ESC HEART FAILURE
ESC Heart Failure 2021; **8**: 4322–4327
Published online 30 June 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13394

SHORT COMMUNICATION

Long-term administration of intravenous inotropes in advanced heart failure

Piero Gentile*, Claudia Marini, Enrico Ammirati, Enrico Perna, Gianluigi Saponara, Andrea Garascia, Luciana D'Angelo, Alessandro Verde, Grazia Foti, Gabriella Masciocco, Maria Frigerio and Manlio Cipriani

De Gasperis Cardio Center, Niguarda Hospital, Piazza dell'Ospedale Maggiore, 3, Milan, 20162, Italy

Abstract

Background Patients in heart transplantation (HTx) waiting list for advanced heart failure (HF) are susceptible to acute deterioration refractory to standard HF medical therapies. Limited data are available on long-term in-hospital continuous intravenous (IV) inotropic therapy as bridge to definite therapies.

Methods and results We reviewed medical records of all heart transplant recipients treated in the pre-HTx phase with in-hospital continuous IV inotropes at our institution between 2012 and 2018. We analysed data before the beginning of continuous IV therapy and at the moment of HTx. We report data of 24 patients (mean age of 43.5 ± 15.7 years) treated with IV inotropes as bridge to HTx (median follow-up of 28 months after HTx). The main length of IV inotropic therapy was 84 ± 66 days (min 22; max 264 days). At the beginning, the most frequently used inotrope was dopamine (median dosage of 3 mcg/kg/min, interquartile range 2.5–3.75), alone (n = 11, 46%) or in combination with other inotropes (n = 13, 54%). In 18 patients, the class of inotropes was changed during the hospitalization. We registered a progressive improvement of perfusion markers and neuro-hormonal activation.

Conclusion In-hospital continuous parenteral inotropic therapy may serve as a temporary pharmacological bridge to HTx in patients with advanced HF that are actively listed to HTx with good reply in terms of prognosis and perfusion markers.

Keywords Advanced heart failure; Intravenous inotropes; Heart transplantation

Received: 11 December 2020; Revised: 18 March 2021; Accepted: 18 April 2021
**Correspondence to: Piero Gentile, De Gasperis Cardio Center and Transplant Center, Niguarda Hospital, Piazza dell'Ospedale Maggiore, 3, 20162 Milano, Italy.*
Email: piero.gentile@ospedaleniguarda.it

Introduction

Advanced heart failure (HF) applies to an estimated 1% to 10% of the overall HF population[1,2] and is usually characterized by low cardiac output with or without congestion.[3] Inotrope therapy may be needed to stabilize the haemodynamics[4] while awaiting for definite therapies such as heart transplantation (HTx) or long-term mechanical circulatory support if myocardial recovery does not manifest.

Limited data are available on long-term in-hospital continuous intravenous (IV) inotropic therapy as bridge to definite therapies.

Aims

The aim of this study is to evaluate the outcomes of patient with advanced HF and actively listed for HTx treated with continuous IV in-hospital inotropes as bridge to HTx.

Methods

Study design

We reviewed medical records of all heart transplanted patients treated in the pre-HTx phase with in-hospital continuous IV inotropes at our institution between 2012 and 2018. Inotrope dependence was defined as exacerbation of HF symptoms, hypotension, deteriorating haemodynamic, or worsening end-organ function on attempted inotrope weaning. We analysed echocardiographic and biochemical data before the beginning of continuous IV therapy and before HTx. Patients received recommended HF or

antiarrhythmic medical treatment as indicated by current guidelines.[5] The choice of inotropes was made according to the clinical presentation of each patient. The addition of a second inotrope or replacement with another one was made according to clinical and laboratory analyses. When we registered a progressive sliding of clinical and biochemical conditions, an upgrade to mechanical circulatory support or higher priority status in HTx waiting list was considered.

