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Atrial and brain natriuretic peptide changes in an experimental model of intra-abdominal hypertension

Eriphyli Argyra, MD,[a] *Kassiani Theodoraki, MD, DEAA,*[a,*] *Panagiota Rellia, MD,*[b] *Athanassios Marinis, MD,*[c] *Dionyssios Voros, MD,*[d] *and George Polymeneas, MD*[d]

[a] *First Department of Anesthesiology, Aretaieion Hospital, University of Athens School of Medicine, Athens, Greece*
[b] *Department of Anesthesiology, Onassis Cardiac Surgery Center, Athens, Greece*
[c] *First Department of Surgery, Tzaneion General Hospital, Pireus, Greece*
[d] *Second Department of Surgery, Aretaieion Hospital, University of Athens School of Medicine, Athens, Greece*

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ABSTRACT

Background: Intra-abdominal hypertension (IAH) can have a profound impact on the cardiovascular system. We hypothesized that natriuretic peptides (Nt-pro-ANP and Nt-pro-BNP) are produced in response to the cardiovascular changes observed in an experimental model of IAH.

Materials and methods: Eleven female pigs were enrolled in this study. Four experimental phases were created: a baseline phase for instrumentation (T_1); two subsequent phases (T_2 and T_3), in which helium pneumoperitoneum was established at 20 and 35 mm Hg, respectively; and the final phase (T_4), in which abdominal desufflation took place. Hemodynamic parameters and concentrations of Nt-pro-ANP and Nt-pro-BNP were measured.

Results: Central venous pressure and pulmonary capillary wedge pressure increased significantly during the elevation of intra-abdominal pressure (IAP) and returned to baseline after abdominal desufflation. Right and left transmural pressures remained unaffected by the elevation of IAP. Cardiac output decreased in phases T_2 and T_3 and was restored to baseline levels after abdominal desufflation. Systemic and pulmonary vascular resistances increased significantly with IAH and decreased after abdominal desufflation. Nt-pro-ANP did not change significantly in comparison to baseline. Nt-pro-BNP increased significantly in comparison to baseline at T_3 and T_4. Peak Nt-pro-BNP levels at T_3 (peak IAP) correlated positively with indices of afterload at this time point, that is, systemic vascular resistance and pulmonary vascular resistance ($r^2 = 0.38$, $P = 0.042$ and $r^2 = 0.55$, $P = 0.009$, respectively). A strong negative correlation between Nt-pro-BNP and cardiac output at T_3 was also demonstrated ($r^2 = 0.58$, $P = 0.006$).

Conclusions: IAH resulted in cardiovascular compromise. The unchanged Nt-pro-ANP concentrations might reflect unaltered atrial stretch with IAH, despite the elevation of right atrial filling pressure. The significant increase of Nt-pro-BNP in response to high levels of IAP may reflect left ventricular strain and dysfunction due to the severe IAH and provide an alternative marker in the monitoring of IAH.

* *Corresponding author*. First Department of Anesthesiology, Aretaieion Hospital, University of Athens School of Medicine, Lambaki 61-63, 111 43 Athens, Greece. Tel.: +30 210 2112672; fax +30 210 7211007.
E-mail address: ktheodoraki@hotmail.com (K. Theodoraki).
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1. Introduction

Elevated intra-abdominal pressure (IAP), although initially described over 150 y ago, has been thoroughly reassessed over the last two decades [1,2]. Intra-abdominal hypertension (IAH) creates a spectrum of pathophysiological sequelae beginning with regional blood flow abnormalities and culminating in the development of the "abdominal compartment syndrome" (ACS), during which end organ perfusion and viability can be seriously threatened. IAH is nowadays considered an independent predictor of morbidity and mortality in critical illness and can lead to multiple system organ failure, if measures to reduce elevated IAP are not urgently undertaken [3,4].

