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Weaning from inotropic support and concomitant beta-blocker therapy in severely ill heart failure patients: take the time in order to improve prognosis

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Aims Beta-blockers improve the prognosis in heart failure (HF), but their introduction may seem impossible in patients dependent on inotropic support. However, many of these patients can be titrated on beta-blockers, but there is little evidence of successful clinical strategies.

Methods and results We analysed the records of inotropy-dependent patients referred for assessment for heart transplantation. Thirty-six patients (45%) could not be weaned (NW) and underwent left ventricular assist device (LVAD) implantation or transplantation, or died. However, 44 (55%) were successfully weaned (SW). Neither the aetiology (ischaemic vs. non-ischaemic) nor cardiac indexes were different in the SW as compared with the NW group (2.27 ± 0.5 vs. 2.15 ± 0.6 L/min/m^2). The NW patients had lower LVEF ($15 \pm 5\%$ vs. $19 \pm 5\%$, $P = 0.001$), higher right atrial pressure (12 ± 6 vs. 8 ± 6 mmHg, $P = 0.02$), and more severe mitral regurgitation ($P < 0.001$) than the SW patients. At discharge, 35 of 44 SW patients were receiving beta-blockers. In 29 of them, a beta-blocker could only be initiated or continued during concomitant support with i.v. enoximone for a duration of 14.1 ± 7.2 days. Patients discharged on a beta-blocker had an LVAD/transplantation-free cumulative survival of 71% during a follow-up of 2074 ± 201 days (confidence interval 1679–2470).

Conclusion It takes time to put severely ill HF patients on beta-blockers and it may require bridging with inotropes which are independent of beta-adrenergic receptors. Whether such a strategy may result in a better clinical outcome warrants further research.

Keywords Heart failure • Inotropes • Beta-blocker • Enoximone

Introduction

Beta-blockers (BBs) have an essential role in reducing mortality and improving functional class in heart failure (HF) of all ranges of severity.[1–3] The Copernicus trial showed that patients at highest risk have the most benefit from BBs.[4,5] However, decompensation is the major concern in patients with severe HF.[6] Although clinical trials showed a survival benefit in the patients that continued BBs at admission for acute HF, continuation of BB treatment in decompensated severe HF is a dilemma in clinical practice because not all patients benefit from it.[7–9]

The European Society of Cardiology (ESC) guidelines recommend cautious use of BBs in recently decompensated patients, and temporary discontinuation of BBs in shocked or severely hypoperfused patients. In patients with severe NYHA class IV HF with persisting signs of congestion and hypotension (systolic blood pressure < 90 mmHg), treatment of congestion and achievement of euvolaemia should be undertaken before starting a BB.[10]

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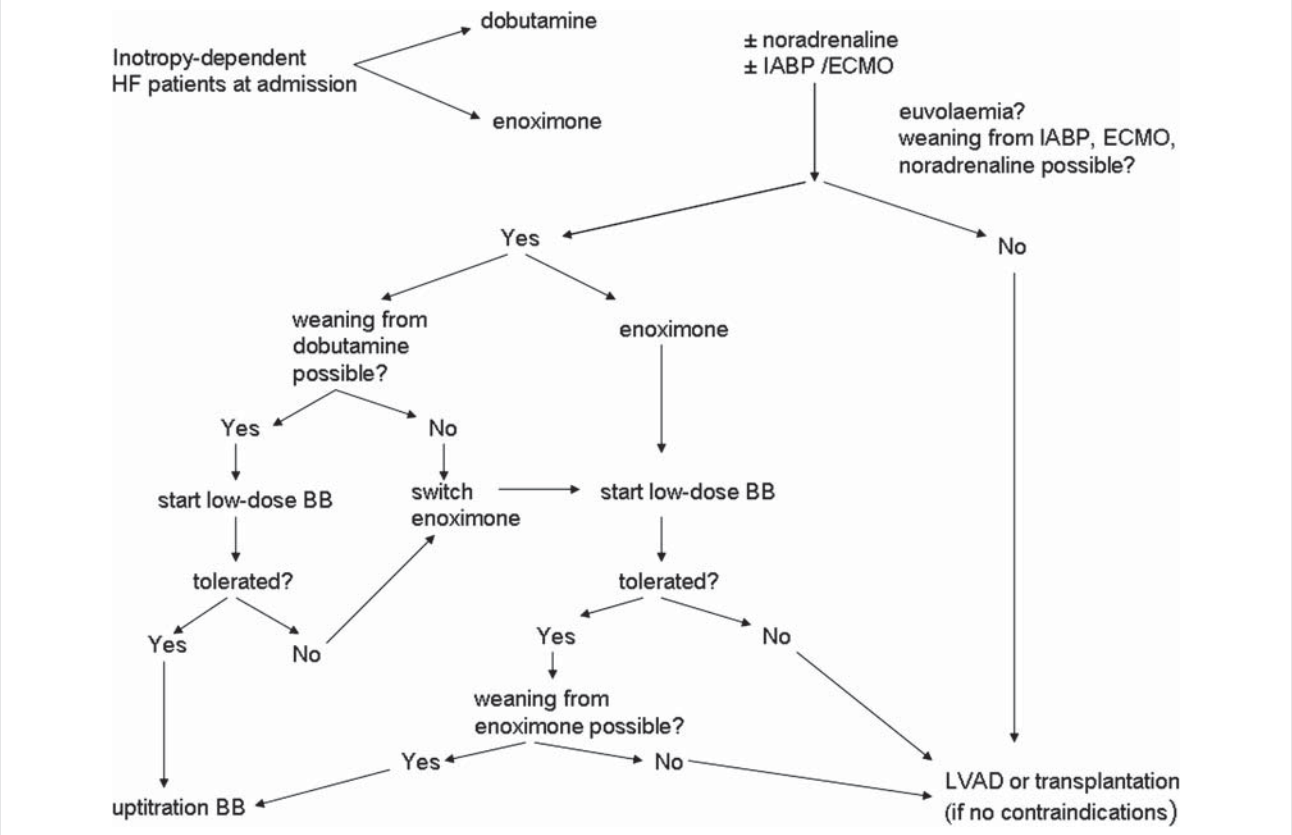

