



**HAL**  
open science

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

Fabrice Vallée, Arthur Le Gall, Jona Joachim, Olivier Passouant, Joaquim Mateo, Arnaud Mari, Sandrine Millasseau, Alexandre Mebazaa, Etienne Gayat

### ► To cite this version:

Fabrice Vallée, Arthur Le Gall, Jona Joachim, Olivier Passouant, Joaquim Mateo, et al.. Beat-by-beat assessment of cardiac afterload using descending aortic velocity–pressure loop during general anesthesia: a pilot study. *Journal of Clinical Monitoring and Computing*, 2017, 113 (5), pp.727 - 735. 10.1007/s10877-017-9982-5 . hal-01629079

**HAL Id: hal-01629079**

**<https://inria.hal.science/hal-01629079v1>**

Submitted on 6 Nov 2017

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

5  
6 Fabrice Vallée\*<sup>1,2,3,4</sup>, MD; Arthur Le Gall<sup>1,2,3</sup>, MD; Jona Joachim<sup>1,2,3,4</sup>, MD; Olivier Passouant<sup>1,2,3</sup>, MD;  
7 Joaquim Matéo<sup>1,3</sup>, MD; Arnaud Mari<sup>5</sup>, MD; Sandrine Millasseau<sup>6</sup>, PhD; Alexandre Mebazaa<sup>1,2,3</sup>, PhD;  
8 Etienne Gayat<sup>1,2,3</sup>, PhD

9  
10 <sup>1</sup> Department of Anesthesiology and Critical Care, St-Louis-Lariboisière-Fernand Widal University Hospitals, Assistance Publique -  
11 Hôpitaux de Paris, Paris, France; <sup>2</sup> INSERM UMR-942, Paris, France; <sup>3</sup> Paris Diderot University, Paris, France; <sup>4</sup> LMS Polytechnique and  
12 M3DISIM, Inria, Saclay, France; <sup>5</sup> Department of Anesthesiology and Intensive Care, Toulouse University Hospitals, Toulouse, France; <sup>6</sup>  
13 Pulse Wave Consulting, St Leu la Foret, France; \* F.V and A.L.G equally contributed to this present study

14  
15  
16  
17  
18 **Running title:** Aortic PU Loop and Cardiac afterload

19  
20  
21  
22  
23 **Corresponding author:** Fabrice Vallée, [vallee.fabrice@gmail.com](mailto:vallee.fabrice@gmail.com), Tel : +33 1 49 95 80 71  
24 Anesthesiology – Intensive care – SMUR department, Saint Louis – Lariboisière- Fernand Widal  
25 University hospitals, 2 rue Ambroise Paré, 75010 Paris

26  
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.

## 35 **Acknowledgments**

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

## 39 **Fundings**

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

## 41 **Disclosures**

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  
46 Servier and fee as member of advisory board and/or steering committee from Cardiorentis,  
47 Adrenomed, MyCartis, ZS Pharma and Critical Diagnostics

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

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 ( $6.1\pm 1.7$  vs  $4.2\pm 0.6$  L/min;  $p = 0.005$ ), higher  
64 Ctot ( $2.7\pm 1.0$  vs  $2.0\pm 0.4$  ml/mmHg,  $p = 0.033$ ), lower AIx and PVR ( $13\pm 10$  vs  $32\pm 11$  % and  
65  $1011\pm 318$  vs  $1390\pm 327$  dyn.s.cm<sup>-5</sup>;  $p<0.001$  and  $p=0.016$ , respectively) and lower GALA  
66 ( $41\pm 15$  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 <sup>1,2</sup>, such as myocardial infarctions <sup>3,4</sup>, acute  
79 kidney injuries <sup>5</sup>, or strokes <sup>6</sup>. To this concern, American and European societies of  
80 anaesthesiology and intensive care have highlighted the importance of perioperative  
81 hemodynamic optimization strategies <sup>7,8</sup>. 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) <sup>9-11</sup>, 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 <sup>12</sup>. 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 <sup>13</sup>. 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.<sup>14</sup>, 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 <sup>15,16</sup>.  
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 <sup>17,18</sup>. 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 CO<sub>2</sub> reached 35 to 38 mmHg, with  
130 Tidal Volume of 6 and PEEP of 4 cmH<sub>2</sub>O. 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 monitor<sup>19-21</sup>. Peripheral Vascular Resistance (PVR)  
150 was calculated using the modified Poiseuille equation:  $PVR \text{ (dyn.s.cm-5)} = MAP \text{ (mmHg)} /$   
151  $CO \text{ (l/min)} * 80$ <sup>22</sup>.

