

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

Pulse wave velocity and short-term outcome in patients requiring intravascular volume expansion: A pilot study

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1728392> since 2020-02-18T22:32:20Z

Published version:

DOI:10.1136/emered-2018-208089

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

Title

Pulse Wave Velocity and short-term outcome in patients requiring intravascular volume expansion: a Pilot Study

Authors

Alberto Milan¹, Pietrantonio Maldari², Andrea Iannaccone¹, Dario Leone¹, Eleonora Avenatti¹, Paola Molino², Sergio Livigni³, Franco Veglio^{1*}, Franco Aprà^{2*}

Affiliations:

1) Dpt of Medical Sciences – Internal Medicine and Hypertension Division - University of Turin – AOU Città della Salute e della Scienza of Turin, Italy.

2) High Dependency Unit, San Giovanni Bosco Hospital, Turin, Italy.

3) S.C. Anestesia e Rianimazione 2, San Giovanni Bosco Hospital, Torino, Italy.

*Joint last authors

Corresponding author:

Alberto MILAN, MD, PhD

Department of Medical Sciences – University of Torino

Via Genova 3 Torino Italy - +390116336952 – e.mail alberto.milan@gmail.com

Contributorship statement:

A. Milan, F. Veglio, F. Aprà: design and review of the work, final approval;

P. Maldari, A. Iannaccone, D. Leone: acquisition, analysis and interpretation of data;

E. Avenatti: analysis and interpretation of data; review of the work;

P. Molino, S. Livigni: design and review of the work.

Word count: 4053

Tables: 3

Figures: 2

Supplementary file: 9 tables. 1 supplementary results paragraph, 1 figure

On behalf of all authors, the corresponding author states that there is no conflict of interest.

ABSTRACT

Background

Fluid therapy plays a pivotal role in the management of acutely ill patients; however, the ideal assessment of a patient's ability to tolerate additional intravascular volume is controversial and optimal strategy is unknown. Carotid femoral Pulse Wave Velocity (cfPWV) evaluates arterial stiffness. We determined if it is able to predict patients' ability to tolerate clinically indicated acute fluid expansion.

Methods

50 consecutive patients requiring intravascular volume expansion were prospectively recruited in intensive care units. All subjects underwent transthoracic echocardiography (TTE), pulmonary ultrasound assessment and cfPWV study at baseline and after 24 hours. Acute outcomes were registered at 24 hours ("soft" end points") and 30 days ("hard" end points: death, acute myocardial infarction, stroke, occurrence of atrial fibrillation, need for dialysis") after initial fluid therapy. Multivariate logistic regression was used to assess association of initial cfPWV with outcomes.

Results

cfPWV was significantly higher (10.6 ± 3.6 vs. 7.4 ± 2.2 m/sec $p < 0.0001$) in subjects who met the pre-specified combined endpoints (hard or soft). After adjustment for confounding factors initial cfPWV was significantly and independently associated with the occurrence of hard events (OR 2.8 (1.36 – 5.97), $p = 0.005$; AUROC 84%). cfPWV less than 9 m/sec had a negative predictive value of 93% excluding hard events associated with fluid expansion.

Conclusion

cfPWV appears to reflect the ability of the patient to tolerate an intravascular fluid expansion when clinically indicated. Increased cfPWV could help in the identification of subject at greater risk of developing signs and symptoms of fluid overload.

Keyword

Intravascular fluid expansion; Pulse Wave Velocity; Arterial Stiffness; Volume overload.

BOX: What this paper adds

What is already known on this subject

- Fluid therapy is a key component of patient management in many acute clinical scenarios, but the optimal strategy for every single patient is still debated;
- Up to now, no study has identified strong predictors of response to volemic filling.

What this study adds

- In this pilot study, we evaluated arterial stiffness using carotid femoral Pulse Wave Velocity (cfPWV,) and found that it is independently associated with outcomes of individuals receiving intravascular fluid expansion;
- Our results suggest a potential role of cfPWV in identifying patients with different elastic reserve and guiding fluid therapy accordingly to obtain a patient tailored approach leading to improved clinical management .

1 **BACKGROUND**

2 Fluid therapy plays a pivotal role in the management of different clinical scenarios, from hypovolemia
3 to renal failure [1] and sepsis [2]. Nevertheless, management of patients' intravascular volume is still
4 a source of doubt for the practicing physician and the optimal strategy[3] is still unknown.