Figure 1 Flow chart of the treatment strategy in inotropy-dependent heart failure (HF) patients. BB, beta-blocker; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic ballon pump; LVAD, left ventricular assist device.

Patients with inotropy-dependent low-output HF have a very high mortality risk.[11–13] Strategies that improve the tolerability of BBs in these patients at highest risk for decompensation are expected to improve prognosis.[14,15] The combination of BB and dobutamine support is hampered by the unpredictability of the haemodynamic response due to competition for the same beta-adrenergic receptors, and the response is influenced by the selectivity of the BB and by the dose of dobutamine.[16] Several combinations of adrenergic-independent inotropes and BBs have been studied, with favourable results.[17–20] However, reports about the use of these therapeutic combinations in the unstable patients in need of prolonged inotropic or mechanical support are scarce.

We reviewed our clinical experience of treatment with BBs in inotropy-dependent patients referred to the Thoraxcenter for heart transplantation. Because we were able to postpone or withdraw the transplant indication in a number of patients, we analysed the clinical characteristics associated with successful weaning from inotropic support and good prognosis. We hypothesized that the bridging of the initial negative inotropic effect of BBs by continuation of inotropic support with the phosphodiesterase inhibitor enoximone given intravenously followed by slow weaning have contributed to an improved prognosis.

Methods

Patient inclusion and data collection

A retrospective study was conducted in a cohort of patients with severe refractory HF who could not be stabilized in the referring hospitals and were transferred to our centre for evaluation for heart transplantation. We reviewed the records of the consecutive patients transferred to the Thoraxcenter Rotterdam between 2004 and 2011. The study was approved by the Medical Ethics Committee at our institution.

Data were acquired from patient medical records and from the local hospital database. Patients referred for heart transplantation because of refractory ventricular tachyarrhythmias and patients who could be managed without the need of inotropic support were excluded. We identified 80 patients with severe low-output HF dependent on inotropic support, who could not be weaned in the referring hospital. During assessment for heart transplantation, these patients underwent optimization of HF therapy while on inotropic support and, when needed, mechanical support by intra-aortic balloon pump (IABP) or extracorporeal membrane oxygenation (ECMO). Patients with new-onset HF and ischaemic aetiology may require substitution of volume to achieve a higher wedge pressure and therefore a higher cardiac output. Most patients with chronic decompensated HF, however, have persistent signs of congestion. According to the Acute Heart Failure Committee of the ESC, pre-discharge clinical assessment of congestion

Table 1 Clinical characteristics at admission (transfer from another hospital to our tertiary centre)

