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Time-course of circulating cardiac and inflammatory biomarkers after Ventricular Assist Device implantation: Comparison between paediatric and adult patients

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ABSTRACT

Background: Ventricular Assist Device (VAD) as bridge to transplantation is a common therapy for adult with heart failure (HF), but VAD use is increasing also in children. Cardiac and inflammatory biomarkers have an important role in the diagnosis and prognosis of HF in adults, but their role in paediatric setting is unknown. The aim of this study was to examine changes in cardiac and inflammatory biomarkers, both in HF paediatric and adult patients, before and following VAD.

Methods: Cardiac (NT-proBNP, cTnI, sST2,Gal-3) and inflammatory (IL-6,IL-8) biomarkers were determined in plasma collected from 12 paediatric patients and 7 adult patients with HF, before and at 4 h,1,3,7,14 and 30 days after VAD implant.

Results: All biomarkers increased up to 1 day after VAD implant and then decreased at pre-VAD levels in 1 month in both groups. Only in children, NT-proBNP decreased significantly after 30 days Post-VAD treatment compared to pre-VAD levels. During the post-operative time-course, NT-proBNP and sST2 were significantly higher in children than adults, while IL-6 was lower.

Conclusions: Cardiac and inflammatory biomarkers were differently modified by VAD implant in children compared to adults. These preliminary data could suggest that different molecular pathways may underlie HF patho-physiology of the two groups, possibly paving the way to a specific and targeted therapeutic intervention in the near future.

1. Introduction

Heart Failure (HF) is a complex clinical syndrome characterized by the reduced ability of the heart to function as a pump to support physiological circulation [1]. In the paediatric population, HF is not common as in adults, affecting approximately 1 on 100,000 children [2]. Several studies have identified congenital heart disease and cardiomyopathy as the major causes of HF in childhood [3, 4].

Although heart transplantation is still the better treatment for end-stage adult patients with HF, the insufficiency of donor organs and the tighter eligibility criteria have necessitated the employ of alternative therapies, such as mechanical circulatory support [5]. Among them, ventricular assist device (VAD) are mechanical pumps that replace ventricle function and ensure regular perfusion of the other organs and tissues. Besides adult patients, in the last decade the number of paediatric patients supported by VAD, as a bridge to cardiac transplantation, has increased considerably. This is a consequence of several factors, including improvements of care after VAD implant, reduction of pump volumes, and evolution of device design [6]. Even if a VAD model for the exclusive paediatric use has not been created yet till now, Blume et al. observed that, in older children and adolescent with HF, VAD was successfully implanted as bridge to transplantation in 80% of cases, and that 87% of those paediatric patients supported on durable device for at least 6 months, showed a favourable outcome after 6 months following heart transplant [7, 8].

Circulating biomarkers are an essential tool in cardiovascular practice for make diagnosis, prognosis of disease, and to monitor the effects of treatment, such as pharmacological therapy and VAD use [9].

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Moreover, from a patho-physiological point of view, bio-humoral markers could help to gain more understandings into the molecular mechanisms of disease, i.e. HF [10]. The 2013 ACCF/AHA guidelines for the management of adult patients with HF suggest in clinical setting the use of biomarkers associated with three different physio-pathological process: cardiac stress [N-terminal pro-brain natriuretic peptide (NT-proBNP) and soluble suppression of tumorigenicity 2 (sST2)], cardiac damage [cardiac Troponin (cTn)] and fibrosis [Galactin-3 (Gal-3)] [11]. On the other hands, it is known that the inflammatory process plays an essential role in the onset and progression of HF, and several studies suggested that the monitoring of inflammatory biomarkers, such as interleukin (IL)-6, IL-8, and tumor necrosis factor-α (TNFα) could be a good strategy for a better risk stratification of HF patients [12, 13].

Unfortunately, the ability to evaluate and monitor the HF evolution over time in paediatric patients is extremely limited due to the lack of available data on changes in blood concentration of markers that reflect disease presence and progression in childhood [14]. Given the differences of physio-pathological mechanisms involved in HF in different age groups [15], it is clear that data collected from HF adults cannot be extrapolated and used for management of paediatric patients [16]. Most available HF biomarkers have not been tested in paediatric patients with HF, and the direction and magnitude of changes in biomarkers after VAD support remain unclear. Moreover, the bio-humoral markers, allowing insights into the molecular patho-physiology of HF, may permit a more sensitive measure of underlying changes after mechanical support implantation.

