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Beat-by-Beat Assessment of Cardiac Afterload Using Descending Aortic Velocity-Pressure Loop During General Anesthesia - A Pilot Study -

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Running title: Aortic PU Loop and Cardiac afterload

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Authors' contribution

F.V., A.L.G., E.G., and A.Me. conception and design of research; F.V., A.L.G., O.P., J.M. and J.J. performed experiments; E.G. and A.L.G. analyzed data; A.L.G. and E.G. interpreted results of experiments; E.G., A.LG. and SM prepared figures; F.V., A.L.G., E.G. and A.Me. drafted manuscript; F.V., A.L.G, E.G., A.Ma and S.M edited and revised manuscript; F.V.,

A.L.G., J.J., O.P., J.M., A.Ma., S.M., A.Me. and E.G. approved final version of manuscript. FV., A.L.G. equally contributed to this present study.

Acknowledgments

We thank Marie-Céline Fournier, research nurse in our department, for her support in the conduct of the present study. We also thank anesthetic nurses for their support in the conduct of the present study.

Fundings

Fabrice Vallée received research grant from Assistance Publique – Hôpitaux de Paris

Disclosures

Fabrice Vallée, Arthur Le Gall, Etienne Gayat and Alexandre Mebazaa co-own the patent describing the PU Loop (WO 2015173785 A1 "Method for the continuous evaluation of the ventriculo-aortic coupling of at-risk patients by analysis of pressure-flow loops")

Alexandre Mebazaa has received speaker honoraria from Abbott, Novartis, Orion, Roche and Servier and fee as member of advisory board and/or steering committee from Cardiorentis, Adrenomed, MyCartis, ZS Pharma and Critical Diagnostics

Etienne Gayat has received consulting fee from Magnisense, research support from Sphingotec, Deltex Medical and Retia Medical.

Abstract

Introduction: Continuous cardiac afterload evaluation could represent a useful tool during general anesthesia (GA) to titrate vasopressor effect. Using beat to beat descending aortic pressure(P)/flow velocity(U) loop obtained from esophageal Doppler and femoral pressure signals might allow to track afterload changes.

Methods: We defined 3 angles characterizing the PU loop (alpha, beta and Global After-Load Angle (GALA)). Augmentation index (AIx) and total arterial compliance (Ctot) were measured via radial tonometry. Peripheral Vascular Resistances (PVR) were also calculated. Twenty patients were recruited and classified into low and high cardiovascular (CV) risk group. Vasopressors were administered, when baseline mean arterial pressure (MAP) fell by 20%.

Results: We studied 118 pairs of pre/post bolus measurements. At baseline, patients in the lower CV risk group had higher cardiac output (6.1±1.7 vs 4.2±0.6 L/min; p = 0.005), higher Ctot (2.7±1.0 vs 2.0±0.4 ml/mmHg, p = 0.033), lower AIx and PVR (13±10 vs 32±11 % and 1011±318 vs 1390±327 dyn.s.cm^{-5}; p<0.001 and p=0.016, respectively) and lower GALA (41±15 vs 68±6°; p<0.001). GALA was the only PU Loop parameter associated with Ctot, AIx and PVR. After vasopressors, MAP increase was associated with a decrease in Ctot, an increase in AIx and PVR and an increase in alpha, beta and GALA (p<0.001 for all). Changes in GALA and Ctot after vasopressors were strongly associated (p=0.004).

Conclusions: PU Loop assessment from routine invasive hemodynamic optimization management during GA and especially GALA parameter could monitor cardiac afterload continuously in anesthetized patients, and may help clinicians to titrate vasopressor therapy.

Keywords :

Blood Flow Velocity; Pressure; Ventricular Function, Left; Arteries; Compliance; Pulse

Introduction

During General Anaesthesia (GA), prolonged hypotensive episodes have been associated with negative postoperative outcomes [1,2], such as myocardial infarctions [3,4], acute kidney injuries [5], or strokes [6]. To this concern, American and European societies of anaesthesiology and intensive care have highlighted the importance of perioperative hemodynamic optimization strategies [7,8]. This management requires understanding of hypotension's aetiologies through hemodynamic monitoring, in order to titrate fluid and/or vasopressor therapies. Although it has been clearly established that fluid therapy should be titrated according to preload or stroke volume (SV) [9–11], monitoring of vasopressor effects is more challenging. Indeed, vasopressors (direct or indirect alpha-1 agonists) restore mean arterial pressure (MAP) by vasoconstriction but also increase cardiac afterload and wave reflections by reducing elastic properties of medium and small arteries. This could lead to undesirable side-effects in failing hearts [12]. Vasopressors might increase oxygen cardiac consumption, reduce coronary perfusion pressure, and hence, be deleterious in cardiac diseases, in case of exaggerated increase of cardiac afterload [13]. In such tight therapeutic context, it could be wise to continuously assess cardiac afterload in order to determine the best balance between beneficial and detrimental effects of vasopressors.

