Effects of different mean arterial pressure targets on plasma volume, ANP and glycocalyx—A randomized trial

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Abstract

Background: Arterial haematocrit (Hct) has been shown to decrease after anaesthesia induction, most probably because of an increased plasma volume (PV). The primary objective was to quantify change in PV if mean arterial pressure (MAP) was kept at baseline level or allowed to decrease to 60 mm Hg. Our secondary objective was to evaluate underlying mechanisms of this response.

Methods: Twenty-four coronary artery bypass patients were randomized to a higher (90 mm Hg, intervention group) or lower (60 mm Hg, control group) MAP by titration of norepinephrine. During the experimental procedure, no fluids were administered. Baseline PV was measured by ¹²⁵I-albumin and the change in PV was calculated from the change in Hct. Changes in MAP, plasma ¹²⁵I-albumin, colloid osmotic pressure, albumin, Mid Regional-pro Atrial Natriuretic Peptide (MR-proANP) and endothelial glycocalyx components were measured from baseline to 50 minutes after anaesthesia induction.

Results: The MAP during the trial was 93 ± 9 mm Hg in the intervention group and 62 ± 5 mm Hg in the control group. PV increased with up to 420 ± 180 mL in the control group and 45 ± 130 mL in the intervention group (P < .001). Albumin and colloid osmotic pressure decreased significantly more in the control group. MR-proANP increased in the control group but no shedding of the glycocalyx layer was detected in either of the groups.

Conclusion: Allowing mean arterial pressure to fall to 60 mm Hg during anaesthesia induction, increases the plasma volume due to reabsorption of interstitial water, with no ANP-induced degradation of the endothelial glycocalyx.
1 | INTRODUCTION

Intraoperative hypotension caused by general anaesthesia induces physiological changes which might lead to organ injury. Maintaining intraoperative mean arterial pressure (MAP) greater than 65 mm Hg may reduce the risk of acute kidney and myocardial injury, the leading causes of 30-day post-operative mortality. Norepinephrine is one vasopressor used to prevent perioperative hypotension. Little is known about the change in plasma volume, atrial natriuretic peptide (ANP) and the glycocalyx layer secondary to changes in MAP during anaesthesia induction.

The Starling principle stipulates that transcapillary fluid exchange depends on a net balance between hydrostatic and oncotic pressure gradients and that fluid is filtered at the arteriolar and reabsorbed at the venular end. Thus, hypotension due to anaesthesia induction could reduce the capillary hydrostatic pressure favouring capillary fluid reabsorption and causing an increased plasma volume. The discovery of the endothelial glycocalyx (EG) layer has, however, questioned the Starling principle and a new model for transcapillary fluid exchange, the Michel-Weinbaum model, has been introduced. The Revised Starling principle stipulates that no net reabsorption occurs in steady state and, instead, filtered fluid is returned to the blood stream by the lymphatic system.

Volume loading has in clinical studies been reported both to elevate and not to elevate the release of ANP. Conflicting results have also been reported on whether ANP induces shedding of the EG or not. Atrial wall stress (eg secondary to hypervolemia) is the major regulator of ANP secretion. The Mid-Regional–pro-Atrial Natriuretic Peptide (MR-proANP) can be detected by a composite assay using binding and signalling antibodies.

The endothelial glycocalyx layer is a web of membrane-bound glycoproteins, proteoglycans and various glycosaminoglycans (GAGs) on the luminal side of the endothelial cells. It is a dynamic layer that is involved in vascular permeability and fluid homeostasis. The presence of circulating glycocalyx fragments such as the GAG hyaluronic acid and the proteoglycan syndecan-1 indicates a loss of glycocalyx integrity and associated endothelial injury. ANP has been suggested to lead to perturbation of the EG during both on-pump and off-pump coronary artery bypass surgery. Whether perioperative hypotension leads to an increased plasma volume that releases ANP and degrades the EG and contributes to fluid shifts and oedema formation is unknown and highlights the need for further knowledge.