Statistical analysis

Clinical and laboratory variables are reported as means and standard deviations, medians and interquartile ranges (IQR), or counts and percentages, as appropriate. Cross-sectional comparisons between groups were made by the analysis of variance test on continuous variables, using the Brown–Forsythe statistic when the assumption of equal variances did not hold, or the non-parametric Mann–Whitney *U* test when necessary. The χ^2 or Fisher exact tests were calculated for discrete variables.

IBM-SPSS (New York, NY) statistical software Version 19 was used for descriptive analyses.

Results

We report data of 24 patients treated with IV inotropes as bridge to HTx. The median follow-up was 28 (IQR 21–41) months after HTx. Mean age was 43.5 ± 15.7 years. Mean left ventricular ejection fraction was 23 ± 7.4%, and right ventricular dysfunction was observed in 96% of cases.

Details of the study population and therapeutic supports are reported in *Tables 1* and *3*. The main length of IV inotropic therapy was 84.2 ± 66.4 days (min 22; max 264 days). In the initial phase after acute HF diagnosis, the most frequently used inotrope was dopamine (median dosage of 3 mcg/kg/min, IQR 2.5–3.75), alone (*n* = 11, 46%) or in combination with other inotropes as adrenaline (*n* = 5, 21%) or adrenaline and milrinone (*n* = 1, 4%). Adrenaline and dobutamine were used as single inotrope respectively, in four (16%) and one patient (4%, dosage of 2.5 mcg/kg/min), while two patients (8%) were treated with a combination of adrenaline and dopamine. The median dosage of adrenaline and milrinone were, respectively, 0.03 mcg/kg/min (IQR 0.02–0.04) and 0.3 mcg/kg/min (IQR 0.2–0.7).

In 18 patients, the class of inotropes was changed during the hospitalization. Regarding the group initially treated with only dopamine (*n* = 8), three patients needed a drug association with adrenaline; in one patient, a periodic infusion of Levosimendan was added, while in four patients, we changed inotrope from dopamine to adrenaline (*n* = 3) and from dopamine to dobutamine (*n* = 1).

Table 1 Characteristics of the study population

Characteristic	Overall (*N* = 24)
Age (years)	43.5 ± 15.7
Gender (male), *n* (%)	13 (54)
Body surface area (m^2)	1.6 ± 0.2
Worsening heart failure, *n* (%)	21 (87.5)
Left ventricle ejection fraction (%)	23 ± 7.4
Right ventricular dysfunction, *n* (%)	22 (96%)
Renal function (eGFR, mL/min/1.73 mq)	61.5 (41.5–77)
Heart failure aetiology	
Ischaemic heart disease, *n* (%)	4 (17)
Dilated cardiomyopathy, *n* (%)	9 (37)
Hypertrophic cardiomyopathy, *n* (%)	5 (21)
Valvular heart disease, *n* (%)	3 (12.5)
Cancer treatment-related cardiomyopathy, *n* (%)	3 (12.5)
Initial intravenous inotropic support	
Only dopamine, *n* (%)	11 (46)
Only dobutamine, *n* (%)	1 (4)
Only adrenaline, *n* (%)	4 (16)
Only milrinone, *n* (%)	0
Adrenaline + dopamine, *n* (%)	5 (21)
Adrenaline + milrinone, *n* (%)	2 (8)
Adrenaline + dopamine + milrinone, *n* (%)	1 (4)
Intravenous inotropic support pre-heart transplantation	
Only adrenaline, *n* (%)	7 (29)
Only milrinone, *n* (%)	1 (4)
Only dopamine, *n* (%)	4 (17)
Only dobutamine, *n* (%)	1 (4)
Adrenaline + dopamine, *n* (%)	9 (37)
Adrenaline + milrinone, *n* (%)	1 (4)
Dopamine + milrinone, *n* (%)	1 (4)

Values are expressed as means and standard deviation, median and interquartile range or counts and percentages, as appropriate.

The median dosage of dopamine and adrenaline before the HTx were, respectively, 3 mcg/kg/min (IQR 2.52–3.87) and 0.035 mcg/kg/min (IQR 0.02–0.06).

