



The evaluation of right ventricular performance in different clinical models of heart failure

Carlo Campana*, Michele Pasotti, Lorenzo Monti, Miriam Revera, Alessandra Serio, Luisa Nespoli, Giulia Magrini, Laura Scelsi, Stefano Ghio, Luigi Tavazzi

Department of Cardiology, IRCCS Policlinico San Matteo, Piazzale Golgi 2, Pavia 27100, Italy

KEYWORDS

Right ventricular function;
End-stage heart failure;
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BNP

Aim To evaluate the role of right ventricular function in different clinical models of heart failure.

Methods 22 patients with pulmonary hypertension (PH) in WHO class III and IV (group A) were evaluated by echocardiography, brain natriuretic peptide (BNP) measurements and right heart catheterization at baseline and after a mean follow-up of 15 ± 4 months. 63 patients with chronic heart failure of different etiology, NYHA class IIIb–IV, followed-up for 18 ± 3 months (group B), underwent echocardiography, BNP measurements, right heart catheterization at study entry and follow-up.

Results In group A patients, among hemodynamic parameters consistent with severe PH, right atrial pressure significantly increased (from 6.7 ± 4.8 to 10 ± 6.5 mmHg, $p < 0.01$); BNP showed a negative correlation with right ventricular ejection fraction ($r^2 = 0.46$). In group B, mean left and right ventricular (thermodilution) ejection fraction (RVEF) were $21 \pm 7\%$ and $18 \pm 9\%$; BNP showed significant correlations with pulmonary wedge pressure ($r = 0.48$, $p = 0.02$) and right ventricular function indices (RVEF and tricuspidal annular plane systolic excursion).

Conclusions A multiparametric right ventricular evaluation is useful even if several diagnostic and prognostic variables which were investigated in this study are not likely to show the same prognostic role in right and biventricular models of heart failure.

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Introduction

Right ventricular function has not been extensively studied until recently, because the right ventricle was con-

sidered to have a secondary role in the prognostic evaluation of several cardiac diseases, including chronic heart failure. In addition, the evaluation of right ventricular function was difficult, because some diagnostic techniques were not efficient or easily reproducible.¹ Radionuclide angiography is currently considered a useful diagnostic method; echocardiography depends on the accuracy of many assumptions about ventricular geometry; the thermodilution technique, able to evaluate stroke volume and ejection fraction by catheter with a

* Correspondence: Carlo Campana, MD, Department of Cardiology, IRCCS Policlinico San Matteo, Piazzale Golgi 2, 27100 Pavia, Italy. Tel.: +39 0382 503460; fax: +39 0382 501279.

E-mail address: unita.sc@smatteo.pv.it (C. Campana).

fast response thermistor, shows good reproducibility in monitoring right ventricular function, but is an invasive technique.²

The aim of this study was to evaluate the evolution of right ventricular performance in two different clinical models of right ventricular dysfunction: the right ventricular impairment observed in patients with end-stage heart failure (HF) and the right ventricular dysfunction seen in patients affected by pulmonary hypertension (PH). The principal objectives were to evaluate the evolution of echocardiographic, Doppler and haemodynamic patterns related to right ventricular impairment and to identify possible correlations with neurohormonal status, as determined by brain natriuretic peptide (BNP) levels.

Methods

Study population

The study population consisted of 85 consecutive patients referred to the Cardiac Failure Unit of the Department of Cardiology, IRCCS Policlinico San Matteo, Pavia from September 2000. The patients were divided into two groups according to the presence of different diagnoses, defining a specific pathophysiological role of the right ventricle.

Group A was formed of 22 patients with a diagnosis of pre-capillary pulmonary hypertension (PH) and a model of isolated right ventricular failure.

Group B was formed of 63 patients with severe chronic HF and a clinical pattern suggesting biventricular dysfunction.

At entry into the study patients underwent a diagnostic evaluation including haemodynamic measurements with right ventricular thermodilution determination and a Doppler echocardiographic study to assess left and right ventricular anatomy and function and to determine the haemodynamic profile in terms of pulmonary pressure and ventricular filling pressures. Functional status was assessed by the 6-min walking test (6MWT) in group A and by cardiopulmonary exercise testing (CPT) in group B.

