Current perspectives

Benefits of beta-blockers in heart failure: a class specific effect?

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There is now compelling evidence in favor of the use of beta-adrenergic antagonists for the treatment of chronic heart failure. In clinically stable patients who remain symptomatic despite the fact that they are already receiving an angiotensin-converting enzyme inhibitor, diuretics and digoxin, the addition of a beta-blocker has been shown to produce further improvements in cardiac function and structure as well as in the quality and quantity of life.

However, although such benefits can be achieved with a number of beta-blockers, the relevant differences in the ability of inhibiting the adrenergic drive among the various agents in the same class could translate into quantitatively different clinical effects. At present, the question whether all beta-blockers confer equal benefit or not to heart failure patients remains unanswered, since only few studies have prospectively addressed the issue and overall evidence does not permit to draw a conclusion that one agent has to be preferred to another. A large ongoing trial, designed to compare the effects of metoprolol and carvedilol on all-cause mortality in chronic heart failure, will provide much of the information required.

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Introduction

The stimulation of neurohormonal pathways (primarily the renin-angiotensin-aldosterone and sympathetic nervous systems), although initially providing hemodynamic support to the failing heart, if prolonged and excessive has many potential detrimental effects which can adversely affect the course of cardiac disease[1].

Therefore, over the past two decades new therapeutic strategies for heart failure (HF) have been tailored to counteract the long-term deleterious consequences of these hyperactivated neurohormonal mechanisms. It has extensively been demonstrated that angiotensin-converting enzyme inhibitors are able to prevent the onset or delay the progression of the HF clinical syndrome[2-5]. Moreover, growing evidence has been accumulated suggesting that the addition of carefully titrated beta-adrenergic antagonists can produce further benefits in terms of cardiac function and structure and of the symptomatic status of HF patients[6-13]. Recently, several large trials have demonstrated that beta-blocker therapy can prolong patient survival[14-16]. As a result, a beta-blocking agent should be recommended as part of standard therapy (in addition to an angiotensin-converting enzyme inhibitor, diuretics and digoxin) for most of clinically stable patients having HF symptoms due to left ventricular systolic dysfunction.

However, several problems concerning the use of beta-blockers are still unresolved[17] and their role in subjects with asymptomatic left ventricular dysfunction is yet to be ascertained. Another important question regards the potential heterogeneity in the clinical effects of different beta-blocking agents. The interest in this issue has grown in recent years with the advent of newer, third-generation compounds characterized by a high antiadrenergic activity (blockade of both the $beta_1$- and $beta_2$-adrenoreceptors) and/or some relevant ancillary properties (such as vasodilation) and, therefore, with a potential for being more effective in the treatment of HF than the second-generation $beta_1$-selective blockers.

This article reviews and discusses current evidence on this issue.

Adrenergic state of the failing human heart

It is well recognized that the sympathetic nervous system, in concert with other neuroendocrine pathways, has a key role in the pathophysiology of the HF syndrome[18].

In the short term, sympathetic activation represents a compensatory mechanism which serves to support circulatory function and, subsequently, to guarantee an adequate organ perfusion in spite of a lowered cardiac output; this hemodynamic goal is pursued by stimulating myocardial contractility and heart rate, as well as by promoting peripheral vasoconstriction, blood flow redistribution, and salt and water retention[19].

In the long term, however, a persistently increased adrenergic drive can cause many potential deleterious effects which contribute to the progression of HF[1]. An excess of norepinephrine enhances cardiac work by means of its inotropic and chronotropic stimulatory effects as well as by exacerbating the hemodynamic stress on the failing heart through an increase in the ventricular preload and afterload (secondary to excessive peripheral vasoconstriction and fluid retention). Since catecholamines augment myocardial energy expenditure but contemporarily diminish myocardial blood flow by promoting coronary vasoconstriction, the metabolic balance of the heart worsens[20].

Moreover, cardiac damage can develop not only in response to these unfavorable hemodynamic actions but also and mainly because catecholamines exert direct toxic effects on the heart. These effects appear to be mediated also by changes in the genetic pathways that regulate myocardial collagen formation, myocyte calcium ion metabolism and myosin isoform expression and growth and programmed death (apoptosis) of muscle cells[21].