In nine patients (37%), an escalation to intra-aortic balloon pump was needed, while one patient required Veno-arterial Extracorporeal Membrane Oxygenation support (*Table 3*). Instead, a therapeutic downgrading was registered in four patients (*Table 3*, ID: 7, 13, 16, and 17).

Biochemical data

In comparison with the beginning of IV inotropes therapy, laboratory findings demonstrated a progressive improvement of perfusion markers and neuro-hormonal activation (*Figure 1*). Level of creatinine, urea, and *N*-terminal pro BNP decreased, respectively, from 1.19 (IQR 0.83–1.72) to 0.9 (IQR 0.7–1.1) mg/dL (*P* = 0.01), from 51.5 (IQR 36–83.7) to 44 (IQR 32–57.5) mg/dL (*P* = 0.03), and from 6394 (IQR 3731–9008) to 2543 (IQR 2215–4876) pg/dL (*P* = 0.004). Central venous oxygen saturation increased from 55.5% (IQR 46.9–59.1) to 64.1% (IQR 59–70.5) ($P < 0.001$), while we registered a decrease of arterial lactate from 1.7 (IQR 1.2–2.1) to 1.1 (IQR 0.9–1.2) mmol/L (*P* = 0.009) and of bilirubin from 1.15 (IQR 0.86–1.94) to 0.7 (IQR 0.44–0.99) mg/dL (*P* = 0.07).

Table 2 Characteristics of the study population according to the ischaemic aetiology

Characteristic	Ischaemic heart disease (n = 4)	No ischaemic heart disease (n = 20)	P
Age (years)	49.1 ± 9.8	42.4 ± 16.7	0.339
Body surface area (m^2)	1.6 ± 0.2	1.7 ± 0.3	0.297
Left ventricle ejection fraction (%)	23 ± 3.6	24.7 ± 10.2	0.667
Right ventricular dysfunction, n (%)	1 (25)	8 (42)	
Total length of intravenous inotropic support (days)	56 (38–110)	55.5 (36–214)	0.929
Use of only one inotropic, n (%)	4 (20)	3 (75)	0.059
Overall mortality, n (%)	1 (25)	2 (10)	0.437

Outcomes

The median follow-up of our study was 28 (IQR 21–41) months after the HTx.

We registered three deaths after the Htx: one patient died for graft and multiorgan failure in the first week after the Htx (*Table 3*, ID patient: 20; *Figure 2* left panel), and two patients died for aspergillosis in the first year post Htx (*Table 3*, ID patients: 6; 24; *Figure 2* right panel). Then, 1 year post-operative freedom from death was 87.5% in this group of patients.

We did not register any difference in terms of biochemical data improvement, need of inotropes change, and need of one or more than one drugs according to the HF ischaemic aetiology (*Table 2*).

Discussion

Inotropic therapy is a first-line treatment in acute, refractory HF, either *de novo* or as worsening of known, chronic disease. Reliable data from randomized clinical trials are substantially lacking in refractory worsening HF. Observational studies on acute HF suggest that the use of inotropes could be associated with a high mid-term mortality rate[6,7] and this prognosis has been claimed to be a consequence both of baseline severe conditions and of the deleterious effects of prolonged inotropic stimulus. Regarding the combination of inotropes in advanced acute HF patients, there are no evidences in the literature. However, a physiopathological rationale supports the use of the smallest dose sufficient to sustain haemodynamics and organ perfusion, limiting adverse events.

The severity of clinical picture of our patient cohort is demonstrated by low left ventricular ejection fraction and a very high prevalence of right-ventricular dysfunction that precluded long-term left ventricular assist device therapy. Biochemical parameters reflect low output state, neurohormonal activation, and end-organ dysfunction, thus justifying the use of inotropes. The fundamental difference between the available studies and our experience is the dosage of IV-inotropes. In the study of Mebazaa *et al.*,[8] the median dosage of IV inotropes was higher than those used in our acute HF patients. Indeed, adrenaline, dobutamine, and dopamine were used respectively at a median dosage of 0.5 (IQR 0.3–7.0), 10 (IQR 5–14), and 3 mcg/kg/min (IQR 2–7), while in our patients, the median pre-HTx dosage were respectively 0.035 (IQR 0.02–0.06), 2.5, and 3 mcg/kg/min (IQR 2.5–3.8). Also regarding dobutamine, we used a lower dosage respect other studies (median dosage of 2.5 as opposed to 9 mcg/kg/min in the Flolan International Randomized Survival Trial[7]).