In a previous study we reported a decrease in haematocrit parallel to a decrease in arterial blood pressure after induction of anaesthesia. In the present study, the primary objective was quantification of plasma volume expansion secondary to arterial blood pressure reduction. Transcapillary escape rate (TER), colloid osmotic pressure and plasma albumin were assessed as dilution markers. To evaluate the effects of the intervention on hormonal release of ANP and its effects on the EG, plasma concentrations of MR-proANP and glycocalyx components were measured as secondary outcomes.

2 | METHODS

2.1 | Ethics

We conducted a single-centre, prospective randomized study at Sahlgrenska University Hospital, Gothenburg, Sweden. The study was approved by the Regional Ethical Review Board in Gothenburg (protocol number: 389-16), by the Sahlgrenska Radiation Safety Committee (protocol number 16-20) and by the Swedish Medical Products Agency (EduraCT number 2016-004961-16). The trial was registered at http://www.ClinicalTrials.gov (NCT02832596) before enrolment and performed according to Good Clinical Practice and the Declaration of Helsinki. Written informed consent was obtained from all patients before inclusion. The trial was audited by an external monitor.

2.2 | Patients

A member of the research team screened patients >40 years of age scheduled for elective coronary artery bypass grafting (CABG) between May 2017 and January 2018. Exclusion criteria were a left ventricular ejection fraction of 45% or less, untreated hypertension, a known carotid artery stenosis or a former stroke, diabetes mellitus, pregnancy and breast-feeding.

2.3 | Randomization

Block randomization with closed envelopes was used to randomize 24 patients into two groups. According to the gender distribution of CABG patients 6 blocks were labelled male and 2 blocks were labelled female. Each block consisted of four envelopes with two envelopes for control and two envelopes for intervention. The blocks were generated by an anaesthesiologist who did not participate in the study. Prior to the anaesthesia induction, a nurse anaesthetist opened the envelope.

Editorial Comment

In this single-centre prospective study, plasma volume, atrial natriuretic peptide and endothelial glycocalyx (EG) components were measured in a group of cardiac surgery patients randomized to a mean arterial pressure (MAP) of 60 or 90 mm Hg using noradrenaline infusion but no fluid boluses. The group randomized to the lower MAP had an increase in plasma volume with no evidence of shedding of the EG. Although a small study, the adherence to a strict protocol and thorough haemodynamic and laboratory measurements give interesting information about the physiological response to hypotension.


2.4 | Clinical management

The basic experimental setup considering premedication, anaesthesia induction and maintenance, bispectral index scores (BIS) with target values of 40–60, electrocardiogram (ECG) monitoring and frontal cerebral oxygenation (INVOs) as previously described in detail. An arterial line was inserted into the radial artery. A central line and a pulmonary artery catheter (Swan-Ganz TD thermomodulation catheter 131F7, Edwards Lifesciences Nordic AB) were inserted into the right jugular vein in local anaesthesia before anaesthesia induction. For patients randomized to the intervention group, an infusion of norepinephrine (NE) (Noradrenalin Abcur, 0.1 mg/mL) was started along with anaesthesia induction at a dose needed to maintain the pre-induction MAP. In the control group, norepinephrine was administered only if MAP decreased below 60 mm Hg. The urine bladder was catheterized. During the experimental procedure, no fluids were administered to the patients.

2.5 | Outcome variables

The primary outcome was the change in PV from measured baseline PV from the start to 50 minutes after anaesthesia induction. Secondary outcomes were changes in TER of radiolabelled albumin, colloid osmotic pressure, albumin, plasma concentration of MR-proANP, the glycocalyx components syndecan-1 and hyaluronic acid, thrombomodulin, urine flow and changes in haemodynamic parameters. Measurements and blood sampling were performed at baseline and 50 minutes after anaesthesia induction. CI and PAWP were measured at baseline, 10 and 50 minutes and COP at baseline and 50 minutes. The passed amount of urine was measured at 50 minutes.

2.6 | Measurements

Arterial pressure, central venous pressure (CVP), pulmonary artery wedge pressure (PAWP) and mean pulmonary artery pressure (MPAP) were measured via the arterial, the central venous and the pulmonary artery catheters. Cardiac index (CI) was measured in triplicate using the thermodilution technique (mean of three 10 mL ice-cold saline injections in the pulmonary artery catheter). Transducers were zeroed at the mid-axillary line.