5 New data have identified deleterious effects of excessive fluid therapy, such as the increase of
6 extravascular lung water, reduced lung compliance and increase in respiratory work load [4, 5] that
7 was associated with an increased mortality [6] in patients with sepsis. Therefore the concept of
8 avoiding positive fluid balance as a tool to improve outcome in intensive care units patients has been
9 suggested.

10 Different patients in similar clinical situations respond differently to volume expansion. The ability
11 to evaluate and predict the individual patient's response to fluid therapy[7] is a constant clinical
12 challenge [8]. A parameter that could guide decision-making in settings in which fluids administration
13 is mandatory, balancing the risk of fluid overload against the benefits of volume expansion[9], would
14 represent the key to a truly patient-tailored management. Different parameters have been tested to
15 this end, with conflicting results [1, 10].

16 The rigidity of the arterial tree (arterial stiffness), evaluated through Pulse Wave Velocity (PWV),
17 has demonstrated an independent role in predicting the cardiovascular mortality[11, 12], but its role
18 in predicting patients' ability to tolerate a fluid expansion has not been investigated.

19

20 Left ventricular systolic contraction propels blood into the aorta but also generates a pressure wave
21 (sphygmic wave) that travels throughout the vascular tree at a higher velocity than the blood itself.
22 In physiological conditions, the sphygmic wave travels at a speed of about 5 m/s: this velocity is
23 called Pulse Wave Velocity (PWV). PWV is influenced by both ventricular function and elastic
24 properties of the aorta and of the whole arterial tree. PWV has a well-established inverse
25 correlation with the arterial tree compliance. PWV is a direct representation of vascular stiffness –
26 i.e. a greater rigidity of the arterial tree corresponds to greater PWV[13]. There are different
27 methods to assess the PWV[14]; the current gold standard uses non-invasive applanation tonometry
28 and measures the time required by the sphygmic wave to travel the distance between the carotid
29 and the femoral artery [cfPWV] [15]. An increased PWV demonstrated independent predictive
30 value for cardiovascular outcomes[16].

31

32 cfPWV can be thought of as the lack of ability of the arterial vessels to accept the systolic increase
33 of intravascular volume without an excessive increase in blood pressure. This lack of compliance

1 imposes an additional burden on the left ventricle, increasing the cardiac work and contributing to
2 systolic and diastolic dysfunction[17].

3

4 Despite this strong physiopathological association, there is no evidence regarding PWV application
5 in the context of intravascular volume expansion. We designed this pilot study to investigate whether
6 cfPWV is able to predict patients' ability to tolerate a clinically indicated increase in intravascular
7 volume.

8

9 **METHODS**

10 Patients requiring intravascular volume expansion were consecutively and prospectively recruited in
11 the Intensive Care Unit and High Dependency Care Unit of the S. Giovanni Bosco Hospital in Turin
12 between April 2015 and April 2016. ~~Acute~~ The volume expansion was defined as the need for an
13 estimated intravenous infusion of at least 2000 ml of liquids in 24 hours. The Regional Ethics
14 Committee (Comitato etico interaziendale AOU San Luigi Gonzaga di Orbassano' n. 29/2015)
15 approved this prospective study and all subjects provided written informed consent.

16 Exclusion criteria were: refusal or inability to provide informed consent, atrial fibrillation or paced
17 cardiac rhythm, inadequate quality of the tracing for the evaluation of PWV.

18 All subjects (Figure S1) underwent transthoracic echocardiography (TTE), lung ultrasound
19 assessment and study of cfPWV at the time of recruitment. cfPWV was assessed before intravascular
20 volume expansion, or during the first phase of fluid therapy in order to avoid a possible delay in
21 delivery of patient care (10 minutes maximum). TTE and lung ultrasound evaluations were repeated
22 at 24h, in order to assess cardiac function and pulmonary congestion. Clinical care of the enrolled
23 patients was deferred to the primary team. Global fluid balance was assessed at 24 hours.

24 The clinicians who were taking care to the patients were not aware about echo, ultrasound or cfPWV
25 results.

26 Acute outcomes were registered at 24 hours ("soft end points") and 30 days ("hard end point"). Soft
27 end points included signs of fluid overload associated with intravascular volume expansion: signs and
28 symptoms of heart failure, onset or worsening of oedema, pleural or pericardial effusion or ascites,
29 appearance of B lines on lung ultrasound or adjustment of diuretic therapy - defined as starting
30 diuretic therapy or increasing initial dose $\geq 100\%$. Hard end points, considered as composite end
31 point, included death (any cause), acute myocardial infarction (AMI), stroke, occurrence of atrial
32 fibrillation and need for dialysis. The operator who performed the outcome evaluation was blinded to
33 the results of cfPWV analysis.