As a result, the aforementioned metabolic, hemodynamic and direct cytotoxic effects of norepinephrine adversely affect cardiac structure and function by accelerating the process of ventricular remodeling and ultimately leading to intractable pump failure[22,23]. In addition, the excess of catecholamines, secondary to its unfavorable effects on myocardial electrophysiologic properties and body electrolyte balance can also precipitate sudden death by lowering the threshold for ventricular arrhythmias[24].

The deleterious actions of the sympathetic nervous system on the heart are mediated by three types of cardiac adrenergic receptors ($beta_1$, $beta_2$, and $alpha_1$). In normal human hearts, the myocyte adrenoreceptor population is predominantly beta, with a $beta_1/beta_2$ ratio of 70-80/20-30. On the other hand, $alpha_1$-adrenoreceptors are much less numerous. $Beta_1$- and $beta_2$-adrenoreceptors are coupled, by the stimulatory Gs protein, to the effector enzyme adenylyl cyclase, which activates the positively inotropic and chronotropic as well as strongly growth-promoting second messenger cAMP. $Alpha_1$-adrenoreceptors are coupled by the stimulatory Gq protein to the effector enzyme phospholipase C, which through the second messenger diacyl glycerol activates the mildly positive inotropic as well as growth-promoting protein kinase C. In the failing human heart, the chronic exposure to high levels of catecholamines induces significant changes in adrenoreceptor number and function. There is a reduction in the beta-receptor population density ("down-regulation") which selectively involves the $beta_1$-subtype such that the $beta_1/beta_2$ ratio is shifted from 70-80/20-30 to 60-65/35-40. Moreover, both the $beta_1$- and $beta_2$-receptors are functionally "uncoupled" from their effector enzyme adenylyl cyclase; therefore, the beta-adrenergic signal transduction is globally reduced with a loss of more than 50% of the total transducing potential in end-stage HF. In contrast to the beta-receptor populations, $alpha_1$-receptor density appears to be increased ("up-regulation"); therefore, in the failing human heart the $beta_1$:$beta_2$:$alpha_1$-receptor profile is approximately 2:1:1[25,26].

Inhibition of adrenergic signal transduction seems to configure a strategy to counteract the long-term harmful effects of sympathetic hyperactivation.

Globally, these data provide the most convincing rationale for the use of beta-blockers in HF.

Classification of beta-blocking agents

There are three generations of beta-blocking agents, which significantly differ in their pharmacological properties.

The first-generation compounds – such as propranolol and timolol – are $beta_1$-$beta_2$-nonselective antagonists and may be poorly tolerated in patients with HF because of their marked myocardial-depressing and afterload-enhancing effects[26].

The second-generation compounds – such as metoprolol, bisoprolol and atenolol – are $beta_1$-selective antagonists. When administered acutely, they reduce cardiac function to a lesser extent than the first-generation agents since the unblocked cardiac $beta_2$-receptors may support myocardial contractility and the unblocked vascular $beta_2$-receptors may mediate vasodilation. Additionally, the second-generation compounds can facilitate the contractile response to sympathetic stimulation during stress, since they possess the property of upregulating the down-regulated cardiac $beta_1$-receptors and recoupling the uncoupled cardiac $beta_2$-receptors[26]. Therefore, they are tolerated well enough to be used in the treatment of HF and two of them, metoprolol and bisoprolol, have been extensively evaluated in clinical trials[6,8,9,15,16].

The third-generation compounds are $beta_1$-$beta_2$-nonselective (carvedilol, bucindolol, labetalol) or $beta_1$-selective (nebivolol, celiprolol) antagonists with potentially relevant ancillary properties such as vasodilation (which can be due to $alpha_1$-receptor blockade (carvedilol, bucindolol, labetalol), nitric oxide production (nebivolol), or $beta_2$-receptor mediated intrinsic sympathomimetic activity (celiprolol)[27]. In the setting of HF, the most widely tested third-generation agent is the nonselective beta-blocker carvedilol[10-14].