The study protocol established that baseline cardiac catheterisation and echocardiographic and Doppler evaluations were performed within a few hours of each other. Right heart catheterisation controls were scheduled yearly; echocardiographic, Doppler, neurohormonal and functional status studies were to be carried out every 6 months.

Cardiac catheterisation

Cardiac catheterisation was achieved via the femoral or internal jugular vein, using a 7F modified Swan-Ganz catheter in conjunction with a computerised detection system of cardiac output and right ventricular ejection fraction (RVEF), model REF-1[®] or Vigilance[®] (Edwards-Lifesciences, Santa Ana, CA, USA). The following measures were recorded or derived during the procedure: pulmonary artery pressure, pulmonary wedge pressure, right atrial pressure, pulmonary vascular and arteriolar resistances, systemic vascular resistances, cardiac output, right ventricular ejection fraction, stroke volume, left and right ventricular stroke work.

Echocardiographic and Doppler studies

Doppler-colour echocardiography was performed with the GE-Vingmed System Five (GE-Vingmed Ultrasound, Horten, Norway) using a multifrequency 2.5–3.5 MHz probe.

In group A the following echocardiographic and Doppler variables were analysed:

- Right and left ventricular end-diastolic and end-systolic areas, measured in the apical four-chamber view.
- The ratio of ventricular areas (RV to LV areas ratio), calculated as the ratio of the right ventricular end-diastolic area to the left ventricular end-diastolic area.
- Right ventricular percent change in area, calculated from the right ventricular end-diastolic and end-systolic area (apical four-chamber view) as: $RV \% \text{ change in area} = 100 \times (RV \text{ end-diastolic area} - RV \text{ end-systolic area}) / RV \text{ end-diastolic area}$.
- Left ventricular eccentricity index, measured at end-diastole and end-systole from the parasternal short-axis views of the left ventricle at the level of the chordae tendineae.
- The minimum diameter of the inferior vena cava during respiration, measured from subcostal images.
- Tricuspid annular plane systolic excursion (TAPSE), measured in the apical four-chamber view.
- Right ventricular acceleration time, measured from the pulsed-wave Doppler flow velocity profile of the right ventricle outflow tract and defined as the interval from the onset to the maximal velocity of forward flow.
- The maximal tricuspid regurgitant jet velocity, measured by determining the peak regurgitant velocity in the continuous-wave Doppler flow profile obtained from the cardiac apex.
- Left ventricle filling, evaluated from pulsed-wave Doppler mitral inflow signals, with measurements of mitral E- and A-wave velocities and the time-velocity integral.

In group B the following echocardiographic and Doppler variables were analysed:

- Left ventricular end-diastolic and end-systolic volumes and ejection fraction, calculated from the apical four-chamber view, using the modified Simpson's single plane method.
- Left ventricular end-diastolic and end-systolic dimensions and wall thickness, measured from the long-axis parasternal view.
- Left ventricle filling, evaluated from pulsed-wave Doppler mitral inflow signals, with measurements of mitral E- and A-wave velocities and the time-velocity integral.
- The severity of mitral regurgitation, assessed from the regurgitant fraction.
- The maximal tricuspid regurgitant jet velocity, measured by determining the peak regurgitant velocity in the continuous-wave Doppler flow profile obtained from the cardiac apex.
- Tricuspid annular plane systolic excursion (TAPSE), measured in the apical four-chamber view.
- The minimum diameter of the inferior vena cava during respiration, measured from subcostal images.

Brain natriuretic peptide

The concentration of brain natriuretic peptide (BNP) was assayed in venous blood samples taken from the patients who had been resting quietly for at least an half-hour; a "point-of-care" test was done, using a rapid BNP immunoassay method

(Triage Cardiac; Biosite Diagnostics, San Diego, CA, USA). The scheduled normal range is 0–50 pg/mL, but in this clinical study a cut-off value of 100 pg/mL was applied.

Statistical analysis

Data are expressed as means \pm SD. Comparisons were made using paired *t*-tests and linear regression analysis. A *p* value of less than 0.05 was considered to be statistically significant.

The percentage variation (from baseline to follow-up visit) of each parameter was calculated and divided by the months of follow-up, searching for similar behaviours between echocardiographic and haemodynamic parameters.

