Brain natriuretic peptide is removed by continuous veno-venous hemofiltration in pediatric patients

Zaccaria Ricci a,*, Cristiana Garisto a, Stefano Morelli a, Luca Di Chiara b, Claudio Ronco b, Sergio Picardo a

Abstract

We wanted to evaluate if brain natriuretic peptide (BNP) is cleared during continuous veno-venous hemofiltration (CVVH) sessions in children with congenital heart disease. A prospective observational single-center study was conducted in a post-cardiac surgery intensive care unit of the city children’s hospital. Ten children requiring CVVH for acute kidney injury following cardiac surgery were enrolled. Seven of them were undergoing postoperative extracorporeal membrane oxygenation. BNP clearance was evaluated by the difference between pre-filter and post-filter BNP blood amount indexed to pre-filter BNP concentration. All CVVH treatments were performed with 0.6 ml \textsuperscript{-1} sodium polycrylonitrile filter, in predilution setting, at a dose of 80 ml/kg/h. Troponin I and myoglobin levels were also measured and CVVH clearances of these markers calculated for comparison with BNP. A significant decrease in post-filter compared with pre-filter levels of BNP was shown in all 10 cases \((P<0.01)\). Median BNP clearance was 35.6 (29–39.3) ml/min. Troponin I and myoglobin levels did not show any significant drop between pre- and post-filter values \((P>0.05)\) and their clearance was significantly lower than BNP \((P=0.0004)\). A daily analysis of BNP levels showed a significant decrease of its blood concentration. BNP levels were significantly reduced after three and four days from CVVH start \((P<0.05)\). During 80 ml/kg/h CVVH, utilizing polycrylonitrile membranes, BNP is efficiently cleared from blood in a small cohort of pediatric post-cardiosurgical patients. In this situation, BNP absolute blood levels may be unpredictable.

E-mail address: zaccaria.ricci@fastwebnet.it (Z. Ricci).

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1. Introduction

Brain natriuretic peptide (BNP) is a 3472 d peptide secreted from the ventricular myocardium. Its function consists in stimulation of natriuresis along with atrial natriuretic peptide (ANP). Its synthetic analogue has been shown to promote diuresis in heart failure patients. The main stimulus for secretion is elevated left ventricular end-diastolic pressure. High levels of BNP represent a compensatory mechanism in heart failure or hypervolemia [1].

BNP plasma levels are a useful biochemical marker of heart failure. Values higher than 100 pg/ml have a 95% specificity in predicting a new onset of heart failure in adults. BNP value has been shown to be more accurate in diagnosis of heart failure than other clinical variables or clinical judgement. A BNP value of 100 pg/ml has been approved by the food and drug administration to differentiate the pulmonary from the cardiac causes of dyspnea [2].

Natriuretic peptide increase is particularly evident in congenital heart defects (CHD) resulting in volume overload and dilation of the left ventricle [3]. In CHD children treated with extracorporeal circulatory support, low BNP levels have been shown to be an expression of effective heart unloading and high levels were considered predictive of worse outcome [4]. The metabolism of both ANP and BNP involves enzymatic degradation and receptor-mediated endocytosis [5]. However, BNP blood levels’ modification during pediatric continuous veno-venous hemofiltration (CVVH) have not been evaluated before. BNP levels may be modified during CVVH due to filtration and clearance from patients, bloodstream. Furthermore, BNP levels may decrease due to hemofiltration optimization of fluid overload in oliguric children. These effects should be considered when BNP is measured in a critically ill patient undergoing continuous renal replacement therapy (CRRT).

The aim of our study was to evaluate BNP levels’ modification in CHD children during CVVH sessions either added to extracorporeal circulatory support or not.

2. Methods

A prospective observational study was conducted. Ten children requiring CVVH for acute kidney injury (AKI) after cardiac surgery were enrolled. In seven patients, CVVH was administered in parallel with an extracorporeal membrane oxygenation (ECMO) machine. For each patient, 3 h after the start of the first CVVH treatment, ‘blood side simultaneous clearance’ calculation was performed: this was obtained by withdrawing blood samples before and after
the filter, in order to evaluate the amount of BNP removed by hemofiltration during a single blood passage through the membrane.

