

Beat-by-beat assessment of cardiac afterload using descending aortic velocity–pressure loop during general anesthesia: a pilot study

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1 **Beat-by-Beat Assessment of Cardiac Afterload**
2 **Using Descending Aortic Velocity-Pressure Loop**
3 **During General Anesthesia**
4 **- A Pilot Study -**

5
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18 **Running title:** Aortic PU Loop and Cardiac afterload

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27
28 **Authors' contribution**

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

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

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

45 Alexandre Mebazaa has received speaker honoraria from Abbott, Novartis, Orion, Roche and
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50

51 **Abstract**

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

56 **Methods:** We defined 3 angles characterizing the PU loop (alpha, beta and Global After-Load
57 Angle (GALA)). Augmentation index (AIx) and total arterial compliance (Ctot) were
58 measured via radial tonometry. Peripheral Vascular Resistances (PVR) were also calculated.
59 Twenty patients were recruited and classified into low and high cardiovascular (CV) risk
60 group. Vasopressors were administered, when baseline mean arterial pressure (MAP) fell by
61 20%.

62 **Results:** We studied 118 pairs of pre/post bolus measurements. At baseline, patients in the
63 lower CV risk group had higher cardiac output (6.1 ± 1.7 vs 4.2 ± 0.6 L/min; $p = 0.005$), higher
64 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
65 1011 ± 318 vs 1390 ± 327 dyn.s.cm⁻⁵; $p < 0.001$ and $p = 0.016$, respectively) and lower GALA
66 (41 ± 15 vs $68 \pm 6^\circ$; $p < 0.001$). GALA was the only PU Loop parameter associated with Ctot,
67 AIx and PVR. After vasopressors, MAP increase was associated with a decrease in Ctot, an
68 increase in AIx and PVR and an increase in alpha, beta and GALA ($p < 0.001$ for all). Changes
69 in GALA and Ctot after vasopressors were strongly associated ($p = 0.004$).

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

73 **Keywords :**

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

75

76 **Introduction**

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

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

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

112

113 **Material and Methods**

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

126 *Procedure*

127 GA was induced with total intravenous anesthesia using propofol (75-150 mg/kg/min) and
128 remifentanil (0.2-0.5 µg/kg/min). Patients were intubated after administration of atracurium
129 (0.5 mg/kg), and ventilation was set up until End Tidal CO₂ reached 35 to 38 mmHg, with
130 Tidal Volume of 6 and PEEP of 4 cmH₂O. The arterial line was inserted via the femoral
131 artery, using 4 French, 20 cm, catheter (Seldicath®, Prodimed, France). Pressure signals were
132 recorded 20cm far from the puncture point so approximatively in the abdominal aorta above
133 the iliac bifurcation. Signals were processed through a Philips MP60 monitor (Philips, NL)
134 and a CombiQ monitor (Deltex Medical®, Chichester, UK). A trans-esophageal Doppler
135 probe was used according to manufacturer recommendations (Deltex Medical®) to record
136 flow velocity (U) at the level of the thoracic aorta. The CombiQ monitor was a specific

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

139 Ascending arterial pressure signal was estimated non-invasively using radial applanation
140 tonometry (SphygmoCor, Atcor Medical, Sydney, Australia). A specific wristband
141 Millartonometer was installed on the radial artery after the induction of anesthesia and kept in
142 position during the whole procedure. Waveforms were calibrated using mean and diastolic
143 iliac pressures obtained by invasive femoral catheterization. The standard commercial well-
144 validated generalized transfer function of SphygmoCor was used to estimate central
145 waveforms. Only recordings with a quality index above 90% were used. The SphygmoCor
146 system then estimates cardiac afterload parameters such as central pulse pressure (CPP) and
147 augmentation index (AIx) which represents the excess pressure due to the reflected waves.
148 Total arterial compliance was calculated as $C_{tot} = SV/ CPP$, where SV was the stroke volume
149 given by the trans-esophageal Doppler monitor¹⁹⁻²¹. Peripheral Vascular Resistance (PVR)
150 was calculated using the modified Poiseuille equation: $PVR \text{ (dyn.s.cm-5)} = MAP \text{ (mmHg)} /$
151 $CO \text{ (l/min)} * 80$ ²².

152 *Intervention*

153 Hypotensive episodes were defined the when MAP fell at least 20% under the pre anesthesia
154 MAP²³. Following standard care protocol of our anesthesia department, when hypotension
155 was identified as a consequence of sedative drugs, as a first line treatment, patients received
156 250 ml sodium isochloride that could be followed by vasopressor as a second line therapy: a
157 bolus dose for Ephedrine (9 mg), Norepinephrine (5 µg), or Phenylephrine (50 µg). For all
158 other etiologic diagnoses, patients were treated according to physician's choice.

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

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

168

169 Hemodynamic measurements:

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

177 *PU Loop (Fig. 1)*

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

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

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

187 B point: corresponding to maximal velocity in the aorta

188 C point: corresponding to maximal pressure in the aorta

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

190

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

195- The Alpha angle representing the angle between the horizontal line and the AB line

196- The Beta angle representing the angle between the AB and AC lines.

197- The Global AfterLoad Angle (GALA) representing the angle between the horizontal and the
198 AC lines (equal to the sum of alpha and beta angle).