With these considerations in mind, in this study we sought to examine baseline levels and time-course changes up to one month in bio-humoral markers representing the key pathways of HF patho-physiology in paediatric patients who underwent VAD placement. In the present study, only the biomarkers recommended by international guidelines for adult patients with HF [11] and inflammatory cytokines were evaluated. Thus, in order to better understand both the possible clinical and patho-physiological role of bio-humoral markers in paediatric patients with HF, specific aims of this study were:

1. to compare the baseline levels of biomarkers from HF paediatric patients with those from a control group of healthy children;
2. to compare biomarker levels during time-course after VAD implant from HF paediatric patients with those from adult patients with HF.

2. Materials and methods

2.1. Study population

The study population included 12 HF paediatric patients undergoing VAD implantation as bridge-to transplantation at the Cardiovascular Department of Ospedale Bambino Gesù of Rome from 2013 to 2015 (Table 1). $N = 9$ patients were implanted with pulsatile-flow pump (Thoratec, Berlin Heart Excor) and $n = 3$ patients were implanted with continuous-flow pump with Jarvik.

Clinical and echocardiographic data were collected at VAD implant (pre-VAD) and at 1 month after implantation. Plasma samples were collected through a peripheral vein into EDTA-containing tubes before VAD implant and during time course at 4 h, 1 day, 3 days, 1 week, 2 weeks, up to 1 month after VAD implant. Plasma was immediately separated by centrifugation for 15 min at 1500 $\times g$ and aliquots of plasma were stored at −80 °C prior to analysis.

The biomarker levels of HF paediatric patients at baseline were compared with a group of 107 healthy children [17.47 (1.8–122) months, 67 males] in which the presence of any significant cardiac disease has been excluded by careful clinical examination and by echocardiography, when necessary [17, 18].

Moreover, the bio-humoral profile of HF paediatric patients was compared with those of 7 end stage HF adult patients supported with VAD [52.36(48.4–60.6) years, 7 males, 24 (18.75–27.25) LVEF%] as bridge-to transplantation (Table 2). Plasma samples were obtained during time course after VAD implantation at the same time points of paediatric group.

This study complied with the principles of the Declaration of Helsinki. Informed consent was given by all parents of children enrolled in this study and the protocol was approved by the local ethic committee.

2.2. Plasma determination

Measurement of NT-proBNP was performed using the electrochemical luminescence immunoassay Elecsys proBNP II by Roche Diagnostics using monoclonal antibodies [19]. Plasma concentrations of cTnI were measured using the high sensitive (hs)-cTnI method on STAT Architect using the Architect i1000SR platform (Abbott Diagnostics) [18]. Plasma sST2 was measured by Presage® ST2 Assay kit (Critical Diagnostic, San Diego, CA, USA). Galectin-3 levels were evaluated using the ARCHITECT Platform (Abbott Diagnostics) [20]. Plasma TNFα, IL-6, IL-8, and IL-10 levels were measured by MILLIPLEX MAP High Sensitivity Human Cytokine Magnetic Bead Panel Kit (Millipore, Billerica, Mass) based on the Luminex xMAP technology (Luminex Corporation, Austin, Tex). Other traditional plasma biomarkers were measured using standard methods.

2.3. Statistical analysis

Quantitative data are presented as median and interquartile range (I-III). Due to not normally distribution of biomarkers, the original data were ln-transformed and parametric tests were used for statistical analysis. Comparison between different points of time-course was performed by t-student test. Difference between several independent groups was compared by two-way ANOVA followed by Fisher's post-hoc test. Statistical analysis was performed using *Statview 5.0.1* software (SAS Institute, Inc., Cary, NC, USA).

Table 1
Clinical features of HF paediatric patients at enrolment.

Patient	Gender	Age (months)	Weight (Kg)	Diagnosis	LVEF% (pre-VAD)	VAD type	VAD duration (day)
1	M	5	4.7	Dilated	10	LVAD	120
2	M	204	85	Dilated	10	LVAD	14
3	M	5	5	LV non compaction	17	LVAD	150
4	F	17	7.7	Dilated	17	LVAD	270
5	M	8	6	Dilated	17	LVAD	63
6	F	32	9	Dilated	20	LVAD	315
7	M	29	15.2	Dilated	16	LVAD	296
8	F	5	4.6	Dilated	19	LVAD	90
9	M	204	47	LV non compaction	19	LVAD	6
10	F	96	20	Restrictive	60	BiVAD	75
11	M	11	7.7	Dilated	15	LVAD	134
12	F	276	44	Dilated	10	LVAD	116