Original article

Clinical and functional effects of beta-blocker therapy discontinuation in patients with biventricular heart failure

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Background Nearly two-thirds of patients with heart failure with reduced ejection fraction (HFrEF) have right ventricular dysfunction, previously identified as an independent predictor of reduced functional capacity and poor prognosis. Beta-blocker therapy (β-BT) reduces mortality and hospitalizations in patients with HFrEF and is approved as first-line therapy regardless of concomitant right ventricular function. However, the exact role of sympathetic nervous system activation in right ventricular dysfunction and the potential usefulness (or harmfulness) of β-BT in these patients are still unclear.

Objectives The aim of the study is to evaluate the medium-term effect of β-BT discontinuation on functional capacity and right ventricular remodelling based on cardiopulmonary exercise testing (CPET), echocardiography and serum biomarkers in patients with clinically stable biventricular dysfunction.

Methods In this single-centre, open-label, prospective trial, 16 patients were enrolled using the following criteria: patients were clinically stable without signs of peripheral congestion; NYHA II-III while on optimal medical therapy (including β-BT); LVEF 40% or less; echocardiographic criteria of right ventricular dysfunction. Patients were randomized 1 : 1 either to withdraw (group 0) or continue (group 1) β-BT. In group 0, optimal heart rate was obtained with alternative rate-control drugs. Echo and serum biomarkers were performed at baseline, after 3 and 6 months; CPET was performed at baseline and 6 months. Mann–Whitney *U* test was adopted to determine the relationships between β-BT discontinuation and effects on right ventricular dysfunction.

Results At 6 months' follow up, S' DTI improved (ΔS': 1.01 vs. −0.92 cm/s; $P = 0.03$), while estimated PAPs (ΔPAPs: 0.8 vs. −7.5 mmHg; $P = 0.04$) and echo left ventricular-remodelling (ΔEDVi: 19.55 vs. −0.96 ml/mq; $P = 0.03$) worsened in group 0. In absolute terms, the only variables significantly affected by β-BT withdrawal were left ventricular EDV and ESV, appearing worse in group 0 (mean EDVi 115 vs. 84 ml/mq; mean ESVi 79 vs. 53.9 ml/mq, $P = 0.03$). No significant changes in terms of functional capacity were observed after β-BT withdrawal.

Conclusion In HFrEF patients with concomitant right ventricular dysfunction, β-BT discontinuation did not produce any beneficial effects. In addition, despite maintenance of optimal heart rate control, β-BT discontinuation induced worsening of left ventricular remodelling. Our study corroborates the hypothesis that improvement in left ventricular function may likewise be a major determinant for improvement in right ventricular function, reducing pulmonary wedge pressure and right ventricular afterload, with only a marginal action of its negative inotropic effect. In conclusion, β-BT appears beneficial also in heart failure patients with biventricular dysfunction.

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Keywords: β-blocker therapy, cardiopulmonary exercise test, echocardiography, left heart failure, right heart failure

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Introduction

Right ventricular function is an independent predictor of functional capacity and a major determinant of morbidity and mortality in patients with heart failure with reduced ejection fraction (HFrEF).[1–7] Moreover, the right ventricle (RV) has received little attention in the past, with cardiologists mainly dealing with left ventricular dysfunction, primarily because the contribution of the RV to overall cardiac hemodynamic was unclear. Thus, most standard heart failure therapies are directed towards left ventricular dysfunction and remodelling. Indeed, beta-blocker therapy (β-BT) is a first-line treatment (Class IA, ESC/HFA HF

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guidelines)[8] in clinically stable patients with HFrEF, resulting in a dose-related improvement in left ventricular ejection fraction (LVEF), patients' functional capacity and survival.[9–14] On the basis of the established beneficial effects of β-BT on left ventricular dysfunction, similar beneficial effects are inferentially recognized for patients with right ventricular dysfunction. However, all studies evaluating β-BT in patients with clinically stable HFrEF have been performed in patients with left ventricular dysfunction, regardless of the presence of right ventricular dysfunction. In the coming era of precision medicine, it would be very useful to determine whether beta blockers (BB) are equally effective in patients with lone left ventricular dysfunction vs. those with biventricular dysfunction, of different magnitude. Generally speaking, treatment strategies for right ventricular dysfunction are still lacking authoritative advise.

