Effects of carvedilol on ventriculo-arterial coupling in patients with heart failure

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Background. **Ventriculo-arterial coupling, defined as the ratio of the effective afterload (Ea) to contractility (Ees), reflects the mechano-energetic performance of the heart and is increased in chronic heart failure (CHF); the aim of treatment is to reduce its value. We studied the effect of carvedilol on the Ea/Ees ratio in patients with CHF treated with ACE-inhibitors, diuretics, and digoxin.**

Methods. **Between November 1999 and October 2001, 36 consecutive ambulatory patients (aged 31 to 76 years) with stable CHF and idiopathic or hypertensive cardiomyopathy, in sinus rhythm and with a left ventricular ejection fraction ≤ 40%, were started on carvedilol and the dose was increased to the maximum tolerated. Ees was calculated as the left ventricular systolic pressure – taken as the systolic arterial pressure measured using the cuff manometer simultaneously with two-dimensional echocardiographic recordings – divided by the left ventricular end-systolic volume. Ea was measured as the ratio of the left ventricular systolic pressure to the stroke volume. All patients were investigated prospectively after 6 and 12 months of treatment.**

Results. **Out of 36 patients, 4 did not tolerate the drug and were dropped out. At 6.35 ± 1 months, the daily dosage of carvedilol was 49.7 ± 21 mg. The NYHA functional class improved from 1.52 ± 0.67 to 1.29 ± 0.53 (p = 0.017), the heart rate markedly diminished from 73.6 ± 13.3 to 60.8 ± 10.8 b/min (p < 0.001) and so did Ea (3.35 ± 0.91 to 2.84 ± 0.93, p = 0.001). Peripheral resistances and Ees did not change. Therefore, the decrease in the Ea/Ees ratio (2.61 ± 0.78 vs 2.19 ± 0.89, p = 0.004) and the related increase in left ventricular ejection fraction (28.8 ± 5.68 vs 33.3 ± 7.5%, p < 0.001) were due to the decrease in Ea, while Ees did not vary significantly. Moreover, the Ea reduction was related linearly to the decrease in heart rate (r = 0.46, p = 0.001). There was no change in diuretic or ACE-inhibitor dosing during carvedilol titration. At 14.7 ± 2 months of follow-up, no further variation occurred, short of a trend toward a slight increase in Ees (1.38 ± 0.49 to 1.58 ± 0.65, p = 0.07).**

Conclusions. **Carvedilol, added to the conventional therapy of CHF, improves left ventricular performance and reduces the Ea/Ees ratio by decreasing Ea, mainly through a reduction in heart rate. This effect is already evident at 6 months and persists later on, while only after 12 months does Ees tend to increase slightly.**

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Introduction

β-blocker therapy is now a mainstay of treatment of patients with heart failure and left ventricular systolic dysfunction[1-6]. However, despite the brilliant clinical success, its mechanism of action has not yet been well established. Clinical improvement seems to be due to an increase in the left ventricular ejection fraction (LVEF). This effect has been recently attributed to an increase in contractility, due to upregulation either of β-receptors[7], or of the sarcoplasmic reticulum calcium ATPase (which is involved in calcium handling), or of the contractile-protein isoform β-myosin heavy chain[8]. However, this improvement in contractility is not apparent before a few months, whereas clinical improvement manifests after some weeks. Ventriculo-arterial coupling offers a conceptual framework[9-11] for an understanding of the adaptation of the left ventricle to a variety of physiological and pathological conditions, and has been successfully used in the setting of left ventricular failure[12-14]. According to this theory, LVEF is determined exclusively by the contractility and the effective afterload (Ea). For this purpose, contractility is measured as the slope of the end-systolic pressure-volume line (Ees), while Ea is measured as the ratio of the left ventricular end-systolic pressure to the stroke volume. On these assumptions, it is easy to demonstrate that LVEF is given by: Ees/(Ea + Ees) (equation 1) (see Appendix). It may also be easily seen that when Ea = Ees (Ea/Ees = 1) LVEF is 50% while, when Ea/Ees = 0.5, LVEF is 67%. Now, the Ea/Ees ratio is the coupling parameter, i.e. the parameter that couples the left ventricle with its own afterload, and it has been con-