More specifically, increased IAP not only compromises regional blood flow in the peritoneal cavity but also has a distinct adverse pathophysiological impact on other organs and systems outside the abdomen. The untoward effects on the cardiovascular system are mediated via increased intrathoracic pressure as a result of rising IAP, affecting preload, contractility, and afterload [5,6]. Thus, the reduction of venous return associated with increased IAP may dramatically reduce preload; due to the cephalad elevation of the diaphragm, intrathoracic pressure (ITP) increases, directly compressing the heart, and thus compromising ventricular contractility and compliance; and, finally, compression of the abdominal aorta may contribute to the increase in cardiac afterload [7].

The natriuretic peptide system consists of a group of neurohormones, including atrial natriuretic peptide (ANP), brain-type natriuretic peptide (BNP), and their biologically inactive N-terminal fragments Nt-pro-ANP and Nt-pro-BNP [8]. BNP was first identified in the porcine brain and later isolated from the porcine heart. ANP is a 28-amino acid peptide primarily synthesized and released by atrial myocytes in response to atrial distension and stretch, whereas BNP is a 32-amino acid synthesized within the ventricles and released in response to ventricular stretch or pressure overload. In response to cardiovascular changes, the atria and ventricles secrete ANP and BNP, respectively, to restore homeostasis by inducing diuresis, natriuresis, and vasodilation through actions in membrane-bound guanylyl cyclase receptors [9]. Nt-pro-ANP and Nt-pro-BNP possess enhanced *in vivo* stability and reduced affinity for receptors compared with that of the biologically active fragments, which are eliminated rapidly from the circulation by receptor binding and enzymatic degradation. This leads to longer half-lives and increased plasma concentrations of the inactive compounds and simplifies handling of samples [10,11].

In this experimental study, we aimed to detect possible changes in serum concentrations of natriuretic peptides following increases of IAP in a porcine model. In specific, we tested the hypothesis that the stable Nt-pro-ANP and Nt-pro-BNP compounds may be produced and detected in response to the profound cardiovascular alterations observed in IAH and provide additional monitoring markers for this syndrome.

2. Materials and methods

The study was performed in the experimental laboratory "Kostas Tountas" of the Second Department of Surgery at Aretaieion University Hospital (Athens School of Medicine, National and Kapodistrian University of Athens). It was conducted in accordance with our institutional standards and took place under the appropriate license of the veterinary authorities and in adherence to National and European regulations for humane care of experimental animals.

Fifteen female pigs (*Sus scrofa domesticus*) with a mean weight of 30 kg (range 25–35 kg) were initially enrolled. The first three animals were used as pilots to develop and standardize our protocol. The corresponding data were not complete so these three animals were excluded from final data analysis. All animals were fasted for 12 h before the experiment, with free access to water.

2.1. Anesthesia

Premedication was achieved by intramuscular injection of ketamine (4–6 mg/kg), atropine (0.02 mg/kg), and midazolam (0.75 mg/kg). This preanesthetic regimen allowed the subsequent establishment of intravenous access via a suitable ear vein. Subsequently, basic monitoring (electrocardiogram, oxygen saturation, noninvasive pulse, and arterial pressure monitoring) was applied. General anesthesia was then induced by thiopental 5 mg/kg and fentanyl 2 μg/kg, and the animal was intubated. After intubation, a bolus dose of vecuronium 0.3 mg/kg was given and anesthesia was maintained by isoflurane 0.5%–1.5%, vecuronium 0.1 mg/kg/h, fentanyl 2 μg/kg/h, and midazolam 3–5 mg/h. The animals were ventilated mechanically (Drager Sulla 808V, type Ventilog-2; Dräger, Berlin, Germany) in a mixture of N_2O and O_2 at a FiO_2 0.4–0.6, respiratory rate varying from 16 to 30 breaths/min and tidal volumes ranging between 250 and 350 mL, aiming at an end-tidal CO_2 between 35 and 45 mm Hg. End-tidal concentration of N_2O and isoflurane was monitored continuously throughout the study to ensure that adequate depth of anesthesia was maintained. Fluid infusion rate was standardized at 5 mL/kg/h during pneumoperitoneum and was modified to 10 mL/kg/h after abdominal desufflation.