As compared to the second-generation compounds, carvedilol exhibits a more comprehensive antiadrenergic activity since it blocks the $beta_1$-, $beta_2$-, and $alpha_1$-receptors, lowers cardiac adrenergic drive and prevents the up-regulation of down-regulated $beta_1$-receptors. Theoretically, the higher degree of adrenergic inhibition should enhance the ability of the drug to counteract the toxic effects of catecholamines on the heart, whereas the property of not restoring the cardiac $beta_1$-population density may impair the contractile response to sympathetic stimulation during stress[27]. The vasodilator action of carvedilol (related to the $alpha_1$-receptor blockade) offsets the negative inotropic effect and improves the acute tolerability by avoiding the drop in cardiac output and the increase in filling pressures[26,27]. It is unclear whether this property may also contribute to the long-term efficacy of the drug by unloading the failing heart. The unique pharmacological profile of carvedilol also includes *in vitro* antioxidant and antiproliferative properties, the clinical relevance of which is still unknown[27,28].

Beta-blocking agents in chronic heart failure

The specific effect of beta-blocking agents is a favorable change in the biology of the myocardium[23] which clinically translates into a time-dependent reversal of left ventricular dysfunction and remodeling[7,8,10-13,29-36]. In the long term, the beta-blockade strategy also results in relief of symptoms and improvement in quality of life, as clearly indicated in a number of small- and medium-size studies[6-13,29-36].

Moreover, following the nonconclusive data of the MDC[8], CIBIS-I[9] and ANZ[13] trials which did not have sufficient power for the accurate assessment of the effects on mortality, in the last years several large studies have definitively proven the ability of beta-blocking agents to prolong the life expectancy of HF patients (Table I)[8,9,13-16].

The US Carvedilol Trial[14] (consisting of four coordinated studies[29-32] that included a total of 1094 patients in New York Heart Association-NYHA functional class II-IV and with a left ventricular ejection fraction-LVEF ≤ 35% and a mean follow-up of 6 months) was prematurely stopped because of a reduction in the overall mortality (relative risk reduction-RRR 65%, 95% confidence interval-CI 39 to 80%, $p < 0.001$) of the carvedilol group as compared to that of the placebo group. Similarly, both the CIBIS-II with bisoprolol[15] (2647 patients, NYHA class III-IV, LVEF ≤ 35%, mean follow-up 16 months), and MERIT-HF with metoprolol[16] (3991 patients, NYHA class II-IV, LVEF ≤ 40%, mean follow-up 12 months) trials were stopped early because of a significant benefit on all-cause mortality in beta-blocker treated groups (with bisoprolol: RRR 34%, 95% CI 19 to 46%, $p < 0.0001$; with metoprolol: RRR 34%, 95% CI 19 to 47%, $p < 0.0001$).

More recently, the COPERNICUS trial with carvedilol (2289 patients, NYHA class IV, LVEF < 25%, mean follow-up 21 months) was prematurely terminated because of evidence of a striking survival benefit (RRR 35%, 95% CI 19 to 48%, $p < 0.0002$) for patients treated with carvedilol (unpublished data; oral presentation at the XXII Congress of the European Society of Cardiology, Amsterdam, The Netherlands, 2000).

In the setting of large mortality trials on beta-blockade in HF, the results of the BEST trial with bucindolol (2708 patients, NYHA class III-IV, LVEF ≤ 35%, mean follow-up 24 months) were not up to expectations. In fact, although the drug was shown to produce favorable effects on a number of secondary endpoints (such as car-

Table I. Design and results of major clinical trials with beta-blockers in heart failure.