1 Individual medical records were reviewed for all patients and used to collect data regarding past
2 medical history and comorbidities as well as the reason for hospitalization.—The body surface area
3 (BSA) was calculated using the formula proposed by Dubois and Dubois [18]. Weight, blood pressure
4 (BP) and heart rate (HR), arterial blood gas analysis at baseline and 24 hours after the volume
5 expansion were measured in all the patients.

6

7 **Transthoracic echocardiography (TTE)**

8 TTE was performed by an expert operator (AI or DL) using a commercially available machine
9 (MyLab 25 Gold, ESAOTE, Italy) equipped with a 2-4 MHz probe. All morphological and Doppler
10 data were digitally stored and analysed offline with a dedicated software.

11 The morphology of the left ventricle (LV) was evaluated using standard 2D TTE views in accordance
12 with current Guidelines [19]. End-diastolic (LVIDd) and end systolic (LVIDs) internal left ventricular
13 diameters were measured, together with the end diastolic thickness of the inferolateral and
14 anteroseptal wall (ILWT and SWT). The LV geometry was defined through the evaluation of the
15 ventricular mass (LVM), calculated with Devereux formula indexed for BSA, considering normal
16 values < 115 g/m² for men and <95 g/m² for women [19]. LV systolic function was evaluated with
17 ejection fraction (EF), computed by the biplane Simpson's method. Stroke volume (SV) and Cardiac
18 Output (CO) were assessed as well with quantitative Doppler analysis.

19

20 **Pulmonary ultrasound**

21 Ultrasonographic evaluation of the chest was performed by an expert operator (DL or AI) with the
22 same ultrasound machine (Esaote myLab Gold, ESAOTE, Italy), equipped with a frequency phased
23 array probe (2.5-4 MHz). Following standard lung ultrasound approach (BLUS), each hemithorax
24 was virtually divided into 4 areas (upper and lower, anterior and lateral) with the patient in the supine
25 position, every section scanned with the probe in longitudinal and oblique positions. The examination
26 was defined as positive for the presence of interstitial edema when more than 3 lines B in at least 2
27 lung areas for each hemithorax were detected[20].

28

29 **Pulse Wave Velocity**

30 The evaluation of the arterial stiffness was performed by an expert operator (PM) in accordance
31 with current international recommendations [15], by the evaluation of the cfPWV with a validated
32 instrument (Sphygmocor system, AtCor Medical, Sydney, Australia) [21]. Blood pressure and HR
33 were measured three times, at 2-min intervals using a validated automatic oscillometric device
34 equipped with a standard arm cuff. (Omron Matsusaka Co., Ltd., Mie, Japan); the mean value of the

1 three measurements was used in the analysis. All BP measurements were performed according to
2 the ESH/ESC recommendations[22] . CfPWV was measured along the descending
3 thoracoabdominal aorta by the foot-to-foot velocity method, as previously published and validated
4 [15]. Waveforms were obtained transcutaneously over the common carotid artery and the femoral
5 artery and the time delay (t, in second) was measured between the feet of the two waveforms. The
6 distance (D, in meters) from the two sampling point on the patient's body surface was divided by
7 the delay time, so that cfPWV was calculated as $PWV=D/t$.

8

9 **Statistical analysis**

10 Statistical analysis was performed using a dedicated software (SPSS Software 20.0, SPSS Inc.,
11 Chicago, IL). Distribution of variables was checked with a Shapiro-Wilkins test. Continuous data are
12 presented as mean \pm standard deviation (SD), or median [25°-75° percentile], where appropriate. The
13 difference between the groups was evaluated using a T-test or Mann-Whitney, where appropriate
14 depending on data distribution; comparison among three groups was performed with an ANOVA test
15 or Kruskal-Wallis where appropriate . For categorical variables, the chi square test or the Fisher exact
16 tests were calculated. The correlation between different variables was evaluated using the Pearson or
17 Spearman test on correlation analysis. The association between outcomes and different variables (e.g.
18 Age, gender, PWV etc.) was studied by univariate and multivariate logistic regression analysis. The
19 risk of events applied separately for soft and hard end points was expressed as odds ratio \pm 95%
20 confidence interval. Receiver operating characteristic (ROC) analysis was performed with the PWV
21 as the test variable and events as the state variable. The calculation of statistical power was made
22 assuming an incidence of events of 30%. We hypothesized to have at least 17 events to be able to
23 detect a significant difference between 2 groups divided according to the PWV. A subgroup analysis
24 was planned for patients not presenting in shock -.i.e patients with mean arterial pressure \geq 65 mmHg
25 and no clinical signs of hypoperfusion as assessed by lactate level.