2.2. Instrumentation

After surgical right neck dissection, the neurovascular bundle was exposed and a 20 G catheter (Arterial Leader-Cath 115.090; Vygon Corporation, Montgomeryville, PA) was introduced in the carotid artery for invasive blood pressure monitoring and blood collection. The ipsilateral internal jugular vein was then exposed and cannulated with an introducer sheath 6-6.5 Fr, followed by the insertion of a thermodilution catheter 5.5 Fr (Pediatric Oximetry Thermodilution Catheter, model 631HF55; Edwards Lifesciences, Irvine, CA). Its correct position in the pulmonary artery was confirmed by the characteristic changes in the transduced pressure waveform. Cardiac output (CO) was measured by the thermodilution method (Oximetrix

3; Abbott, North Chicago, IL). Moreover, a single lumen venous catheter (Leader-Cath 15 cm 119; Vygon Corporation) was introduced in the femoral vein for blood sampling.

2.3. Experimental phases

After instrumentation, animals were left to stabilize for 45–60 min (baseline phase T_1). Then, hemodynamic parameters were recorded and blood samples were collected. The next phase (T_2) started with the introduction of a Veress needle through a small horizontal infra-umbilical incision into the peritoneal cavity. After connecting the Veress needle to the laparoscopic insufflator, a preset IAP of 20 mm Hg was established mimicking IAH grade II. IAP of 20 mm Hg was maintained for 45–60 min and then hemodynamics were recorded and samples collected as in phase T_1. Phase T_3 included an additional rise of IAP by establishing pneumoperitoneum of 35 mm Hg for another 45–60 min, mimicking ACS, after which pressures were recorded and samples collected. Finally, the abdomen was desufflated by opening the Veress needle to the air (phase T_4). After 45–60 min of animal stabilization, hemodynamic variables were recorded and samples collected.

The hemodynamic parameters evaluated were CO, heart rate, systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), mean arterial pressure, central venous pressure (CVP), and pulmonary capillary wedge pressure (PCWP). Finally, for the estimation of transmural pressures, true transmural right atrial pressure was considered as the measured CVP minus the extracardiac pressure and true transmural left atrial pressure was considered as the measured PCWP minus the extracardiac pressure and were calculated, respectively, according to the formulae: CVPtm = CVP − IAP/2 and PCWPtm = PCWP − IAP/2 [5]. At the end of the procedure, all animals were subjected to euthanasia with a lethal dose of thiopental.

2.4. Measurement of natriuretic peptides

Samples were collected in sterile tubes (Vacutainer; Becton-Dickinson, Heidelberg, Germany) and were immediately centrifuged, and the supernatant was stored at −60°C until assay. Nt-pro-ANP and Nt-pro-BNP were measured with an enzyme immunoassay test kit incorporating immunoaffinity–purified specific polyclonal antibodies (Biomedica Gruppe, Wien, Austria). Nt-pro-ANP and Nt-pro-BNP serum levels were quantitated by enzyme-catalyzed color changes detectable on an ELISA reader (Biotrend, Cologne, Germany). The amount of color developed is directly proportional to the amount of Nt-pro-ANP and Nt-pro-BNP present in the serum samples. Detection sensitivity was 50 fmol/mL for Nt-pro-ANP and 171 fmol/mL for Nt-pro-BNP. The coefficients of variability were 6%–7% and 6%–8% for Nt-pro-ANP and Nt-pro-BNP, respectively.

2.5. Study end points

The main aim of this study was to demonstrate changes of natriuretic peptides Nt-pro-ANP and Nt-pro-BNP during an experimentally induced model of IAP and to correlate them with the hemodynamic changes observed.

2.6. Statistical analysis

Variables were tested for normality of distributions with the Shapiro-Wilk test. Hemodynamic variables over time were analyzed with one-way analysis of variance with repeated measures. Serial levels of Nt-pro-ANP and Nt-pro-BNP were analyzed with Friedman-repeated measures analysis of variance on ranks. The Tukey test was used *post hoc* for pairwise multiple comparisons. Correlation between data was tested by using the Pearson product–moment correlation coefficient test. Results are expressed as mean ± standard deviation or as median [25th–75th percentiles] depending on normality of distributions. A value of $P < 0.05$ was considered as statistically significant. Statistical analysis was performed by the use of SigmaPlot for Windows v.11.0 statistical software (Systat Software, Inc., San Jose, CA).

