Copeptin assessment to predict vasoplegia after cardiopulmonary by-pass. An observational cohort study.

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Daniela Pasero
Azienda Ospedaliero Universitaria di Sassari
danielacristina.pasero@gmail.comCorresponding Author
ORCiD: https://orcid.org/0000-0002-9921-7562

Alessandro Maria Berton
University Hospital "Città della Salute e della Scienza di Torino"

Giovanna Motta
University Hospital "Città della Salute e della Scienza di Torino"

Riccardo Raffaldi
Università degli Studi di Torino Dipartimento di Scienze Chirurgiche

Giancarlo Fornaro
Azienda Ospedaliero Universitaria Città della Salute e della Scienza di Torino

Andrea Costamagna
Azienda Ospedaliero Universitaria Città della Salute e della Scienza di Torino

Anna Chiara Trompeo
Azienda Ospedaliero Universitaria Città della Salute e della Scienza di Torino

Claudia Filippini
Università degli Studi di Torino Dipartimento di Scienze Chirurgiche

Giulio Mengozzi
Azienda Ospedaliero Universitaria Città della Salute e della Scienza di Torino

Nunzia Prencipe
University Hospital "Città della Salute e della Scienza di Torino"

Marco Zavattaro
University Hospital "Città della Salute e della Scienza di Torino"
Abstract

Background

Post-cardiotomy vasoplegic syndrome is a vasodilatory shock characterized by a decrease of vascular tone with a normal or increased cardiac output. A relative deficit in vasopressin secretion in the postoperative was hypothesized. Copeptin is secreted in equimolar ratio with vasopressin but it is more stable and easier to measure. The aim of the present study was to investigate whether perioperative copeptin was associated with post-cardiotomy vasoplegic syndrome.

Methods

All patients scheduled for cardiac surgery were evaluated. Exclusion criteria were age < 18 years old, corticosteroids therapy, heart transplantation, extra-circulatory life support, sepsis, preoperative use of vasoactive drugs, off-pump surgery, chronic hepatic and renal failure, paraneoplastic syndrome, lack of informed consent. Post-cardiotomy vasoplegic syndrome was defined as a mean arterial pressure < 60 mmHg, a reduction of systemic vascular resistances < 1200 dyn*s/cm 5 *m 2 and/or the need of nor-epinephrine ³ 0.1 µg/kg/min. All patients underwent a preoperative evaluation of the corticotropin stimulation test; then, before surgery (T0), on day one after surgery (T1) and after 7 days (T2) copeptin and NT-proBNP concentration were measured.

Results

Among 55 enrolled patients, 9 (16.3%) developed post-cardiac surgery vasoplegia. Patients with vasoplegia had higher preoperative level of copeptin (19.2 pmol/L, IQR 17.89 – 21.29 vs 11.39 pmol/L, IQR 6.33 - 14.78; p < 0.001) and NT-proBNP (1435 pg/ml, IQR 721.75 – 1836.25 vs 365.5 pg/ml, IQR 141 - 977); p = 0.006) compared to the control group. At the multivariable analysis, preoperative copeptin resulted a significant predictor of vasoplegia (OR 1.56, 95% CI 1.002-1.33) and the ROC analysis showed an accurate copeptin cut off able to identify vasoplegic patients (> 16.9 pmol/L, AUC = 0.86, 95% CI 0.73-0.94). Otherwise, a lack of response to the low dose corticotropin test was not a predictor of PCVS; no patient presented a pathological response to the standard dose test.

Conclusions

Increased preoperative copeptin and NT-proBNP levels might be associated with an increased risk to
develop post-cardiotomy vasoplegic syndrome. Our results suggest that patients with a
decompensated neuroendocrine control of cardiovascular function are more prone to develop
postoperative vasoplegia.

