Beta-blocker therapy in unstable severe heart failure, evidence or experience?

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Abstract Currently, no evidence exists on the effects of beta-receptor blocker (BRB) treatment in patients with unstable severe heart failure. When confronted with this specific patient category, clinical experience in our centre has consistently guided us to lower the dose or stop BRB therapy. To share this experience, we present three clinical case scenarios and discuss background literature motivating our approach in these patients.

Keywords Heart Failure · Beta-blockers · Inotropics

Introduction

For quite some years, beta-receptor blockers (BRB) have been implemented in guidelines on chronic heart failure (HF). The first report of BRB therapy by Waagstein and colleagues [1] in 1975 was followed by a report in 1979 from Swedberg [2] on improved survival. Present recommendations are based on many randomised controlled trials showing mortality rate reductions of up to 30 % in patients using metoprolol, bisoprolol or carvedilol versus those on placebo [3–5]. Moreover, BRB therapy conveys a significant reduction in patients' morbidity and improvement in quality of life [5].

Initiation of BRB treatment in HF patients may transiently worsen the haemodynamic situation, leading to a temporary increase in HF symptoms. On the longer run, however, BRBs effectuate an improvement in systolic left

ventricular performance. A concomitant decrease in heart rate facilitates a better diastolic ventricular performance. While in HF plasma catecholamine concentrations are typically elevated and cardiac beta-receptors are downregulated and also less responsive [6], BRBs paradoxically reverse these alterations. The reduction in sympathetic drive and an increased cardiac susceptibility after initiation of BRB therapy, provide a higher inotropic reserve, improving physical exercise capacity. A reduction in sympathetic drive also protects against ventricular arrhythmias as a cause of sudden cardiac death [5].

This journal has recently paid attention to the treatment of patients with heart failure [7–11]. Evidence favouring the use of BRBs has typically been gathered in HF patients with New York Heart Association (NYHA) class I to III, but also in those presenting with NYHA class IV [4]. NYHA IV delineates a very heterogeneous group, however, comprising severely limited yet stable, euvoelaemic patients but also those presenting with cardiogenic shock and/or severe decompensation. This latter category, from now on referred to as '*unstable severe heart failure*', was collectively excluded from participation in all trials. Therefore, evidence for the use of BRBs in this specific population is lacking. Clinical experience in our centre has consistently guided us to stop BRBs in these unstable patients. In a previous editorial [12], we cautioned on the use of BRBs in these patients. Here, we present three patients in whom we encountered severe difficulties as a result of beta-blocker treatment.

Case 1. Decompensation in unstable severe heart failure

A male patient, aged 58, was admitted because of progressive exercise intolerance and dyspnoea at rest. He was known with an idiopathic dilating cardiomyopathy and his

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HF medication comprised metoprolol 150 mg once daily. His current admission was for acute decompensation and he was treated with intravenous diuretics. This strategy appeared to be unsuccessful because his renal function deteriorated rapidly. Echocardiography revealed a dilated left ventricle with very poor systolic function. After cessation of the BRB, excess fluid could be easily mobilised and his symptoms improved quickly. After implantation of a biventricular pacemaker and optimisation of ACE inhibition and oral diuretics, the patient could be discharged from hospital. In the outpatient clinic, BRBs could be reinstituted again in a low dose.

In a recent randomised clinical trial in acutely decompensated HF patients, investigating the effects of stopping versus continuing BRBs on length of hospital stay and 30-day mortality, no differences were found between the two groups [13]. Based on the potential need for inotropic therapy, our patient would have been excluded from this study. For these patients, in order to profit from longer term neurohumoral benefits of BRBs, the clinical haemodynamic status must permit a (temporary) decrease in myocardial contractility [14]. While considered beneficial in stable and euvoletic states, negative chronotropic effects of BRBs may be disadvantageous in decompensated states. In these patients, an increase in heart rate is the only compensatory mechanism available to them to maintain cardiac output. In the present case, to prevent the need for intravenous inotropic support, the dosage of BRB was lowered and eventually stopped. In general, it is advised to start reducing the dose first. Intolerance to BRB therapy should be considered as a strong adverse prognostic sign which likely indicates severe underlying disease.

Case 2. Poor right ventricular function in context of unstable severe heart failure

A 72-year-old female patient was seen with right-sided decompensation due to an arrhythmogenic cardiomyopathy. The deterioration was partly explained by recurrent atrial fibrillation. On admission, besides a severely compromised left ventricular function (LVF), echocardiography also revealed a very poor right ventricular function (RVF). At that time, she was still using a low dose of carvedilol. Following weaning of carvedilol, clinical status, renal function and liver-enzyme disturbances gradually improved. Also, right ventricular performance partly improved.

BRBs have been shown to improve both LVF and RVF in patients with HF [15, 16]. These studies were conducted in haemodynamically stable patients not requiring inotropic support. The current scenario illustrates our clinical experience

with right-sided HF as a predictor for a poor tolerance to BRBs. This is supported by a subset analysis from the BEST trial [17] in which the long-term beneficial effects of bucindolol in patients with chronic HF were dependent on RVF. Patients with a relatively preserved RVF ($EF > 20\%$) profited significantly from BRBs while in the subgroup with poorer RVF ($EF \leq 20\%$), BRB therapy was associated with increased mortality rates.

Case 3. Beta-blockers combined with intravenous inotropics

A 40-year-old female patient, known with a long-standing dilating (peripartum) cardiomyopathy, presented to another hospital with acutely decompensated HF. After recompensation, a mitral valvuloplasty was performed because of a severe regurgitation. Postoperatively, however, she could not be weaned off intravenous inotropic medication. Subsequently, she was referred to our centre for heart transplantation or left ventricular assist device implantation. Inotropic support at that time consisted of dobutamine 5 $\mu\text{g/kg/min}$, and dopamine 3 $\mu\text{g/kg/min}$. Remarkably, she was still on 6.25 mg of carvedilol, three times daily. During lowering of the BRB therapy, her haemodynamics improved considerably, enabling careful lowering of inotropics. Unfortunately, she died of a sepsis a few days after referral, very likely due to the central line which had been inserted for administration of inotropics.

It seems logical that simultaneous inhibition and stimulation of the same receptors (β_1 , β_2 and α) is inefficient. This reasoning is in accordance with studies examining the effect of inotropics in euvoletic HF patients already receiving BRBs. It appeared that dobutamine was not able to increase cardiac index and heart rate when combined with carvedilol and only to a limited extent when patients were on selective β_1 receptor inhibition [18, 19].

Phosphodiesterase inhibitors (PDE-I), being independent of beta-receptor signalling, indirectly promote myocardial contractility by raising intracellular cyclic adenosine monophosphate (cAMP) and thereby cytosolic calcium concentrations [18]. Temporary PDE-I infusion enabled introduction of BRB therapy in unstable severe HF [20].

A drawback of the administration of intravenous inotropics is the necessity for central venous access with its inherent risks for a line sepsis. The possibility of such a complication is further promoted by the increased proneness of these patients for developing infections. As illustrated in our patient, the consequences of a line-related sepsis can be severe. Therefore, the possibility of this complication should weigh heavily in the consideration of inserting a central venous line.

Conclusions

Evidence for the use of BRBs is lacking in patients with unstable severe HF. Temporary lowering or discontinuation of BRB therapy may be necessary and life saving in patients with unstable severe HF, especially in those with signs of right-sided HF. Before starting intravenous beta-agonists, BRBs should always be stopped. In addition, central line-related complications such as infections and genesis of (supra) ventricular arrhythmias by intravenous beta-agonists should weigh heavily in the decision of initiating inotropic medication.

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