Cardiac afterload evaluation remains complex during daily clinical practice. Indeed, as described by O Rourke et al.[14], it includes the combination of three components: arterial compliance, aortic wave reflections and vascular resistances, all of which should be assessed separately using specific usually invasive tools. Analysis of central pressure waveforms has been used to monitor arterial function and properties during various vasodilatation states [15,16]. Augmentation index (AIx), a parameter related to the amount of wave reflections occurring during systole and SEVR (subendocardial viability ratio), a measure of coronary perfusion,

have been related to cardiac workload and afterload. However, this type of analysis requires high fidelity ascending aortic pressure waveforms which are usually obtained via intra-aortic catheters or non-invasive tonometry. During routine GA, these technics are not practical: the invasive line usually rests on brachial or iliac artery where waveform morphology is altered and more difficult to interpret in terms of waveform analysis and cardiac afterload [17,18]. We hypothesized that abdominal aortic pressure (P) coupled with flow waveform (U) into pressure-flow velocity (PU) loop diagram could allows a beat to beat assessment of cardiac afterload. We have conducted a pilot study to compare cardiac afterload parameters obtained from PU loops, with parameters obtained from central pressure analysis estimated by non-invasive arterial tonometry. To this concern, we have assessed the changes of these parameters during GA, in high or low cardiovascular risks patients as well as before and after vasopressor administration.

Material and Methods

This prospective observational study was performed on patients undergoing GA for neurosurgery. Between November 2013 and April 2014, the patients admitted at Lariboisiere University Hospital (Paris, France) for elective removal of intra-cranial tumours, or for intracranial aneurysm surgery, were screened for inclusion. Only patients in whom preoperative anesthesia's consultation had indicated continuous arterial pressure through femoral puncture and cardiac output monitoring during the procedure, were eligible for the study. What is more, only patients who medically required vasopressors to maintain their MAP during the intervention were included in the study. Exclusion criteria were age < 18 year, pregnancy or contraindication for the use of transesophageal Doppler. This study was approved by the Institutional Review Board of the « Société de Réanimation de Langue Française » (CE SRLF 11-356), that exempted signed informed consent. Every subject was orally informed for its inclusion in this study.

Procedure

GA was induced with total intravenous anesthesia using propofol (75-150 mg/kg/min) and remifentanil (0.2-0.5 µg/kg/min). Patients were intubated after administration of atracurium (0.5 mg/kg), and ventilation was set up until End Tidal CO_2 reached 35 to 38 mmHg, with Tidal Volume of 6 and PEEP of 4 cmH_2O. The arterial line was inserted via the femoral artery, using 4 French, 20 cm, catheter (Seldicath®, Prodimed, France). Pressure signals were recorded 20cm far from the puncture point so approximatively in the abdominal aorta above the iliac bifurcation. Signals were processed through a Philips MP60 monitor (Philips, NL) and a CombiQ monitor (Deltex Medical®, Chichester, UK). A trans-esophageal Doppler probe was used according to manufacturer recommendations (Deltex Medical®) to record flow velocity (U) at the level of the thoracic aorta. The CombiQ monitor was a specific

prototype allowing to record simultaneously and continuously arterial pressure and aortic velocity signals at a sampling frequency of 180Hz

Ascending arterial pressure signal was estimated non-invasively using radial applanation tonometry (ShygmoCor, Atcor Medical, Sydney, Australia). A specific wristband Millartonometer was installed on the radial artery after the induction of anesthesia and kept in position during the whole procedure. Waveforms were calibrated using mean and diastolic iliac pressures obtained by invasive femoral catheterization. The standard commercial well-validated generalized transfer function of SphygmoCor was used to estimate central waveforms. Only recordings with a quality index above 90% were used. The SphygmoCor system then estimates cardiac afterload parameters such as central pulse pressure (CPP) and augmentation index (AIx) which represents the excess pressure due to the reflected waves. Total arterial compliance was calculated as Ctot = SV/CPP, where SV was the stroke volume given by the trans-esophageal Doppler monitor [19–21]. Peripheral Vascular Resistance (PVR) was calculated using the modified Poiseuille equation: PVR (dyn.s.cm-5) = MAP (mmHg) / CO (l/min) * 80 [22].