## 152 *Intervention*

153 Hypotensive episodes were defined the when MAP fell at least 20% under the pre anesthesia  
154 MAP<sup>23</sup>. 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 2<sup>nd</sup>  
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<sup>-5</sup> 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<sup>-5</sup> ; respectively ;  $p < 0.001$  for each), and to a decrease in  
251 CO and Ctot ( $-1.0 \pm 0.9$  L/min ;  $-0.8 \pm 0.5$  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  $5.2 [-8.7 - -1.7]^\circ$  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 <sup>17</sup>, 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 <sup>24</sup> 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 <sup>20,25-27</sup>, 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 <sup>28,29</sup> 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 <sup>30</sup>.

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 <sup>15,16</sup>, 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 <sup>31</sup>. During physical exercise, a strong vasoactive  
303 stimulus, Thiebaud et al. <sup>32</sup> 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'Rourke<sup>17</sup>, 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 blocker<sup>33</sup>. 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 dogs<sup>34</sup>, the correlation coefficient between the two  
322 algorithm were 0.78. Chemla et al. have also observed this finding in humans<sup>20</sup>. 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 observations<sup>35-37</sup>.

326 As mentioned above, central pressure analysis can be used as a surrogate of afterload  
327<sup>38</sup>, in particular to quantify vasoactive drug effects<sup>15</sup>. 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<sup>17,18</sup>. 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 loop<sup>39</sup>. 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<sup>37,40</sup>, 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

376

377

378

379

380

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)