The plasma volume before intervention and the TER were determined using 125I-labelled human serum albumin (SERALB-125®, CIS bio international, Gif-Sur-Yvette Cedex, France). Each patient received an IV injection of 0.3 mL 125I-albumin (50 kBq) in the central line 5 minutes before anaesthesia induction. Plasma samples were collected from the arterial line 10 minutes before anaesthesia induction and at 0 (just before anaesthesia induction), 10 and 30 minutes after induction. The administered 125I activity, \(A_{\text{inj}}\) was individually determined by weighing the syringe before \(m_{\text{before}}\) and after \(m_{\text{after}}\) injection, in combination with measurement of the activity concentration in a standard sample, \(C_{\text{standard}}\) (with an activity, \(A_{\text{standard}}\) of ca 20 kBq, and a mass, \(m_{\text{standard}}\) of ca 0.1 g) collected from the same vial, \(C_{\text{standard}} = A_{\text{standard}} / m_{\text{standard}}\). Possible 125I activity adsorbed to the syringes was determined and found negligible. Thus:

\[
A_{\text{inj}} = (m_{\text{before}} - m_{\text{after}}) \times C_{\text{standard}} \tag{1}
\]

The plasma volume before intervention was determined as:

\[
PV_0 = A_{\text{inj}} / C_{\text{plasma,0}} \tag{2}
\]

where \(A_{\text{inj}}\) is the activity injected at time \(t = 5\), \(C_{\text{plasma,0}}\) is the measured 125I concentration in plasma at time 0, assuming total distribution in plasma and negligible (or similar) TER during these 5 minutes.

TER was determined as \(\lambda\) by fitting a monoexponential curve to the measured plasma concentrations of 125I at times 0, 10 and 30 minutes versus time for each patient.

TER was calculated both without (uncorrected TER) and with correction (corrected TER) for plasma volume changes with time. Determination of corrected TER was made using the measured 125I-albumin concentrations at 10 and 30 minutes post-injection multiplied by the relative change in plasma volume at respective time point. The 125I activity in plasma and standard samples were measured in a gamma counter (Wizard 1480; Wallac Oy). Corrections were done for detector background signal and physical decay. Changes in plasma volume after anaesthesia induction were calculated with standard formula\(^{16,100}\times (\text{Hct}_{\text{pre}} / \text{Hct}_{\text{post}} - 1) / (1 - \text{Hct}_{\text{pre}} )\), where Hct is expressed as a fraction.

The colloid osmotic pressure was measured by the OSMOMAT 050 (Colloid Osmometer, Gonotec GmbH). Plasma concentrations of albumin (Roche Diagnostics), MR-proANP (Brahms), syndecan-1 (Human sCD138, Diaclone SAS), hyaluronic acid (Echelon Biosciences Inc) and thrombomodulin (Human sCD141, Diaclone SAS) were determined by immunologic assays according to the manufacturer’s instructions. Large vessel total Hb (tHb) and lactate were measured using a blood gas analyser (RAPIDPoint 500). Light absorbance is measured by a spectrophotometer to calculate the tHb level and Hct is then calculated by the formula: Hb\((\text{g/L}) \times 0.2941\). At our institution the measured coefficient of variation for Hb at the RAPIDPoint 500 machine is 0.4%-0.7%.

Plasma samples were stored at −80°C until analysis. Measurement of plasma volumes, TER and plasma concentrations of hormones and glycocalyx components were made blinded to treatment.

2.7 | Statistical analysis

The statistical analyses were made using the GraphPad Prism, version 8.3.1 (332) (GraphPad Software) and SPSS Statistics version 25 (IBM). Assessment of normality was performed using the Shapiro-Wilk test and histograms. Baseline data were compared using Student’s t-test. Categorical baseline data were compared using Fisher’s exact test. A repeated measures one-way ANOVA was used for assessment of...
intragroup changes and two-way ANOVA for repeated measurements for assessment of differences between groups. A repeated measures correlation was used for assessment of correlation between PV and MAP as well as PV and NE. A P-value < .05 was considered statistically significant. The data are presented as mean ± SD.