Background
Postoperative vasodilatory shock is a common complication after major cardiac surgery, ranging from
5–45% of the procedures and it has been observed mostly among on-pump cardiac surgery [1–4]. This
condition has been defined as vasodilatory post-cardiotomy shock or post-cardiotomy vasoplegic
syndrome (PCVS) and is characterized by reduced vascular tone, tissue hypoperfusion and metabolic
acidosis [1, 5, 6, 4]. PCVS represents the second cause of vasoplegic shock after sepsis; other well-
known associated conditions are major surgical interventions (i.e. organ transplantation), organ
failure, as a result of burns and multiple traumas, severe pancreatitis [1, 7].
The factors responsible for impaired vasomotor tone after cardiopulmonary by-pass (CPB) are only
partially understood. An increased incidence of PCVS in patients with a preoperative history of
congestive heart failure has been previously described, probably due to vasodilatory factors such as
tumor necrosis factor and nitric oxide [8, 9].
The preoperative use of angiotensin-converting enzyme (ACE) inhibitors has also been described as
independently associated with an increased risk of vasodilatory shock after CPB [2, 8].
Arginine vasopressin (AVP) and natriuretic peptides are some of the most important neuroendocrine
regulators of the hydro-electrolyte balance. In heart failure, the increased release of AVP, due to the
reduced effective circulating blood volume, is partially involved in the water retention process and in
the development of hypotonic hyponatremia [10]. A downregulation of V1 AVP receptors (V1R),
mainly expressed on vascular smooth muscle cells and responsible of a calcium-mediated
vasoconstriction mechanism, was described during the septic shock; moreover, a relative
postoperative deficiency of AVP, probably due to progressive depletion in chronic hyperstimulation
conditions, was hypothesized in the postoperative after CPB [11–13]. On this basis, it has been
assumed that a relative AVP insufficiency may contribute to the failure in restoring vascular tone in
post-cardiac surgery vasodilatory shock [6]. However, the reasons why only some patients are prone
to develop an AVP deficiency after cardiac surgery remain unclear.

The AVP measurement is cumbersome and not reliable, mainly due to preanalytical variability and, ultimately, not suggested [14]. Copeptin, which derives from the same hypothalamic precursor of AVP (pre-proAVP), is more stable, easier to measure and characterized by longer half-life [14]. Because copeptin is released in equimolar ratio by neurohypophyseal granules, it has been recently promoted as a reliable marker of AVP release [15]. High copeptin level has been associated with chronic heart failure and acute myocardial infarction [16]; moreover the prognostic value of copeptin has been described in critically ill patients suffering from coronary artery disease and advanced heart failure.

Patients undergoing CPB often experience profound physiologic responses to the extracorporeal circulation with alterations in hypothalamic-pituitary-adrenal (HPA) axis as well as the activation of the inflammatory system [17, 18]. On this basis, another endocrinological mechanism supposed to be implicated in PCVS is an acquired adrenal insufficiency (AI) [18, 19]. Glucocorticoids are, in fact, necessary for the physiological action of angiotensin II, epinephrine and nor-epinephrine (NE) and, consequently, for maintaining an adequate vascular tone in response to surgical stress [20]. The incidence of post-cardiotomy AI is estimated in 38–60% of surgical procedures, depending on the criteria used for the diagnosis, and is associated to vasopressor resistance with necessity of a prolonged period of amino-pharmacological support [18]. The Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) Guidelines for the Diagnosis and Management of Critical Illness Related Corticosteroid Insufficiency (CIRCI), currently consider CPB surgery a condition at risk of CIRCI and suggest prophylactic treatment with hydrocortisone; this practise in fact demonstrated a reduction in mortality and atrial fibrillation occurrence [19]. On the other hand, no evidence about the role of a presurgical HPA axis impairment or exhaustion in the development of PCVS is currently available.