The role and safety of low-to-moderate doses of IV inotropic agents were described also in the experience of Hastenteufel *et al.*,[9] in which they described a safety--focused protocol for hospitalized advanced HF patients outside the intensive care unit. As in our experience, the positive effect was correlated with use of low-to-moderate doses of IV inotropic, with a median dose of dobutamine and milrinone in their patients of respectively 5.7 and 0.25 mcg/kg/min. The main difference with our study is the length of inotropic therapy, with a median of days 23.5 days (IQR 13.75–45.5), while in our study the median length was much longer.

Besides inotropes, we reported an extensive use (n = 7, 29%) of vasodilators, in particular sodium nitroprusside. The rationale of vasodilators in acute decompensated HF presenting with increased LV filling pressure and no too low blood pressure is strong and, according to Elkayam *et al.*,[10] the use of vasodilators was not associated with adverse outcomes.

These patients clearly represent a selected group of HTx-eligible and listed subjects with chronic advanced HF, who deteriorated to low-output state, and who survived until HTx was possible. Although >40% showed some deterioration leading to additional non-pharmacological support, as a whole, an improvement of indexes of end-organ function, tissue perfusion, neuroendocrine activation, and cardiac output was observed from admission to HTx. The excellent post-HTx survival underscores that pre-operative patient conditions, rather than the type or amount of therapies that are on board, do influence postoperative outcome, as suggested by several observations.[11]

Further investigations are required to confirm these hypotheses in larger cohorts of patients.

Table 3 Details of patients' characteristics and therapies (at admission and 'pre-heart transplantation')