The sample size was based on a power calculation of a previous study with a similar study protocol investigating pressure-dependent changes in haematocrit and plasma volume. The power analysis revealed a sample size of six patients in each group for detecting a calculated difference in plasma volume change of 50% with a power of 80% and a significance level of 0.05.

3 | RESULTS

A total of 26 patients were enrolled between June 2017 and January 2018. Two patients were excluded due to postponed surgery. The baseline characteristics for the two randomization groups are presented in Table 1. No adverse events or serious adverse events were reported. The study ended when the predefined number of patients to participate in the trial had been included.

3.1 | Anaesthesia

The anaesthesia level during the experimental procedure, measured by BIS, was 39 ± 7 (range 15-58) in the control group and 40 ± 4 (range 28-66) (n.s.) in the intervention group. End-tidal sevoflurane was 1.8 ± 0.6 (range 0.9-3.1) in the control group and 2.1 ± 0.6 (range 1.0-3.1), (n.s.) in the intervention group.

3.2 | Haemodynamics

Changes in haemodynamic variables in the control and intervention groups are presented in Table 2. Baseline MAP, before induction of anaesthesia, was 94 ± 14 mm Hg in the control group and 92 ± 12 mm Hg in the intervention group (P = .735). In the control group, seven of 12 patients needed NE at a maximal dose of 0.01-0.12 μg/kg/min to maintain MAP above 60 mm Hg. All patients in the intervention group required NE at a maximal dose of 0.09-0.26 μg/kg/min. The MAP during the trial was 93 ± 9 mm Hg in the intervention group and 62 ± 5 mm Hg in the control group. MAP decreased after anaesthesia induction (P < .001), in the control group, as expected, while MAP was maintained at pre-induction levels in the intervention group (Figure 1). CVP increased in both groups after anaesthesia induction with no difference between groups (P = .251). MPAP increased in the intervention group to a greater extent than the control group (P = .01). CI and SV decreased in both groups after induction with no differences between groups (P = .306 and 0.414 respectively). PAWP was not affected in the control group but increased in the intervention group (P = .046). SVR decreased in the control group and increased in the intervention group (P < .001). There were no differences in heart rate (P = .784), regional cerebral oxygen saturation (INVOS) (P = .702) and arterial blood lactate (P = .089) between the groups after anaesthesia induction.

The urine output was 2.4 ± 1.3 mL/min in the control group and 2.5 ± 1.8 mL/min in the intervention group (P = .614).

3.3 | Changes in plasma volume, colloid osmotic pressure, MR-proANP and glyocalyx products

The baseline plasma volume measured with 125I-albumin was 3.0 ± 0.4 L, in the control group and 3.2 ± 0.7 L, in the intervention group (P = .293). Weight-indexed baseline plasma volume was 37 ± 6 mL/kg, in the control group, and 38 ± 4 mL/kg, in the intervention group (P = .754). Arterial blood haemoglobin and haematocrit decreased in the control group with no change in the intervention group (P < .001) (Table 3). The calculated plasma volume increased by 13 ± 4% in the control group, and by 1.6 ± 4.4% in the intervention group (P < .001) (Figure 2). There was a significant correlation between the change in MAP and PV (P < .001), whereas NE was not significantly correlated with the change in PV (P = .537). Furthermore, there was no difference in the PV change in the control group between patients receiving or not receiving norepinephrine, P = .842. Serum albumin decreased in both groups but to a greater extent in the control group (P = .001). Changes in colloid osmotic pressures 50 minutes after anaesthesia induction were −2.4 ± 1.6 and −0.8 ± 1.2 mm Hg in the control and intervention group respectively (P = .013). The mean value of uncorrected TER for 125I-albumin was 22 ± 6%/h in the control group and 6.9 ± 5.9%/h in the intervention group (P < .001). There was a close correlation between TER and calculated plasma volume change at 30 minutes (r = .838). Corrected TER, adjusted for the plasma volume change was −0.1 ± 5.4% per hour and 5.7 ± 8.3% per hour in the control and intervention groups respectively (mean difference, 5.8 ± 2.9% per hour [95% CI, −0.13 to 11], P = .055).