Results

Group A (patients with PH)

Twenty-two patients (eight males, mean age 50 ± 11 years) affected by precapillary PH, of whom eight (40%) in WHO class III and 14 (60%) in WHO class IV, were evaluated at study entry and followed-up for 15 ± 4 months. The aetiology of the PH was: primary in 10 patients, thromboembolic in four, HIV-related in two and related to systemic sclerosis in six. Significant variations in therapy and drug dosages were not made during the follow-up, except for, in some cases, the daily dosages of epoprostenol infusion or diuretics. Eighteen patients

received epoprostenol as a continuous infusion; this treatment started at baseline and drug titration was performed until a mean dosage of 20 ± 8 ng/kg/min was reached. The demographic and clinical characteristics of these patients are reported in Table 1. The echocardiographic and Doppler data and BNP values recorded at baseline and during the follow-up are reported in Table 2, whereas the haemodynamic parameters evaluated at baseline and during the follow-up are reported in Table 3. The haemodynamic profile at baseline was consistent with a severe PH (mean systolic pulmonary arterial pressure 80 ± 21 mmHg) and very high pulmonary vascular resistances (1021 ± 814 dynes/s/cm⁻⁵). During the follow-up right atrial pressure increased significantly, rising from 6.7 ± 4.8 to 10 ± 6.5 mmHg ($p < 0.01$) without there being significant variations in RVEF, cardiac index and pulmonary arterial pressure. The TAPSE decreased from 17.3 ± 4.4 to 15.5 ± 4.4 mm. The pulmonary vascular resistances decreased from 1021 ± 814 to 645 ± 380 dynes/s/cm⁻⁵ ($p < 0.4$). Functional status improved during the follow-up (at the end of follow-up 15/22 patients in WHO class III and 7/22 in WHO class IV); patients also obtained an improvement in 6MWT (from 281 ± 144 to 351 ± 154 m, $p = 0.06$). Among these patients the average plasma BNP level at baseline was 246 ± 162 pg/mL; at follow-up, the BNP level averaged 256 ± 180 pg/mL, which was not significantly different from the baseline value. Nevertheless plasma BNP levels (log BNP) showed a significant negative correlation with RVEF ($r^2 = 0.46$) (Fig. 1), whereas weak, non-significant correlations were found among BNP levels (log BNP) and cardiac index ($r^2 = 0.2$), mean pulmonary arterial pressure ($r^2 = 0.1$), right atrial pressure ($r^2 = 0.09$) and TAPSE ($r^2 = 0.005$).

With regard to the outcome, of the 22 patients with precapillary PH, 19 survived with a clinical improvement in functional class, one patient successfully underwent a double-lung transplantation and two patients died because of end-stage heart failure.

Group B (patients with end-stage heart failure)

Sixty-three patients (56 males, mean age 54 ± 9 years) with dilated cardiomyopathy of various aetiology and chronic heart failure, of whom 41 (65%) in NYHA class

Table 1 Baseline demographic and clinical characteristics in group A

Age (years)	50 ± 11
Women	15/22 (68%)
Aetiology	
Primary	10/22 (45%)
Thromboembolic	4/22 (18%)
HIV-related	2/22 (9%)
Scleroderma associated	6/22 (27%)
WHO functional class	
III	8/22 (36%)
IV	14/22 (64%)

Legenda: WHO, World Health Organization.

Table 2 Echocardiographic – Doppler characteristics and BNP levels at baseline and during follow-up in group A (PH patients)

		RVEDD (mm)	RV thickness (mm)	TAPSE (mm)	RV% area	RV-RA ΔP (mm/Hg)	EDLV eccentricity index	BNP (pg/mL)
Baseline	Mean	36	6.6	17.3	0.26	70	1.37	246
	SD	7.5	1.6	4.4	0.10	25	0.32	162
Follow-up	Mean	39	6.7	15.2	0.23	70	1.38	256
	SD	7.3	1.7	4.4	0.08	19	0.36	180
<i>p</i> -Value		0.09	0.6	0.04	0.8	0.8	0.3	0.9

Legenda: RVEDD, right ventricular end-diastolic diameter; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; RA, right atrial; EDLV, end-diastolic left ventricular; BNP, brain natriuretic peptide.