Diagnosis of secondary AI is based on a basal cortisol evaluation early in the morning, implemented by the response to a corticotropin (ACTH) stimulation test, in presence of basal values in the grey area defined as 30–150 µg/L [21]. The usage of a standard dose (SD) of ACTH (250 µg) in order to identify secondary AI has been criticized because supraphysiologic and able to induce false normal
response; otherwise, a low dose (LD) ACTH stimulation test (1 μg) was advocated in these cases [22]. Thus, the aims of the present study were to estimate the incidence of PCVS after CPB surgery and to investigate whether preoperative copeptin or a presurgical impairment of the HPA axis were associated with PCVS.

Materials And Methods

Study design

We performed an observational prospective cohort study at “Città della Salute e della Scienza di Torino” University Hospital in Turin, Italy. The local ethical committee “Comitato Etico Interaziendale” in Turin, approved the study protocol on 12th October 2015 (protocol n. 0099127) and the study has been conducted in accordance with the Declaration of Helsinki.

Patients

All patients scheduled for cardiac surgery with CPB and admitted to the Cardiac Intensive Care Unit after the intervention were consecutively evaluated for enrolment. Exclusions criteria were age less than 18 years old, off pump surgery, cardiac transplantations, extracorporeal membrane oxygenation (ECMO), dialysis, end stage hepatic disease, endocarditis, sepsis, septic shock, preoperative use of vasoactive or inotropic drugs and lack of consent.

Variables and data measurements

We defined PCVS as the simultaneous occurrence of a mean arterial blood pressure (MAP) < 60 mmHg together with a systemic vascular resistance index (SVRI) < 1,200 dyn*s/cm⁵*m², resulting in the need for a NE infusion with dosages ≥ 0.1 μg/kg/ minute for at least 12 hours and within the first 24 hours after cardiac surgery [1, 7].

We collected demographic and clinical data, as following: age, gender, EuroSCORE[23], SAPS II[24] and SOFA[25] score, type of surgery, CPB and cross clamping time, preoperative left ventricular ejection fraction (LVEF), anti-hypertensive drugs assumed before surgery (if suspended or not), renal failure (AKIN classification[26]). Additionally, we evaluated if patients needed inotropic and/or vasoactive drugs after CPB and dose. Systolic and mean arterial pressure, central venous pressure, left atrial pressure, when available, and systemic vascular resistance index were also collected.
Before surgery (T0), one day (T1) and 7 days after surgery (T2), copeptin and NT-proBNP levels were measured together with routine biochemical analysis, hemodynamic monitoring (MAP, SVRI, CO) and NE infusion were also recorded.

Moreover, at T0, early in the morning, all patients underwent to HPA axis evaluation with a LD, followed by a SD, ACTH stimulation test as follows: after baseline cortisol measurement, i.v. Cortrosyn 1 μg bolus was administrated with collection of venous blood sample for cortisol at 30 minutes and 60 minutes (LD ACTH test); immediately after, i.v. Cortrosyn 250 μg was administrated with collection of venous blood samples for cortisol at 120 minutes (SD ACTH test). A lack of response to both tests was defined for a peak cortisol level < 180 μg/L.

Finally, we evaluated the intensive care unit length of stay (ICU-LOS), expressed as days free from ICU stay, considering 28 days as the maximum length of ICU stay.

Copeptin determination

Blood from an EDTA-containing tube was centrifugated at 4,000 rpm for 5 minutes and a plasma aliquot was immediately frozen and stored at −80 °C until analysis. Copeptin concentrations were then determined with the B.R.A.H.A.M.S. KRYPTOR compact PLUS (ThermoFisher Scientific, Hennigsdorf, Germany) automated method. Copeptin is measured using TRACE (Time-Resolved Amplified Cryptate Emission) technique, an immune fluorescent analysis that measures the delayed fluorescent signal transferred from donor molecules when bound in an immunocomplexes. The signal is proportional with the concentration of copeptin in the sample. The limit of detection of the assay is 0.9 pmol/L, while intra-assay coefficients of variation were below 7% and below 12% for inter-assay coefficients.