Our single-centre prospective study is aimed to evaluate the medium-term effect of β-BT withdrawal on functional capacity assessed by cardiopulmonary exercise testing (CPET) in symptomatic patients with clinically stable HFrEF and right ventricular dysfunction and evaluate how β-BT discontinuation impacts biventricular function and remodelling based on echocardiographic and serum biomarkers.

Materials and methods

Patient selection

This is a single-centre, prospective, open-label trial encompassing 16 patients referred to our Heart Failure Outpatients clinic with clinically stable HFrEF with associated right ventricular dysfunction.

Eligibility requirements were age of at least 18 years; patients were clinically stable without signs of peripheral congestion; NYHA Class II- III despite optimal guideline directed medical therapy (including RAAS-I and β-BT, titrated to maximal tolerated dose; diuretics); left ventricular ejection fraction (LVEF) of 40% or less; echocardiographic criteria of right ventricular dysfunction (TDI S $<$ 10 cm/s and/or TAPSE $<$ 1.6 cm); PAPs $\geq$ 40 mmHg.

Exclusion criteria were pulmonary embolism in the previous 3 months; CRT-D implanted in the previous 6 months; acute coronary syndrome or recent coronary revascularization within less than 1 month; history of arrhythmias necessitating β-BT (i.e. FA/FLA $>$130 bpm, ventricular tachycardia); end-stage renal disease (eGFR $<$ 15 ml/min/1.73 m^2); active neoplasia and serious comorbidities associated with less than 1 year of life expectancy; indication for β-BT for extracardiac disease (i.e. oesophageal varices).

Study design

Patients were randomized 1 : 1 into two groups, either to withdraw (group 0, eight patients) or continue (group 1, eight patients) β-BT. Randomization was based on random assignation of letters A or B, corresponding to a group: A = B-BT continuation and B = B-BT withdrawal. In group 0 optimal heart rate (HR $>$50, $<$70 bpm) was then obtained with alternative rate-control drugs (ivabradine in patients in sinus rhythm, digoxin in patients in atrial fibrillation), introduced after 24 h of ECG monitoring performed after 7 days of β-BT withdrawal. Both arms were re-evaluated after 3 weeks of enrolment to ascertain proper heart rate achievement.

During follow-up, no significant changes in cardiovascular therapy were made; the only variation was the introduction of ivabradine or digoxin in group 0, at baseline, in order to maintain optimal heart rate. More specifically, no changes in diuretic therapy were allowed during the study period. In the eventuality of decompensation and ensuing therapy variation, including diuretic dose increment, patients were excluded from the study and analysis.

Patients were assessed at baseline and after 6 months, with clinical evaluation, 12-lead ECG, echocardiography, CPET, and serum biomarkers (electrolytes, creatinine, NT pro-BNP).

Echocardiography measurements

Conventional TTE was systematically performed using a commercially available system (Philips Ultrasound; Philips Medical Systems, Bothell, Washington, USA). We measured the linear left ventricular dimension (LV EDD) using B-mode with the parasternal long-axis view at the papillary muscle level, and thereafter the biplane (modified Simpson's) method to measure left ventricular EDV, ESV and ejection fraction (LVEF). Mitral regurgitation was evaluated by vena contracta measurement.[15–17]

Right ventricular remodelling was evaluated by right ventricular basal diameter (right ventricular EDD) measurement in apical four-chamber view; right ventricular systolic function was evaluated with M-mode images to obtain TAPSE and a value less than 16 cm was considered as the cut-off value for right ventricular dysfunction. Right ventricular longitudinal function was also obtained through TDI-derived tricuspid lateral annular systolic velocity wave (S′) and S′ less than 10 cm/s was considered as pathological. Tricuspid regurgitation was estimated by vena contracta measurement. The pressure gradient between the right ventricular and right atrium during systole was measured using the simplified Bernoulli equation (right ventricular systolic pressure).[16]

Cardiopulmonary exercise testing

The cycle ergometer CPETs were performed in an upright position, with a standardized ramp protocol, designed with the aim of reaching maximum tolerated exercise.

Gas exchange was evaluated at rest for 3 min, during warm-up of 2 min set at 60 W followed by progressive workload increase by 30 W/min until volitional fatigue and finally after the third minute of recovery (Cardiopulmonary Metabolic Cart; Sensormedics Vmax Spectra, Sensormedics Corp, USA). Blood pressure, heart rate, 12-lead electrocardiogram and SpO_2 were continuously monitored.