Table 3 Haemodynamic characteristics at baseline and during follow-up in group A (PH patients)

	sPAP (mmHg)	dPAP (mmHg)	mPAP (mmHg)	RAP (mmHg)	CI (L/min/m ²)	SVRI (dynes/s/cm ⁻⁵ /m ²)	PVR (dynes/s/cm ⁻⁵ /m ²)	RVEF (%)
Baseline	Mean 80	36	52	6.7	2.53	2830	1021	18
	SD 21	13	15	4.8	0.91	1114	814	9.6
Follow-up	Mean 79	34	50	10	2.48	2578	645	18
	SD 22	10	12	6.5	0.72	757	380	10
<i>p</i> -Value	0.6	0.8	0.7	0.01	0.9	0.5	0.4	0.8

Legenda: sPAP, systolic pulmonary arterial pressure; dPAP, diastolic pulmonary arterial pressure; mPAP, mean pulmonary arterial pressure; RAP, right atrial pressure; CI, cardiac index; SVRI, systemic vascular resistance index; PVR, pulmonary vascular resistance; RVEF, right ventricular ejection fraction.

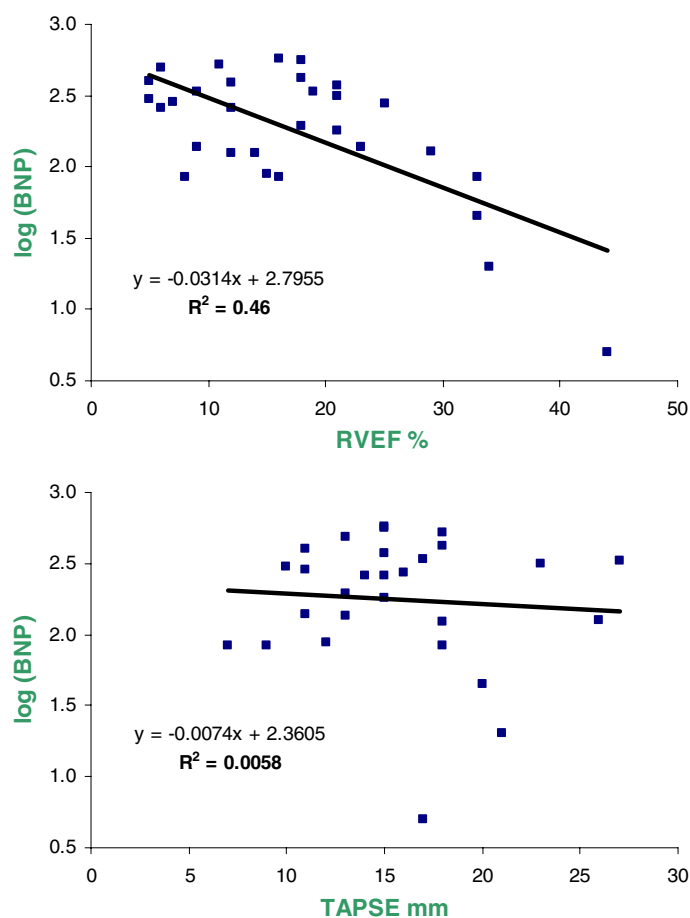


Fig. 1 Relationship between BNP levels and tricuspid annular plane systolic excursion (TAPSE) ($r = 0.4$, $p < 0.05$) and between BNP levels and right ventricular ejection fraction (RVEF) ($r = 0.5$, $p < 0.0006$) in patients with pre-capillary pulmonary hypertension.

IIIb and 22 (35%) in NYHA class IV, were consecutively enrolled into this study when they were to undergo medical therapy optimisation and prognostic evaluation. The aetiology of the HF was primary dilated cardiomyopathy in 26 patients (41%), coronary artery disease in 32 (51%), valvular in 4 (6%), and hypertension in 1 (2%) (Table 4). Forty-three patients were in sinus rhythm, five patients in atrial fibrillation and 15 patients in a rhythm controlled by a pacemaker (12 patients underwent biventricular pacemaker implantation) (see Tables 5 and 6).

These patients were followed-up for a mean period of 18 ± 3 months; they received optimised medical therapy including low dosage β -blocker therapy. The patients' functional class did not improve significantly during the study. Forty-six patients were entered into the waiting list for a heart transplant. Of the initial 63 patients, 47 were alive without transplantation at the end of follow-up, nine had died and seven had undergone heart transplantation.

