Preoperative Biological Determinants Of Postoperative Vasoplegia After First Time Long-term LVAD Insertion.

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SUMMARY

- Search for biomarkers associated with vasoplegia after Left Ventricular Assist Device (LVAD) insertion
- Single centre retrospective cohort study
- Patients scheduled for first time long-term LVAD implantation
- Preoperative concentrations of 6 biomarkers were significantly higher in patients who developed postoperative vasoplegia, which might support the inflammation and endothelial activation concept of vasoplegia.

BACKGROUND

Vasoplegia after Left Ventricular Assist Device (LVAD) insertion occurs frequently and is associated with increased morbidity and mortality. Previous cardiothoracic surgery, preoperative dopamine use, increased bilirubin levels and decreased creatinine clearance have been identified as independent predictors¹. The current work focuses on fundamental biological mechanisms and explores the hypothesis that preoperative molecular events are associated with and help to predict post-LVAD vasoplegia.

Area of interest	Biomarker
Pro-inflammatory	IL-1b; IL-2; IL-6; IL-8; TNF α ; elastase; C5a; MCP-1 (CCL2); MIP-1a (CCL3); Rantes (CCL5);
Anti-inflammatory	IL-10; IL-1RA; LAP; TNF-R1; TNF-R2; TIMP-1
Endothelial activation	ANG1; ANG2; sICAM; sVCAM; E selectin; Syndecan-1
Apoptosis	FAS
Hormonal axes	Copeptin; thyroxin

table 1. Analyzed biomarkers

	No vasoplegia N = 90 (70.9%)	Vasoplegia N = 37 (29.1%)	P-value
TNF-R1 (ng/ml)	5.3 [4.1 – 6.9]	7.1 [5.6 – 9.8]	< 0.01
TNF-R2 (ng/ml)	2.4 [1.9 – 2.9]	3.3 [2.6 – 4.3]	< 0.01
TIMP-1 (ng/ml)	2.7 [2.0 – 3.3]	3.1 [2.4 – 4.4]	< 0.01
ANG2 (ng/ml)	8.9 [4.5 – 13.4]	12.5 [8.1 – 18.7]	0.01
sVCAM (ng/ml)	22.5 [17.7 – 30.9]	26.1 [22.4 – 32.3]	0.03
FAS (ng/ml)	1.3 [1.0 – 1.7]	1.7 [1.2 – 2.6]	< 0.01

table 2. Biomarkers included in the initial prediction model

Data are presented as median [IQR]

1. De Waal EEC et al., Vasoplegia after implantation of a continuous flow left ventricular assist device: incidence, outcomes and predictors. Submitted.

METHODS

Patients undergoing first time long-term LVAD implantation from 2006 to 2016 with complete preoperative blood sample collection were included. Vasoplegia was defined by a vasodilation criterion (MAP $\leq$ 50 mmHg or SVR $\leq$ 800 dyns $\cdot$ s $\cdot$ cm⁵); a hemodynamic criterion (CI $\geq$ 2.5 l $\cdot$ min⁻¹ $\cdot$ m⁻²); and a high vasopressor requirement (use of norepinephrine $\geq$ 200 ng $\cdot$ kg⁻¹ $\cdot$ min⁻¹ or equivalent doses of other vasopressors as proposed in the ATHOS-3 trial²) during the first 48 hours post-operatively. We quantified 25 biomarkers (table 1), employed R-Studio for supervised cluster analysis and SPSS to compare differences in levels of biomarkers in patients with and without postoperative vasoplegia. ROC analysis was used to investigate if the addition of these preoperative biomarkers could improve the initial clinical prediction model¹.

figure 1. Supervised cluster analysis
Showing the discriminating capacity of the mentioned biomarkers

RESULTS AND DISCUSSION

We included 127 patients of which 37 (29.1%) developed vasoplegia. Patients who developed vasoplegia have undergone more often previous cardiothoracic surgery (29.7 % vs. 13.3%), were preoperatively more often treated with dopamine (32.4% vs 13.3%), and had preoperatively higher bilirubin (33.6 ± 13.4 vs. 25.4 ± 13.8 μ mol/L) and creatine levels (143 ± 52 vs. 116 ± 37 μ mol/L). Supervised cluster analysis showed that several biomarkers can explain differences between patients with and without postoperative vasoplegia (figure 1, table 2). This implicates potential involvement of anti-inflammation, endothelial activation, apoptosis and extracellular matrix in vasoplegia. Inclusion of these 6 biomarkers into the initial model resulted in a non significant increase in predictive value (figure 2) ($p = 0.12$). While these findings appear to support the inflammation and endothelial activation concept of vasoplegia, the predictive value of these biomarkers is low. Either intraoperative and early postoperative changes in these pathways may contribute to vasoplegia or this condition is mediated by different mechanisms.

figure 2. ROC curves
 • Initial model AUC 0.76 (95%CI 0.67-0.86)
 • Initial model combined with 6 biomarkers AUC 0.80 (95%CI 0.72-0.89)

CONCLUSION

Preoperative plasma levels of TNF-R1, TNF-R2, ANG2, sVCAM, FAS and TIMP-1 were significantly higher in patients developing post-LVAD vasoplegia compared to patients without vasoplegia. However, these biomarkers failed to predict postoperative vasoplegia on their own, and only tended to improve the preoperative prediction model based solely on clinical parameters.

2. Chawla LS et al. Angiotensin II for the Treatment of High-Output Shock 3 (ATHOS-3): protocol for a phase III, double-blind randomised controlled trial. Crit Care Resusc 2017;19:43-9