Intervention

Hypotensive episodes were defined the when MAP fell at least 20% under the pre anesthesia MAP [23]. Following standard care protocol of our anesthesia department, when hypotension was identified as a consequence of sedative drugs, as a first line treatment, patients received 250 ml sodium isochloride that could be followed by vasopressor as a second line therapy: a bolus dose for Ephedrine (9 mg), Norepinephrine (5 µg), or Phenylephrine (50 µg). For all other etiologic diagnoses, patients were treated according to physician's choice.

As each patient may have received several boluses of vasoconstrictors, only boluses administered to treat general anesthesia-induced arterial hypotension with following

characteristics were analyzed: (1) stable hemodynamic state with no acute change of MAP or CO 1 minute before bolus (2) no clear evidence of hypovolemia or acute hemorrhage, (3) no concomitant rapid fluid administration, (4) no change in respiratory or ventilator parameters or anesthesia infusion rate 3 minutes before or during bolus and (4) in case of multiple boluses in a short interval were administered, we analyzed only the first bolus if the delay between the first and the second boluses was more than 5 minutes to try to eliminate the confounding factors such as synergism between the drugs and repetitive boluses.

Hemodynamic measurements:

Hemodynamic recordings, including standard measurements, tonometer derived parameters, and PU loop assessments were started a few seconds before the anesthetist administered vasopressor and run for a few seconds after the mean arterial pressure started to decrease. The investigator identified the baseline as the period corresponding to the few second before the administration of the treatment. The peak effect sample was defined as the heart beat with the maximal mean arterial pressure following vasopressor administration. Each vasopressor administration was thus associated with a couple of baseline and peak assessment.

PU Loop (Fig. 1)

In order to plot PU loops: one pressure pulse and its simultaneous flow velocity pulse were manually selected. Only good visual quality pulses were used in the off-line analysis (Matlab, Mathworks, US). Due to equipment filtering and processing, there was a systematic delay between the 2 signals which could go up to 20ms. Pressure and flow velocity pulses were hence visually aligned using the upstroke of the pressure pulse (maximum of the 2^{nd} derivative) and the point when flow becomes different from 0. PU loop were plotted for each subject before and at maximal vasopressor effect.

In order to characterize PU loops, we defined 4 characteristic points (Fig. 1):

A: End Diastole: corresponding to the last point when flow in the aorta equals zero

B point: corresponding to maximal velocity in the aorta

C point: corresponding to maximal pressure in the aorta

D point: End Systole when the flow in the aorta goes back to zero

Fig. 2 and 3 present some examples of PU loops. The area covered by the loop did not properly described its shape as an "elongated" loop (such as in low risk patient) could have the same area than a more "rounded" loop (such as in high risk patient). Hence, to quantify the tilt and the opening of the loop, we defined 3 angles (Fig. 1B):

- The Alpha angle representing the angle between the horizontal line and the AB line
- The Beta angle representing the angle between the AB and AC lines.
- The Global AfterLoad Angle (GALA) representing the angle between the horizontal and the AC lines (equal to the sum of alpha and beta angle).

Statistical analysis

Results are expressed as mean and standard deviation for continuous variables. Discontinuous variables are expressed in number and percentage.

As arterial properties are known to differ according to patient cardiovascular (CV) risk, patients were separated into two groups depending on their number of CV risk factors. Risk factors taken into account were: age> 55 years old, arterial hypertension, current smoking, history of previous cardiovascular event, diabetes mellitus, dyslipidemia or congestive heart

failure. Patients with 0 or 1 CV risk factor constituted the “Low CV Risk” group, while the “High CV Risk” group was composed with patients with 2 or more CV risk factors.

Patients’ characteristics were compared 1) between Low CV Risk and High CV Risk groups and 2) between Baseline and Peak effect of vasopressor. During GA, several vasopressor boluses might be administered. To take into account multiple measures per patients, hemodynamic measurement analysis was conducted using mixed effect models for repeated measures where the weight corresponded to the number of measurements per patients. Comparisons were performed using a weighted student test (for paired or unpaired variables).

