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(Article begins on next page)

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Title

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

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

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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 .

BACKGROUND

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

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

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

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

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

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

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

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

METHODS

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

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

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

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

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

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

Transthoracic echocardiography (TTE)

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

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

Pulmonary ultrasound

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

Pulse Wave Velocity

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

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

Statistical analysis

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

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

RESULTS

Characteristics of the study patients

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

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

Population Outcomes

Hard endpoints

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

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

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

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

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

Table 3 . Multivariate logistic regression analysis Hard events

	Hard events
Variables	**R^2=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)	113 (0.8 - 15500), p=0.06
Body surface area (m2)	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

Cf:carotido-femoral

Soft endpoints

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

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

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

Subgroup analysis (patients without shock)

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

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

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

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

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

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

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

LIMITATIONS

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

undergoing fluid therapy for different reasons, and that could thus be widely applicable. Future studies will be needed to determine the value of cfPWV in specific clinical scenarios.

Lastly, we acknowledge that there are intrinsic technical limitations to the applicability of the proposed evaluation. Assessment of cfPWV requires trained operators as well as specific equipment that is at present of limited availability and significant cost. Moreover, the technology itself might not yet be completely optimised for the acute care setting- as exemplified by the fact that in about one third of the study subjects, cfPWV could not be assessed because of suboptimal quality of tracing.

However, the encouraging performances of cfPWV in predicting outcomes in our study could encourage its use and wider application, and provide ground for further technical development.

CONCLUSIONS

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

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

Figure Legend

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

Figure 2. Pulse Wave Velocity and event: ROC curve for hard (Figure 2A) and soft (Figure 2B) prediction events (logistic regression analysis)

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Statements

a. **Ethics approval statements** – All Authors state that any necessary ethics committee approval was secured for the study reported. This study was approved by ‘Comitato etico interaziendale AOU San Luigi Gonzaga di Orbassano’ n. 29/2015.

b. **Clinical Trial Registration**- Our clinical trial has been registered n. 29/2015.

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d. **Competing Interests** – Authors did not have conflict of interest to declare for this paper;