vincingly demonstrated, both on theoretical and experimental grounds, that this parameter is strictly related to the mechano-energetic properties[15-17] of the left ventricle. Theoretically, it may be assumed that in physiological conditions the left ventricle and its afterload constitute a matched system. Indeed, previous experimental studies showed that the heart and vascular system are considered matched when either optimal external work or mechanical efficiency is provided by the contraction[15,16]. In a failing heart operating at the limit of the preload reserve, the left ventricle faces increased peripheral resistances and decreased vascular compliance, secondary to adrenergic adaptations. This results in ventricular-load mismatch, which equally explains both the decrease in LVEF and in the work efficiency.

An effective therapy of heart failure, aiming at increasing LVEF should reduce the Ea/Ees ratio toward normal values. This may be accomplished by increasing Ees or reducing Ea. However, since Ea results from the product of the peripheral resistance (R) per heart rate[9] (see Appendix), both a decrease in resistance or in heart rate should be able to decrease Ea and increase LVEF. Carvedilol is able to block α_1, β_1, and β_2-receptors, and is now widely and successfully used in the treatment of patients with heart failure. The aim of this study was to investigate whether the improvement in the clinical conditions (NYHA functional class) and LVEF induced by carvedilol are obtained through an action on Ees or Ea and, in the latter case, whether the peripheral resistance, heart rate or both are affected.

Methods

Patients. The study subjects were 36 ambulatory patients, who were started on carvedilol at our department from November 1999 to October 2001. All patients had stable chronic heart failure (CHF) in NYHA functional class II-III, and idiopathic or hypertensive cardiomyopathy, were in sinus rhythm and had a LVEF ≤ 40%. Coronary artery disease was excluded by coronary angiography. No patient had mitral regurgitation above +/4.

Patients were excluded if they had an absolute contraindication to β-blocker therapy, significant valvular disease, previous revascularization, acute myocarditis or excessive alcohol intake. All patients were in clinically stable conditions on a regimen comprehensive of ACE-inhibitors (100%), diuretics (91%), and digitalis (61%). The mean duration of heart failure symptoms was 18 months (range 6 to 36 months).

β-blocker therapy. All patients were on standard medical therapy before initiation of carvedilol (Table I). A test dose of 3.125 mg was given first; if tolerated, the dosage was increased every 1 or 2 weeks up to the target or maximum tolerated dose. The target dose for carvedilol was 25 mg twice daily for patients weighing < 85 kg, otherwise 50 mg twice daily.

Table I. Baseline parameters.

No. patients	36
Age (years)	57.5 ± 12.0
Body surface area (m^2)	1.7 ± 0.2
Sex (M/F)	26/6 (81%/19%)
Diabetes	3 (9%)
Left bundle branch block	20 (62%)
Left ventricular mass/volume	0.7 ± 0.1
NYHA functional class	2.30 ± 0.67
Heart rate (b/min)	73.7 ± 13.3
Systolic blood pressure (mmHg)	131.7 ± 16.8
Diastolic blood pressure (mmHg)	83.3 ± 8.6
Left ventricular ejection fraction (%)	28.8 ± 5.7
End-diastolic volume (ml/m^2)	148.4 ± 47.7
End-systolic volume (ml/m^2)	105.6 ± 32.43
Peripheral resistance (UWm^2)	35.7 ± 12.0
Ea ($mmHg/[ml/m^2]$)	3.36 ± 0.91
Ees ($mmHg/[ml/m^2]$)	1.38 ± 0.50
Ea/Ees ratio	2.62 ± 0.78
Digoxin	22 (61%)
Furosemide	33 (91%)
mg/die	47.1 ± 55.3
Spironolactone	7 (22%)
ACE-inhibitors	32 (100%)
Angiotensin II receptor antagonists	0

Ea = effective afterload; Ees = contractility.