Patient ID	Age	HF aetiology	Pre-heart transplantation pharmacotherapy and mechanical circulatory support		
			At admission	Pre-heart transplantation	Total length (days)
1	42	DCM	Dopamine 2.5 mcg/kg/min	Dopamine 2.5 mcg/kg/min, Levosimendan	22
2	56	VHD	Dopamine 4 mcg/kg/min, SNP	Adrenaline 0.02 mcg/kg/min, Dopamine 5 mcg/kg/min	85
3	50	IHD	Dopamine 2.5 mcg/kg/min	Dobutamine 2.5 mcg/kg/min	45
4	46	DCM	Dopamine 3 mcg/kg/min Adrenaline 0.04 mcg/kg/min	Dopamine 2.6 mcg/kg/min Adrenaline 0.03 mcg/kg/min	39
5	36	HCM	Dopamine 5 mcg/kg/min	Adrenaline 0.02 mcg/kg/min Dopamine 5 mcg/kg/min	108
6	56	DCM	Dopamine 2.5 mcg/kg/min	Adrenaline 0.04 mcg/kg/min	111
7	54	HCM	Adrenaline 0.02 mcg/kg/min, SNP, IABP	Adrenaline 0.02 mcg/kg/min, SNP	44
8	56	DCM	Adrenaline 0.03 mcg/kg/min, Dopamine 2.5 mcg/kg/min SNP	Adrenaline 0.04 mcg/kg/min, Dopamine 2.7 mcg/kg/min, IABP	36
9	56	VHD	Adrenaline 0.02 mcg/kg/min, Dopamine 3.3 mcg/kg/min	Adrenaline 0.02 mcg/kg/min, Dopamine 3.3 mcg/kg/min	75
10	60	CTRC	Adrenaline 0.03 mcg/kg/min, Dopamine 4 mcg/kg/min	Adrenaline 0.03 mcg/kg/min, Dopamine 4 mcg/kg/min, IABP	156
11	44	CTRC	Dopamine 2.5 mcg/kg/min, SNP	Adrenaline 0.07 mcg/kg/min, SNP, IABP	88
12	17	DCM	Adrenaline 0.04 mcg/kg/min, SNP, IABP	Dopamine 3 mcg/kg/min, Milrinone 0.3 mcg/kg/min, IABP	36
13	22	HCM	Adrenaline 0.12 mcg/kg/min, Milrinone 0.7 mcg/kg/min	Milrinone 0.25 mcg/kg/min	140
14	34	DCM	Dopamine 3 mcg/kg/min	Dopamine 3 mcg/kg/min	29
15	43	IHD	Dopamine 3.5 mcg/kg/min	Dopamine 3.5 mcg/kg/min	67
16	49	DCM	Adrenaline 0.03 mcg/kg/min Milrinone 0.3 mcg/kg/min Levosimendan, IABP	Adrenaline 0.06 mcg/kg/min, Milrinone 0.7 mcg/kg/min IABP	28
17	21	CTRC	Adrenaline 0.03 mcg/kg/min, Dopamine 6 mcg/kg/min, Levosimendan	Adrenaline 0.02 mcg/kg/min, Dopamine 2 mcg/kg/min	169
18	61	DCM	Dopamine 2.5 mcg/kg/min	Adrenaline 0.03 mcg/kg/min, Dopamine 2 mcg/kg/min, SNP, IABP	60
19	32	HCM	Adrenaline 0.03 mcg/kg/min, Levosimendan SNP	Adrenaline 0.06 mcg/kg/min, IABP	51
20	19	HCM	Adrenaline 0.02 mcg/kg/min, Dopamine 3 mcg/kg/min, SNP, Milrinone 0.3 mcg/kg/min	Adrenaline 0.2 mcg/kg/min, Dopamine 3 mcg/kg/min, Levosimendan, IABP, VA-ECMO	30
21	23	DCM	Adrenaline 0.04 mcg/kg/min SNP	Adrenaline 0.12 mcg/kg/min	33
22	59	IHD	Dobutamine 2.5 mcg/kg/min IABP	Adrenaline 0.06 mcg/kg/min, SNP, Levosimendan	36
23	55	VHD	Dopamine 2.5 mcg/kg/min	Adrenaline 0.07 mcg/kg/min, Levosimendan, IABP	47
24	63	IHD	Dopamine 3 mcg/kg/min	Dopamine 3 mcg/kg/min	264

CTRC, cancer treatment-related cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HF, heart failure; IABP, intra-aortic balloon pump; IHD, ischemic heart disease; SNP, sodium nitroprusside; VA-ECMO, Veno-arterial Extracorporeal Membrane Oxygenation; VHD, valvular heart disease.

Figure 1 Graphical illustration of biochemical data trend (at admission vs. pre-heart transplantation). BUN, blood urea nitrogen.