3. Results

With the exception of one animal (pig #5 died after inducing pneumoperitoneum due to massive pulmonary embolism and

Table – Changes of hemodynamic parameters during the four experimental phases.

Parameters	T1 (baseline)	T2 (IAP = 20 mm Hg)	T3 (IAP = 35 mm Hg)	T4 (desufflation)
CVP (mm Hg)	7.4 ± 3.2	11.5 ± 3.8*	15.2 ± 4.7*	7.8 ± 3.3
CVPtm (mm Hg)	5.5 ± 3.3	7.9 ± 2.6	8.3 ± 2.6	7.8 ± 3.4
PCWP (mm Hg)	10.7 ± 3.5	19.7 ± 5.9*	27.7 ± 7.2*	9.6 ± 4.1
PCWPtm (mm Hg)	7.7 ± 3.7	10.5 ± 4.4	11.7 ± 3.8	7.3 ± 4.7
MAP (mm Hg)	87.9 ± 11.2	81.4 ± 10.8	90.4 ± 15.5	87.6 ± 13.7
HR (beats/min)	123.6 ± 25.2	134.6 ± 30.7	141.2 ± 33.8	130.1 ± 20.8
CO (L/min)	3.1 ± 0.4	2.6 ± 0.3*	2.5 ± 0.2*	3.0 ± 0.3
SVR (dyn s/cm^5)	1869 ± 256	2535 ± 345*	2716 ± 418*	1960 ± 234
PVR (dyn s/cm^5)	253 ± 45	383 ± 58*	397 ± 113*	241 ± 69

Data are displayed as mean ± standard deviation. Parameters included are traditionally measured CVP and pulmonary capillary wedge pressure (PCWP), calculated transmural intracardiac filling pressures (CVPtm and PCWPtm), mean arterial pressure (MAP), heart rate (HR), CO, SVR, and PVR.

* $P < 0.05$ in comparison to baseline.

was excluded from the study), 11 animals were included for the analysis of experimental data, which are as follows:

3.1. *Hemodynamic parameters*

Hear rate and mean arterial pressure remained relatively stable over the course of IAH. CVP and PCWP increased significantly during the elevation of IAP and returned to baseline after abdominal desufflation. Right and left transmural pressures (CVPtm and PCWPtm) remained unaffected by the elevation of IAP. CO and cardiac index decreased in phases T_2 and T_3 and were restored to baseline levels after abdominal desufflation. Finally, SVR and PVR increased significantly with IAH and decreased after abdominal desufflation (Table).

3.2. *Natriuretic peptides*

Nt-pro-ANP did not change significantly in comparison to baseline at any time point (Fig. 1). Nt-pro-BNP increased significantly in comparison to baseline at time point 3 (IAP = 35 mm Hg) and time point 4 (abdominal desufflation) (Nt-pro-BNP values 1308 [1014–1515] and 1037 [1012–1161] as compared with 347 [288–493] fmol/mL, respectively, $P < 0.05$) (Fig. 2). Peak Nt-pro-BNP levels at time point 3 (peak IAP) correlated positively with indices of afterload at this time point, that is, SVR and PVR ($r^2 = 0.38$, $P = 0.042$ and $r^2 = 0.55$, $P = 0.009$, respectively). A strong negative correlation between Nt-pro-BNP and CO at time point 3 was also demonstrated ($r^2 = 0.58$, $P = 0.006$) (Fig. 3).

4. Discussion

In the present experimental study, we analyzed the changes in serum concentrations of natriuretic peptides Nt-pro-ANP and Nt-pro-BNP during a controlled increase in IAP to determine their relationship with the observed hemodynamic changes. The main findings of this experimental study were as follows: first, Nt-pro-ANP did not change significantly over the course of experimentally induced IAH; second, there was a sustained increase in Nt-pro-BNP levels when IAH became severe, whereas Nt-pro-BNP correlated significantly with indices of ventricular dysfunction; and finally, IAH had an overall negative impact on cardiovascular function, as this was documented by an increase in SVR and PVR and a decrease in CO.