Procedure. All patients underwent a thorough clinical examination, electrocardiography and two-dimensional echocardiography at T0, before starting carvedilol, and at two follow-up visits, 6 months apart. Their demographic and clinical variables were recorded. Echocardiograms were obtained using an HP Sonos 5500 machine (Hewlett-Packard, Loveland, CO, USA) equipped with a 2.5 MHz probe with the patient in the left lateral position. The left ventricular volumes were measured in the 4-chamber view using the area-length method[18,19]. Ees was computed as the left ventricular systolic pressure – taken as the systolic arterial pressure obtained using a cuff manometer during echocardiographic recordings – to the left ventricular end-systolic volume ratio, a reasonable approximation of the true end-systolic pressure-volume slope for intrapatient comparison[18,20,21]. Ea was measured as the systolic pressure to the stroke volume ratio. The latter was obtained by subtracting the left ventricular end-systolic volume from the left ventricular end-diastolic volume. In order to compute the peripheral resistance, the mean aortic pressure was estimated as[22] (D + (S - D)/3), where D is the aortic diastolic pressure and S is the aortic systolic pressure measured using a cuff manometer as previously described. The cardiac output was obtained by multiplying the stroke volume by the heart rate, as obtained during echocardiography. The resistance was then computed by dividing the

mean estimated aortic pressure by the cardiac output. To assess reproducibility, the echocardiographic parameters were independently evaluated by two observers (GT, SO). The interobserver agreement was 95%.

Statistical analysis. Continuous variables are expressed as mean ± SD. The unpaired Student's t-test was used for comparison of continuous variables between groups and the repeated measures analysis of variance for comparison within groups using Bonferroni's correction. The Fisher exact probability test was used to compare frequencies. In order to investigate the separate influence of resistance and heart rate in changing Ea, and the role of Ees in changing LVEF, we normalized these variables to time T0. Simple linear regression analysis was used to examine the relation between aortic elastance and heart rate changes during follow-up. A two-sided p value < 0.05 was considered statistically significant. Data were analyzed using SPSS for windows, release 10.0 (SPSS Inc., Chicago, IL, USA).

Results

Of 36 patients, 4 (11%) did not tolerate the drug and were eliminated. The resting heart rate tended to be lower in patients who did not tolerate carvedilol (73.7 ± 13.4 vs 64 ± 5.6 b/min, p = 0.08). At the first clinical follow-up performed at 6.35 ± 1 months, the attained daily dose of carvedilol was 49.7 ± 21 mg. The period from the initiation of β-blocker therapy until attainment of the final dose was 1.4 ± 0.5 months. The baseline and follow-up clinical and echocardiographic features of the patients are listed in tables I and II. The changes in the parameters with respect to baseline are represented in figure 1. The NYHA class improved from 1.52 ± 0.67 to 1.29 ± 0.53 (p = 0.017), the heart rate diminished markedly from 73.6 ± 13.3 to 60.8 ± 10.8 b/min (p < 0.001) and so did Ea (from 3.35 ± 0.91 to 2.84 ± 0.93, p = 0.001). The peripheral resistances and Ees did not change. Therefore, the decrease in the Ea/Ees ratio (2.61 ± 0.78 vs 2.19 ± 0.89, p = 0.004) and the related increase in LVEF (28.8 ± 5.68 vs 33.3 ± 7.5%, p < 0.001) were due to the decrease in Ea, while Ees did not vary significantly. Moreover, the decrease in Ea after carvedilol therapy was significantly correlated with the decrease in heart rate (r = 0.46, p = 0.001) (Fig. 2). There was no change in diuretic or ACE-inhibitor dosing with carvedilol titration. At 14.7 ± 2 months of follow-up, no further variation occurred, except for a trend toward a slight increase in Ees (1.38 ± 0.49 to 1.58 ± 0.65, p = 0.07) after 6 months of therapy. However, if we consider patients (18/32) in whom LVEF increased by > 5 units after 12 months of therapy with carvedilol, a significant increase in Ees is also evident (1.44 ± 0.54 to 1.99 ± 0.73, p = 0.008).