Breath data of VE, VO_2 and VCO_2 were collected and analysed every 10 s using a metabolic recording system calibrated with room air and standardized gas before each test. VO_2max was calculated as the highest O_2 consumption during stress with VO_2max less than 15 ml O_2/kg/min as the cut-off value. The anaerobic threshold was measured by the V-slope method from the plot of VCO_2 vs. VO_2 on equal scales. The VE/VCO_2 ratio was measured at the anaerobic threshold. The VO_2/workload slope and the HR/VO_2 slope were calculated from rest to maximal exercise. The VE/VCO_2 slope was calculated from rest to the respiratory compensation point as recommended. The slope of the relationship between ventilation and carbon dioxide production obtained during symptom-limited ramp exercise testing reflects exercise ventilatory efficiency, with less than 30 considered normal with a slight increase with advanced age possible.

Statistical analysis

Continuous variables were expressed as median and interquartile range-IQR (25–75%). Pre and postchanges in parameter values were compared between group 0 and group 1 using the nonparametric Mann–Whitney *U* test. *P*-values less than 0.05 were considered statistically significant. All statistical analyses were performed using RStudio 2022.02.1 + 461.

The study was approved by our Institutional Committee on Human Research (Studio DESTRO 03032011, EudraCT 2011–000890–29).

Results

Population

Patients' characteristics are reported in Table 1. After randomization, no significant differences at baseline were observed between the two groups (Table 2). In the overall population, nearly a half of the patients presented atrial fibrillation, only 18% were female and the mean age was 79 years. In group 0, three patients were in atrial fibrillation and received digoxin 0.125 mg/die. The remaining five patients were in sinus rhythm and were prescribed ivabradine at 6.5 ± 1.4 mg twice a day. The doses were effectively adjusted to maintain heart rate more than 50 to less than 70 bpm.

During the study period no patient needed variations in therapy, which could have eventually led to exclusion from the study.

Table 1 Study population characteristics at baseline

Population ($n = 16$)	Median IQR (25–75%) or *n* (%)
Age (years)	79 (71–82)
Sex (% women)	3/16 (18%)
Heart rate (bpm)	64 (59–71)
Atrial fibrillation (%)	7 (44%)
Pro-BNP (pg/dl)	3518 (2600–6455)
LVEF (%)	28 (25–36)
LVEDV (ml/mq)	89 (83–104)
LVESV (ml/mq)	66 (49–76)
MR VC (mm)	5.0 (4.8–5.5)
RV EDD (mm)	34 (30–40)
TAPSE (mm)	13 (12–15)
S' DTI RV (cm/s)	8.5 (7.6–9.5)
PAPs (mmHg)	55 (42–63)
VO_2 max (ml O_2/kg/min)	9.9 (8.1–13.2)
VE/VCO_2 slope	41 (35–46)
VE/VO_2 at peak exercise	39 (35–45)

Values are median (interquartile range) or *n* (%). EDD, end-diastolic diameter; LVEDV, left ventricle end-diastolic volume; LVEF, left ventricle ejection fraction; LVESV, left ventricle end-systolic volume; MR VC, mitral regurgitation vena contracta; PAPs, pulmonary artery systolic pressure; VCO_2, CO_2 production; VE, minute ventilation; VO_2, O_2 consumption.

Echo remodelling after beta-blocker discontinuation

Under β-BT discontinuation, several echo parameters significantly changed. Right ventricular systolic function based on TDI-derived tricuspid lateral annular systolic velocity improved in group 0 compared with group 1 (ΔS' DTI: 1.01 vs. −0.92 cm/s; $P = 0.03$). Conversely, worsening of estimated pulmonary arterial hypertension (ΔPAPs: 0.8 vs. −7.5 mmHg; $P = 0.04$) and left ventricular-remodelling parameters (ΔEDVi bp: 19.55 vs. −0.96 ml/mq; $P = 0.03$) were observed in group 0 compared with group 1, respectively.

No change was observed in right ventricular remodelling assessed by EDD (median EDD RV 37 vs. 32 mm, $P = 0.19$).

As summarized in Table 3, at the end of the study, the only two variables significantly affected by β-BT withdrawal were LV EDVi and ESVi, appearing worse in group 0 (median EDVi bp 115 vs. 84 ml/mq, $P = 0.03$; median ESVi bp 79 vs. 53.9 ml/mq, $P = 0.03$). See Table 3.