Among several echocardiographic variables, mean values of left ventricular ejection fraction and TAPSE were

Table 4 Demographic and clinical characteristics at baseline in group B (HF patients)

Characteristics	
Age (years)	54 ± 9
Women	7 (11%)
Aetiology	
DCM	26 (41%)
CAD	32 (51%)
Valvular heart disease	4 (6%)
Hypertension	1 (2%)
NYHA functional class	
IIIb	41 (65%)
IV	22 (35%)

Legenda: DCM, dilated cardiomyopathy; CAD, coronary artery disease; NYHA, New York Heart Association.

21 ± 7% and 15 ± 4 mm, respectively. The haemodynamic parameters measured at baseline right heart catheterisation were the following: mean pulmonary arterial pressure 33 ± 12 mmHg, pulmonary wedge pressure 23 ± 9 mmHg, right atrial pressure 8.5 ± 5 mmHg, cardiac index 1.9 ± 0.4 L/min/m², RVEF 18 ± 9%. The mean concentration of BNP was 738 ± 448 pg/mL.

No significant differences were recorded between the baseline and follow-up values, calculating the percentage of variation for the studied variables. The haemodynamic results observed at baseline and confirmed at follow-up showed a low cardiac output in the presence of mild pulmonary hypertension and a moderate increase of left ventricular filling pressure.

A series of weak but statistically significant correlations was found among BNP levels and pulmonary wedge pressure values ($r = 0.48$; $p = 0.02$), RVEF ($r = 0.5$, $p < 0.006$), and TAPSE ($r = 0.46$; $p < 0.04$) (Fig. 2).

Discussion

Right ventricular function is generally difficult to assess using standard techniques; in the present study we evaluated whether careful monitoring of right ventricular impairment in the evolution of two different clinical models of heart failure could be a critical part of the assessment and decision-making process of these diseases. Moreover, we analysed the potential relationship between the data derived from repeated echocardiographic and haemodynamic evaluations and plasma BNP levels, since this peptide is an effective prognostic marker in heart failure in patients with mild to moderate symptoms.^{3,4}

The role of the right ventricle in PH, as a model of isolated right ventricular dysfunction

In recent years medical treatments have been developed, targeting both vasodilation and anti-remodelling mechanisms in PH. Careful outpatient clinical monitoring of affected persons and prostacyclin administration recently produced an improved survival.⁵ In our experience PH patients showed a significant improvement in WHO class, in agreement with the significant longer 6-min walked distance. Moreover the trend of reduction in pulmonary vascular resistances, measured by right heart catheterisation, was certainly consistent with the chronic effect of the therapy (prostacyclin) administered in a greater number of patients. No signs of further remodelling were noted during the follow-up; however right atrial pressure significantly increased. The data derived from the haemodynamic study, in terms of a trend towards a decrease in pulmonary vascular resistances,

Table 5 Echocardiographic and Doppler characteristics and BNP levels at baseline and during follow-up in group B (HF patients)

		LVEDV (mL ³)	LVESV (mL ³)	LVEF (%)	LVEDD (mm)	LVESD (mm)	TAPSE (mm)	BNP (pg/mL)
Baseline	Mean	314.64	250.59	21.28	72.88	64.32	14.96	738.02
	SD	104.51	104.47	7.54	9.95	11.52	3.88	448.02
Follow-up	Mean	320.16	244.92	21.48	72.79	66.25	16.22	678.95
	SD	114.02	107.47	6.72	10.24	9.69	5.18	576.81
<i>p</i> -Value		0.83	0.92	0.88	0.77	0.60	0.23	0.82

Legenda: LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; TAPSE, tricuspid annular plane systolic excursion; BNP, brain natriuretic peptide.

Table 6 Haemodynamic characteristics at baseline and during follow-up in group B (HF patients)

		mPAP (mmHg)	PCP (mmHg)	RAP (mmHg)	CI (L/min/m ²)	RVEF (%)
Baseline	Mean	33.39	23.58	8.51	1.86	17.96
	SD	12.65	9.60	5.36	0.43	9.60
Follow-up	Mean	28.23	19.45	6.74	1.95	22.49
	SD	10.67	8.35	4.46	0.48	11.09
<i>p</i> -Value		0.13	0.10	0.21	0.50	0.14

Legenda: mPAP, mean pulmonary arterial pressure; PCP, pulmonary capillary pressure; RAP, right atrial pressure; CI, cardiac index; RVEF, right ventricular ejection fraction.