Discussion

The use of β-blockers in heart failure dates back to the pioneering researches of Swedberg et al.[23] and Waagstein et al.[24], and was confirmed after the introduction of ACE-inhibitors. Numerous clinical trials have demonstrated that β-blockers produce consistent benefits in patients with CHF[1-3,25-29]. It soon appeared clear that this favorable action rests upon an increase in LVEF[30-32], which occurs in about 60 to 70% of treated patients, and is more pronounced than that obtained after ACE-inhibitors. This fact was unexplainable on the basis of the well known pharmacologic action of β-blockers, i.e. a decrease in contractility and a small, if any, influence on peripheral resistance. Ventriculo-arterial coupling offers a conceptual framework to explain the favorable action of β-blockers soon after administration as simply due to the reduction in Ea. In fact, in our experience Ea was significantly reduced

Table II. Follow-up.

	T0	T1	p (T0-T1)	T2	p (T0-T2)	p (T1-T2)
Carvedilol	32 (100%)	31 (97%)		32 (100%)		
mg/die	0	49.7 ± 21.0		53.5 ± 18.6		
NYHA functional class	1.52 ± 0.67	1.29 ± 0.53	0.017*	1.25 ± 0.52	0.01*	0.64
Heart rate (b/min)	73.66 ± 13.35	60.8 ± 10.8	< 0.001*	63.0 ± 10.98	0.001*	0.20
Systolic blood pressure (mmHg)	131.72 ± 16.83	126.4 ± 22.7	0.17	129.8 ± 15.26	0.55	0.44
Diastolic blood pressure (mmHg)	83.28 ± 8.58	76.9 ± 11.2	0.003*	79.4 ± 7.33	0.01*	0.32
Left ventricular ejection fraction (%)	28.81 ± 5.68	33.3 ± 7.5	< 0.001*	34.7 ± 7.79	< 0.001*	0.25
End-diastolic volume (ml/m^2)	148.44 ± 47.68	151.6 ± 56.2	0.63	148.7 ± 49.96	0.96	0.71
End-systolic volume (ml/m^2)	105.6 ± 32.43	100 ± 32.5	0.51	97.1 ± 32.8	0.18	0.22
Peripheral resistance (UWm^2)	35.70 ± 12.05	35.5 ± 12.0	0.94	34.47 ± 9.83	0.65	0.58
Ea (mmHg/[ml/m^2])	3.36 ± 0.91	2.84 ± 0.93	0.001*	2.85 ± 0.80	0.008*	0.99
Ees (mmHg/[ml/m^2])	1.38 ± 0.49	1.46 ± 0.62	0.27	1.58 ± 0.65	0.07	0.11
Ea/Ees ratio	2.62 ± 0.78	2.19 ± 0.89	0.004*	2.10 ± 0.88	0.001*	0.54

Ea = effective afterload; Ees = contractility. * p < 0.05.