Figure 1 shows trajectories of left ventricular remodelling, showing statistically significant maladaptive remodelling based on left ventricle dilatation ($P = 0.02$).

Functional capacity after beta-blocker discontinuation

No significant improvements in terms of functional capacity were obtained, and peak oxygen uptake did not change between the two groups (median ΔVO_2max: 13 vs. 10.6 ml O_2/kg/min, $P = 1$). Notably, the VE/VCO_2 slope was not

Table 2 Comparisons between groups at baseline

Variables	Group 0 ($n=8$) Median IQR (25–75%)	Group 1 ($n=8$) Median IQR (25–75%)	P
Heart rate (bpm)	61 (57–69)	64 (60–71)	0.821
Pro-BNP (pg/dl)	5233 (4381–7658)	2890 (1398–3518)	0.073
LVEF (%)	26 (24–30)	29 (25–41)	0.370
LVEDV (ml)	94 (89–112)	87 (74–92)	0.268
LVESV (ml)	74 (65–78)	50 (48–68)	0.149
MR VC (mm)	5.0 (4.8–5.5)	4.4 (3.9–4.9)	0.407
RV EDD (mm)	39 (38–41)	30 (27–36)	0.085
TAPSE (mm)	14 (12–15)	14 (13–15)	0.935
S' DTI RV (cm/s)	8.3 (7.2–8.9)	9.1 (8.4–9.6)	0.192
PAPs (mmHg)	55 (51–60)	56 (46–63)	0.935
VO2 Max (ml O_2/kg/min)	13.2 (8.0–13.3)	10.5 (9.0–11.9)	0.755
VE/VCO_2 slope	42 (41–58)	37 (34–46)	0.268
VE/VO_2 at peak exercise	41 (39–54)	35 (33–43)	0.255

Values are median (interquartile range). EDD, end-diastolic diameter; LVEDV, left ventricle end-diastolic volume; LVEF, left ventricle ejection fraction; LVESV, left ventricle end-systolic volume; MR VC, mitral regurgitation vena contracta; PAPs, pulmonary artery systolic pressure; VCO_2, CO_2 production; VE, minute ventilation; VO_2, O_2 consumption.

Table 3 Comparisons between groups at 6 months' follow-up

Variables	Group 0 ($n=8$) Median IQR (25–75%)	Group 1 ($n=8$) Median IQR (25–75%)	P
Heart rate (bpm)	68 (62–71)	65 (59–67)	0.128
Pro-BNP (pg/dl)	3996 (3967–5003)	2262 (1610–2883)	0.111
LVEF (%)	23 (20–35)	31 (26–41)	0.202
LVEDV (ml)	115 (98–129)	84 (71–90)	**0.030**
LVESV (ml)	79 (72–82)	54 (48–65)	**0.030**
MR VC (mm)	4.5 (4.0–4.8)	4.5 (4.0–4.9)	0.905
RV EDD (mm)	37 (34–39)	31 (28–36)	0.191
TAPSE (mm)	16 (15–18)	16 (11–16)	0.755
S' DTI RV (cm/s)	9.1 (8.8–10.1)	8.4 (7.5–8.8)	0.142
PAPs (mmHg)	57 (49–59)	46 (39–54)	0.268
VO_2 Max (ml O_2/kg/min)	13.3 (10.1–15.1)	10.6 (9.9–15.5)	0.998
VE/VCO_2 slope	39 (36–45)	39 (33–40)	0.623
VE/VO_2 at peak exercise	37 (33–43)	35 (33–39)	0.730

Values are median (interquartile range). EDD, end-diastolic diameter; LVEDV, left ventricle end-diastolic volume; LVEF, left ventricle ejection fraction; LVESV, left ventricle end-systolic volume; MR VC, mitral regurgitation vena contracta; PAPs, pulmonary artery systolic pressure; VCO_2, CO_2 production; VE, minute ventilation; VO_2, O_2 consumption. Statistically significant values are highlighted in bold characters.

different between β-blocked patients and patients not receiving β-blockers ($P=0.6$). See Table 4.

No difference in heart rate was observed between the two groups.