NT-proBNP determination

Blood samples were collected in an EDTA-containing tube and processed on Cobas e602 automated platform (Roche Diagnostics), including centrifugation at 3,500 rpm for 5 minutes and determination by sandwich immunoassay with two monoclonal antibodies directed against N-terminal portion (1–76) of proBNP molecule (Elecsys proBNP II), using electrochemiluminescence detection (ECLIA). The limit of detection of the assay was 5 pg/mL (0.6 pmol/L), with a 5–35,000 (0.6-4,130) dynamic range as
well as intra-assay and inter-assay coefficients of variation of less than 5% at three different concentrations (46, 125 and 14,150).

Other determinations

All the remaining routine laboratory measurements on serum, plasma and urine samples were performed with automated biochemical assays in the local laboratory (Baldi & Riberi Laboratory, University Hospital “Città della Salute e della Scienza di Torino”, Turin, Italy).

Statistical analysis

All continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR), while categorical variables were expressed as number and percentage (%). Inter-group comparisons for continuous variables were performed with the T-test or the Wilcoxon-Mann-Whitney test depending on type of distribution. The Chi square test or the Fisher’s exact test were used to analyse categorical variables, when appropriate. The Receiver Operating Curves (ROC) analysis was used to assess copeptin and NT-proBNP cut-offs able to discriminate patients who developed PCVS. Logistic regression models were calculated in order to identify the predictors of PCVS among the preoperative or intraoperative variables. A multiple linear regression model was also calculated to define the best predictor of log-normalized copeptin values at 7 days post-surgery. As outcome variable we evaluated the ICU length of stay (ICU-LOS), with a follow up at 28 days.

Statistical analysis was performed using Stata/IC 14.2, version 29 Jan 2018. Figures were made using GraphPad Prism™, version 8.01.

Results

We consecutively evaluated 350 patients admitted to the cardiac surgery ward; 253 of them were not eligible according with the exclusion criteria. Among the 97 eligible patients, 55 were enrolled and completed the study (Fig. 1).

All demographic variables and the main preoperative and intraoperative data are described in Table 1.
# Table 1
Demographic and pre-operative variables

|                      | All (N = 55) | PCVS (N = 9) | Not PCVS (N = 46) |
|----------------------|-------------|-------------|-------------------|
| **Age, Median (IQR)** | 72 (60–78)  | 76 (60–80)  | 71 (61–78)        |
| **Gender, Female, N(%)** | 18 (38)    | 2 (22)      | 16 (35)           |
| **BMI, Median (IQR)**  | 25.12 (22.8–29) | 21.9 (20.7–27.3) | 25.3 (23.4–29)   |
| **EuroSCORE II**      | 1.28 (0.98–1.83) | 1.31 (0.88–1.68) | 1.27 (1.03–1.83) |
| **SAPS II**           | 23 (19–28)  | 31 (19–35)  | 22 (19–26)        |
| **LVEF %**            | 60 (57–65)  | 61 (53–65)  | 60 (57–66)        |
| **SOFA**              | 4 (2–6)     | 8 (3–9)     | 4 (2–6)           |
| **ACEi, n (%)**       | 5 (9)       | 3 (33.3)    | 2 (43)            |
| **Beta-Blocker, n (%)** | 21 (38)    | 5 (55.5)    | 16 (34.8)         |
| **Diagnosis**         |             |             |                   |
| **Mitral Valve Disease, n(%)** | 26 (47)  | 7 (78)      | 19 (41)           |
| **Aortic valve Disease, n(%)** | 29 (53) | 5 (55.5)    | 24 (52)           |
| **CAD, n(%)**         | 9 (16)      | 1 (11)      | 8 (17)            |
| **Surgery**           |             |             |                   |
| **Mitral valve surgery, n(%)** | 24 (43)  | 7 (78)      | 17 (37)           |
| **Aortic valve surgery, n(%)** | 29 (53) | 5 (55.5)    | 24 (52)           |
| **Combined valve surgery, n(%)** | 7 (13)   | 3 (33.3)    | 4 (9)             |
| **CABG, n(%)**        | 12 (22)     | 3 (33.3)    | 9 (19)            |
| **Cortisol, median (IQR)** |         |             |                   |
| **T0**                | 11.7 (8.71–14.91) | 12.4 (5.72–14.47) | 11.5 (9.03–14.91) |
| **T30**               | 20.4 (16.4–24.13) | 16.4 (11.3–21.12) | 21.01 (16.5–24.5) |
| **T60**               | 18.14 (14.6–21.9) | 15.8 (12.13–18.25) | 18.62 (14.7–22.6) |
| **T120**              | 26.29 (23.1–32.9) | 25 (20.07–25.53) | 27.8 (23.29–32.95) |