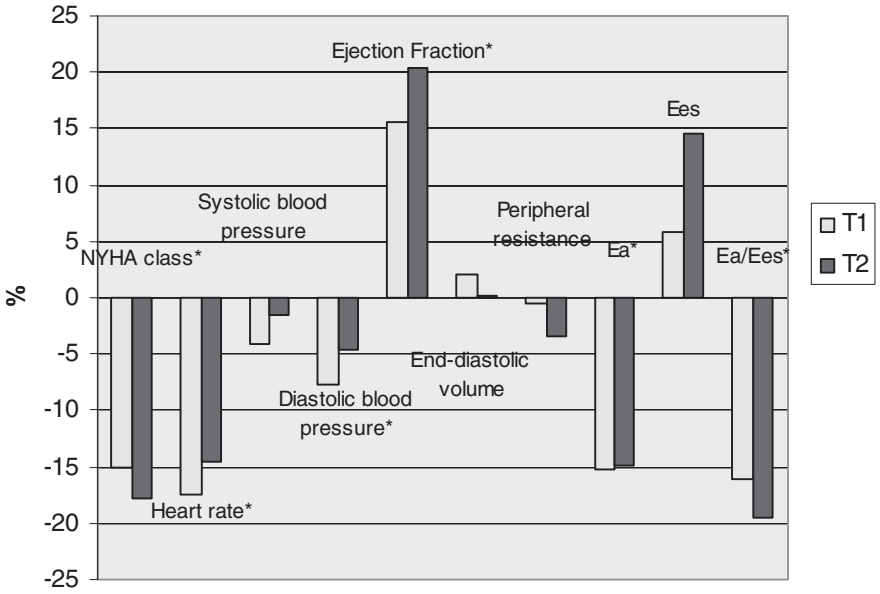

Figure 1. *Percent variation in the hemodynamic parameters after 6 (T1) and 12 months (T2) of carvedilol with respect to baseline. Note that the peripheral resistances are unchanged, and that the contractility (Ees) increases especially after 12 months. Ea = effective afterload. * p < 0.05.*

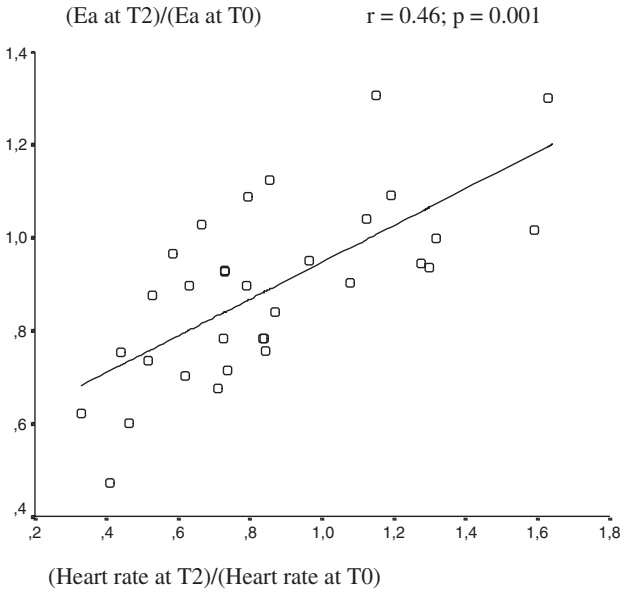

Figure 2. *Variations in the effective afterload (Ea) are linearly related to the variations in heart rate.*

soon after the administration of carvedilol, and LVEF was significantly increased at a time when the resistance and Ees were unchanged. Therefore, according to equation (1) (see Appendix), this increase in LVEF is uniquely due to the decrease in Ea. But Ea is the product of the peripheral resistance per heart rate, and since the peripheral resistance was unchanged, it follows that the increase in LVEF was solely due to the decrease in heart rate. After 12 months Ees showed a trend to increase, and was significantly increased in patients whose LVEF increased by > 5 units. Thus, the increase in LVEF seems to be initially mediated by a decrease in Ea, due to the decrease in heart rate, and later to a slight increase in contractility, at least in patients who respond to therapy. The decrease in heart rate has long been known as the most powerful predictor of an improvement in left ventricular function[33,34] in heart failure patients treated with β-blockers. The MDC trial has shown that an increase in LVEF of 13 units vs 6 units was predicted by the decrease in heart rate after metoprolol[24]. In the CIBIS trial, the baseline heart rate and especially its reduction after bisoprolol correlated with survival[35]. Recently, Packer et al.[2] demonstrated that patients with a baseline rest heart rate > 82 b/min benefited most from carvedilol. On the contrary, Eichhorn et al.[36] do not mention heart rate among the predictors of hemodynamic improvement, and the values of heart rate and heart rate variations are not reported. Lowes et al.[8] report that patients who respond to carvedilol, i.e. those whose LVEF increases by at least 5 units, have a greater decrease in resting heart rate after the drug. However, they do not comment this finding. The usual explanation for the beneficial role of a heart rate reduction is that bradycardia allows the heart to save energy and contract more efficiently. The "energy starving" myocardium can slowly recover and ameliorate its function. A decrease in myocyte loss, and an increased expression of β-receptors and of calcium regulating proteins has been demonstrated[37,38] in animal experiments. More recently, in a model of heart failure in dogs, it has been demonstrated that the institution of bradycardia is a major mechanism by which β-blockers effectively restore the contractile function as measured *in vivo* and in isolated cardiocytes[37]. Finally, Lowes et al.[8] have shown that LVEF increased by at least 5 units in 26 out of 32 patients treated with carvedilol. These respon-