Subgroup analysis

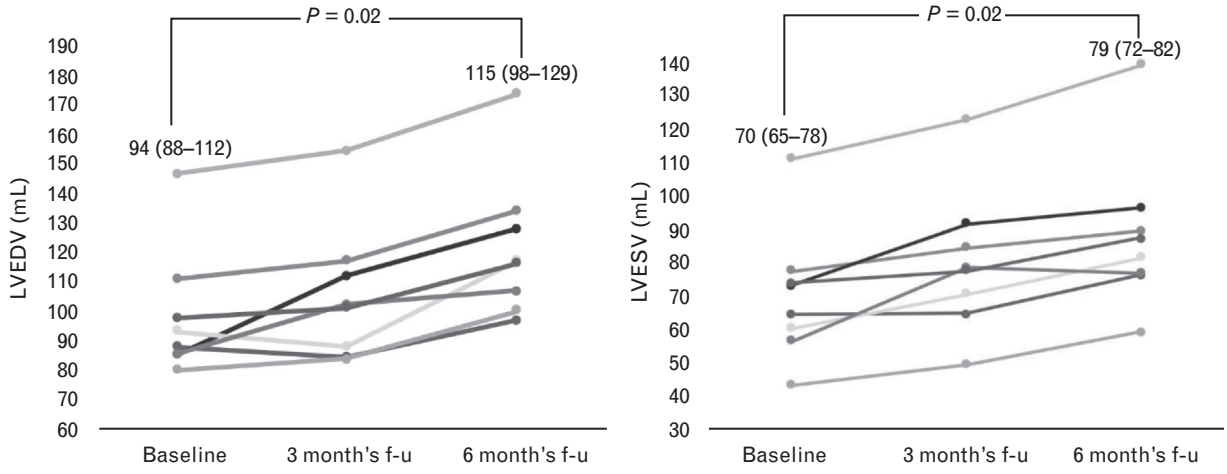
As half of the study patients had atrial fibrillation and digoxin was therefore prescribed, leading to a potential confounding effect due its positive inotropic effect, a subgroup analysis including only sinus rhythm patients was conducted. Similarly to the whole study group, in this subgroup of patients, adverse remodelling of the left ventricle (median EDVi bp 117 vs. 88 ml/mq, $P=0.04$; median ESVi bp 79 vs. 56 ml/mq, $P=0.04$) remained the only significant effect of β-BT discontinuation. See Table 5.

Discussion

In this study, we investigated the effect of β-BT discontinuation on right ventricular function in ambulatory patients with biventricular heart failure. β-BT discontinuation does not appear to lead to right ventricular shape and function improvement but rather yields a detrimental effect on left ventricular remodelling. Moreover, β-BT withdrawal did not produce variations in terms of functional capacity assessed by CPET.

In nearly two-thirds of patients with HFrEF, the concomitance of right ventricular dysfunction complicates the pathophysiology of HFrEF and represents a strong predictor of mortality.[1–3] Right ventricular dysfunction in HFrEF often results from the development of pulmonary congestion and subsequent pulmonary arterial hypertension (PAH), reflecting the backward transmission of elevated left heart filling pressure (postcapillary PAH).

Fig. 1



Trajectories of adverse remodelling of left ventricle after β-BT discontinuation at baseline, 3 and 6 months' follow-up, showing significant trend towards dilatation of both LVEDV (left) and LVESV (right). Data are reported as median (IQR 25–75%).

Table 4 Variables variation after 6 months' follow-up

Variables variations at 6 months of follow-up	Group 0 ($n=8$) Median IQR (25–75%)	Group 1 ($n=8$) Median IQR (25–75%)	*P*
Δ Heart rate (bpm)	−1 (−4 to 2)	3 (−1 to 4)	0.394
Δ Pro-BNP (pg/dl)	−2655 (−3505 to 1069)	204 (−433 to 410)	0.730
Δ LVEF (%)	−1.4 (−3.1 to 2.3)	2.2 (−1.2 to 3.4)	0.453
Δ LVEDV (ml)	19.6 (10.2–29.0)	−1.1 (−5.7 to 3.2)	0.038
Δ LVESV (ml)	13.9 (6.3–22.4)	0.7 (−6.8 to 5.6)	0.054
Δ MR VC (mm)	−0.13 (−0.20 to −0.05)	0.04 (−0.04 to 0.05)	0.111
Δ RV EDD (mm)	−0.8 (−2.3 to 0.9)	0 (−1.8 to 1.0)	0.745
Δ TAPSE (mm)	0.6 (−0.2 to 1.7)	0.2 (−0.1 to 0.2)	0.914
Δ S' DTI RV (cm/s)	1.0 (−0.1 to 2.3)	−0.8 (−1.9 to −0.9)	0.032
Δ PAPs (mmHg)	−0.8 (−2.3 to 0.9)	−7.5 (−11.4 to −4.0)	0.042
Δ VO2 Max (ml O_2/kg/min)	0.1 (−1.4 to 1.7)	0.1 (−0.1 to 2.5)	0.905
Δ VE/VCO_2 slope	−3.1 (−11.2 to 5.3)	2.2 (1.1–2.8)	0.709
Δ VE/VO_2 at peak exercise	−4.6 (−12.1 to 6.3)	1.1 (0.3–2.6)	0.712