26 The level of significance was considered by accepting an error $\alpha < 0.05$.

27

28

29

1 RESULTS

2 Characteristics of the study patients

3 A total of 71 patients were evaluated for enrolment in the study, but 21 patients (29.5%) were
4 excluded because of inadequate tracing of the cfPWV. Excluded patients were similar to the overall
5 group in terms of age and gender distribution. There were no excluded patients for other reasons (ie
6 no consent). The resulting population thus consisted of 50 subjects (table 1)

7 Most of the subjects underwent fluid therapy for hypovolemia (40%) and/or sepsis (20%); detailed
8 reasons for fluid therapy and hospitalization of patients are summarized in Table S1 and S2
9 respectively. The average infused volume was 3.2 ± 0.3 liters with an average infusion rate of
10 118 ± 46 cc/h.

11

12 Population Outcomes

13 Hard endpoints

14 Hard endpoints occurred in 40% (n=20) of patients: atrial fibrillation (18%, n=9), acute heart failure
15 (12%, n=6), need for dialytic therapy (10%, n=5), death 18% (n=9) - with sepsis being the most
16 common cause (10%, n= 5)-. Patients who experienced hard events were older (table 1) but remaining
17 clinical characteristics were similar to those of patients that did not experience any event.

18 Table 1 **Clinical characteristics of study population:** Hard end point vs no Hard end point

Variables	Global population	No Hard Events	Hard Events*	P
n	50	32	18	
Age (years)	64±17	56±18	72±8	0.0001
Male gender, n (%)	30 (60)	56%	65%	0.34
Weight (Kg)	74±15.5	73±16	75±16	0.58
Height (m)	169±10.1	168±10	169±9	0.97
Body mass index (kg/m ²)	26.1±4.6	25.7±4.9	26.6±4	0.6
Body surface area (m ²)	1.84±0.22	1.82±0.23	1.85±0.19	0.39

SBP (mmHg)	126±25	123±25	131±25	0.67
DBP (mmHg)	66±13	66±14	65±10	0.61
PP (mmHg)	60±22	56±19	66±25	0.11
HR (beats per minutes)	85±16.9	84±17	87±15	0.58
Creatinine (mg/dl)	0.9 [0.7 – 1.5]	0.9 [0.7-1.4]	0.85[0.6-1.7]	0.65
GFR, (ml/min)	78 [40 - 114]	76 [53-128]	83 [37-107]	0.77
Volume infused, (L)	3.2 [2.6 - 4]	3[2.4-4]	3.2[2.8-3.9]	0.68
Infusion velocity, (ml/h)	100 [84 - 150]	100 [84-150]	120[84-140]	0.6
Urinary output, (L/24h)	1.2 [1 – 2.4]	1.2[1-2.4]	1.2[1-2.3]	0.7
Pulse Wave Velocity (m/s)	9.3±3.4	7.8±2.5	11.5±3.5	0.0001

1 SBP: Systolic blood pressure; DBP: Diastolic BP; PP: Pulse pressure; HR: Heart rate; GFR: Glomerular
2 filtration rate.

3 Data are expressed as median [25th-75th ile] or mean±standard deviation.

4

5 PWV was significantly higher before volume expansion in patients that met hard and soft end points
6 (Figure 1): indeed, in a logistic regression analysis (Table 3) PWV strongly (OR 2.7 (1.004-2.9),
7 p=0.04) predicted occurrence of such events. The ROC analysis yielded an AUC of 84% (Figure
8 2A): a cut off value of 9 m/s demonstrated a sensitivity of 88% (IC 67%-96%) with a specificity of
9 81% (IC 64%-91%) identifying the hard events.