Trial	No. patients	Disease etiology	NYHA class	LVEF (%)	Follow-up (months)	Hospitalizations (RR, 95% CI)	All-cause deaths (RR, 95% CI)	Pump failure deaths (RR, 95% CI)	Sudden deaths (RR, 95% CI)
MDC[8], 1993 (metoprolol)	383	ID	II-III	≤ 40	12-18	↓ 29 p = 0.04*	↓ 34 (6 to 62) p = 0.058§§	– p = NS	– p = NS
CIBIS-I[9], 1994 (bisoprolol)	641	M	III	≤ 35	23	↓ 34 p < 0.01**	↓ 20 (-15 to 44) p = NS	↓ p = NS	– p = NS
ANZ Trial[13], 1997 (carvedilol)	415	IS	I-III	≤ 45	19	↓ 23 (0 to 41) p = 0.05§	↓ 24 (-36 to 58) p = NS	– p = NS	↓ p = NS
US Trial[14], 1996 (carvedilol)	1094	M	II-IV	≤ 35	6	↓ 27 (3 to 45) p = 0.036*	↓ 65 (39 to 80) p < 0.001	↓ p = not specified	↓ p = not specified
CIBIS-II[15], 1999 (bisoprolol)	2647	M	III-IV	≤ 35	16	↓ 20 (9 to 29) p = 0.0006§	↓ 34 (19 to 46) p < 0.0001	↓ 26 (-14 to 52) p = NS	↓ 44 (20 to 61) p = 0.0011
MERIT-HF[16], 1999 (metoprolol)	3991	M	II-IV	≤ 40	12	Not evaluated	↓ 34 (19 to 47) p < 0.0001	↓ 49 (21 to 67) p = 0.0023	↓ 41 (22 to 55) p = 0.0002
BEST, 1999 (bucindolol)	2708	M	III-IV	≤ 35	24	↓ 8 p = NS	↓ 10 p = NS	↓ p = NS	↓ p = NS
COPERNICUS, 2000 (carvedilol)	2289	M	IV	< 25	21	↓ 20 p = 0.0017	↓ 35 (19 to 48) p < 0.0002	Not available	Not available

CI = confidence interval (when available); ID = idiopathic; IS = ischemic; LVEF = left ventricular ejection fraction; M = mixed; NYHA = New York Heart Association; RR = relative risk (when available). * due to cardiovascular reasons; ** due to worsening heart failure; § due to all cause; §§ all-cause deaths + heart transplant. ↓ reduced; – unchanged.

diovascular deaths and hospitalizations), the study failed to prove its primary hypothesis, that is to say a significant benefit of bucindolol on all-cause mortality (unpublished data; oral presentation at the 71st Scientific Sessions of the American Heart Association, Dallas, TX, 1998). Several explanations have been advocated to account for the lesser benefits observed with bucindolol in comparison to metoprolol, bisoprolol and carvedilol[14-16]. The latter have been attributed to pharmacological differences existing among the various agents in the class (in contrast to other beta-blockers, bucindolol might have appreciable intrinsic sympathomimetic activity).

The salutary effects of beta-adrenergic antagonists as a class have been well summarized in a recent meta-analysis by Lechat et al.[37] (including 17 randomized and controlled trials on beta-blocker therapy in HF for a total of 3023 patients). The pooled data showed that the addition of a beta-blocker to conventional HF therapy was associated with significant benefits on symptoms (32% improvement in NYHA functional class, $p < 0.04$), cardiac function (29% increase in LVEF, $p < 0.0001$), morbidity indices (41% reduction in the risk of being hospitalized because of worsening HF, $p < 0.001$), and survival of patients (32% reduction in all-cause mortality, $p = 0.003$).

Do different agents in the class work in different way?

Although beta-blocker therapy has been shown to be beneficial in HF, it cannot be assumed that all beta-blocking agents are "equally" effective. In fact, the beta$_1$- and beta$_2$-blockade plus vasodilator and other ancillary effects of third-generation compounds could confer a clinical advantage compared to beta$_1$-blockade alone by second-generation compounds. Which evidence is currently available regarding this issue?