Characteristics	Not weaned ($n = 36$)	Weaned from inotropic support ($n = 44$)	*P*-value
Age (years, mean ± SD)	43 ± 13	44 ± 13	0.79
Gender			
Male	20 (56%)	32 (73%)	0.15
Female	16 (44%)	12 (27%)	—
Heart disease			
Ischaemic	18 (50%)	12 (27%)	0.06
Non-ischaemic	18 (50%)	32 (73%)	—
Heart failure			
Newly developed	24 (67%)	22 (50%)	0.17
Decompensated chronic	12 (33%)	22 (50%)	—
Mechanical ventilation	21 (58%)	12 (27%)	0.006
Systolic BP (mmHg, mean ± SD)	85 ± 9	93 ± 8	0.001
Diastolic BP (mmHg, mean ± SD)	56 ± 7	61 ± 8	0.014
Heart rate (b.p.m., mean ± SD)	101 ± 21	104 ± 20	0.85
Sinus rhythm	31 (86%)	39 (89%)	0.74
QRS duration (ms, mean ± SD)	119 ± 33	122 ± 41	0.073
Haemoglobin (mmol/L, mean ± SD)	7.04 ± 1.2	7.9 ± 1.2	0.002
Serum creatinine (μmol/L, mean ± SD)	117 ± 53	133 ± 57	0.19
Urea (mmol/L, mean ± SD)	12.6 ± 7.2	13.2 ± 9	0.69
Sodium (mmol/L, mean ± SD)	133 ± 6	134 ± 6	0.41
Potassium (mmol/L, mean ± SD)	4.2 ± 0.7	4.2 ± 0.7	0.85
Bilirubin (μmol/L, mean ± SD)	31 ± 24	27 ± 23	0.4
C-reactive protein (mg/L, mean ± SD)	78 ± 87	51 ± 73	0.13

BP, blood pressure; SD, standard deviation.

Table 2 Invasive haemodynamic and echocardiographic measurements

Parameters	Not weaned ($n = 36$)	Weaned from inotropic support ($n = 44$)	*P*-value
Cardiac index (L/min/m^2, mean ± SD)[a]	2.15 ± 0.57	2.27 ± 0.47	0.38
PCWP (mmHg, mean ± SD)[a]	22 ± 8	20 ± 8	0.45
RA pressure (mmHg, mean ± SD)[a]	12 ± 6	8 ± 6	0.02
PAP systolic (mmHg, mean ± SD)[a]	43 ± 14	37 ± 10	0.06
Echocardiogram			
LVEDd (mm, mean ± SD)	64 ± 12	66 ± 10	0.36
LVESd (mm, mean ± SD)	57 ± 13	58 ± 11	0.71
LVEF (%, mean ± SD)	15 ± 5	19 ± 5	0.001
LA diameter (mm, mean ± SD)	46 ± 9	47 ± 9	0.87
Mitral inflow			
E/A ratio (mean ± SD)	2.2 ± 0.8	2.1 ± 0.9	0.83
DET (ms, mean ± SD)	125 ± 23	130 ± 33	0.55
Mitral regurgitation			
Absent, *n* (%)	—	1 (2%)	—
Mild, *n* (%)	7 (19%)	17 (39%)	—
Moderate, *n* (%)	5 (14%)	15 (34%)	0.002
Severe, *n* (%)	24 (67%)	11 (25%)	—

DET, deceleration time; LA, left atrial; LVEDd, left ventricular end-diastolic diameter; LVESd, left ventricular end-systolic diameter; PAP, pulmonary artery pressure; RA, right atrial; SD, standard deviation.
[a]Only 56 patients (70%) had invasive measurement of cardiac index, PCWP, RA, and PAP pressure

is often not systematically performed and therefore many patients are discharged with symptoms and signs of congestion.[21]

The strategy included achievement of euvolaemia (as assessed by physical examination and Doppler measurements of filling pressures) followed by a trial of weaning from inotropic support. Our strategy is presented in *Figure 1*. After achievement of euvolaemia and if the vasopressors could be weaned, weaning of dobutamine was attempted. When this was successful, a BB was initiated. If the patients did not tolerate the lowest BB dose after withdrawal of dobutamine, i.v. enoximone (in a dose of 1–2 μg/kg/min, without a loading dose) was started. Sequentially, another trial of alow dose BB was made. In patients on inotropic support with enoximone, a low dose of a BB was started, and thereafter enoximone was gradually withdrawn. If withdrawal of enoximone was not tolerated, enoximone was restarted and a longer period of combination of enoximone and BB was allowed before a new attempt to wean enoximone was undertaken.