Meta regression was performed at baseline for static association assessment between parameters. Absolute difference between baseline and maximal effect of vasopressor was used for dynamic association assessment between parameters. Meta regression results were expressed as slope and 95% confidence interval.

Microsoft Excel (Microsoft, US) and Matlab software (Mathworks, US) were used to plot and analyse PU loops. The Metafor package from the R project software (The R Foundation for Statistical Computing, Vienna, Austria) was used for meta regression analysis.

Results

Patients' main characteristics are presented in table 1 (n = 20). Eleven patients were in the low CV risk group and 9 in the high CV risk group. Low CV risk patients were younger and presented a lower ASA score compared to the high CV risk group. No patients suffered for heart failure.

Hemodynamic profile of patients at baseline

One hundred and eighteen PU loops were performed at baseline in the whole population, before any vasopressor administration. As expected, at baseline, high risk patients had higher Aix and PVR; and lower Ctot and CO (table 1) but, there was no statistical significant difference in MAP. Fig. 2A and 2B present examples of low and high risk patients' PU loops.

All defined angles - Alpha, Beta and GALA - were greater in the high risk group compared to the low risk group (56 ± 11° vs 36 ± 16 ° ; p=0.004, 7 ± 5° vs. 2 ± 3 ° ; p = 0.017, and 68 ± 6° vs. 41 ± 15 ° ; p<0.001, for alpha, beta and GALA angles respectively, table 1).

When comparing PU Loop parameters, a negative association has been found between Ctot and GALA (Fig. 4). Indeed, GALA increased by 11.9 [3.8 - 20] °, for 1 ml/mmHg decrease in Ctot (p = 0.004). Furthermore, a positive association has been found between both GALA and Beta, and Aix: GALA increased by 8.8 [3.8 - 13.7] °, and Beta increased by 2 [0.7 - 3.2] °, for 10 % increase in AIx (p < 0.001 and p = 0.002, respectively). We also found a positive association between PVR and both GALA and Beta: GALA increased by 2.2 [0.2 - 4.2] °, and Beta increased by 0.9 [0.2 - 1.5] °, for 100 dyn.s.cm-5 increase in PVR (p = 0.033 and p = 0.006 respectively).

Assessment of dynamic alteration of cardiac afterload during vasopressors administration (table 2):

One hundred and eighteen boluses of vasopressors were studied. In our population, vasopressor administration led to an increase in MAP, in Aix and in PVR (+18 ± 6 mmHg ; +4 ± 4% and ; +715 ± 357 dyn.s.cm^{-5} ; respectively ; $p < 0.001$ for each), and to a decrease in CO and Ctot (-1.0 ± 0.9 L/min ; -0.8 ± 0.5 ml/mmHg, $p<0.001$; respectively). Fig. 3 shows changes in pressure, flow velocity and PU loop after vasopressor bolus. These changes occurred within a few heart beats (15 heart beats on patient presented on Fig. 3B). Vasopressors significantly increased GALA (+8 ± 4°, $p < 0.001$), as well as Alpha and Beta angles ($p < 0.001$).

Vasopressor-induced increases in GALA were negatively associated with changes in Ctot (-5.2 [-8.7 - -1.7] ° for 1ml/mmHg increase in Ctot, $p = 0.004$, Fig. 4), whereas no association was observed between changes in GALA, Alpha or Beta, and changes in Aix or PVR.

Discussion

This study describes a method to define cardiac afterload parameters derived from aortic pressure – flow velocity (PU) loop plotted with standard hemodynamic signals, recorded during general anesthesia. These parameters: alpha, beta and the Global AfterLoad Angle (GALA) angles quantify the tilt and shape of the PU loop.

Our study showed that those angles 1) varied adequately according to the presence of cardiovascular risk factors and 2) allowed us to track changes in afterload after vasopressor administration.

Afterload is described as a combination of 3 constitutive components [17], acting together to counteract heart's ejection forces: Arterial Stiffness, Aortic Reflection Waves and Arterial Resistances. In our study, we used AIx, Ctot and PVR calculation as estimates of these 3 cardiac afterload components. Indeed, even if general monitoring parameters such as MAP, CO and HR are of course available, their interpretation in terms of cardiac afterload is tricky, as they are fully interlinked and dependent on CV risk. The novelty of our approach is to propose a quantification of afterload during general anesthesia through a combined analysis of Pressure and flow using the angles of the PU loops. Our work aimed to describe a continuous and reactive method which could offer visual assessment of cardiac afterload, and guide anesthetist to dose vasoactive drugs.