10 **Table 3 . Multivariate logistic regression analysis Hard events**

Hard events	
Variables	R²=0.7, (p<0.0001)
	Standardized B (95% CI)
Age (years)	1.03 (0.94 – 1.13), p=0.4
Gender (Male=1; Female=0)	1.13 (0.8 - 1.5500), p=0.06
Body surface area (m ²)	0.01 (0 – 11.6), p=0.12
Glomerular Filtration Rate (ml/min)	1.0 (0.97 – 1.03), p=0.9

Ejection fraction (%)	1.06 (0.97 – 1.16), p=0.21
CfPulse Wave Velocity (m/s)	2.8 (1.36 – 5.97), p=0.005

1 Cf:carotido-femoral

2

3 **Soft endpoints**

4 Soft endpoints occurred in 54% of patients: 46 % (n=23) developed B Lines on lung ultrasound, 41%
5 (n=20) clinically evident edema, 38% (n=19) needed to start or increase the dosage of diuretic
6 therapy.

7 Patients who experienced soft events were older (table S4) but remaining clinical characteristics were
8 similar to those of patients that did not experience any event. Again PWV was significantly higher
9 in patients that met soft end points, but in logistic regression analysis (Table S4 and S5) PWV did not
10 predict occurrence of such end points (OR 1.46 (0.92 – 2.31), p=0.11).

11 Anyway the ROC analysis yielded an AUC of 76% (Figure 2B): a cut off value of 9 m/s demonstrated
12 a sensitivity of 62% (IC 44%-78%) with a specificity of 78% (IC 58%-90%) identifying the soft
13 events.

14

15 **Subgroup analysis (patients without shock)**

16 In the subgroup analysis considering only patients that did not present in shock (n. 41) at baseline,
17 again cfPWV was significantly different between individuals with (n=23) and without
18 (n=18) events [(10 [8.5 - 13] vs. 6.95 [5.7 - 8.7] m/s respectively, p = 0.001)]. The univariate analysis
19 confirmed the association between cfPWV and the risk of events after intravascular volume
20 expansion in this subset. This held true considering hard (OR 1.4 [1.1 – 1.8]; p 0.01), and soft (OR
21 1.56 [1.1 – 2.1] p 0.007) end-points.

22 The ROC analysis in this subgroup yielded an AUC of 74% and 80% for hard and soft end points
23 respectively. cfPWV values <9 m/s showed a negative predictive value of 91% for hard events,
24 with a positive predictive value of 73%. In this context, the sensitivity and specificity were similar
25 (84%). On the other hand, considering the soft events, cfPWV of 9 m/s had a positive predictive
26 value for events associated with volume expansion of 80%, with a sensitivity of 72% (IC 51%-86%)
27 and a specificity of 80% (IC 69%-92%).

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34

DISCUSSION

This pilot study supports the use of cfPWV, when feasible, as a potential new parameter able to identify subjects at increased risk of events and deleterious clinical consequences of fluid overload, in particular, after intravascular expansion. cfPWV was the only parameter able to predict events in our population, independently of age; no TTE- or BLUS- derived parameters showed a similar performance.

Fluid therapy is a key component of patient management in many acute clinical scenarios but the optimal strategy in every single patient is still debated [3]. The SOAP study demonstrated that a positive water balance in septic patients was associated with an increased mortality and length of stay in the Intensive Care Units [6]. Along the same line, the FACTT trial [23] demonstrated that patients with low values of Central Venous Pressure (CVP) benefitted from a conservative management of liquid infusion and that high doses of diuretic in patients with high CVP did not lead to an improvement of the outcomes [24].

The key to a successful clinical management is to titrate the fluid therapy based on the individuals' ability to tolerate it. Consistent with previous reported data, no ultrasonographic parameters in our population (including assessment of IVC) showed a significant association with the occurrence of any event. IVC is considered a useful index in assessing the blood volume of the patient, but the more acute complications related to volume expansion may depend on vascular failure [25, 26].

We found that cfPWV was able to predict events in our population: patients with an increased PWV (> 9 m/sec) had an increased risk of developing major (OR 1.64) or minor (OR 1.5) events in the short term showing a lower tolerance to fluid challenge. The performance of cfPWV in predicting any type of event was good: 74% for hard and 80% for soft end points.

cfPWV has emerged as useful marker in stratification of cardiovascular risk[12, 27, 28]: patients with an increased cfPWV have increased risk of cardiovascular disease independently from other common risk factors. Increased stiffness is the hallmark of diastolic dysfunction as well, and of individual with heart failure with preserved ejection fraction (HFpEF). In these subjects during exercise the reduced elastic reserve of the cardiovascular system leads to an increase of afterload

1 and cardiac work and a significant increase in pulmonary capillary wedge pressure [29] . Similarly
2 in the setting of reduced compliance, fluid expansion-induced increase in preload could act as a
3 trigger, imposing a similar albeit less intense burden [30] on patients with a stiff cardiovascular
4 system.