The weaning of the inotropic support was attempted after achieving euvolaemia without signs of hypoperfusion. Weaning was considered successful if the patients remained stable without peripheral organ failure, and if they remained euvolaemic after complete withdrawal of inotropic support. Our final cohort of patients was divided into two groups according to whether weaning from inotropic support was successful or not. Introduction of a BB was carried out starting with very small doses, e.g. 3.125 mg carvedilol or 1.25 mg bisoprolol once daily, with a preference for bisoprolol when hypotension became symptomatic or resulted in an increase in creatinine levels. The BB was up-titrated until a decrease in heart rate of at least 15 b.p.m. occurred.

The decision to assign a patient to the not weaned (NW) group was made when any attempt to introduce a BB or to wean the inotropic support was complicated by signs of severe hypoperfusion. The decision to proceed with left ventricular assist device (LVAD) implantation or direct listing for urgent transplantation was taken after it became clear that these patients could not be weaned from i.v. inotropic support. Some patients died during inotropic support and while awaiting the transplantation, and were not excluded from the analysis because death was due to severe haemodynamic impairment.

Table 3 Mechanical support and intravenous inotropic and oral medication during hospitalization and at discharge

	Not weaned ($n = 36$)	Weaned from inotropic support ($n = 44$)	*P*-value
IABP	18 (50%)	10 (23%)	0.018
ECMO	10 (28%)	4 (9%)	0.039
Inotropic support			
Dobutamine at admission	34 (95%)	42 (96%)	1
Switch dobutamine/ enoximone	16 (44%)	32 (73%)	0.013
Enoximone	18 (50%)	34 (77%)	0.018
Noradrenaline	22 (67%)	11 (25%)	<0.001
Dopamine	12 (36%)	12 (27%)	0.46
Duration inotropic support (days, mean ± SD)	40 ± 34	36 ± 20	0.48
Oral medication			
ACE inhibitors	17 (47%)	41 (93%)	<0.001
ARBs	12 (33%)	21 (48%)	0.25
Digoxin	26 (72%)	35 (80%)	0.59
Amiodarone	12 (33%)	13 (30%)	0.81
Heparin/coumadines	33 (92%)	42 (96%)	0.65
ASA/clopidogrel	16 (44%)	9 (21%)	0.03
Loop diuretics	35 (97%)	44 (100%)	0.45
Beta-blockade			
BB at admission	7 (19%)	11 (25%)	0.6
BB newly introduced	7 (19%)	30 (68%)	<0.001
BB continued or introduced while on enoximone	14 (39%)	29 (66%)	0.02
Days on BB + enoximone (mean ± SD)	23 ± 35	14 ± 7	0.18
BB at discharge	n.a	35 (80%)	—

ASA, acetylsalicylic acid; BB, beta-blocker; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; SD, standard deviation.

Study definitions

All patients included in the analysis received inotropic support at admission to our department. For each patient, demographic characteristics, aetiology of HF, acute presentation vs. decompensation of chronic HF, mechanical ventilation, blood pressure, heart rate, the presence of sinus rhythm, and QRS duration were collected from the chart as recorded at admission to our department. The first laboratory measurements in our hospital were obtained from the local database.

Echocardiographic parameters were obtained from the local database. LVEF was derived from the wall motion score index. The LV and left atrial dimensions were measured from the parasternal long axis window. The E/A ratio and deceleration time (DET) were obtained by pulsed wave Doppler at the mitral inflow. Mitral regurgitation has been graded as absent, mild, moderate, or severe using established echocardiography criteria. Haemodynamic invasive measurements were available in 70% of the patients. Cardiac index, capillary wedge pressure, pulmonary artery pressure, and central venous pressures were collected as the first measurements recorded in the chart during the period of inotropic support.

Information on the use of a mechanical device (IABP or ECMO) and inotropic drugs, the duration of inotropic therapy, and the concomitant use of diuretics, ACE inhibitors, aldosterone blockers, digoxin, amiodarone, and anticoagulation during inotropic support was collected. Continuation and introduction of a BB and the time course of BB therapy during and after discontinuation of inotropic support until hospital discharge were recorded.

A patient was regarded as being intolerant of BBs if they suffered haemodynamic deterioration with hypotension, cold extremities, decreased urinary output, impairment of renal function, and/or pulmonary congestion after starting or continuing a BB. A patient was also regarded as BB intolerant if he could not be weaned from support by noradrenaline or short-term mechanical support by IABP or ECMO, as in this situation a BB could not be started.

Follow-up was performed until 1 July 2012 or until an event occurred, i.e. death, LVAD implantation, or heart transplantation. In patients receiving LVAD or heart transplantation, data were censored after that time.