Three separate meta-analyses have attempted to resolve the issue about the benefits, in terms of mortality, of pharmacologically distinct beta-blocking agents. No significant differences were found between vasodilating and nonvasodilating agents by Doughty et al.[38] or between carvedilol and other beta-blockers by Heidenreich et al.[39]. On the contrary, in their meta-analysis, Lechat et al.[37] observed a more favorable effect, in terms of survival, among patients submitted to nonselective beta-blocker therapeutic regimens compared to those treated with selective beta-blocking agents (49 vs 18% reduction in all-cause deaths, $p < 0.05$). However, it must be noted that this was primarily attributable to the effect of the four trials[29-32] included in the US Program on carvedilol[14]. Thereafter, it was shown that even the selective beta$_1$-blockers bisoprolol and metoprolol significantly reduce mortality in HF[15,16]. It is conceivable that the differences in survival benefit between selective and nonselective beta-blocking agents observed in the meta-analysis by Lechat et al. would not be confirmed by adding the data from the two large CIBIS-II and MERIT-HF trials.

With few exceptions[40,41], most of the evidence from single comparative studies concerns metoprolol and carvedilol (Table II)[40-46]. In an early report by Gilbert et al.[42], carvedilol treatment was associated with a greater symptomatic improvement and tended to produce more favorable effects in terms of hemodynamics and left ventricular function than metoprolol treatment. However, that study did not include a direct comparison of the two drugs since the data were from two different placebo-controlled trials conducted with metoprolol and carvedilol in a similar but not identical manner[8,11].

To date, there are only few published reports which have directly compared the effects of metoprolol and carvedilol in HF patients. Kukin et al.[43] and Sanderson et al.[44] studied the effects of the two drugs in symptomatic

Table II. Design and results of comparative studies with third-generation beta-blockers versus the second-generation agent metoprolol.

	Heesh et al.[40] 1995	Sanderson et al.[41] 1998	Gilbert et al.[42] 1996	Kukin et al.[43] 1999	Sanderson et al.[44] 1999	Di Lenarda et al.[45] 1999	Metra et al.[46] 2000
Tested drug vs metoprolol	Bucindolol	Celiprolol	Carvedilol	Carvedilol	Carvedilol	Carvedilol	Carvedilol
Drug dosage (mean, mg/die)	200 bucindolol 100 metoprolol	400 celiprolol 100 metoprolol	79 carvedilol 127 metoprolol	50 carvedilol 50 metoprolol	50 carvedilol 100 metoprolol	74 carvedilol 142 metoprolol	44 carvedilol 115 metoprolol
Follow-up (months)	3	12	4-6	6	3	12	13-15
No. patients	30	40	44	67	51	30	150
Patient age (years)	49	59	50	57	59	Not reported	56
Disease etiology (IS/ID/H/V)	3/27/0/0	17/18/5/0	0/44/0/0	28/34/0/5	23/11/17/0	0/30/0/0	57/93/0/0
NYHA class (I/II/III/IV)	Not reported	0/17/21/2	1/22/20/1	0/13/48/6	0/17/33/1	0/8/19/3	0/46/90/14
LVEF (%)	22	28	22	18	26	29	21
Comparative effects on symptoms	Not evaluated	–	↑	–	–	–	–
Comparative effects on exercise tolerance	Not evaluated	–	–	–	–	↓	↓
Comparative effects on LV function	↑	–	–	–	–	↑	↑
Comparative effects on LV dimensions	Not evaluated	–	–	Not evaluated	–	↑	–

H = hypertensive; LV = left ventricular; V = valvular. Other abbreviations as in table I. ↑ significant difference in favor of the tested drug vs metoprolol; ↓ significant difference in favor of metoprolol; – no significant between-drug difference.

patients with moderate to severe left ventricular systolic dysfunction and already receiving conventional HF therapy. Both beta-blocking agents showed beneficial effects on the parameters regarding symptoms, exercise performance and ventricular function, but no significant difference between metoprolol and carvedilol treatments was found at the end of the two studies.