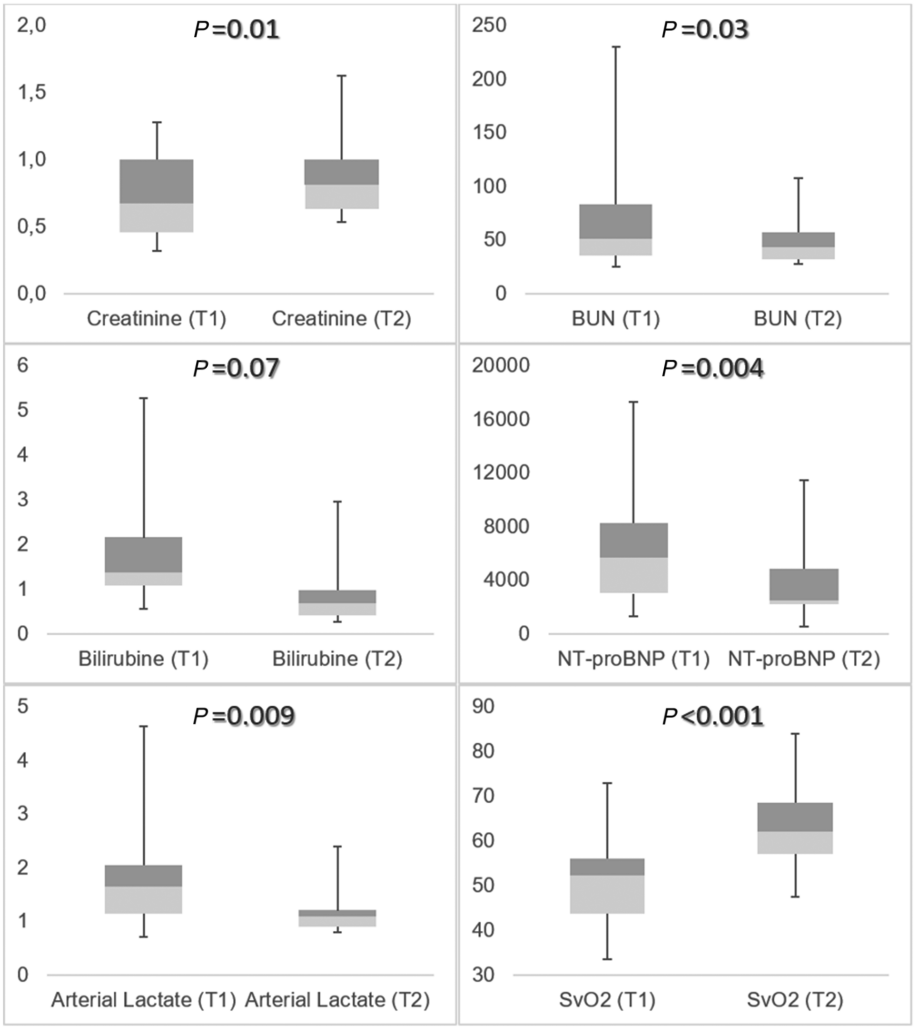
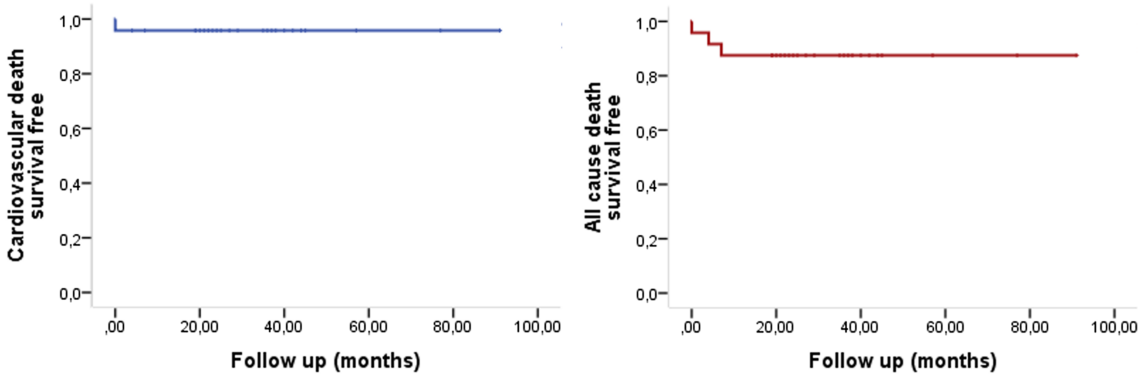


Figure 2 Kaplan–Meier curve of survival free from cardiovascular death (left panel)/all cause death (right panel).



DOI: 10.1002/ehf2.13394

Limitations

The retrospective nature of the study and the small number of population are limitations of this experience. However, to the best of our knowledge, this is one of the largest population in which the impact of multiple IV inotropic drugs is studied in advanced HF patients that are actively listed to HTx. Further investigations are required to confirm our data in larger cohorts of patients.