ders had an increase in sarcoplasmic reticulum calcium ATPase mRNA and in α-myosin mRNA, and a decrease in β-myosin mRNA after 6 months of therapy. Metra et al.[39] showed an increase in LVEF of at least 15 units in 22% of their patients, with an excellent prognosis. These data point to an increase in contractility as the final mechanism by which β-blockers improve hemodynamics and clinical status. We indeed found an increase in contractility – i.e. an increase in Ees – in responders (LVEF increase > 5 units) after 12 months, but we also found an increase in LVEF at 6 months, before the increase in Ees took place. At that time, only Ea and heart rate were decreased. Thus, since the resistance remained unchanged, we believe that the early increase in LVEF was due to an unloading effect of β-blockers (decrease in Ea) exclusively attributable to the decrease in heart rate.

In summary, our results seem to demonstrate that carvedilol, added to conventional therapy, exerts a favorable unloading effect on the left ventricle, leading to an increase in LVEF and a better ventricular arterial coupling. The observed important decrease in the Ea/Ees ratio was due, early, to a significant reduction in Ea combined, later on, with a trend to an augmentation of Ees. This effect appeared to be primarily due to the decrease in heart rate, at least in our study patients who were on ACE-inhibitor therapy, which mainly acts on the peripheral resistance. After 1 year, Ees showed a trend toward an increase, and was significantly increased in patients who respond to therapy (LVEF increase > 5 units). Vasodilating properties do not seem to be important in inducing hemodynamic improvement, at least in patients already on full doses of ACE-inhibitors. β-blocking treatment may be anticipated to be particularly useful in patients in sinus rhythm whose heart rate can decrease substantially and decrease Ea, and whose contractility reserve is not fully exhausted so as to allow a partial restoration after 12 months. These results should be considered when managing the hemodynamic environment of CHF.

Study limitations. An important limitation of the present study was the use of the peak systolic pressure instead of the left ventricular end-systolic pressure in the evaluation of Ees and Ea. This error is evident in the separate computation of these two parameters, but their ratio eliminates the pressure and therefore is unaffected. We believe that for intrapatient comparisons this error should not modify the main results. The same considerations apply to the use of the peak systolic pressure to the end-systolic volume ratio as an index of contractility. A further limitation consisted of the fact that we inferred the hemodynamic parameters from echocardiographic data. Recently, not many studies report a correlation between the two techniques, especially for more sophisticated parameters, and we had to rely on rather old data.

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Appendix

Relationship between peripheral resistance, heart rate and effective afterload

The relationship between peripheral resistance (R), heart rate (HR) and effective afterload (Ea) may be understood by considering the following equations:

$$Ea = Pes/SV$$

where Pes is the left ventricular end-systolic pressure and SV is the stroke volume, and

$$R = Pmean/Q$$

where Pmean is the mean aortic pressure and Q is the cardiac output. But Q = SV*HR, and since the dichrotic notch is rather close to the mean aortic pressure, Pes ≅ Pmean. Therefore

$$R = Pes/(SV*HR)$$

$$Ea = R*HR$$

Thus Ea equals the product of the resistance per HR.

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