Statistical analysis

Data were analysed using SPSS software, version 16.0. Continuous variables are presented as the mean ± standard deviation (SD) and were compared using Student's *t*-test or one-way analysis of variance (ANOVA). Categorical variables are presented as percentages, and were compared using Fisher's exact test. Cumulative survival was estimated according to the Kaplan–Meier method. Kaplan–Meier survival curves were compared using the log-rank test. A Cox regression analysis was used to evaluate the effect of BBs on the outcome of LVAD or transplantation. All statistical tests were two-tailed and a $P < 0.05$ was considered statistically significant.

Results

From 80 patients dependent on inotropic support at transfer to our department, 44 (55%) were eventually successfully weaned (SW), while 36 (45%) could not be weaned (NW). Baseline characteristics at admission in our department were compared between the two groups of patients (*Table 1*). There was no significant difference between the distributions of the non-ischaemic vs. ischaemic aetiology in the SW as compared with the NW patients, although there was a higher proportion of patients with non-ischaemic aetiology of HF in the SW group. Blood pressure and haemoglobin level were significantly lower in the NW group. Mechanical ventilation was more often necessary in the NW group. Echocardiographic and invasive haemodynamic measurements showed a lower LVEF, a more severe mitral regurgitation, and a higher right atrial pressure in the NW group, but no significant differences in the cardiac indexes in the two groups (*Table 2*).

Inotropic medication, mechanical device support, and oral medication are presented in *Table 3*. In the NW group, there were more patients who needed support with a mechanical device (IABP, ECMO, or both), and needed a vasopressor drug (noradrenaline). There were 46 patients with new-onset HF. Fourteen of these patients needed volume substitution after admission to our Intensive Care Cardiac Unit (ICCU), 5 patients in the SW group

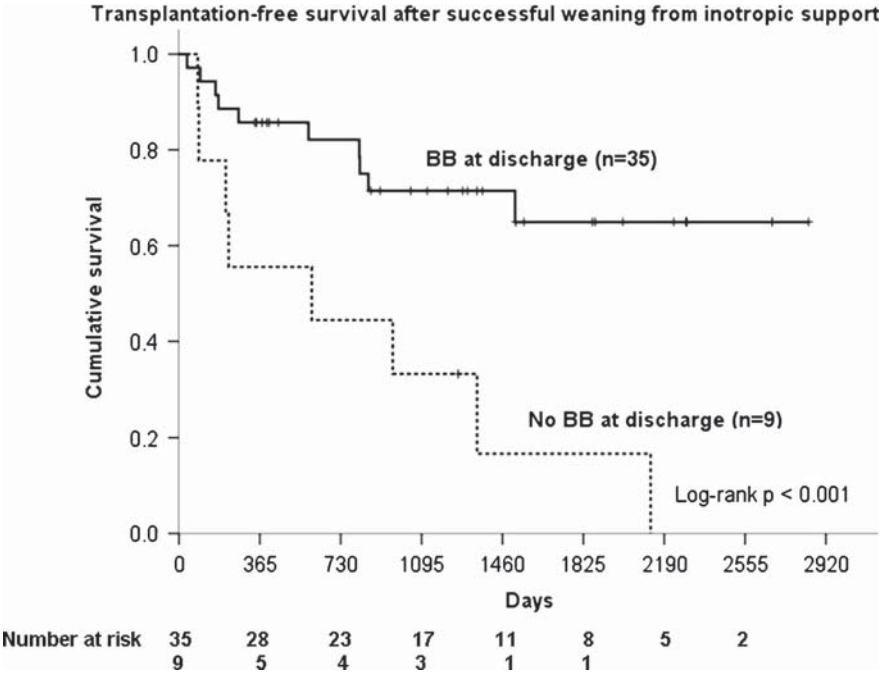

Figure 2 Cumulative survival without heart transplantation or left ventricular assist device of patients weaned from inotropic support according to the presence of beta-blocker therapy (BB) at discharge.

(2.2 ± 2.1 L/24 h) vs. 9 patients in the NW group (1.2 ± 0.6 L/24 h, $P = 0.2$). All other patients with new-onset HF and the 34 patients with decompensated chronic HF needed an increased diuretic dose in order to achieve euvolaemia. We attributed 1 diuretic unit (1 UD) to 40 mg of furosemide or 1 mg of bumetanide.

The diuretic dose was 3.5 ± 3.7 UD and 4.3 ± 3.7 UD ($P = 0.3$) at admission and discharge, respectively, in the SW group, and 3.3 ± 3.7 and 7 ± 9.7 ($P = 0.058$) at admission and before a clinical event (LVAD, transplantation, or death), respectively, in the NW group. There were no significant differences in the diuretic dose between the SW and NW group.