BNP blood side clearance was evaluated utilizing the formula [6]:

$$\text{Cbi} \times \frac{\text{Qbi} - \text{Cbo}}{\text{Qbo}} = \frac{\text{Cbi} \times \text{Qbi}}{\text{Cbi}}$$

where, Cbi is pre-filter BNP level, Cbo is post-filter BNP level, Qbi is pre-filter blood flow rate and Qbo is post-filter blood flow rate. BNP concentration was measured every 24 h for the whole CRRT period in all patients.

All CVVH treatments were performed by a Prisma machine (Hospal, Lyon), with 0.6 m² polycrylonitrile filter. Replacement solution was infused before the filter, in predilution hemofiltration, at a dose of 80 ml/kg/h. Net ultrafiltration was decided upon clinical needs. All BNP measurements were performed utilizing The Triage® test (Biosite, Inc, San Diego, CA, USA). With the same kit, troponin I (24,000 d peptide) and myoglobin (16,700 d) levels are also measured and CVVH clearances for these markers calculated for comparison with BNP. Samples for the analysis of BNP (1 ml whole blood) were drawn into standard vials with EDTA as required for the Triage system.

The institutional review board approved the protocol and waived the need for consent from patient parents because of the observational nature of the study.

All data are expressed as median (interquartile range). Mann–Whitney non-parametric test was utilized when necessary. One way analysis of variance was utilized in order to compare clearances of troponin, myoglobin and BNP. Bonferroni post test was utilized in order to compare couples. A P-value <0.05 was considered significant. Statistical analysis was performed with the GraphPad Prism 4.00 software package (GraphPad Software, San Diego, CA, USA).

3. Results

Demographic and baseline characteristics of the 10 patients are expressed in Table 1. BNP baseline level was 584 (361–1016) pg/ml. An analysis of baseline BNP levels in seven ECMO patients did not show significant differences with three non-ECMO patients (P >0.05). A significant decrease in the post-filter compared with pre-filter levels of BNP was shown in all 10 cases: post-filter BNP levels were 211 (157–245) pg/ml (P: 0.0028) (Fig. 1). BNP drop percentage (calculated as [BNP pre–BNP post]/BNP pre x100) was 67.4%. BNP clearance was 35.6 (29–39.3) ml/min (Fig. 2). Troponin I and myoglobin levels showed the smallest drop between pre- and post-filter values and their clearance was significantly lower than BNP (P: 0.0004), being, respectively 2.5 ml/min (1.6–3.5) and 4.5 ml/min (1.9–6.2) (Figs. 1 and 2). Median BNP level after four CVVH days (at this time there were no censored patients) was significantly reduced to 190 (136–215) pg/ml (P: 0.002). A day-to-day analysis of BNP levels in these patients is represented in Fig. 3. BNP levels decreased significantly in days three and four after the CVVH start. No significant difference in BNP levels after four CVVH days was observed between seven ECMO and three non-ECMO patients (P >0.05). Only five patients recovered renal function (two ECMO and three non-ECMO patients). They were all weaned from CVVH and discharged from the ICU (Table 1). An analysis of baseline BNP levels of survived patients showed a (non-statistical) difference with non-surviving patients (485 vs. 785 pg/ml, P >0.05). When BNP levels of survived patients after four CVVH days were compared to those of non-surviving ones this difference was not present (208 vs. 198 pg/ml, P >0.05).

4. Discussion

BNP is an established marker of heart failure. Many centers are also administering this molecule with therapeutic purposes [7]. BNP plasma levels are frequently utilized...
in order to monitor the progression of chronic heart failure or the efficacy of therapy in critically ill patients [8]. A number of studies explored the use of BNP in chronic dialysis patients [9]. The utilization of dialysis or CRRT in critically ill post-cardiosurgical children with AKI ranges from 1 to 30% of cases [10]. In our cohort of 10 children with congenital heart disease requiring postoperative renal replacement, CVVH showed to achieve a surprisingly high concentration of BNP.

These results are in contrast with a report from Balik and co-authors who did not find significant elimination of BNP by CVVH [11]. However, Kazory and co-workers hypothesized that filtration might have a role in BNP reduction in a subset of heart failure patients undergoing therapy with intermittent hemodiafiltration [12]. The reason for our results might be explained by the fact that a high hemofiltration dose (80 ml/kg/h) was administered to our pediatric cohort: in a 3–9 kg patient (especially when CVVH is administered in parallel with ECMO) it is relatively easy to reach such level of blood purification [13]. Furthermore, we utilized only convective techniques (pure hemofiltration) that are known to have better efficiency in middle and high molecule removal than osmotic or combined therapies (dialysis or hemodiafiltration). Finally, we always utilized polycrylonitrile membranes that have a relatively high cut-off point and are considered to have also good adsorptive properties [14]. Interestingly, troponin I and myoglobin levels did not show any significant drop between pre- and post-filter values and their clearance was significantly lower than BNP: this finding may be also correlated to the higher molecular weight of these two molecules that approaches the membrane filtration cut-off.