5
6 Beside cfPWV, only age and diastolic BP (DBP) were associated with the risk of complications.
7 Unsurprisingly age per se showed a significant association with hard and soft end-points.
8 Correlation between aging and cfPWV is well characterized in the literature. However, cfPWV
9 correlation with events remained significant after adjustment for age in our multivariate analysis.
10 When considering both PWV and age as dichotomous variables, only PWV remained significantly
11 associated to clinical events in our population. These data suggest a pathophysiological connection
12 that exceeds the effects of age alone. It has to be remarked, however, that the number of patients in
13 our population aged < 60 years was relatively small (n=16) and as such, the performance of PWV in
14 this specific group of patients will need to be further evaluated.

15
16 Beside age, the only other parameter that showed a significant (and inverse) correlation with the
17 development of any event was the DBP, which is closely related to arterial stiffness and
18 consequently to the PWV[31]. Indeed if usually the Central Venous Pressure reflects the
19 hydrostatic pressure and the preload, the PWV could add information about the variation of
20 afterload and may give us a glimpse into the patient's physiology after fluid expansion.
21 Our results suggest a potential use of cfPWV assessment in patients who require volume expansion
22 in order to identify those in which a reduced elastic reserve (cfPWV > 9 m/sec) would indicate the
23 need of a more cautious approach to fluid therapy , especially if > 60 yo.

24
25 The predictive capacity of cfPWV was confirmed also in the subgroup of patients that did not
26 present in shock. While in patients with circulatory failure, fluid therapy is often mandatory, this is
27 not always true for patients who present with more stable hemodynamics. In these individuals, an
28 assessment of the risk-benefit ratio of the intravenous fluid infusion could have greater relevance to
29 clinical-therapeutic management.

30 31 **LIMITATIONS**

32 A few limitations in this pilot study need to be highlighted. Firstly, we report data on a mixed
33 patient population, presenting with different clinical conditions. We sought this type of design, as
34 we aimed at evaluating parameters able to guide the physician in the risk stratification of patients

1 undergoing fluid therapy for different reasons, and that could thus be widely applicable. Future
2 studies will be needed to determine the value of cfPWV in specific clinical scenarios.
3 Lastly, we acknowledge that there are intrinsic technical limitations to the applicability of the
4 proposed evaluation. Assessment of cfPWV requires trained operators as well as specific
5 equipment that is at present of limited availability and significant cost. Moreover, the technology
6 itself might not yet be completely optimised for the acute care setting- as exemplified by the fact
7 that in about one third of the study subjects, cfPWV could not be assessed because of suboptimal
8 quality of tracing.
9 However, the encouraging performances of cfPWV in predicting outcomes in our study could
10 encourage its use and wider application, and provide ground for further technical development.

11 **CONCLUSIONS**

12 Our pilot study demonstrated that the arterial stiffness, evaluated with cfPWV prior to fluid
13 infusion, reflects the ability of individuals to tolerate an intravascular fluid expansion. Increased
14 cfPWV can identify patients at greater risk of developing signs and symptoms of fluid overload
15 after fluid therapy. A risk assessment “a priori” may be important especially for patients not in
16 acute circulatory insufficiency, for which the risk-benefit analysis might indeed suggest a more
17 conservative approach.

18 Our data will need to be validated in a larger cohort of patients, including more patients < 60 years
19 of age. To ensure this, a technical development that would allow easier acquisition of PWV data,
20 ensuring its feasibility in the acute care setting will be pivotal. Future studies will need to verify
21 whether cfPWV values could be used to determine the amount of fluid required, helping to
22 customize therapy based on the patients’ characteristics.
23

24 **Figure Legend**

25 **Figure 1.** Carotid-femoral Pulse Wave Velocity distribution among different event groups

26 **Figure 2.** Pulse Wave Velocity and event: ROC curve for hard (Figure 2A) and soft (Figure 2B)
27 prediction events (logistic regression analysis)
28
29
30
31