Values are median (interquartile range). EDD, end-diastolic diameter; LVEDV, left ventricle end-diastolic volume; LVEF, left ventricle ejection fraction; LVESV, left ventricle end-systolic volume; MR VC, mitral regurgitation vena contracta; PAPs, pulmonary artery systolic pressure; VCO_2, CO_2 production; VE, minute ventilation; VO_2, O_2 consumption.

Thereafter, chronic vascular changes within the pulmonary circulation, pulmonary vasculature remodelling and endothelial dysfunction translate into elevated PVR combined pre and postcapillary PAH. On the other hand, mechanisms underlying heart failure involve the sympathetic nervous system with numerous theoretical deleterious effects, including vasoconstriction, increased left ventricular afterload, cardiac remodelling and fibrosis.[18,19]

In addition, disease processes affecting both ventricles could play an important role in the development of RVD.[20–23] In this context, sympathetic nervous system overactivation is a main feature of progressive left ventricular dysfunction and maladaptive remodelling, having detrimental effects also on RV.[24] The benefit from β-BT in HFrEF is mainly related to reduction of detrimental effects of chronic catecholamine stimulation and chronic blockade of beta-adrenergic receptors improves symptoms, reduces hospitalization and enhances survival in HFrEF.[9–14]

However, less is known about the potential usefulness of β-BT in the treatment of associated right ventricular dysfunction and some concerns regarding its effects in this patient subgroup are still present. Heart rate plays a relevant role in right ventricular function and right ventricular output, due to limited inotropic reserve of the RV. In fact, the relative negative inotropic effects exerted by β-BT could play an additional detrimental effect on the thin-

Table 5 Subgroup analysis in sinus rhythm patient at 6 months' follow-up

Variables	Group 0 ($n=8$) Median IQR (25–75%)	Group 1 ($n=8$) Median IQR (25–75%)	*P*
Heart rate (bpm)	66 (63–70)	69 (65–71)	0.321
Pro-BNP (pg/dl)	4493 (3207–7664)	3670 (1940–5324)	0.234
LVEF (%)	20 (19–31)	27 (23–41)	0.471
LVEDV (ml)	117 (100–152)	88 (71–98)	0.048
LVESV (ml)	79 (77–111)	56 (45–79)	0.046
MR VC (mm)	4.8 (3.9–5.1)	4.5 (2.0–5.4)	0.765
RV EDD (mm)	37 (35–38)	32 (25–38)	0.165
TAPSE (mm)	15 (12–20)	14 (11–16)	0.840
S' DTI RV (cm/s)	9.2 (8.4–9.8)	8.4 (6.8–9.5)	0.234
PAPs (mmHg)	53 (47–74)	49 (40–56)	0.450
VO_2 Max (ml O_2/kg/min)	12.6 (11.9–14.8)	10.6 (9.7–16.1)	0.574
VE/VCO_2 slope	41 (39–44)	37 (32–40)	0.113
VE/VO_2 at peak exercise	39 (35–42)	41 (35–43)	0.678

Values are median (interquartile range). EDD, end-diastolic diameter; LVEDV, left ventricle end-diastolic volume; LVEF, left ventricle ejection fraction; LVESV, left ventricle end-systolic volume; MR VC, mitral regurgitation vena contracta; PAPs, pulmonary artery systolic pressure; VCO_2, CO_2 production; VE, minute ventilation; VO_2, O_2 consumption.