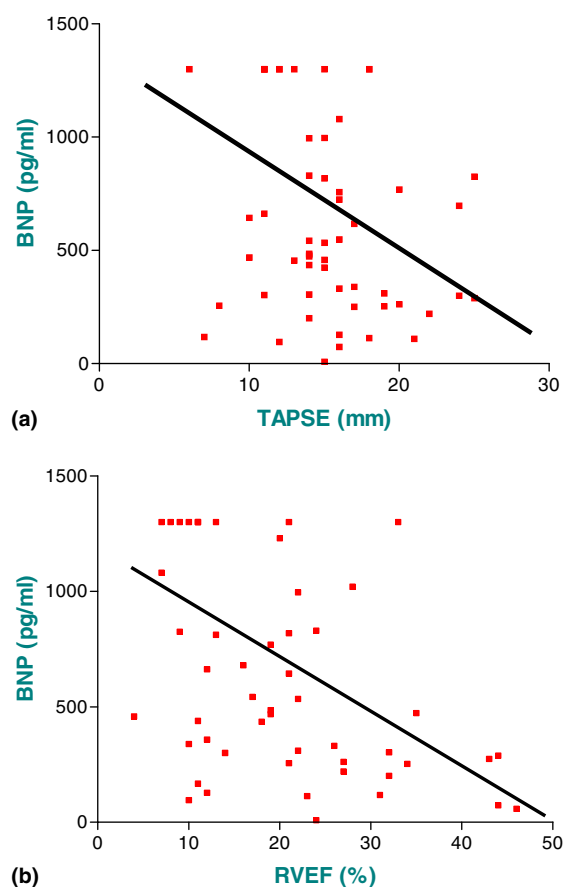


Fig. 2 Relationship between BNP levels and tricuspidal annular plane systolic excursion (TAPSE) (a) ($r = 0.4$, $p < 0.05$) and between BNP levels and right ventricular ejection fraction (RVEF) (b) ($r = 0.5$, $p < 0.0006$) in patients with end stage heart failure.

could represent a favourable response of the pulmonary circulation in agreement with the improvement in clinical status; this effect is often observed in the patients who are treated with epoprostenol therapy.^{5,6} The increase of right ventricular filling pressure and a trend toward a reduction of TAPSE can, respectively, be signs of right ventricular function deterioration, in the presence of a preload increase, and a reduction of contractility. Raymond et al.⁷ on behalf of the "Primary PH Hypertension Study Group", prospectively followed 81 patients with severe primary PH. These authors identified pericardial effusion and indexed right atrial area as predictors of mortality; in addition, septal diastolic shift was able to identify patients at higher risk of death or lung transplantation. In our series we did not observe significant pericardial effusion, which is frequently detected in severe PH.⁸ The plasma BNP levels increased slightly, but not significantly, during the follow-up; the higher BNP levels in our patients than among normal subjects can be ascribed to the volume overload and to the increased pressure of the right ventricle. The influence of right ventricular haemodynamic variables and function on BNP secretion was investigated by Nagaya et al.⁹ in patients with right ventricular volume overload (atrial septal defect) and right ventricular pressure overload

(primary or thromboembolic PH); plasma BNP levels were significantly higher in the presence of pressure overload and increased in proportion to the extent of right ventricular dysfunction, with a good correlation among BNP values and pulmonary artery pressure, total pulmonary resistances, mean right atrial pressure, RV end-diastolic pressure and RV myocardial mass.