The impact of CRRT on biomarkers blood concentration has previously been reported by Level and co-authors that showed how median plasma levels of procalcitonin were not altered during CVVH at a ‘conventional’ substitution rate (2.5 l/h) [15]. Nonetheless, they found a (non-significant) decrease in procalcitonin plasma levels after a few CVVH days and admitted that procalcitonin clearance measurement and its impact on plasma concentration should be evaluated in studies with high-volume hemofiltration. The BNP levels decreased significantly over the four examined days. This effect may also be influenced by the elevated number of ECMO patients in this study: artificial support of circulation and atrioventricular unloading may be responsible for a rapid decrease of BNP levels [4]. Nevertheless, extracorporeal circulation is also responsible for BNP increases when the heart is not adequately drained, and BNP is an important marker for assessment of adequacy of mechanical circulatory support [4]. It must be remarked that eight patients out of 10 weighed 5 kg or less: an investigation on CVVH in such a cohort of small-weight children necessarily includes ECMO patients. Baseline BNP levels between ECMO and non-ECMO children were, however, comparable and hemofiltration rate was the same in both groups. Apart from the presence of ECMO, finally,
decrease of BNP levels over time might have been caused by hemofiltration beneficial effects on cardiac function and patients volume status. Nevertheless, in our opinion, the unexpectedly high pre- and post-filter difference of marker concentration indicates a considerable filter removal of BNP and might play a major role in modifying BNP levels: CVVH clearance might have caused the absence of difference in BNP levels between surviving and non-surviving patients after four renal replacement days. As a matter of fact, operators should be aware that when using BNP as cardiac failure marker in pediatric patients undergoing high dose CVVH, added to ECMO or not, BNP blood level may be unreliable.

5. Conclusion

In conclusion, we showed that 80 ml/kg/h CVVH delivered with polyacrylonitrile membranes is able to efficiently clear BNP from blood in a small cohort of pediatric post-cardio-surgical congenital heart disease patients. A larger CVVH patients cohort and adjustment of results for different covariates, such as disease progression (improvement or worsening) and pharmacological treatment, are needed in order to confirm if hemofiltration significantly affects BNP levels.

References


EComment: Re: Brain natriuretic peptide is removed by continuous veno-venous hemofiltration in pediatric patients

Authors: Leo A. Bockeria, Bakoulev Scientific Center for Cardiovascular Surgery, Roublevskoye Sh 135, 12552 Moscow, Russia; Mikhail Yarustovsky
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The paper by Zaccaria Ricci et al. [1] deals with the problem of complex intensive care in infants after surgical correction of complex congenital heart defects. In particular, the authors consider the question of the optimization of brain natriuretic peptide (BNP) concentration during continuous high volume veno-venous hemofiltration (CVVH). The authors present data on high BNP clearance (over 35.6 ml/min) with CVVH, while the clearance of high-molecular-weight substances (myoglobin, troponin) is significantly lower. In our opinion, good elimination of BNP can be explained by several factors: (1) Low (3472 dalton) molecular mass of BNP facilitating its free passage through the hemofilter membrane; (2) the use of synthetic polyacrylonitril membrane with perfect adsorption properties; (3) the use of high volume hemofiltration, which significantly increases the clearance of low- and medium-molecular weight substances.

On the other hand, the authors used CVVH in combination with ECMO, which makes it very difficult to reveal the cause of blood BNP concentration decrease. It can be due either to the improvement of the circulatory system’s function (it is well known that BNP is a maker of heart failure) in response to ECMO addition, or to CVVH conduction. Unfortunately, the clinical state of patients during ECMO and CVVH virtually is not presented in this article, thus an adequate evaluation of the efficacy of the technique used is quite difficult. This appears to be an initial stage of a big work made by the anaesthesiologist Zaccaria Ricci from the Ospedale Bambino Gesu in Rome.

Reference