On the other hand, Di Lenarda et al.[45] addressed the specific question whether carvedilol may provide additional benefits in HF patients with persistent moderate to severe left ventricular systolic dysfunction in spite of long-term standard therapy plus metoprolol. At 12-months of follow-up, the most relevant finding was that patients who were switched to carvedilol presented a reversal of left ventricular dysfunction and remodeling. This, in contrast to those continuing on metoprolol. Conversely, a negative effect on maximal exercise tolerance was seen in the carvedilol treated group. These results are strongly consistent with the theoretical background[27]. Since the cardiac protection against the harmful effects of catecholamines afforded by beta$_1$-, beta$_2$- and alpha$_1$-blockade versus beta$_1$-blockade alone is more complete, a greater effect of carvedilol in improving left ventricular structure and function may be expected. At the same time, since beta-receptor down-regulation and desensitization appear to contribute to the loss of the inotropic/chronotropic response to catecholamines, this may explain why only treatment with metoprolol, which is capable of restoring cardiac beta-receptor density and function, may improve the response to maximal exercise.

The results from these trials are quite different but the characteristics of study populations (number of enrolled subjects, baseline demographics, type and severity of the disease) and designs (double-blind[43] versus open-label[44,45] randomization, drug dosage, treatment duration) should be borne in mind when interpreting them. Two aspects seem to be particularly relevant. Firstly, the study by Di Lenarda et al.[45] only included patients with idiopathic dilated cardiomyopathy, whereas in the studies by Kukin et al.[43] and Sanderson et al.[44], patients with ischemic, hypertensive or valvular heart disease were also enrolled. With regard to this, some data suggest the existence of potential differences in the adrenergic pathophysiological mechanisms of ischemic and idiopathic dilated cardiomyopathy[47] and a less impressive clinical response to beta-blockade in patients with ischemic heart disease[48]. These differences might have been responsible for the bias in favor of metoprolol. This is particularly true for the Kukin's trial where the prevalence of patients with idiopathic dilated cardiomyopathy was greater, even though not significantly, in the metoprolol group compared with the carvedilol group.

Secondly, the follow-up period was significantly longer in the study by Di Lenarda et al. With regard to this, a number of previous placebo-controlled studies have provided evidence that favorable changes in LVEF, left ventricular mass and geometry become significant within 6 months but may continue beyond 1 year of treatment[8,29,35,36,49]. Therefore, the duration of treatment is of critical importance for the maximal expression of these benefits. This, in particular, when comparing the effects of two different beta-blocking agents. In fact, since both metoprolol and carvedilol are expected to improve left ventricular function, it is conceivable that the ability to reveal any difference between one treatment and the other may be enhanced by longer exposure to the drugs. Interestingly, similar to the findings of Kukin et al. and of Sanderson et al., in the study by Di Lenarda et al., no significant difference between the effects of the two drugs on left ventricular function was detectable within 6 months of follow-up. It cannot be excluded that the small number of patients studied by Kukin et al. and Sanderson et al. may have contributed to the decrease in the ability to reveal a statistically significant difference over that short period of observation.

A study published more recently by Metra et al.[46] seems to strengthen this belief. In that long-term and double-blind study, 150 patients were randomized to treatment with metoprolol or carvedilol; at 13-15 months of follow-up, carvedilol produced a more marked improvement in LVEF and hemodynamics (increase in stroke volume and stroke work indexes, decrease in mean pulmonary artery pressure and pulmonary wedge pressure) compared to metoprolol but no different effect on symptoms. On the other hand, a significant benefit on exercise tolerance in favor of metoprolol was observed. The results of Metra et al. are very similar to those of Di Lenarda et al.; notably, the two studies are the only ones which lasted more than 6 months and, at the same time, the only ones which were able to reveal statistically significant differences between the two treatments.

Conclusion

Considering their pharmacological properties including a more comprehensive antiadrenergic activity and potentially relevant ancillary characteristics, the newer, third-generation beta-blockers (primarily the beta$_1$-beta$_2$-blocking and vasodilating agent carvedilol) are theoretically more advantageous for the treatment of HF compared to the older second-generation compounds (such as the beta$_1$-blocking agent metoprolol).

Currently available data are limited by the small number of studies which directly addressed this issue. Therefore, whether the second- and third-generation adrenergic antagonists significantly differ in clinical tolerability and efficacy has yet to be established. Further major insights on this issue will be provided by the large ongoing COMET trial which is directly comparing the effects of the second-generation beta-blocker metoprolol to those of the third-generation beta-blocker carvedilol on all-cause mortality in HF.

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