The changes in MR-proANP, hyaluronic acid and syndecan-1 are presented in Table 4. MR-proANP increased in the control group but not in the intervention group. There was no difference in the ANP response in the control group between patients receiving or not

### TABLE 1 Patient demographics and characteristics

|            | Control (n = 12) | Intervention (n = 12) |
|------------|-----------------|-----------------------|
| Age (years)| 66 ± 4.5        | 62 ± 8.6              |
| Gender (F/M)| 3/9             | 2/10                  |
| Weight (kg)| 80 ± 8.5        | 86 ± 18               |
| BSA (Dubois)| 1.9 ± 0.1      | 2.0 ± 0.2             |
| MAP (mm Hg)| 94 ± 14         | 92 ± 12               |
| Haematocrit (%)| 41 ± 2        | 39 ± 3                |
| Calculated PV (L)| 3.5 ± 0.5 | 3.8 ± 0.9             |

Note: Values are mean ± SD.

Abbreviations: BSA, body surface area; MAP, mean arterial pressure; PV, plasma volume.
receiving NE \((P = .998)\). Changes in hyaluronic acid and syndecan-1 after anaesthesia induction did not differ between groups \((P = .222\) and .513 respectively). Altogether, 52 of 96 thrombomodulin samples were under the limit of detection of the Diaclone CD141 ELISA kit \((0.31 \text{ ng/mL})\) and, therefore, no data analysis was performed.

No adverse effects were encountered during the study protocol on heart rate, ST-segment, cerebral oxygenation or arterial lactate.

### 4 DISCUSSION

In this trial, we investigated effects of anaesthesia induction-related hypotension on plasma volume expansion, ANP release and EG degradation in patients going through elective CABP surgery. Two distinct MAP strategies were compared (maintaining pre-operative MAP vs allowing MAP to decline to 60 mm Hg) during 50 minutes from anaesthesia induction. Pressure levels were targeted with intravenous norepinephrine administration. Anaesthesia induction-related hypotension expanded the plasma volume with 420 mL which corresponds to a 13% increase in the plasma volume, while plasma volume was not changed in the intervention group.

A sudden decrease in MAP (such as following anaesthesia induction) lowering the capillary hydrostatic pressure could transiently shift the steady state in the Starling equilibrium and cause a transcapillary fluid reabsorption of short duration explaining the increase in plasma volume. A rapid restoration of plasma volume is supported by earlier studies showing a 40% restored plasma volume 15-20 minutes after reduction in the circulating blood volume.\(^{17}\) Furthermore, Michel and Phillips\(^{18}\) showed that an abruptly lowered capillary pressure caused an reabsorption of fluid from the tissues to the capillary.
which supports our finding of a hypotension-induced transient fluid absorption. Finally, we have in a previous study reported a similar decrease in Hct and an increase in PV in parallel to a decrease in MAP, which is in line with studies by Sano and Saito.

Our data on TER, the disappearance rate of radiolabelled albumin from plasma, are in line with previous studies showing a diffusion of albumin over endothelial structures with a rate of 5.0% per hour. TER may be influenced by hydrostatic blood pressure, glycocalyx degradation and plasma leakage. In the present study, there was a significant difference between the groups in uncorrected TER. Since differences in glycocalyx degradation were not shown, plasma dilution by reabsorption of interstitial fluid most probably explains the higher uncorrected TER in the control group. By adjusting for the individual changes in plasma volume, corrected TER in the low-pressure group and intervention group was 0% per hour and 6% per hour respectively. These results are in compliance with studies from Parving et al showing highly significant correlation between the TER of albumin and blood pressure. The difference in TER, although not significant, may be explained by lower hydrostatic capillary pressure for convective transport of albumin in the low-pressure group. Both colloid osmotic pressure and serum albumin decreased significantly more in the control group, supporting the idea of expansion of plasma volume by fluid of low protein content, most probably from the interstitial space. The haemodilution seen in our patients during lowered MAP can hardly be explained by increased lymph return. About 8-12 L of
lymph is returned in an adult each day, making this explanation unlikely to cause haemodilution with approximately 400 mL within 10-30 minutes, as shown in the present study.\textsuperscript{23}