405

406

407

## References:

- 409 1. Monk TG, Saini V, Weldon BC, Sigl JC: Anesthetic Management and One-Year Mortality After  
410 Noncardiac Surgery: *Anesthesia & Analgesia* 2005; 100:4–10
- 411 2. Sessler DI, Sigl JC, Kelley SD, Chamoun NG, Manberg PJ, Saager L, Kurz A, Greenwald S: Hospital Stay  
412 and Mortality Are Increased in Patients Having a “Triple Low” of Low Blood Pressure, Low Bispectral  
413 Index, and Low Minimum Alveolar Concentration of Volatile Anesthesia: *Anesthesiology* 2012;  
414 116:1195–203
- 415 3. Waes JAR van, Klei WA van, Wijeysondera DN, Wolfswinkel L van, Lindsay TF, Beattie WS: Association  
416 between Intraoperative Hypotension and Myocardial Injury after Vascular Surgery: *Anesthesiology*  
417 2016; 124:35–44
- 418 4. Kheterpal S, O’Reilly M, Englesbe MJ, Rosenberg AL, Shanks AM, Zhang L, Rothman ED, Campbell DA,  
419 Tremper KK: Preoperative and Intraoperative Predictors of Cardiac Adverse Events after General,  
420 Vascular, and Urological Surgery: *Anesthesiology* 2009; 110:58–66
- 421 5. Sun LY, Wijeysondera DN, Tait GA, Beattie WS: Association of intraoperative hypotension with acute  
422 kidney injury after elective noncardiac surgery. *Anesthesiology* 2015; 123:515–23
- 423 6. Bijker JB, Persoon S, Peelen LM, Moons KGM, Kalkman CJ, Kappelle LJ, Klei WA van: Intraoperative  
424 hypotension and perioperative ischemic stroke after general surgery: a nested case-control study.  
425 *Anesthesiology* 2012; 116:658–64
- 426 7. Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof EL, Fleischmann KE, Freeman WK, Froehlich JB,  
427 Kasper EK, Kersten JR, Riegel B, Robb JF, Smith SC, Jacobs AK, Adams CD, Anderson JL, Antman EM,  
428 Buller CE, Creager MA, Ettinger SM, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Lytle BW,  
429 Nishimura R, Ornato JP, Page RL, Riegel B, et al.: ACC/AHA 2007 Guidelines on Perioperative  
430 Cardiovascular Evaluation and Care for Noncardiac Surgery. *Journal of the American College of*  
431 *Cardiology* 2007; 50:e159–242
- 432 8. Vallet B, Blanloeil Y, Cholley B, Orliaguet G, Pierre S, Tavernier B: Guidelines for perioperative  
433 haemodynamic optimization. *Annales Françaises d’Anesthésie et de Réanimation* 2013; 32:e151–8
- 434 9. Hamilton MA, Cecconi M, Rhodes A: A Systematic Review and Meta-Analysis on the Use of  
435 Preemptive Hemodynamic Intervention to Improve Postoperative Outcomes in Moderate and High-  
436 Risk Surgical Patients: *Anesthesia & Analgesia* 2011; 112:1392–402
- 437 10. Navarro LHC, Bloomstone JA, Auler JOC, Cannesson M, Rocca GD, Gan TJ, Kinsky M, Magder S, Miller  
438 TE, Mythen M, Perel A, Reuter DA, Pinsky MR, Kramer GC: Perioperative fluid therapy: a statement  
439 from the international Fluid Optimization Group. *Perioperative Medicine* 2015; 4
- 440 11. Grocott MPW, Dushianthan A, Hamilton MA, Mythen MG, Harrison D, Rowan K, Optimisation  
441 Systematic Review Steering Group: Perioperative increase in global blood flow to explicit defined  
442 goals and outcomes after surgery: a Cochrane Systematic Review. *British Journal of Anaesthesia*  
443 2013; 111:535–48
- 444 12. Singer M: Catecholamine treatment for shock—equally good or bad? *The Lancet* 2007; 370:636–637
- 445 13. Mebazaa A, Parissis J, Porcher R, Gayat E, Nikolaou M, Boas FV, Delgado JF, Follath F: Short-term  
446 survival by treatment among patients hospitalized with acute heart failure: the global ALARM-HF  
447 registry using propensity scoring methods. *Intensive Care Medicine* 2011; 37:290–301
- 448 14. Nichols WW, O’ROURKE M, Vlachopoulos C: Aortic Input Impedance as ventricular load, McDonald’s  
449 blood flow in arteries: theoretic, experimental, and clinical principles. pp 311–20
- 450 15. Kelly RP, Millasseau SC, Ritter JM, Chowienczyk PJ: Vasoactive drugs influence aortic augmentation  
451 index independently of pulse-wave velocity in healthy men. *Hypertension* 2001; 37:1429–33
- 452 16. Kelly RP, Gibbs HH, O’Rourke MF, Daley JE, Mang K, Morgan JJ, Avolio a P: Nitroglycerin has more  
453 favourable effects on left ventricular afterload than apparent from measurement of pressure in a  
454 peripheral artery. *European heart journal* 1990; 11:138–44
- 455 17. Nichols WW, Nichols WW, McDonald DA: McDonald’s blood flow in arteries: theoretic, experimental,  
456 and clinical principles, 6th ed. London, Hodder Arnold, 2011
- 457 18. Temmar M, Jankowski P, Peltier M, Mouquet V, Debicka-Dabrowska D, Hamida F, Kawecka-Jaszcz K,  
458 Safar ME: Intraortic Pulse Pressure Amplification in Subjects at High Coronary Risk. *Hypertension*  
459 2010; 55:327–32