Cardiovascular changes during IAH have been thoroughly studied and reported in the last two decades [7,12–14]. Rising IAP displaces the diaphragm cephalad leading to an increase in intrathoracic pressure (ITP). This is called abdominothoracic transmission, with ITP generally assumed to correspond to IAP/2 [5]. In our experimental model, we demonstrated a reduction in CO in response to IAP elevation. Decreased venous return, as ITP rises, causes a significant reduction of preload. Moreover, diaphragmatic elevation and rising ITP apart from significantly impeding venous return can compress the heart directly, reducing ventricular compliance and contractility [6,15]. We also demonstrated increases in SVR and PVR in response to rising IAP. Afterload increase is probably mediated through compression of the aorta and the systemic vasculature as well as the activation of the renin–angiotensin–aldosterone pathway [15–18]. The increase in PVR might be attributed to the compression of pulmonary parenchyma, as ITP rises. We did not observe a statistically significant change of blood pressure as its

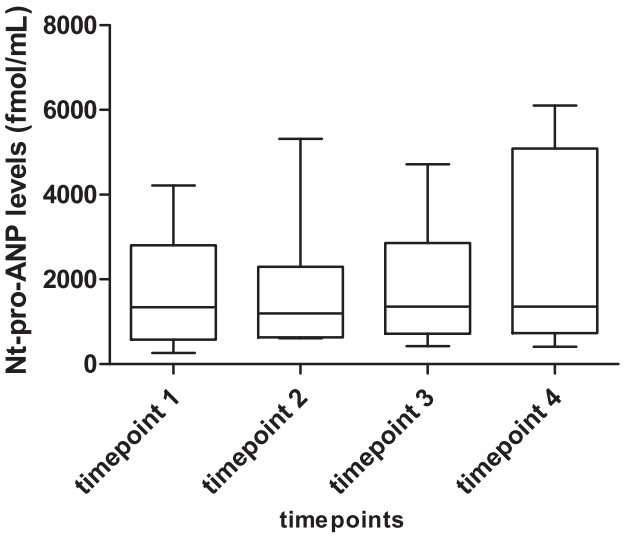

Fig. 1 – Box-and-whisker plot of changes in serum concentrations of Nt-pro-ANP (atrial natriuretic peptide) during the four experimental phases (T_1–T_4). No significant change from baseline was demonstrated.

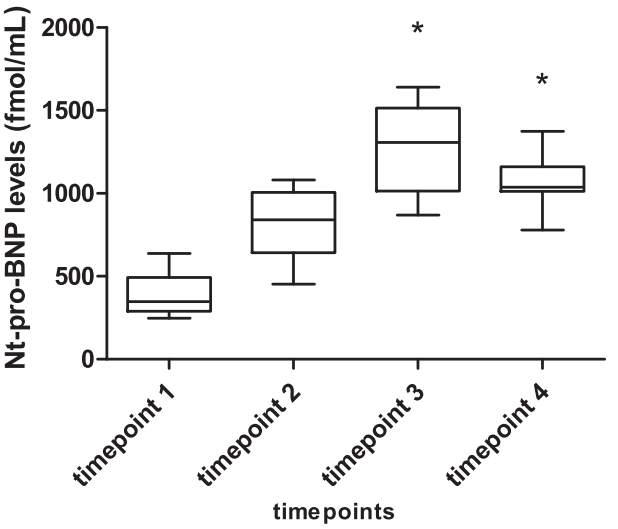

Fig. 2 – Box-and-whisker plot of changes in serum concentrations of Nt-pro-BNP (brain natriuretic peptide) during the four experimental phases (T_1–T_4). Nt-pro-BNP increased significantly in comparison to baseline at time point 3 (IAP = 35 mm Hg) and time point 4 (abdominal desufflation). (Nt-pro-BNP values 1308 [1014–1515] and 1037 [1012–1161] as compared with 347 [288–493] fmol/mL, respectively, $^*P < 0.05$).