1 REFERENCES

- 2
- 3 1. Roberts, D.A. and A.D. Shaw, Impact of volume status and volume therapy on the kidney. *Best*
4 *Pract Res Clin Anaesthesiol*, 2017; 31;3: 345-352.
- 5 2. Rhodes, A., L.E. Evans, W. Alhazzani, M.M. Levy, M. Antonelli, R. Ferrer, et al., *Surviving Sepsis*
6 *Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016*. *Crit Care*
7 *Med*, 2017; 45;3: 486-552.
- 8 3. Myburgh, J.A. and M.G. Mythen, *Resuscitation Fluids*. *New England Journal of Medicine*, 2013;
9 369;13: 1243-1251.
- 10 4. Ghosh, S., A. Chawla, K. Mishra, R. Jhalani, R. Salhotra, and A. Singh, *Cumulative Fluid Balance*
11 *and Outcome of Extubation: A Prospective Observational Study from a General Intensive Care Unit*.
12 *Indian J Crit Care Med*, 2018; 22;11: 767-772.
- 13 5. Boyd, J.H., J. Forbes, T.A. Nakada, K.R. Walley, and J.A. Russell, *Fluid resuscitation in septic*
14 *shock: a positive fluid balance and elevated central venous pressure are associated with increased*
15 *mortality*. *Crit Care Med*, 2011; 39;2: 259-65.
- 16 6. Vincent, J.L., Y. Sakr, C.L. Sprung, V.M. Ranieri, K. Reinhart, H. Gerlach, et al., *Sepsis in*
17 *European intensive care units: results of the SOAP study*. *Crit Care Med*, 2006; 34;2: 344-53.
- 18 7. Huang, C.C., J.Y. Fu, H.C. Hu, K.C. Kao, N.H. Chen, M.J. Hsieh, et al., *Prediction of fluid*
19 *responsiveness in acute respiratory distress syndrome patients ventilated with low tidal volume and*
20 *high positive end-expiratory pressure*. *Crit Care Med*, 2008; 36;10: 2810-6.
- 21 8. Hasanin, A., *Fluid responsiveness in acute circulatory failure*. *J Intensive Care*, 2015; 3: 50.
- 22 9. Monnet, X., P.E. Marik, and J.L. Teboul, *Prediction of fluid responsiveness: an update*. *Ann*
23 *Intensive Care*, 2016; 6;1: 111.
- 24 10. Seymour, C.W., F. Gesten, H.C. Prescott, M.E. Friedrich, T.J. Iwashyna, G.S. Phillips, et al.,
25 *Time to Treatment and Mortality during Mandated Emergency Care for Sepsis*. *New England Journal*
26 *of Medicine*, 2017; 376;23: 2235-2244.
- 27 11. Ben-Shlomo, Y., M. Spears, C. Boustred, M. May, S.G. Anderson, E.J. Benjamin, et al., *Aortic*
28 *pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis*
29 *of prospective observational data from 17,635 subjects*. *J Am Coll Cardiol*, 2014; 63;7: 636-46.
- 30 12. Boutouyrie, P., A.I. Tropeano, R. Asmar, I. Gautier, A. Benetos, P. Lacolley, et al., *Aortic*
31 *stiffness is an independent predictor of primary coronary events in hypertensive patients: a*
32 *longitudinal study*. *Hypertension*, 2002; 39;1: 10-5.
- 33 13. Milan, A., F. Tosello, A. Fabbri, A. Vairo, D. Leone, M. Chiarlo, et al., *Arterial stiffness: from*
34 *physiology to clinical implications*. *High Blood Press Cardiovasc Prev*, 2011; 18;1: 1-12.