*Wilcoxon-Mann-Whitney test, p < 0.001. SAPS II, simplified acute physiology score; SOFA, sequential organ failure assessment; EF, ejection fraction; CKD, chronic kidney disease; ACEi, angiotensin-converting enzymes inhibitor.*

Among the included patients, 9 (16.3%) developed PCVS. No patients showed a pathological response to the SD ACTH test; moreover there was no significant difference neither in basal or stimulated cortisol level between patients who developed PCVS and those who did not (Table 1); nevertheless, a greater proportion of patients developing PCVS (55.5% vs 24%) presented a reduced response to the LD ACTH test.

Patients who developed PCVS had a significantly longer CPB (p = 0.005) and clamping time (p = 0.0004) and needed more often inotropic support, with epinephrine or dobutamine (p = 0.008) (Table 2). Mean dosage of dobutamine was slightly higher among patient who developed PCVS compared to those who did not (3.68 ± 2.92 vs 1.42 ± 1.96; p = 0.01).
Table 2

|                      | All (N = 55) | PCVS (N = 9) | Not PCVS (N = 46) |
|----------------------|--------------|--------------|-------------------|
| **CPB median (IQR)** | 132 (108–158)| 170 (149–209)| 131 (105–145)*    |
| **CLAMP, median (IQR)** | 99.5 (82.5)  | 137.5 (111–172)| 97 (82–107)*      |

**Hemodynamic support**

|                      |              |              |                   |
|----------------------|--------------|--------------|-------------------|
| **Nor-epinephrine, n(%)** | 21 (38)     | 7 (78)       | 16 (35)#          |
| **Epinephrine, n(%)**          | 4 (7)       | 2 (22)       | 2 (4)             |
| **Dobutamine, n(%)**           | 20 (36)     | 7 (78)       | 13 (28)#          |

|                      |              |              |                   |
|----------------------|--------------|--------------|-------------------|
| **Na + 1st day**     | 141 (138–144)| 144 (139.5–145.5)| 141 (138–144) |
| **2nd day**          | 139 (137–143)| 140 (139–147)   | 138.5 (136–142) |
| **3rd day**          | 139 (137–141)| 141 (139–144)   | 138 (137–140)  |
| **4th day**          | 139 (136–142)| 138 (137–145)   | 139 (136–142)  |
| **5th day**          | 139 (137–141.5)| 140 (138–146)| 139 (137–141)  |
| **6th day**          | 140 (137–141)| 144.5 (140–149)| 139 (137–140)  |

*Wilcoxon-Mann-Whitney test, p < 0.001; # Fisher exact test, p = 0.008. CPB, cardiopulmonary by pass; CLAMP, clamping time.