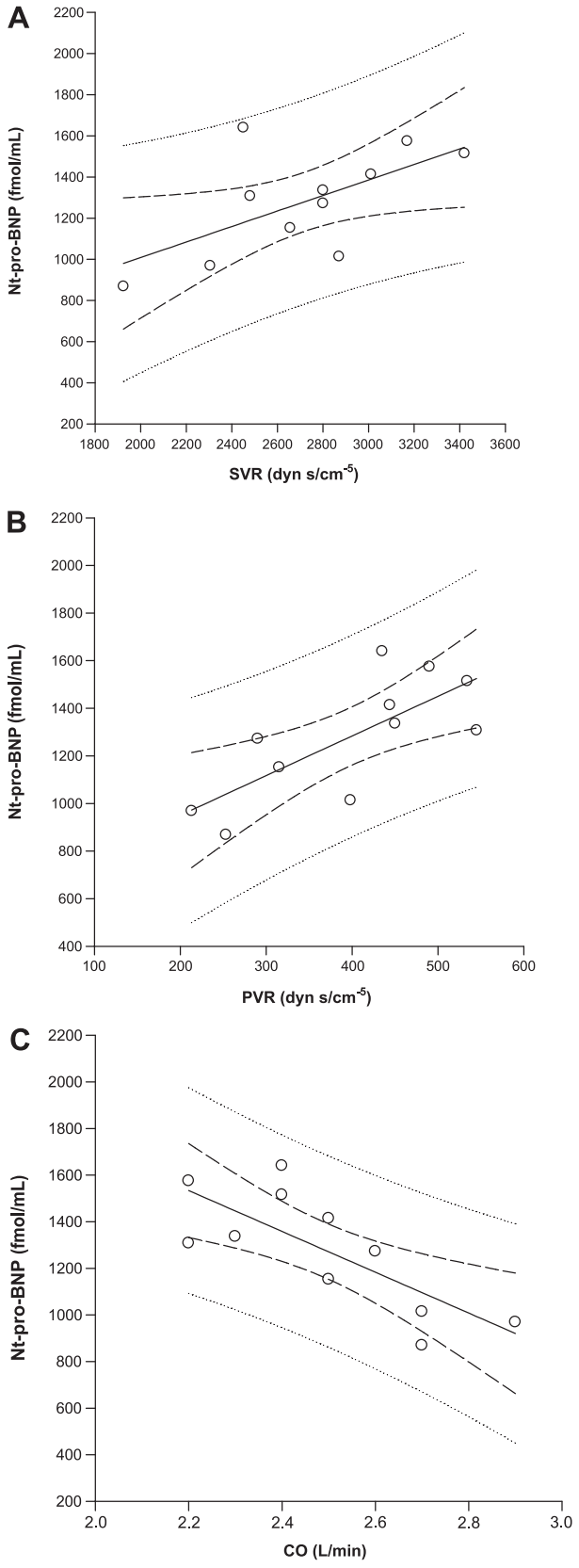

Fig. 3 – Scatter plot diagram of peak Nt-pro-BNP levels at time point 3 (situation mimicking ACS) in relation to hemodynamic parameters at this time point. Nt-pro-BNP correlated positively with indices of afterload at this time point, that is (A) SVR and (B) PVR ($r^2 = 0.38$, $P = 0.042$ and $r^2 = 0.55$, $P = 0.009$, respectively). A strong negative correlation between (C) Nt-pro-BNP and CO at time point 3 was also demonstrated ($r^2 = 0.58$, $P = 0.006$).

measurement at the end of each stabilization period might reflect the opposing effects of a reduced CO and increased SVR, as equilibrium is reached [18].

The induction of IAP in our experimental model was clearly mechanical, without developing conditions either of capillary leakage, which could interfere with the interpretation of plasma levels of natriuretic peptides or intravascular depletion (i.e., hemorrhage) interfering with hemodynamic measurements. We did not use a gradual increase of IAP but rather a first level of 20 mm Hg, commonly seen in clinical settings, and then an abrupt increase to 35 mm Hg to augment the impact of IAH on the cardiovascular system and draw safer conclusions for this relationship. IAP levels of 35 mm Hg in phase T_3, although extreme, are not unrealistic as they are considered as ACS, according to the definitions of the World Society of Abdominal Compartment Syndrome [2].