199

200 *Statistical analysis*

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

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

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

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

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

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

222

223

224 **Results**

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

229 *Hemodynamic profile of patients at baseline*

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

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

237 When comparing PU Loop parameters, a negative association has been found between Ctot
238 and GALA (Fig. 4). Indeed, GALA increased by $11.9 [3.8 - 20]^\circ$, for 1 ml/mmHg decrease in
239 Ctot ($p = 0.004$). Furthermore, a positive association has been found between both GALA and
240 Beta, and Aix: GALA increased by $8.8 [3.8 - 13.7]^\circ$, and Beta increased by $2 [0.7 - 3.2]^\circ$, for
241 10 % increase in Aix ($p < 0.001$ and $p = 0.002$, respectively). We also found a positive
242 association between PVR and both GALA and Beta: GALA increased by $2.2 [0.2 - 4.2]^\circ$, and
243 Beta increased by $0.9 [0.2 - 1.5]^\circ$, for 100 dyn.s.cm⁻⁵ increase in PVR ($p = 0.033$ and $p =$
244 0.006 respectively).

245

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

248 One hundred and eighteen boluses of vasopressors were studied. In our population,
249 vasopressor administration led to an increase in MAP, in Aix and in PVR ($+18 \pm 6$ mmHg ;
250 $+4 \pm 4\%$ and ; $+715 \pm 357$ dyn.s.cm⁻⁵ ; respectively ; $p < 0.001$ for each), and to a decrease in
251 CO and Ctot (-1.0 ± 0.9 L/min ; -0.8 ± 0.5 ml/mmHg, $p < 0.001$; respectively). Fig. 3 shows
252 changes in pressure, flow velocity and PU loop after vasopressor bolus. These changes
253 occurred within a few heart beats (15 heart beats on patient presented on Fig. 3B).
254 Vasopressors significantly increased GALA ($+8 \pm 4^\circ$, $p < 0.001$), as well as Alpha and Beta
255 angles ($p < 0.001$).

256 Vasopressor-induced increases in GALA were negatively associated with changes in Ctot (-
257 $5.2 [-8.7 - -1.7]$ ° for 1ml/mmHg increase in Ctot, $p = 0.004$, Fig. 4), whereas no association
258 was observed between changes in GALA, Alpha or Beta, and changes in Aix or PVR.

259 **Discussion**

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

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

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

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

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

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

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

308 Interestingly, PVR did not show any association with PU loops angles during
309 vasopressor agent administration. However, as discussed expansively by Nichols and
310 O'Rourke¹⁷, PVR can find a physiological meaning in terms of cardiac afterload only in
311 steady flow conditions, ie at a distal level of the arterial tree, and not at the aortic level. Thus,
312 our PU loop which is a dynamic, and beat by beat analysis of Pressure and Flow in Aorta, is
313 probably not the most adequate algorithm to track changes in PVR.

314 In our data, only decrease in Ctot has remained strongly associated with increase in
315 GALA in response to vasopressor agents. Several comments can be addressed about this
316 finding. First, in literature, data relating effects of vasopressors on total arterial compliance
317 are very scarce. However, the SV on PP ratio has been shown to be reliably linked to decrease
318 in cardiac afterload in a population of hypertensive patients taking daily calcium channel
319 blocker³³. We hence used the SV on PP algorithm as an estimator of Total Arterial
320 Compliance. Even if such a method has expressed poor agreement with the area method
321 (more accurate measurement of Ctot) in dogs³⁴, the correlation coefficient between the two
322 algorithm were 0.78. Chemla et al. have also observed this finding in humans²⁰. Finally, Ctot
323 is thought to represent Windkessel model of arterial circulation and which is known to have
324 some imperfection, but at a global arterial system point of view, this model is sufficient to
325 explain arterial circulation observations³⁵⁻³⁷.

326 As mentioned above, central pressure analysis can be used as a surrogate of afterload
327³⁸, in particular to quantify vasoactive drug effects¹⁵. However high quality invasive central
328 pressure recordings or estimated central waveforms from carotid or transformed radial
329 applanation tonometry are not easily available during GA. We wanted a method to quantify

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

342 Another potential source of inaccuracy of our PU loops relates to the re-alignment of
343 pressure and velocity waveforms. In our pilot study, this process was performed manually. An
344 error of a few sample during the re-alignment might be possible. Swalen et al have studied the
345 influence of the re-alignment on the PU loop³⁹. While it can greatly modify the onset of PU
346 loop and hence calculation of local wave speed, it however has little influence on the position
347 of B and C and hence on the angles made by these points from the horizontal.

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

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

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

366

367 **Conclusion**

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

375

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381 **Figures Legend**

382 **Fig.1:** Definition of analysis parameters

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

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

388

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

391

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

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

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

397

398 **Fig.4:** Association of GALA with AIx, Ctot and Peripheral Vascular Resistances (PVR)
399 (Panel A.1-3, respectively), and changes of GALA after bolus versus change of AIx, change
400 of Ctot and change of PVR (Panel B.1-3, respectively) 118 measurements were performed in
401 20 patients. Each circle represents the weighted mean of repeated measure for one patient.
402 The radius of the circle represents the number of measurements perform for each patient.
403 (Slopes are expressed in ° per 1 ml/mmHg increase in Ctot, in ° per 10 % increase in AIx or in
404 ° per 100 dyn.s.cm-5 increase with their respective 95% interval confidence)

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521 **Abbreviations**

- 522 AIx : Augmentation Index
- 523 CPP : central pulse pressure
- 524 Ctot : Total Arterial Compliance = SV/ CPP
- 525 CV risk: Cardiovascular risk
- 526 GA : general anesthesia
- 527 GALA: Global After-Load Angle
- 528 MAP : Mean arterial pressure
- 529 P : Aortic pressure
- 530 PU loop: pressure/flow velocity loop
- 531 PVR : Peripheral Vascular Resistances
- 532 SV : Stroke Volume
- 533 U : Flow velocity
- 534