The duration of inotropic support was considerable and not significantly different between the two groups. A switch from dobutamine to enoximone was more frequently undertaken in the SW group. In the NW group, there were in total 18 patients who received enoximone, 2 of them at transfer to our department and 16 patients after switching from dobutamine to enoximone. In the SW group, there were 34 patients receiving enoximone, 2 patients at transfer to our department, and 32 after switching from dobutamine to enoximone. The use of concomitant medication other than a BB during inotropic support was only different with respect to the ACE inhibitors and platelet aggregation inhibitors.

Administration of a BB was attempted in 14 patients from the NW group during concomitant enoximone, but had to be withdrawn due to the haemodynamic deterioration (*Table 3*). In the SW group, the switch from dobutamine to enoximone allowed continuation or introduction of a BB during inotropic support. A BB was successfully continued or introduced during concomitant enoximone in 29 patients, while 6 more patients were titrated on a BB after direct weaning from dobutamine support. The 29 patients who received a BB in combination with enoximone could be divided into three groups: (i) patients on chronic BB therapy who, therefore, immediately after admission were switched to enoximone as inotropic medication instead of dobutamine; (ii) patients weaned from dobutamine, who had a negative BB test and were thereafter put on enoximone in order to allow a new attempt to introduce a BB; and (iii) patients receiving primarily enoximone as inotropic support who could be started directly on a BB without prior weaning from enoximone.

Thus, there were 35 patients receiving a BB at discharge. In the remainder of the patients from the SW group (nine patients), the BB had to be withdrawn because of worsening of HF and was not attempted again before discharge. From the 35 patients on a BB at discharge, 25 patients used bisoprolol at a dosage of 3.2 ± 1.6 mg/day, seven patients used carvedilol at 50 ± 36 mg/day, and three patients used metoprolol succinate at 100 ± 50 mg/day. At discharge, the heart rate of patients was considerably lower than the rate at admission, which had been >100 b.p.m. The heart rate at discharge was not significantly different in the group of patients that received a BB during concomitant enoximone support as compared with the small group of patients that received a BB after weaning from dobutamine (72.3 ± 12.3 vs. 77.8 ± 9.5 b.p.m., $P = 0.3$).

In the group of 36 patients that could not be weaned from inotropic support, 18 received an LVAD as bridge to heart transplantation, 4 underwent urgent transplantation, and 14 died during inotropic support of 44 ± 39 days. In the group of 44 patients weaned from inotropic support, there were 6 deaths, 1 LVAD implantation, and 2 transplantations in the first year, and 2 deaths

Table 4 Univariate and multivariate Cox regression analysis on the outcome of left ventricular assist device or transplantation, and transplantation-free survival

	LVAD/transplantation			Transplantation-free survival	
BB tolerated		*P-value*	*BB tolerated*		P-value
Univariate	HR 0.16 (0.04–0.28)	<0.001	Univariate	HR 3.2 (0.4–24)	0.2
Multivariate	HR 0.15 (0.05–0.38)	<0.001			
ACE inhibitor/ARB tolerated			ACE inhibitor/ARB tolerated		NA[a]
Univariate	HR 0.15 (0.06–0.35)	<0.001			
Multivariate	HR 0.36 (0.14–0.9)	0.03			
Noradrenaline			*Noradrenaline*		
Univariate	HR 3.3 (1.6–6.8)	0.001	Univariate	HR 0.54 (0.2–1.4)	0.2
Multivariate	HR 1.3 (0.5–3.2)	0.57			
IABP			*IABP*		
Univariate	HR 3.3 (1.6–6.8)	<0.001	Univariate	HR 0.8 (0.3–2.4)	0.7
Multivariate	HR 1.5 (0.6–3.5)	0.32			
ECMO			*ECMO*		
Univariate	HR 2.5 (1.1–5.8)	0.034	Univariate	HR 1.9 (0.6–5.6)	0.2
Systolic BP			*Systolic BP*		
Univariate	HR 0.9 (0.86–0.95)	<0.001	Univariate	HR 0.97 (0.9–1)	0.3
Multivariate	HR 0.94 (0.89–0.98)	0.008			
LVEF			*LVEF*		
Univariate	HR 0.88 (0.82–0.95)	0.001	Univariate	HR 1.1 (1.01–1.2)	0.02
Multivariate	HR 0.91 (0.84–0.99)	0.03			
RA pressure			*RA pressure*		
Univariate	HR 1.04 (0.97–1.1)	0.2	Univariate	HR 1.02 (0.9–1.1)	0.5
Mitral insufficiency			*Mitral insufficiency*		
Univariate	HR 1.3 (0.9–2)	0.1	Univariate	HR 0.8 (0.5–1.3)	0.5