At a physiological point of view, a small GALA angle reflects a low afterload: cardiac ejection produces a high flow velocity for a relatively low pressure. On the opposite, a high GALA angle implies that a relatively low ejected volume ends up creating a high pressure pulse. Alpha angle could be more related to local wave velocity through the water hammer equation [24] and beta angle to wave reflections.

These interpretations corroborate the differences observed between low and high CV risk groups as regard to Alpha, Beta and GALA angles (table 1) as well as with the correlations found with Ctot, AIx and PVR (Fig. 4). Indeed, as expected and previously reported [20,25–27], AIx and PVR were higher and Ctot lower with high CV risk patients. They also have higher Alpha, Beta and GALA angles indicating higher cardiac ~~a~~fterload (table 1). Interestingly, GALA was the only parameter significantly associated with the 3 components of cardiac afterload (Fig. 4) while Beta showed a strong relationship with AIx. Those results, while encouraging, should be tempered by the classification used to separate population. Indeed, we used a non-validated classification based on the number of CV risks the patients expressed. While a stratification according to the surgical risk should be more intuitive in terms of post-operative outcomes, to our knowledge, no statistical score is especially designed to evaluate the arterial stiffness or the cardiac afterload. While ASA Classification or Revised Cardiac Index [28,29] could fit our clinical purposes, those score doesn't integrate the age that is known to be the most influent factor in terms of cardiac afterload [30].

After rapid pharmacological vasopressor bolus, AIx, Ctot and PVR were altered. As were the 3 novel angle parameters of the PU loop. However, the association between changes in AIx or PVR and changes in GALA did not reach statistical significance. This surprising result might be explained by the potential inaccuracy of the comparators. Indeed, while AIx has been shown to be a reliable marker during vasoactive challenges [15,16], those results have only been observed in a young population, free of CV risk factors. In older population, AIx might not be such a sensitive parameter [31]. During physical exercise, a strong vasoactive stimulus, Thiebaud et al.[32] have shown that AIx has only been linked to alteration of cardiac afterload in the youngest population. Unfortunately, our study is underpowered to analyze the effect of age on vasopressor agents' effect. Another limitation could arise because

Sphygmocor system used to estimate central pressure has only been validated in awaken patients, under the scope of hypertension pathology, and not during general anesthesia.

Interestingly, PVR did not show any association with PU loops angles during vasopressor agent administration. However, as discussed expansively by Nichols and O'Rourke [17], PVR can find a physiological meaning in terms of cardiac afterload only in steady flow conditions, ie at a distal level of the arterial tree, and not at the aortic level. Thus, our PU loop which is a dynamic, and beat by beat analysis of Pressure and Flow in Aorta, is probably not the most adequate algorithm to track changes in PVR.

In our data, only decrease in Ctot has remained strongly associated with increase in GALA in response to vasopressor agents. Several comments can be addressed about this finding. First, in literature, data relating effects of vasopressors on total arterial compliance are very scarce. However, the SV on PP ratio has been shown to be reliably linked to decrease in cardiac afterload in a population of hypertensive patients taking daily calcium channel blocker [33].We hence used the SV on PP algorithm as an estimator of Total Arterial Compliance. Even if such a method has expressed poor agreement with the area method (more accurate measurement of Ctot) in dogs[34], the correlation coefficient between the two algorithm were 0.78. Chemla et al. have also observed this finding in humans[20]. Finally, Ctot is thought to represent Windkessel model of arterial circulation and which is known to have some imperfection, but at a global arterial system point of view, this model is sufficient to explain arterial circulation observations [35–37].

As mentioned above, central pressure analysis can be used as a surrogate of afterload [38], in particular to quantify vasoactive drug effects [15]. However high quality invasive central pressure recordings or estimated central waveforms from carotid or transformed radial applanation tonometry are not easily available during GA. We wanted a method to quantify

afterload based on GA routine care in order to be easily applicable. For this reason, we used flow velocity obtained by a trans-esophageal Doppler probe, and pressure waveforms recorded through fluid-catheters. One limitation of this approach could be the remoteness of the pressure measurement, at an arterial location slightly different from flow velocity point of measurement. Indeed, pressure wave shape and amplitude are greatly dependent on measurement site [17,18]. This is the reason why we decided to select only patients with invasive femoral line in order to use pressures recorded as close as possible to flow recording point. However, femoral access for pressure measurement isn't out of risk of complication, and should be used only for selected patients. This aspect limits the clinical application of our method. Nevertheless, improvement in technical aspect of PU loop could probably be done and work on the design of a specific transfer function from iliac and/or radial to aortic arch is currently in progress in our research unit.