- 460 19. Chemla D, Lamia B: Monitoring hémodynamique non-invasif en réanimation: intérêt potentiel de la  
461 tonométrie artérielle. *Réanimation* 2009; 18:197–200
- 462 20. Chemla D, Hébert J-L, Coirault C, Zamani K, Suard I, Colin P, Lecarpentier Y: Total arterial compliance  
463 estimated by stroke volume-to-aortic pulse pressure ratio in humans. *American Journal of Physiology-  
464 Heart and Circulatory Physiology* 1998; 43:H500
- 465 21. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C,  
466 Wilkinson I, Struijker-Boudier H, on behalf of the European Network for Non-invasive Investigation of  
467 Large Arteries: Expert consensus document on arterial stiffness: methodological issues and clinical  
468 applications. *European Heart Journal* 2006; 27:2588–605
- 469 22. KUHN LA, TURNER JK: Alterations in pulmonary and peripheral vascular resistance in immersion  
470 hypothermia. *Circulation research* 1959; 7:366–374
- 471 23. Bijker JB, Klei WA van, Kappen TH, Wolfswinkel L van, Moons KGM, Kalkman CJ: Incidence of  
472 Intraoperative Hypotension as a Function of the Chosen Definition: Literature Definitions Applied to a  
473 Retrospective Cohort Using Automated Data Collection. *Anesthesiology* 2007; 107:213–20
- 474 24. Khir AW, O'Brien A, Gibbs JS, Parker KH: Determination of wave speed and wave separation in the  
475 arteries. *JBiomech* 2001; 34:1145–55
- 476 25. McVeigh GE, Bratteli CW, Morgan DJ, Alinder CM, Glasser SP, Finkelstein SM, Cohn JN: Age-related  
477 abnormalities in arterial compliance identified by pressure pulse contour analysis aging and arterial  
478 compliance. *Hypertension* 1999; 33:1392–1398
- 479 26. Kelly R, Hayward C, Avolio A, O'Rourke M: Noninvasive determination of age-related changes in the  
480 human arterial pulse. *Circulation* 1989; 80:1652–9
- 481 27. McEniery CM, Yasmin null, Maki-Petaja KM, McDonnell BJ, Munnery M, Hickson SS, Franklin SS,  
482 Cockcroft JR, Wilkinson IB, Anglo-Cardiff Collaboration Trial Investigators: The impact of  
483 cardiovascular risk factors on aortic stiffness and wave reflections depends on age: the Anglo-Cardiff  
484 Collaborative Trial (ACCT III). *Hypertension* 2010; 56:591–7
- 485 28. Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, Sugarbaker DJ, Donaldson  
486 MC, Poss R, Ho KK, others: Derivation and prospective validation of a simple index for prediction of  
487 cardiac risk of major noncardiac surgery. *Circulation* 1999; 100:1043–1049
- 488 29. Wolters U, Wolf T, Stutzer H, Schroder T: ASA classification and perioperative variables as predictors  
489 of postoperative outcome. *British Journal of Anaesthesia* 1996; 77:217–22
- 490 30. Nilsson PM: Early vascular aging (EVA): consequences and prevention. *Vasc Health Risk Manag* 2008;  
491 4:547–52
- 492 31. McEniery CM, Yasmin, Hall IR, Qasem A, Wilkinson IB, Cockcroft JR: Normal vascular aging:  
493 differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative  
494 Trial (ACCT). *JAmCollCardiol* 2005; 46:1753–60
- 495 32. Thiebaud RS, Fahs CA, Rossow LM, Loenneke JP, Kim D, Mouser JG, Beck TW, Bembem DA, Larson RD,  
496 Bembem MG: Effects of age on arterial stiffness and central blood pressure after an acute bout of  
497 resistance exercise. *European Journal of Applied Physiology* 2016; 116:39–48
- 498 33. Schmieder RE, Messerli FH: Compliance großer elastischer Arterien nach blutdrucksenkender  
499 Therapie mit einem Calciumantagonisten. *DMW - Deutsche Medizinische Wochenschrift* 1995;  
500 120:907–11
- 501 34. Segers P, Verdonck P, Deryck Y, Brimiouille S, Naeije R, Carlier S, Stergiopoulos N: Pulse pressure  
502 method and the area method for the estimation of total arterial compliance in dogs: sensitivity to  
503 wave reflection intensity. *Ann Biomed Eng* 1999; 27:480–5
- 504 35. Chirinos JA, Segers P, Raina A, Saif H, Swillens A, Gupta AK, Townsend R, Emmi AG, Kirkpatrick JN,  
505 Keane MG, Ferrari VA, Wiegers SE, St. John Sutton MG: Arterial pulsatile hemodynamic load induced  
506 by isometric exercise strongly predicts left ventricular mass in hypertension. *AJP: Heart and  
507 Circulatory Physiology* 2010; 298:H320–30
- 508 36. Chirinos JA: Arterial Stiffness: Basic Concepts and Measurement Techniques. *Journal of  
509 Cardiovascular Translational Research* 2012; 5:243–55
- 510 37. Chirinos JA, Segers P: Noninvasive Evaluation of Left Ventricular Afterload: Part 2: Arterial Pressure-  
511 Flow and Pressure-Volume Relations in Humans. *Hypertension* 2010; 56:563–70

- 512 38. Chirinos JA, Segers P: Noninvasive evaluation of left ventricular afterload: part 1: pressure and flow  
513 measurements and basic principles of wave conduction and reflection. *Hypertension* 2010; 56:555–  
514 62
- 515 39. Swalen MJP, Khir AW: Resolving the time lag between pressure and flow for the determination of  
516 local wave speed in elastic tubes and arteries. *J Biomech* 2009; 42:1574–7
- 517 40. Borlotti A, Khir AW, Rietzschel ER, De Buyzere ML, Vermeersch S, Segers P: Noninvasive  
518 determination of local pulse wave velocity and wave intensity: changes with age and gender in the  
519 carotid and femoral arteries of healthy human. *J Appl Physiol* 2012; 113:727–35  
520

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