BB, beta-blocker; BP, blood pressure; ECMO, extracorporeal membrane oxygenation; HR, hazard ratio; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; RA, right atrial.
[a]NA, not applicable due to co-linearity of ACE inhibitor/ARB and transplantation-free survival.

and 7 transplantations in the following years. The transplantation-free survival of patients discharged on a BB was significantly better than the survival of the patients from the SW group without a BB at discharge (*Figure 2*). The patients discharged on a BB had an LVAD/transplantation-free cumulative survival of 71.4% during a follow-up period of 2074 ± 201 days (95% confidence interval 1679–2470 days). We performed a Cox regression analysis to evaluate the effect of BBs on the outcome of LVAD or transplantation. One major limitation of this analysis is the small number of patients. The hazard ratio for LVAD or transplantation was significantly lower when a BB was tolerated (*Table 4*). However, none of the parameters, with the exception of LVEF, could be identified as a predictor of transplantation-free survival.

Discussion

In this study, we showed that a BB was tolerated in a proportion of patients with low-cardiac output HF, allowing weaning from inotropic support. Patients who remained dependent on inotropic support did not tolerate a BB and survived only due to LVAD implantation or urgent transplantation. The patients who stabilized and tolerated a BB had a high transplantation-free survival. This is important for clinical practice for two reasons: suitable donor hearts are very scarce and should be allocated to the most urgent cases and, secondly, transplantation prolongs life but does not normalize life expectancy so postponement of transplantation contributes to a longer life span.

Determinants of weaning from inotropic support

Although the cardiac index was low in both groups, the persistently unstable patients had a lower blood pressure, and more often needed noradrenaline as a vasopressor and mechanical support by IABP or ECMO and mechanical ventilation. Although the proportion of patients with non-ischaemic aetiology of HF tended to be higher in the group weaned from inotropic support, this difference was not statistically significant. There was no difference in the weaning success in patients with the first presentation vs. decompensated chronic HF.

A lower LVEF and a higher degree of mitral regurgitation were associated with persistent haemodynamic instability. Right atrial pressures measured invasively were higher in the group that could not be weaned from inotropic support, although there were no significant differences in the pulmonary artery and the capillary wedge pressures. This may indicate that patients with additional right ventricular dysfunction are less likely to be weaned from inotropic support. Mortality in patients not weaned from inotropic support

Table 5 Overview of studies on concomitant administration of adrenergic-independent inotropic medication and beta-blockers

Study	Population (*n*)	Patients (*n*)	Drugs	Duration	Outcome
Galie[25]	NYHA III/IV	10	Enoximone	2 h	Increase in HR and CI, myocardial O_2 consumption ↓ mean PCWP ↓
Shakar,[17] retrospective	NYHA IV, failure to wean inotropic support	30	Enoximone (oral) metoprolol	±9 months	80% tolerated BB 48% weaned 80% survival (including 30% transplantation, at 20.9 ± 3.9 months).
Metra,[30] ESSENTIAL randomized	NYHA III/IV 86% chronic BB	1854	Enoximone (oral)	16 months	Safe, major clinical outcomes not improved
Kumar,[20] prospective	NYHA IIIb/IV	17	Milrinone (i.v. intermittent 4 h/day), carvedilol	8 weeks	88 tolerated BB 53% weaned
Berger,[19] prospective randomized	NYHA IIIb/IV, intolerant to BB up-titration	75	Levosimendan or i.v. PGE1, bisprolol	12 weeks	Up-titration possible in 77% of levosimendan, and 94% of PGE1 group
Zewail,[26] retrospective	NYHA IV	51 14	Milrinone i.v. + BB Milrinone i.v. + BB (BB intolerant)	3 years	↑ survival, 47% weaned 0 weaned
Gattis,[27] post-hoc OPTIME-CHF	NYHA IV, BB at admission, 212 milrinone i.v.	212	Milrinone + BB BB withdrawn	60 days	↓ mortality ↑ mortality

BB, beta-blocker; CI, cardiac index; HR, heart rate; h, hours; i.v., intravenous; n, number of patients; NYHA, New York Heart Association class; O_2, oxygen; PCWP, pulmonary capillary wedge pressure; PGE1, prostaglandin E1.

was high, and this is in line with data from registries of acute decompensated HF.[11–13] The multicentre ADHERE registry in the USA showed that the mortality risk increases several times at low blood pressures, and the Euro Heart Failure Survey II showed that in-hospital mortality from cardiogenic shock in Europe was 39%.[11,12]