Another potential source of inaccuracy of our PU loops relates to the re-alignment of pressure and velocity waveforms. In our pilot study, this process was performed manually. An error of a few sample during the re-alignment might be possible. Swalen et al have studied the influence of the re-alignment on the PU loop[39]. While it can greatly modify the onset of PU loop and hence calculation of local wave speed, it however has little influence on the position of B and C and hence on the angles made by these points from the horizontal.

Thiele et al. described a similar setting to ours but they used radial arterial catheter pressures that have been averaged to plot velocity-pressure loop. While their loop is inverted compared to the PU loop usually referred in the literature [37,40], their proposed setting brings, to our standpoint, additional drawbacks: 1) the use of radial pressure waveforms will alter the overall loop shape, 2) the use of average flow and pressure waveforms precludes analysis of acute afterload changes and, 3) to our experience, area of the PU loop does not rendered correctly loop characteristics. Indeed, same surfaces can be found for PU loops of different

shapes. The novelty of our approach resides in the definition of alpha, beta and GALA angles which are simple sensitive parameters to describe the PU loop and its changes across CV risk and vasopressor drugs.

This study was designed on a pragmatic approach based on routine procedures of standard neurosurgical cares including the use of vasopressors in non-hypovolemic patient to maintain cerebral perfusion. While our results support the feasibility of PU loop as a tool to monitor cardiac afterload, this pilot study only included 20 subjects preventing us to further evaluate the specific effect of the various vasopressors effects. Thus, further studies are required to confirm that GALA and GALA changes after vasopressor could be used to optimized perioperative hemodynamic strategies during GA during different volemic conditions.

Conclusion

While our analysis was performed off-line, PU Loop assessment could potentially allow beat-to-beat quantitative analysis of cardiac afterload in clinical settings. This is achieved without any supplementary material, using signals already requested for hemodynamic optimization management in operating room and may help to better understand hemodynamics of high risk surgical patients during GA. Further work on the use of the alpha, beta and GALA angle during GA in particular in patients with failing heart are however required.

Figures Legend

Fig.1: Definition of analysis parameters

Panel A: Example of synchronized arterial pressure and aortic flow velocity with the definition of augmentation index AIx and the A, B, C and D points as described in the methods section.

Panel B: Schematic representation of PU Loop with the 4 characteristics points and definition of the alpha, beta and Global AfterLoad Angles (GALA)

Fig.2: Examples of pressure, flow and PU Loops at baseline (A and B) in low (A and B) and high (C and D) Cardio Vascular (CV) risk patients.

Fig.3: Example of vasopressor effect of aortic pressure, aortic flow velocity and PU loop.

Panel A: Example of aortic pressure (in black) and aortic flow velocity (in gray) before and at peak vasopressor effect.

Panel B: beat to beat PU loops evolution from baseline (gray) to peak vasopressor effect (black)

Fig.4: Association of GALA with AIx, Ctot and Peripheral Vascular Resistances (PVR) (Panel A.1-3, respectively), and changes of GALA after bolus versus change of AIx, change of Ctot and change of PVR (Panel B.1-3, respectively) 118 measurements were performed in 20 patients. Each circle represents the weighted mean of repeated measure for one patient. The radius of the circle represents the number of measurements perform for each patient. (Slopes are expressed in ° per 1 ml/mmHg increase in Ctot, in ° per 10 % increase in AIx or in ° per 100 dyn.s.cm-5 increase with their respective 95% interval confidence)

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Abbreviations

AIx : Augmentation Index

CPP : central pulse pressure

Ctot : Total Arterial Compliance = SV/CPP

CV risk: Cardiovascular risk

GA : general anesthesia

GALA: Global After-Load Angle

MAP : Mean arterial pressure

P : Aortic pressure

PU loop: pressure/flow velocity loop

PVR : Peripheral Vascular Resistances

SV : Stroke Volume

U : Flow velocity