- 1 14. Milan A, Z.G., Leone D, Tosello F, Buraioli I, Schiavone D, Veglio F, Current assessment of
2 Pulse Wave Velocity: comprehensive review of validation studies. *Journal of Hypertension*, 2019,
3 accepted.
- 4 15. Laurent, S., J. Cockcroft, L. Van Bortel, P. Boutouyrie, C. Giannattasio, D. Hayoz, et al., Expert
5 consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart*
6 *J*, 2006; 27;21: 2588-605.
- 7 16. Zoungas, S. and R.P. Asmar, Arterial stiffness and cardiovascular outcome. *Clin Exp Pharmacol*
8 *Physiol*, 2007; 34;7: 647-51.
- 9 17. Borlaug, B.A. and D.A. Kass, Ventricular-vascular interaction in heart failure. *Cardiol Clin*, 2011;
10 29;3: 447-59.
- 11 18. Du Bois, D. and E.F. Du Bois, A formula to estimate the approximate surface area if height and
12 weight be known. 1916. *Nutrition*, 1989; 5;5: 303-11; discussion 312-3.
- 13 19. Lang, R.M., L.P. Badano, V. Mor-Avi, J. Afilalo, A. Armstrong, L. Ernande, et al.,
14 Recommendations for cardiac chamber quantification by echocardiography in adults: an update from
15 the american society of echocardiography and the European association of cardiovascular imaging. *J*
16 *Am Soc Echocardiogr*, 2015; 28;1: 1-39 e14.
- 17 20. Volpicelli, G., M. Elbarbary, M. Blaivas, D.A. Lichtenstein, G. Mathis, A.W. Kirkpatrick, et al.,
18 International evidence-based recommendations for point-of-care lung ultrasound. *Intensive Care*
19 *Med*, 2012; 38;4: 577-91.
- 20 21. Milan, A., F. Tosello, D. Naso, E. Avenatti, D. Leone, C. Magnino, et al., Ascending aortic
21 dilatation, arterial stiffness and cardiac organ damage in essential hypertension. *J Hypertens*, 2013;
22 31;1: 109-16.
- 23 22. Williams, B., G. Mancia, W. Spiering, E. Agabiti Rosei, M. Azizi, M. Burnier, et al., 2018
24 ESC/ESH Guidelines for the management of arterial hypertension. *European Heart Journal*, 2018:
25 ehy339-ehy339.
- 26 23. Semler, M.W., A.P. Wheeler, B.T. Thompson, G.R. Bernard, H.P. Wiedemann, and T.W. Rice,
27 Impact of Initial Central Venous Pressure on Outcomes of Conservative Versus Liberal Fluid
28 Management in Acute Respiratory Distress Syndrome. *Crit Care Med*, 2016; 44;4: 782-9.
- 29 24. National Heart, L., N. Blood Institute Acute Respiratory Distress Syndrome Clinical Trials, H.P.
30 Wiedemann, A.P. Wheeler, G.R. Bernard, B.T. Thompson, et al., Comparison of two fluid-
31 management strategies in acute lung injury. *N Engl J Med*, 2006; 354;24: 2564-75.
- 32 25. Asahi, T., M. Nakata, N. Higa, M. Manita, K. Tabata, and M. Shimabukuro, Respiratory Collapse
33 of the Inferior Vena Cava Reflects Volume Shift and Subsequent Fluid Refill in Acute Heart Failure
34 Syndrome. *Circ J*, 2016; 80;5: 1171-7.

- 1 26. Viau, D.M., J.A. Sala-Mercado, M.D. Spranger, D.S. O'Leary, and P.D. Levy, The
2 pathophysiology of hypertensive acute heart failure. *Heart*, 2015; 101;23: 1861-7.
- 3 27. Laurent, S., S. Katsahian, C. Fassot, A.I. Tropeano, I. Gautier, B. Laloux, et al., Aortic stiffness
4 is an independent predictor of fatal stroke in essential hypertension. *Stroke*, 2003; 34;5: 1203-6.
- 5 28. Vlachopoulos, C., K. Aznaouridis, and C. Stefanadis, Prediction of Cardiovascular Events and
6 All-Cause Mortality With Arterial Stiffness: A Systematic Review and Meta-Analysis. *Journal of the*
7 *American College of Cardiology*, 2010; 55;13: 1318-1327.
- 8 29. Reddy, Y.N.V., M.J. Andersen, M. Obokata, K.E. Koepp, G.C. Kane, V. Melenovsky, et al.,
9 Arterial Stiffening With Exercise in Patients With Heart Failure and Preserved Ejection Fraction.
10 *Journal of the American College of Cardiology*, 2017; 70;2: 136-148.
- 11 30. Andersen, M.J., T.P. Olson, V. Melenovsky, G.C. Kane, and B.A. Borlaug, Differential
12 hemodynamic effects of exercise and volume expansion in people with and without heart failure. *Circ*
13 *Heart Fail*, 2015; 8;1: 41-8.
- 14 31. Protogerou, A.D., M.E. Safar, P. Iaria, H. Safar, K. Le Dudal, J. Filipovsky, et al., Diastolic Blood
15 Pressure and Mortality in the Elderly With Cardiovascular Disease. *Hypertension*, 2007; 50;1: 172-
16 180.

17

18 **Statements**

- 19 a. **Ethics approval statements** – All Authors state that any necessary ethics committee approval
20 was secured for the study reported. This study was approved by ‘Comitato etico interaziendale
21 AOU San Luigi Gonzaga di Orbassano’ n. 29/2015.
- 22 b. **Clinical Trial Registration**- Our clinical trial has been registered n. 29/2015.
- 23 c. **Funding statement** – The authors did not had source of funding to declare.
- 24 d. **Competing Interests** – Authors did not have conflict of interest to declare for this paper;