Atrial wall stress is the major regulator of ANP secretion.\textsuperscript{12} Volume loading as a blood-sparing procedure has been shown to increase the release of ANP and has been suggested to cause shedding of the EG.\textsuperscript{7} We, therefore, hypothesized that a rapid increase in the plasma volume due to anaesthesia induction could release ANP and induce shedding of glycocalyx components. However, the issue on the role of ANP on glycocalyx is controversial. A 750-mL crystalloid fluid bolus has been shown to disrupt the EG without a significant increase in ANP.\textsuperscript{8} Furthermore, in post-operative patients with signs of hypoperfusion, a rapid infusion of 5% albumin caused an increase in MR-proANP but not glycocalyx shedding.\textsuperscript{11}

The CVP increased in both groups but there was no difference between the groups over time. Explanations for increased CVP include increased plasma volume in the control group and recruitment of peripheral volume by norepinephrine-induced vasoconstriction in the intervention group. There was a more pronounced increase in MR-proANP in the control group with increased PV. Mechanical stretch, like increased preload, is probably the most important factor affecting ANP secretion, but also increasing aortic pressure (afterload) has been shown to stimulate ANP secretion from the heart.\textsuperscript{24} In the intervention group, PAWP increased to a greater extent compared to the control group, but the increase in MR-proANP was modest. Also norepinephrine has been suspected to increase plasma levels of ANP, but it is more likely an effect due to increased afterload.\textsuperscript{25} No shedding of the glycocalyx layer was, however, observed in either of the groups and the hypothesis that ANP induces shedding of EG components is, hence, not supported by our results.

The free-flowing plasma volume could possibly be diluted by glycocalyx-bound fluid with a protein concentration between the free-flowing plasma and the endothelial intercellular clefts.\textsuperscript{4} The volume of the EG in humans is estimated to be between 15 and 20 mL/kg body weight.\textsuperscript{26} Degradation of glycocalyx has been shown in adults undergoing cardiac surgery both with and without cardiopulmonary bypass.\textsuperscript{10} That means that other reasons (eg plasma volume expansion secondary to anaesthesia induction) for initiating the endothelial surface damage than extracorporeal circulation has to be sought. Glycocalyx degradation, measured by hyaluronic acid and syndeacan-1, was not found in this trial and does, therefore, not support that the observed increase in plasma volume emanates from the glycocalyx layer.

This study with 12 patients in each group has several limitations. This study design cannot distinguish between the effects of different blood pressure targets and the NE dose itself on the changes in plasma volume. However, seven patients in the control group received NE during the experimental procedure and there was no difference in the PV change in the control group between patients receiving or not receiving NE. Furthermore no correlation was shown between NE and the change in PV, whereas the change in MAP and PV was significantly correlated with each other. Thus, the lack of change in plasma volume in the intervention group is most probably due to maintained capillary hydrostatic pressure and maintained arterial blood pressure, and not by the norepinephrine itself. The time frame may be too short for showing a difference in ANP secretion between the groups and its effects on glycocalyx degradation. The atria have, however, intracellular reserves of ANP and an atrial wall stress induces a rapid release of ANP and, therefore, the duration of the study period of 50 minutes after anaesthesia induction should be long enough. In our study, clinical outcomes due to the different target pressures were not assessed, but reports on the use of perioperative NE to treat vasodilation has been associated with less intraoperative anaemia and reduced red cell transfusion, and further clinical outcome studies on target pressures during anaesthesia are needed.\textsuperscript{27} All patients had ischaemic heart disease and medicated with beta-blockers which might affect the haemodynamic effects on anaesthesia and of norepinephrine infusion, thus, generalization of the study to other patient groups must be done with caution. The strengths of the study include the low risk of bias due to the randomized design, the blinded measurement of plasma volume and plasma concentrations and the external auditing of study conduct.

5 | CONCLUSIONS

Maintaining blood pressure with norepinephrine after anaesthesia induction maintains the plasma volume. Allowing blood pressure to fall to 60 mm Hg after anaesthesia induction, increases the plasma volume due to transient changes in the Starling forces. Different blood pressure targets after anaesthesia induction have little effect on ANP release and no effect on the endothelial glycocalyx degradation.

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CONFLICT OF INTEREST

None declared.

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