Long-term administration of intravenous inotropes in advanced heart failure

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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

Introduction

Advanced heart failure (HF) applies to an estimated 1% to 10% of the overall HF population and is usually characterized by low cardiac output with or without congestion. Inotropic therapy may be needed to stabilize the haemodynamics 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. Inotropic 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. 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 $\chi^2$ 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%. Level of creatinine, urea, and N-terminal pro BNP decreased, respectively, from 1.19 (IQR 0.83–1.72) mg/dL (P = 0.01) to 0.7 (IQR 0.44–0.99) mg/dL (P = 0.07). 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).

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**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 (m²)         | 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.
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 rate6,7 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 there are no evidences in the literature. However, a physiopathological rationale supports the use of the smallest dose that is 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 Trial9).

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.

| 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 (m²) | 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) | 0.929 |
| Total length of intravenous inotropic support (days) | 56 (38–110) | 55.5 (36–214) | 0.059 |
| Use of only one inotropic, n (%) | 4 (20) | 3 (75) | 0.437 |
| Overall mortality, n (%) | 1 (25) | 2 (10) | 0.929 |

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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          | Adrenaline 4 mcg/kg/min, SNP                                               | Dopamine 2.5 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                 | 39 |
| 5          | 36  | HCM          | Dopamine 5 mcg/kg/min                                                      | Adrenaline 0.03 mcg/kg/min              | 108 |
| 6          | 56  | DCM          | Adrenaline 0.02 mcg/kg/min                                                  | Adrenaline 0.02 mcg/kg/min, SNP         | 44 |
| 7          | 54  | HCM          | Adrenaline 0.03 mcg/kg/min, Dopamine 2.5 mcg/kg/min, SNP, IABP             | Adrenaline 0.02 mcg/kg/min, Dopamine 2.7 mcg/kg/min, IABP | 36 |
| 8          | 56  | DCM          | 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 |
| 9          | 56  | VHD          | Adrenaline 0.03 mcg/kg/min                                                  | Adrenaline 0.03 mcg/kg/min, Dopamine 4 mcg/kg/min | 156 |
| 10         | 60  | CTRC         | Adrenaline 0.03 mcg/kg/min                                                  | Adrenaline 0.07 mcg/kg/min, SNP, IABP   | 88 |
| 11         | 44  | CTRC         | Dopamine 2.5 mcg/kg/min, SNP                                               | Levosimendan, IABP                      | 140 |
| 12         | 17  | DCM          | Adrenaline 0.04 mcg/kg/min, SNP, IABP                                      | Milrinone 0.25 mcg/kg/min               | 29 |
| 13         | 22  | HCM          | Adrenaline 0.12 mcg/kg/min, Milrinone 0.7 mcg/kg/min                       | Dopamine 3 mcg/kg/min                   | 67 |
| 14         | 34  | DCM          | Dopamine 3 mcg/kg/min                                                      | Dopamine 3 mcg/kg/min                   | 28 |
| 15         | 43  | IHD          | Dopamine 3.5 mcg/kg/min                                                    | Dopamine 3.5 mcg/kg/min                 | 169 |
| 16         | 49  | DCM          | Milrinone 0.3 mcg/kg/min                                                   | Adrenaline 0.06 mcg/kg/min, Milrinone 0.7 mcg/kg/min, IABP | 60 |
| 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, Levosimendan | 51 |
| 18         | 61  | DCM          | Dopamine 2.5 mcg/kg/min                                                    | Adrenaline 0.03 mcg/kg/min, SNP, IABP   | 30 |
| 19         | 32  | HCM          | Adrenaline 0.03 mcg/kg/min, Levosimendan SNP                              | Adrenaline 0.2 mcg/kg/min, Dopamine 3 mcg/kg/min, IABP | 33 |
| 20         | 19  | HCM          | Adrenaline 0.02 mcg/kg/min, Dopamine 3 mcg/kg/min, SNP, Milrinone 0.3 mcg/kg/min | Levosimendan, IABP, VA-ECMO | 36 |
| 21         | 23  | DCM          | Adrenaline 0.04 mcg/kg/min, SNP                                            | Adrenaline 0.03 mcg/kg/min               | 47 |
| 22         | 23  | IHD          | Dobutamine 2.5 mcg/kg/min                                                  | Adrenaline 0.06 mcg/kg/min, SNP, Levosimendan | 264 |
| 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                                                      | Adrenaline 0.03 mcg/kg/min, SNP, Levosimendan | 47 |

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).
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.

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Conflict of interest

None declared.

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