At T1 copeptin (median value 211.8 pmol/L [50.25 to 318.9]) was significantly higher than at T0 (12.7 pmol/L [8 to 17.9]) and at T2 (11.7 pmol/L [8.7 to 21.3]) (p < 0.0001). At T1, no difference was found in median copeptin between PCVS and non-PCVS (Fig. 2). Copeptin was significantly higher among PCVS both at T0 (19.2 pmol/L [17.89 to 21.29] vs 11.39 pmol/L [6.33 to 14.78]; p = 0.001) and at T2 (30.23 pmol/L [19.7 to 99.85] vs 10.4 pmol/L [7.63 to 19.87]; p = 0.002), compared to those who did not developed PCVS. The observed difference in copeptin between PCVS and non-PCVS at baseline was also confirmed considering mean values after log-normalization (2.36 ± 0.56 pmol/L vs 3.03 ± 0.36 pmol/L; p = 0.001) (Table 3).

Table 3

| Variable              | Coefficient | r-partial | p-value |
|----------------------|-------------|-----------|---------|
| PCVS                 | 0.58        | 0.27      | 0.067   |
| CPB                  | 0.0026      | 0.077     | 0.61    |
| Aortic clamp         | -0.0045     | -0.1      | 0.5     |
| NT-proBNP T2         | 0.000037    | 0.43      | 0.0025  |
| CKD                  | 0.49        | 0.23      | 0.12    |

Additionally, NT-proBNP was higher among PCVS at T0 (1,435 pg/ml [721.75 to 1,836.25] vs 365.5 pg/ml [141 to 977]; p = 0.006) and at T1 (2,053 pg/ml [1,365.25 to 3,465.75] vs 581 pg/ml [220.5 to 1,259]; p = 0.003), while there was no difference in median NT-proBNP between the two groups at T2 (3,571 pg/ml [1,687.5 to 8,316] vs 1,733 pg/ml [954 to 2,957]; p = 0.06) (Fig. 3).

Noteworthy, no significant difference was observed in serum sodium levels between the two groups at...
any observation time (Table 2).

The univariate analysis showed that CPB (OR 1.23, 95% CI 1.005–1.04), copeptin at T0 (OR 1.17, 95% CI 1.04–1.32) and NT-proBNP at T0 (OR 1.001, 95% CI 1.0002–1.001) were associated with the development of PCVS, while at the multivariable analysis only copeptin at T0 was independently associated with PCVS (OR 1.56, 95% CI 1.002–1.33).

The ROC analysis identified in a preoperative copeptin value > 16.9 pmol/L the cut-off associated to the best accuracy (AUC 0.86, 95% CI 0.73–0.94, Se 0.8, 95% CI 0.52-1.00, Sp 0.86, 95% CI 0.73–0.95) and likelihood ratios (+ LR 6.52, -LR 0.13) in predicting PCVS (Fig. 4). Similarly, the best preoperative cut-off for NT-proBNP was > 598 pg/ml (AUC 0.79, 95% CI 0.66–0.89, Se 0.89, 95% CI 0.52-1.00, Sp 0.61, 95% CI 0.45–0.75, +LR 2.27, -LR 0.18) (Fig. 5). The comparison of the two AUC did not show any significant difference (difference 0.0682, 95% CI -0.116 to 0.252, p = 0.47).

The outcome results showed that among patients who developed PCVS the ICU-LOS was longer compared to the control group (3 days [2 to 8] vs 1 days [1 to 2]).

Discussion

In the present study, preoperative copeptin was found to be a good predictor of PCVS after CBP.

Preintervention basal copeptin showed a strong association with PCVS onset within 7 days after CPB surgery. The correlation was clearly confirmed in a logarithmic regression model considering both preoperative variables, as basal NT-proBNP or severe renal disease comorbidity, and intraoperative predictors, as CPB duration. Our results support the previous observation of Colson et al. [27] about the predictive role of copeptin in patients waiting for on-pump cardiac surgery; furthermore, we identified a more specific copeptin cut-off, in an homogeneous cohort of cardiopathic subjects.

No differences were observed between PCVS and non-PCVS in the prevalence of previously reported preoperative risk factors for the syndrome (ACE inhibitors or beta-blockers administration, cardiosurgical risk, LVEF).