Conclusion

In-hospital continuous parenteral inotropic therapy may serve as a temporary pharmacological bridge to HTx in patients with advanced HF that are actively listed to HTx with good reply in terms of perfusion markers and prognosis. Avoidance of traditional high doses of inotropes and the administration of one or multiple IV vasoactive drugs under careful monitoring conditions are fundamentals in this setting.

Acknowledgements

We would like to thank Fondazione Angelo De Gasperis for the support.

Conflict of interest

None declared.

References

1. Bjork JB, Alton KK, Georgiopoulou VV, Butler J, Kalogeropoulos AP. Defining advanced heart failure: a systematic review of criteria used in clinical trials. *J Card Fail* 2016; **22**: 569–577.
2. Fang JC, Ewald GA, Allen LA, Butler J, Westlake Canary CA, Colvin-Adams M, Dickinson MG, Levy P, Stough WG, Sweitzer NK, Teerlink JR, Whellan DJ, Albert NM, Krishnamani R, Rich MW, Walsh MN, Bonnell MR, Carson PE, Chan MC, Dries DL, Hernandez AF, Hershberger RE, Katz SD, Moore S, Rodgers JE, Rogers JG, Vest AR, Givertz MM. Advanced (stage D) heart failure: a statement from the heart failure society of America Guidelines Committee. *J Card Fail* 2015; **21**: 519–534.
3. Crespo-Leiro MG, Metra M, Lund LH, Milicic D, Costanzo MR, Filippatos G, Gustafsson F, Tsui S, Barge-Caballero E, De Jonge N, Frigerio M, Hamdan R, Hasin T, Hülsmann M, Nalbantgil S, Potena L, Bauersachs J, Gkouziouta A, Ruhparwar A, Ristic AD, Straburzynska-Migaj E, McDonagh T, Seferovic P, Ruschitzka F. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2018; **20**: 1505–1535.
4. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola V-P, Parissis J, Laroche C, Piepoli MF, Fonseca C, Mebazaa A, Lund L, Ambrosio GA, Coats AJ, Ferrari R, Ruschitzka F, Maggioni AP, Filippatos G. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail England* 2017; **19**: 1574–1585.
5. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2016; **37**: 2129–2200.
6. Cuffe MS, Califf RM, Adams KF, Benza R, Bourge R, Colucci WS, Massie BM, O'Connor CM, Pina I, Quigg R, Silver MA, Gheorghiade M. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. *JAMA* 2002; **287**: 1541–1547.
7. O'Connor CM, Gattis WA, Uretsky BF, Adams J, McNulty SE, Grossman SH, McKenna WJ, Zannad F, Swedberg K, Gheorghiade M, Califf RM. Continuous intravenous dobutamine is associated with an increased risk of death in patients with advanced heart failure: insights from the Flolan International Randomized Survival Trial (FIRST). *Am Heart J* 1999; **138**: 78–86.
8. Mebazaa A, Parissis J, Porcher R, Gayat E, Nikolaou M, Boas FV, Delgado JF, Follath F. Short-term survival by treatment among patients hospitalized with acute heart failure: the global ALARM-HF registry using propensity scoring methods. *Intensive Care Med* 2011; **37**: 290–301.
9. Hastenteufel LCT, Clausell N, Neyeloff JL, Domingues FB, Caballero LG, da Silva ERR, Goldraich LA. Continuous intravenous inotropes in ward units: expanding therapy outside intensive care using a safety-oriented protocol. *Arq Bras Cardiol* 2019.
10. Elkayam U, Tasissa G, Binanay C, Stevenson LW, Gheorghiade M, Warnica JW, Young JB, Rayburn BK, Rogers JG, Demarco T, Leier CV. Use and impact of inotropes and vasodilator therapy in hospitalized patients with severe heart failure. *Am Heart J* 2007.
11. Cantrelle C, Legeai C, Latouche A, Tuppin P, Jasseron C, Sebbag L, Bastien O, Dorent R. Access to heart transplantation: a proper analysis of the competing risks of death and transplantation is required to optimize graft allocation. *Transplant Direct* 2017; **3**: e198.