The role of the right ventricle in severe chronic HF, as a model of biventricular dysfunction

Left ventricular ejection fraction is a powerful predictor of mortality in mild and moderate heart failure and in patients after myocardial infarction;¹⁰ nevertheless there is increasing awareness that his prognostic role is weak in the presence of severe systolic heart failure and a severely depressed left ventricular ejection fraction; in this setting the right ventricular function can be determinant in the clinical evolution and RVEF gains a very important prognostic significance.^{11,12,13}

In patients with chronic HF caused by dilated cardiomyopathy, reduced RVEF, (<38%) assessed using gated pool scanning, was related to an increased mortality only in subjects with lower left ventricular ejection fraction (<30%);¹² in patients with coronary artery disease, RVEF is considered a powerful prognostic indicator in the presence of left ventricular ejection fraction <40%.¹¹ In a previous experience involving more than 300 patients with severe chronic HF of mixed aetiology evaluated for heart transplantation, RVEF (with a cut-off of 24%) resulted as an independent prognostic indicator of mortality in a multivariate model.¹³

DiSalvo et al.¹⁴ in a study of patients with advanced heart failure and very low left ventricular ejection fraction (mean value: 22%), showed that a normal value of resting RVEF (>35%) was the most powerful independent predictor of survival in a multivariate model including conventional prognostic markers.

Our data confirm that RVEF is strongly reduced (RVEF $20 \pm 11\%$) in patients with advanced heart failure (left ventricular ejection fraction $22 \pm 7\%$). Among the different parameters analysed by echocardiography, TAPSE showed a weak correlation with RVEF.

Recently, assays of plasma BNP levels have been suggested to be an easy, and cost-effective method in the differential diagnosis of dyspnoea and in risk stratification of patients with congestive HF. The evolution of BNP levels in chronic HF was investigated in the Valsartan Heart Failure Trial (Val-HeFT), the largest neurohormone study in patients with symptomatic HF, in NYHA class II-III and with a LVEF <40%.⁴ BNP values were analysed during a 24-month follow-up in 3919 patients enrolled and randomised to receive valsartan treatment or placebo; BNP levels rose significantly in the control group over the course of the study and resulted as the most reliable indicator of outcome. Koglin et al.¹⁵ found a significant correlation between plasma BNP levels and the heart failure survival score (HFSS) in 78 patients with moderate HF (LVEF $36 \pm 15\%$) referred for a multiparametric evaluation; during the follow-up Kaplan–Meier estimates of

freedom from clinical events were significantly different for patients whose plasma BNP concentrations were above or below the 75th percentile. Recent reports show that repeated BNP measurements improve the predictive value of this assay and scheduled determinations during the follow-up might be useful for detecting heart failure progression.¹⁶

Moreover, in a large population of patients with left ventricular ejection fraction <35% and a careful follow-up programme, Berger et al.¹⁷ showed that BNP was a strong independent predictor of sudden death; among several clinical and haemodynamic variables those related to right ventricular function were not specifically analysed. A recent study¹⁶ was designed to evaluate whether right ventricular systolic dysfunction in the presence of a reduced LVEF is associated with higher BNP levels. Eighty-five patients with different degrees of left and right ventricular dysfunction were studied and it was found that BNP levels were negatively correlated with RVEF for all subgroups; for patients with LVEF <40% plasma BNP levels correlate with RVEF but not with LVEF and were significantly higher in those patients with more severe right ventricular impairment.

In a group of patients with advanced HF we observed a significant correlation between BNP levels and pulmonary wedge pressure and TAPSE. However, when the analysis was restricted to higher BNP values (>500 pg/mL) the correlation lost its statistical power.¹⁸ A weaker but statistically significant relationship was found between BNP levels and TAPSE, confirming that these values are related and that they could be effectively used in non-invasive prognostic evaluation.¹⁸

Conclusions

Invasive and non-invasive diagnostic and prognostic investigations usually used to study right ventricular function are not likely to show the same prognostic role in both right and biventricular models of heart failure. In patients affected by pulmonary hypertension a diagnostic and prognostic work-up based on haemodynamic evaluation seems to be still effective; the invasive study can accurately measure pulmonary vascular resistances, the most important prognostic variable, strongly influenced by the therapy. BNP concentrations show a weak relationship with RVEF, even if the range of variability of the plasma BNP levels is narrow. In patients affected by end-stage heart failure the distribution of BNP levels is wide and the levels are weakly correlated with other indices usually considered strong predictors of prognosis in advanced heart failure, such as RVEF, TAPSE and pulmonary wedge pressure.

In conclusion, these results offer several pieces of information on the evolution of right ventricular impairment in two different models of heart failure; further

investigations are certainly required to obtain a better understanding of these pathophysiological mechanisms.

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