PCVS represents a serious complication after CPB, requiring a large amount of vasoactive agents, often burden by relevant side effects. The presurgical identification of subjects at high risk of developing PCVS would be useful in order to select these patients to a precocious usage of 1-
deamino, 8-D arginine-vasopressin (dDAVP) in case of hypotension induced by CPB [28]. A recent meta-analysis of 8 randomized controlled trials showed that a low dose of dDAVP would reduce the rate of perioperative complications in patients undergoing elective and emergency cardiac surgery (OR 0.33, 95% CI 0.20–0.54) [29]. A wide heterogeneity was present among the selected papers and most of them had a small sample size, were monocentric trial and at high risk of bias. Furthermore, the inclusion criteria were different and only two trials started the infusion of dDAVP after the vasodilatory shock [30, 31]; all the other studies used, instead, the drugs prophylactically to prevent post-CPB hypotension in patients chronically treated with ACE inhibitors [29]. However, the VANCS trial [31], a Brazilian double blind RCT with the biggest sample size (300 patients), showed a significant reduction in mortality and in several postoperative complications (stroke, requirement for mechanical ventilation for longer than 48 hours, deep sternal wound infection, reoperation, or acute renal failure) in patients with postoperative vasoplegia treated with dDAVP (0.01–0.06 UI/min) instead of NE (10–60 µg/min) (unadjusted HR 0.55, 95% CI 0.38–0.80); p = 0.0014).

On this basis, our results, corroborating the predictive role of preoperative to identify patients at risk of PCVS, might help to optimize the weaning from CPB.

Our data confirm a marked copeptin increase in the early postoperative [32]. As known, significant psycho-physical stresses represent effective triggers for AVP release from neurosecretory granules stored in the neurohypophysis [33]. In our cohort of patients, median copeptin levels were higher in PCVS than in non-PCVS at the baseline as well as in the early postoperative, although this last difference was not clearly significant (190.3 pmol/L vs 154.3 pmol/L). Consequently, under an etiopathogenetic point of view, our observation is not consistent with the hypothesis of an early postoperative AVP deficiency, eventually induced by chronic hyperstimulation in chronic heart failure [11].

A good correlation between AVP and copeptin levels was observed, in fact, during vasodilatory shock for the first 7 days after cardiac surgery [6]. On the other hand, some degree of V1R insensitivity, eventually consequent to the systemic inflammatory response induced by CPB, could exacerbate the effect of just a partial AVP insufficiency not identifiable by copeptin measurements.

Finally, patients who developed PCVS maintained a significantly higher copeptin even at 7 days after
the intervention, with median levels almost 50% increase compared to basal values. In a linear regression model, NT-proBNP resulted the best predictor of postoperative copeptin values, even more significantly than the PCSV occurrence.

As previously mentioned, recent observationsefforted the increasing role of copeptin as a reliable prognostic marker in cardiopathic patients, mostly in association with NT-proBNP values [16]. Thus, the progressive return of copeptin as closer as possible to the presurgical levels could represents a reliable marker of recovery of the cardiac function after intervention. To our knowledge, this is the first study reporting observations about the postoperative trend of neuroendocrine biomarkers of hydro-electrolyte balance, suggesting a supplemental utility of copeptin measurement in cardiosurgical patients.

The demonstration of a reduced response of the HPA axis to the LD ACTH test, in our cohort, was not significantly associated with the PCSV. Although it could be intriguing to speculate if a presurgical HPA axis impairment could facilitate the development of a CIRCI induced by CPB, it does not seem that a lack of response to LD ACTH test could facilitate PCSV. Finally, it is more relevant insist on the usefulness of a short-term prophylactic treatment with hydrocortisone in patients undergoing CPB in order to reduce surgical complications [19].