Concomitant beta-blockade and inotropic support with intravenous enoximone

Clinical trials have shown that patients with NYHA class IV HF are more likely to develop worsening of HF leading to permanent withdrawal of BB. However, these patients are most likely to show symptomatic improvement by one or more functional classes in the long term.[5,6] The favourable effect of carvedilol on reducing mortality and hospitalization was apparent as early as 14–21 days following the initiation of the treatment in the COPERNICUS study, and this time window also applied to the highest risk patients with recent or recurrent decompensation or very depressed cardiac function.[5] A smaller study including 63 patients with NYHA class IV HF treated with carvedilol showed that 59% of the patients improved at 3 months by one or more functional class.[6]

Overcoming the short-term intolerance of BBs is rewarding in the patients with severe low-cardiac output HF in whom the functional status can be improved above the limit where heart transplantation is indicated. It has been shown that the positive inotropic effect of dobutamine is severely decreased after chronic administration of a BB, which may lead to decreased survival in patients hospitalized with acute decompensation.[18,22,23] Several studies, presented in *Table 5*, have shown the results of concomitant administration of a BB and inotropic support with phosphodiesterase inhibitors or levosimendan. A review of earlier studies using milrinone in combination with a BB in patients with advanced HF showed that the combination appeared to be well tolerated and favourable for the weaning of inotropic support, although the data were insufficient to reach a firm conclusion on clinical benefit.[24]

Our report shows that combination of i.v. enoximone and a BB was used in 43 of 80 patients included in the study. This combination was successful in two-thirds of these patients, because 29 patients were successfully weaned from enoximone after a support of 14 ± 7 days, and remained stable thereafter on a BB. In the other 14 patients, the combination of enoximone and a BB did not succeed, and the inotropic support had to be intensified. Several patients died, while others received an LVAD as bridge to transplantion or received a direct transplant. It could be argued that the start of BB therapy could have contributed to the adverse outcome by unmasking a very fragile haemodynamic balance. The novelty of our study consists of the finding that we identified a subgroup of severe HF patients who could be bridged to a BB although they at first seemed far too sick for the introduction of this initially negative inotropic medication. This approach required a considerable number of days in hospital.

Implications for clinical practice

Inherent to a tertiary referral centre for heart transplantation is the young age of the patients included in the present study. Compared with the mean age in large registries of acute decompensated HF, which is 70 years, the mean age in our group of patients was 43 years.[11,12] Thus, our strategy has been used in a selected group of patients who are potential candidates for heart transplantation. The applicability of this strategy may, however, be much wider. A strategy of switching from dobutamine to i.v. enoximone can also be considered for older patients dependent on inotropic support in order to allow the introduction of BB therapy and increase its tolerability during the first weeks.

Our experience is largely based on the phosphodiesterase inhibitor enoximone because we consider the dose–response effect of enoximone easier to handle in practice than that of milrinone. We used low dosages of enoximone of 1–2 μg/kg/min in continued infusion considering that the inotropic effect already occurs at the lowest infusion rate, while higher dosages are associated with more vasodilation.[28,29] The duration of enoximone infusion was extended over several weeks (without infusion-related complications except the need to change the venous line because of crystallization), and was gradually withdrawn, in order to counteract the negative inotropic effect of BBs in these haemodynamically fragile patients. Therefore, HF clinics should be prepared to hospitalize those patients for a longer period of time, although this may be contrary to the general goal of lowering the length of hospital stay in order to lower the healthcare costs. Ultimately, the benefit in terms of survival and quality of life without more expensive treatments such as LVAD implantation or heart transplantation can lower the overall costs.

Study limitations

Our study has the limitations of a retrospective study in which the therapy was driven by clinical practice. Therefore, the association of clinical factors with successful weaning and BB use may be biased by non-standardized moments of clinical assessment. However, invasively measured and echocardiographic data were recorded as the first measurements reported in the chart in all patients, and therefore we consider them to be representative of the unstable situation that determined the referral hospitals to transfer the patients for the assessment for transplantation. Another limitation is the small number of patients included in the analysis, which does not allow identification of strong associations. However, this category of inotropy-dependent severe HF patients is haemodynamically unstable, and therefore rarely used in clinical trials.

Conclusion

The fact that a number of initially unstable patients improved considerably and remained stable in the long term if they could be titrated on a BB in our opinion justifies the investment in time and effort to optimize the therapy by using a bridge with the phosphodiesterase inhibitor enoximone.

Conflict of interest: none declared.

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