damy et al, the investigators demonstrated the superiority of Stv, compared with other echocardiographic indices of RV systolic function, in predicting survival and event-free survival in patients with chronic systolic HF. The possible reasons for the superiority of Stv involve either the limited accuracy in assessment by other indices, because of RV geometry (as in the case of TAPSE and RVFA), or weaker correlation between those indices and RVEF, when assessed invasively. Given the aforementioned results, we sought to evaluate the prognostic significance of impaired RV function, when assessed by means of tricuspid annulus Stv, in stabilized, newly diagnosed, systolic HF patients. The rationale for specifically enrolling newly diagnosed patients was to allow us to validate the concept that RV dysfunction, whenever it occurs in the course of the disease, leads to a vicious cycle of reduced LV output, reduced coronary perfusion and RV volume and pressure overload, thereby negatively affecting prognosis. Based on the estimated model, Stv values were an independent prognostic factor for CVD events (fatal or not), which supports the concept of the cycle just described, because the worse the initial RV systolic function is, the sooner the threshold of RV compensatory mechanisms will be reached. Additionally, none of the commonly available indices for assessing LV diastolic function was found to have prognostic significance, which contrasts with previous studies in which the ratio of E of the transmural flow to the Emv tissue Doppler derived index was found to have prognostic significance, as it correlated with LV diastolic filling pressure in patients with either preserved or impaired LV systolic function. The lack of any significant relationship between E/Emv accords with the results of Damy et al. A possible explanation for this result may be that patients with newly diagnosed HF have rather increased LV filling pressures and so the E to Emv ratio cannot distinguish those patients with a high likelihood of recurrent hospitalizations or death.

Ventricular interaction has been shown to affect the RV filling pattern, resulting, in combination with post-capillary elevated pulmonary artery pressure and reduced LV output, in reduced RVEF. Additionally, in the clinical course of various cardiomyopathies, the RV myocardium appears to be affected in the same manner as the LV. The study by Fujimoto et al revealed the differences in the mechanisms of diastolic filling between the ventricles. In the RV, the inflow velocities and thus stroke distances are lower, the effective orifice area is larger, and the contribution of the tricuspid annulus motion to stroke volume is greater. Thus, the tissue Doppler-derived index of tricuspid annulus systolic velocity can express the systolic ability of the RV. On the other hand, the echocardiographic evaluation of RV function in the arena of LV systolic dysfunction has several limitations because of morphologic alterations of the RV, compared with the LV. Although the normal RV filling is accomplished with lower pressure gradients, compared with LV filling, this pattern changes in dilated cardiomyopathy, with increased transvalvular velocities in the same manner as those documented in the left side of the heart.

Another deviation between our study and previously reported findings is the role of HF etiology in establishing patient prognosis. Ischemic systolic HF was found in these patients to be associated with worse prognosis, compared with dilated cardiomyopathy, as opposed to previous reports. However, this deviation may be attributed to the differences in the patients’ characteristics. Specifically, it is conceivable that in newly diagnosed ischemic HF, with a recent major event causing a more abrupt increase in RV afterload, the RV has had little time to adapt to the pressure overload while affected by an atheromatous coronary circulation. In contrast, dilated cardiomyopathy generally increases afterload more gradually, potentially allowing compensatory mechanisms to act. Hence, this discrepancy can perhaps be attributed to a survival effect, as other studies enrolled ischemic HF patients with coronary events that did not affect the RV as much, as in patients who died soon after the event.

Renal dysfunction also has a significant prognostic role in the clinical course of HF, because it leads to fluid retention and volume overload, which in turn causes LV filling pressures to rise, adding to RV afterload. As RV function becomes
impaired, the reduced renal perfusion pressure leads to diminished glomerular filtration and consequent neurohormonal mechanisms, such as the renin–angiotensin system and catecholamine pathways, are activated in order to preserve the effective blood volume. In this study, CrCl was used as a surrogate for renal function, incorporating both age, gender and BMI. In our multivariate data analysis, CrCl was found to have borderline prognostic significance; moreover, when patients were stratified according to their renal function (CrCl ≤ 60 ml/min), Stv did not lose significance even in patients with more than mildly impaired renal function.

Notably in this study, cardiac resynchronization therapy (CRT, applied after patient enrollment during the follow-up period) did not confer a survival/event-free survival benefit. Although the response to CRT remains an unresolved issue, as nonresponders are estimated to be approximately 30%, in the case of this study the lack of a relationship between event-free survival and CRT may imply that RV dysfunction occurs with the same frequency in patients both with and without ventricular dyssynchrony. Although there are no data for CRT quality (% of biventricular pacing, cardiac performance following therapy), it could be suspected that CRT improves interventricular but worsens intraventricular (within the right ventricle) dyssynchrony, because the RV free wall, contributing equally with the interventricular septum in RV output, is seldom paced. As a result, in patients with sufficient RV function, the net effect of improved interventricular and worse right intraventricular synchrony may favorably affect outcome. In contrast, when RV dysfunction coexists, the aforementioned combination potentially adversely affects patient outcome. Furthermore, patients with severe mitral regurgitation, which may benefit from CRT, were excluded from this study. Clearly, more studies are needed to clarify this issue.

Future developments in the field of RV dysfunction in the setting of systolic HF may be directed towards 3 objectives. The first would be to assess the potential of other indices to accurately describe RV function, ideally being preload- and afterload-independent (such as acceleration of the RV free wall during isovolumic contractions). The second would be to examine whether reduced Stv values in decompensated HF patients (as opposed to stabilized patients included in studies to date) may confer additional prognostic value to “stable” Stv. The rationale for this would be that a reduced “strained” Stv value would suggest that the RV is reaching the limit of its compensatory mechanisms. Finally, more studies are needed to establish the appropriate therapeutic approach to patients with systolic HF demonstrating impaired RV systolic function, in order to improve patient prognosis.

Study Limitations

Because we did not include in this study a second cohort of HF patients with preserved LV function, or patients with severe valvular disease, prosthetic valves and congenital causes of HF, we cannot generalize our results to the whole spectrum of HF patients, independent of LV function.

Conclusions

The present study revealed that in a cohort of patients with newly diagnosed systolic HF, the Stv in the lateral tricuspid annulus, reflecting RV systolic performance, has long-term prognostic significance of CVD events, regardless of LV systolic and diastolic functions. This relation was not moderated by renal function. Another independent prognostic factor was the etiology of HF, with ischemic HF having a worse prognosis than dilated cardiomyopathy and NYHA classification. These results highlight the important role of the RV in left-sided HF and the need for an early assessment of its function in left systolic HF patients, in order to modify treatment strategies to improve the patients’ outcomes.

References

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