Our study presents some limitations. First, the study was designed to perform the ACTH tests 24 hours before surgery, therefore, all patients admitted less than 24 hours before surgery and all emergencies cases were not included. Hence, we might have lost some information on a proportion of this population. Second, the sample size is relatively small, maybe reducing the predictivity value of preoperative copeptin. Third, the HPA axis assessment was not repeated in the early postoperative period, losing the information of possible CIRCI induced by CPB or the intervention itself.

Conclusion

Our results confirm the role of copeptin as cardiovascular prognostic marker in patients suffering from chronic heart failure. Furthermore, preoperative copeptin predicts the occurrence of PCVS even better than previously reported risk factors. CPB duration, however, remains to be considered the principal intraoperative determinant of PCVS. Secondary corticosteroid insufficiency seems not to have a role in
the pathogenesis of PCVS and a routinely preoperative assessment of HPA axis function might be useless. Nevertheless, hydrocortisone prophylactic administration in patients undergoing CPB surgery should be considered because of the high risk of CIRCI induced by extracorporeal circulation.

Abbreviations
PCVS
post-cardiotomy vasoplegic syndrome
CPB
cardiopulmonary by-pass
AVP
Arginine vasopressin
V1R
V1 AVP receptors
HPA
hypothalamic-pituitary-adrenal
AI
adrenal insufficiency
NE
nor-epinephrine
CIRCI
Critical Illness Related Corticosteroid Insufficiency
ECMO
extracorporeal membrane oxygenation
LVEF
left ventricular ejection fraction
MAP
mean arterial pressure
SVRI
systemic vascular resistance index
CO
cardiac output
ICU
intensive care unit
Declarations
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Availability of data and material’s statement
The datasets collected and analysed during the current study are available from the corresponding author on reasonable request.

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Author information

Affiliations
Cardiac Anesthesia Unit, Department of Anesthesia and Intensive Care Medicine, University Hospital “Città della Salute e della Scienza”, Turin, Italy
Daniela Pasero, Giancarlo Fornaro, Andrea Costamagna, Anna Chiara Trompeo, Luca Brazzi
Division of Endocrinology, Diabetology and Metabolism, Department of Medical Science, University Hospital “Città della Salute e della Scienza”, Turin, Italy
Alessandro Maria Berton, Giovanna Motta, Nunzia Prencipe, Marco Zavattaro, Fabio Settanni, Ezio Ghigo, Andrea Silvio Benso
Department of Surgical Science, University of Turin, Turin, Italy
Riccardo Raffaldi, Claudia Filippini, Luca Brazzi
Clinical Biochemistry Laboratory, University Hospital “Città della Salute e della Scienza”, Turin, Italy
Giulio Mengozzi

Contributions
DP, GM, EG, and ASB conceived and design the study. DP, GM, RR, GM, GF, AC, ACT, NP, MZ and FS collected and analyzed the data. DP, AMB, CF, EG, LB and ASB did the statistical analysis and interpreted the data. DP, AMB, GM and ASB wrote the manuscript. All authors revised the manuscript.
for important intellectual content and approved the final version.

**Corresponding author**

Correspondence to Daniela Pasero

**Ethics declarations**

**Ethics approval and consent to participate**

The Institutional Review Board, the local committee “Comitato Etico Interaziendale” in Turin, approved the study protocol on 12th October 2015 (protocol n. 0099127) and all enrolled patients gave the consent to participate to the study.

**Consent for publication**

All patient included in the analysis gave the consent for publication.

**Competing interests**

The authors declare that they have no competing interests.

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Figures
Figure 1

Flow diagram illustrating the selection criteria.
Figure 2

Copeptin at different observation times, post cardiac surgery vasoplegia (PCSV) vs non-PCSV (* p=0.001; § p=0.002).
Figure 3

NT-proBNP at different observation times, post cardiac surgery vasoplegia (PCSV) vs non-PCSV (* p=0.006; § p=0.003).
ROC curve calculated for copeptin at T0 associated to the best preoperative cut-off.
Figure 5

ROC curve calculated for NT-proBNP at T0 associated to the best preoperative cut-off.