walled RV. In this context, negative inotropic and chronotropic effects of β-BT could be detrimental in these patients and could explain a potential different susceptibility of the RV to β-BT compared with the LV. However, the RV and LV are highly independent of each other, and as left ventricular function improves, the left ventricular filling pressures decrease and, consequently, pulmonary artery pressure also decreases, thereby reducing right ventricular afterload. Small-scale, single-centre studies support the use of β-blockers in right ventricular dysfunction. A small series of studies previously demonstrated that carvedilol and bisoprolol improved right ventricular function in patients with heart failure.[25–28] Several trials evaluated the effects of empirical β-BT (mainly carvedilol) in patients with repaired congenital heart disease (mainly TGA and systemic RV), showing improvement of symptoms and right ventricular ejection fraction.[29–32] More recently, Galves *et al.*[33] showed that under β-BT, right ventricular function parameters evaluated by Doppler echo significantly improved in HFrEF patients.

To the best of our knowledge, this is the first study evaluating the effects of β-BT discontinuation in patients with biventricular dysfunction. Worsening of left ventricular remodelling after β-BT discontinuation despite optimal heart rate control, in absence of positive effects on right ventricular systolic function and remodelling, is the most important finding of our study. Right ventricular systolic function variations were observed during follow-up but at the end of the study no significant differences were observed between the two groups. These results highlight the importance of C in clinically stable biventricular heart failure, where left ventricular function is often the primum movens of right ventricular dysfunction.

In our study, nearly half of the patients had atrial fibrillation. There are no high-quality systematic reviews evaluating the evidence for digoxin use in clinically stable patients with right ventricular dysfunction. As a result, the role of digoxin in this setting remains unknown. In left ventricular failure, the DIG trial concluded that chronic digoxin therapy does not yield mortality benefit, although it could reduce heart failure hospitalization. However, the DIG study excluded patients with right ventricular failure.[34] Moreover, most previous studies have been conducted in patients with right ventricular failure secondary to chronic obstructive pulmonary disease and pulmonary hypertension, where a significant increase in cardiac output was found following a single dose of digoxin therapy.[35] A recent meta-analysis on the role of digoxin therapy by Alajaji *et al.*[36] showed no improvement in RVEF, exercise capacity or NYHA class in this subset of patients. However, considering a potential confounding effect of digoxin on right ventricular function due to its positive inotropic effect, we limited potential treatment biases by performing a subgroup analysis including only sinus rhythm patients, and confirmed the result found in the overall population.

Right ventricular function has usually been associated with functional capacity (measured by peak oxygen consumption) and reduced exercise tolerance is one of the hallmark symptoms in clinically stable heart failure patients, measured objectively as decreased peak oxygen uptake (VO_2peak) during maximal aerobic exercise.[37–39] Exercise capacity is a robust prognostic variable that predicts total and cardiac mortality.[40–43] A consequence of reduced VO_2 peak is that simple daily activities may require near maximal effort and result in further deconditioning.[44–50]

In our study, VO_2peak and VE/VCO_2 slope (main prognostic factors) were impaired in the overall population, being that these parameters related to right ventricular function. However, after β-BT discontinuation no

significant functional capacity variations could be observed, coherently with the observed lack of improvement in right ventricular systolic function.

Limitations

The absence of blinding and the small sample size represent significant limitations of the present study. Therefore, further studies are warranted to confirm the present findings in a larger randomized fashion. Secondly, the adoption of more sensitive measures of right ventricular function (right ventricular strain, right ventricular 3D but also right ventricular FAC) could have certainly augmented the value of our results. However, the measured parameters are those generally adopted in clinical practice and, therefore, we believe they fairly approximate right ventricular function. Lastly, the use of echocardiographic defined right ventricular dysfunction instead of identifying and including patients with right ventricular failure may have limited the study results, as they might not be applicable in this clinically relevant subgroup. However, all study patients according to our entry criteria were clinically stable without signs of congestion. The entry criterion was right ventricular dysfunction, without clinically relevant right ventricular failure.

Conclusion

In patients with biventricular dysfunction, β-BT discontinuation did not produce any beneficial effects. In addition, despite maintenance of optimal heart rate control, β-BT discontinuation induced worsening of left ventricular remodelling. Our study corroborates the hypothesis that improvement in left ventricular function may likewise be a major determinant for improvement in right ventricular function, reducing pulmonary wedge pressure and right ventricular afterload, with only a marginal action of its negative inotropic effect. In conclusion, β-BT appears beneficial also in heart failure patients with biventricular dysfunction.

Conflicts of interest

There are no conflicts of interest.

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