In our study, we also demonstrated an increase in right and left cardiac filling pressures as reflected by CVP and PCWP over the course of the elevation of IAP. There are contradictory views, however, on whether increased filling pressures during IAH represent increased central blood volume or rather increased intrathoracic pressure caused by IAP elevation [19]. In fact, it has been suggested that due to abdominothoracic transmission of pressure, traditional intracardiac filling pressures are erroneously elevated during IAH and cannot be used as cardiac preload parameters. Both measurements are the sum of intravascular pressure and ITP and thus do not reflect the preload status. Therefore, volumetric parameters, such as right ventricular end-diastolic volume or global end-diastolic volume, are superior predictors of intravascular volume status because their accuracy is unaffected by abdominothoracic transmission of pressure. In the absence of volumetric data, transmural right and left atrial pressures (CVP minus ITP and PCWP minus ITP, respectively) can be calculated, as they have been proposed to reflect intravascular pressures more accurately [5,18,20].

In our experimental model, we did not observe any significant change in Nt-pro-ANP levels in response to the elevation of IAP. The most important stimulus for the release of ANP into the circulation is stretch of the myocyte fibers [21]. An increase in atrial intraluminal pressure without an increase in atrial transmural pressure does not trigger ANP release [22]. This is in accordance with our findings, because, throughout our experiment, atrial transmural pressure did not change significantly and the unchanged Nt-pro-ANP concentrations might reflect unaltered atrial stretch with IAH, despite the elevation of right atrial filling pressure.

In contrast to the unaffected levels of Nt-pro-ANP, Nt-pro-BNP increased significantly when IAH became severe and remained increased even after the resolution of high levels of IAP. BNP is secreted by the ventricular myocardium in response to volume or pressure overload [23]. Its concentration correlates with the degree of ventricular functional impairment and has prognostic significance [24–26]. The significant increase of Nt-pro-BNP in response to high levels of

IAP may reflect left ventricular strain and dysfunction due to the severe IAH. BNP concentrations have also been found to increase in conditions that lead to isolated acute or chronic right ventricular overload [27]. Therefore, the elevated concentrations of Nt-pro-BNP in our experiment might also be partially attributed to the acute right ventricular dysfunction caused by increased IAP. The correlation of BNP with ventricular strain is further supported by its correlation with markers of ventricular dysfunction (CO, SVR, and PVR), when IAH became extreme, mimicking ACS. The persisting high levels of Nt-pro-BNP even after the resolution of IAH and restoration of hemodynamic variables (time point 4) might be explained by its kinetic behavior and its resistance to enzymatic degradation [28].

Our study has a few limitations like the small sample size and the absence of a control group. Furthermore, we do not have hemodynamic data and natriuretic peptide measurements beyond time point 4 and, therefore, we cannot speculate about the behaviour of these peptides in a longer time span. Numerous serial measurements of natriuretic peptides throughout the experiment would most probably provide more accurate information regarding their time course. Unfortunately, this was not a realistic option when designing our experimental protocol due to the high cost of the measurement kits and to hospital budget limitations. Therefore, we restricted our measurements to a few characteristic stages in the continuum of IAH, assuming that any alterations in natriuretic peptide levels would be more easily detectable as a response to distinct IAP changes. In spite of the limited number of measurements, we do believe that our findings are of value because, from our literature search and to the best of our knowledge, we could not find any reports of natriuretic peptide measurements in the clinical context of severe IAH.

In conclusion, under the present study design, we demonstrated unaltered plasma levels of Nt-pro-ANP and elevated levels of Nt-pro-BNP in an experimental model of mechanically induced IAH. The former might be related to a lack of trigger for ANP release due to unaffected atrial transmural pressure and the latter might be attributed to the ventricular functional compromise accompanying elevated IAP. Because the prognostic significance of both peptides has been documented in several studies, further research is warranted to define whether this interesting pathophysiological observation could have any potential clinical implications as well as to determine the optimal use of natriuretic peptides in the context of severe IAH.

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