Research Article

A Novel Fluorescent Clinical Method to Rapidly Quantify Plasma Volume

Bruce A. Molitoris[a, d]   Anthony G. George[b]   Patrick T. Murray[c]
Daniel Meier[d]   Erinn S. Reilly[d]   Erin Barreto[e]   Ruben M. Sandoval[a, d]
Dana V. Rizk[f]   Andrew D. Shaw[b]   W. Frank Peacock[g]

[a]Indiana University, Indianapolis, IN, USA; [b]Department of Anesthesiology and Pain Medicine, University of Alberta, Edmonton, AB, Canada; [c]School of Medicine, University College Dublin, Dublin, Ireland; [d]FAST BioMedical, Carmel, IN, USA; [e]Mayo Clinic, Rochester, MN, USA; [f]University of Alabama at Birmingham, Birmingham, AL, USA; [g]Baylor College of Medicine, Houston, TX, USA

Abstract

Objectives: To determine the performance of a rapid fluorescent indicator technique for measuring plasma volume (PV). *Methods:* This was an open-label, observational evaluation of a two-component intravenous visible fluorescent dye technique to rapidly measure PV in 16 healthy subjects and 16 subjects with chronic kidney disease (8 stage 3 and 8 stage 4 CKD), at 2 clinical research sites. The method consisted of a single intravenous injection of 12 mg of a large 150-kDa carboxy-methyl dextran conjugated to a fluorescent rhodamine-derived dye as the PV marker (PVM), and 35 mg of a small 5-kDa carboxy-methyl dextran conjugated to fluorescein, the renal clearance marker. Dye concentrations were quantified 15 min after the injections for initial PV measurements using the indicator-dilution principle. Additional samples were taken over 8 h to evaluate the stability of the PVM as a determinant of PV. Blood volumes (BV) were calculated based on PV and the subject's hematocrit. Pharmacokinetic parameters were calculated from the plasma concentration data taken over several days using noncompartmental methods (Phoenix WinNonlin®). Linear correlation and Bland-Altman plots were used to compare visible fluorescent injectate-measured PV compared to Nadler's

Bruce A. Molitoris, MD
R-2, Room 266
950 West Walnut St.
Indianapolis, IN 46202 (USA)
E-Mail bmolitor@iu.edu

KARGER

CardioRenal Medicine

Cardiorenal Med 2019;9:168–179

DOI: 10.1159/000496480 | © 2019 S. Karger AG, Basel
www.karger.com/crm

Molitoris et al.: A Novel Fluorescent Clinical Method to Rapidly Quantify PV

169

formula for estimating PV. Finally, 8 healthy subjects received 350 mL infusion of a 5% albumin solution in normal saline over 30 min and a repeat PV determination was then carried out. **Results:** PV and BV varied according to weight and body surface area, with PV ranging from 2,115 to 6,234 mL and 28.6 to 41.9 mL/kg when weight adjusted. Both parameters were stable for >6 h with repeated plasma measurements of the PVM. There was no difference between healthy subjects and CKD subjects. Overall, there was general agreement with Nadler's estimation formula for the mean PV in subjects. A 24-h repeat dose measurement in 8 healthy subjects showed PV variability of 98 ± 121 mL (mean = 3.8%). Additionally, following an intravenous bolus of 350 mL of a 5% albumin solution in normal saline in 8 healthy subjects, the mean (SD) measured increase in PV was 356 (±50.0) mL post-infusion. There were no serious adverse events reported during the study. **Conclusions:** This minimally invasive fluorescent dye approach safely allowed for rapid, accurate, and reproducible determination of PV, BV, and dynamic monitoring of changes following fluid administration.

© 2019 S. Karger AG, Basel

Background

In patients presenting with the potential of volume abnormalities, an accurate evaluation is critical for appropriate diagnosis and management. Unfortunately, volume assessment is challenging. Studies demonstrate that 10–20% of non-heart failure (HF) dyspneic patients are initially diagnosed with HF, i.e. they are incorrectly diagnosed with volume overload despite its absence [1, 2]. Similarly, in the 1,586 patient Breathing Not Properly study [3], adding bovine natriuretic peptide (BNP) to the history, physical exam, and chest X-ray improved the misdiagnosis rate, which remained high at 18%. These error rates occur because the clinical estimate of volume status is difficult and highly dependent on clinician experience and ability. These errors occur because the signs and symptoms usually considered suggestive of volume overload suffer from extremely poor inter-rater reliability. In a study of 68 emergency department patients, the kappa measurement of inter-rater agreement had an overall dismal performance. Although there was substantial agreement [4] for edema ($\kappa = 0.67$), agreement was only moderate for ascites ($\kappa = 0.47$) and crepitations ($\kappa = 0.43$), and was nonexistent for orthopnea ($\kappa = 0.20$), jugular venous distention ($\kappa = 0.08$), or the presence of a third heart sound (S3) ($\kappa = 0.10$) [5]. With such low inter-rater agreement, the practice of relying solely on clinical grounds for volume assessment is questionable.

Readily available rapid and accurate bedside techniques for measurement of a patient's volume are limited. Bedside ultrasound can evaluate vena cava size, with consideration of respiratory variation, to aid in the assessment. However, the skill set to obtain these measures is not universally available. A number of hemodynamic measurements [6–9] that measure physiological surrogates of volume, e.g. pulse pressure [10, 11] and stroke volume [12, 13] variations – both indicators of fluid responsiveness, have been promoted. The currently available options for volume assessment include capillary refill, peripheral temperature, skin color, mean arterial pressure, urine output, creatinine, lactate, lung sounds, chest X ray, edema, weight changes, central venous oxygen saturation, and cardiac output monitoring [9, 14–17]. All of these parameters are surrogate markers of the adequacy of the circulating blood volume (BV) [14, 15]. Ultimately, the decision to administer or remove volume is almost always predicated on an assessment of volume status *in the absence of a direct measurement*.

Because of the need to accurately assess volume in real time, studies evaluating a new application of dye dilution technology to objectively determine its status offer promise [16–18]. Filtration assessment and surveillance technology (FAST) is able to measure the variables of plasma volume (PV) and glomerular filtration rate (GFR). These parameters are

CardioRenal Medicine

Cardiorenal Med 2019;9:168–179

DOI: 10.1159/000496480 | © 2019 S. Karger AG, Basel
www.karger.com/crm

170

Molitoris et al.: A Novel Fluorescent Clinical Method to Rapidly Quantify PV

determined by dye dilution calculation after the injection of a pair of fluorescent molecules. In this application, a visible fluorescent injectate (VFI™), containing 12 mg of a large (150 kDa) carboxy-methylated dextran conjugated to a fluorescent rhodamine derivative, is the PV marker (PVM). It is simultaneously administered with 35 mg of a small (5-kDa) carboxy-methylated dextran conjugated to fluorescein that serves as the renal clearance marker (RCM). As the large molecule is retained in the intravascular space, its concentration reflects real-time PV, and since the small molecule is freely filtered across the glomerulus, its change represents the GFR.

As results for GFR measurements in this study population have been previously reported [19], the purpose of the present analysis is to assess the relationship of measured PV to that estimated by Nadler's equation [20] and the serum stability of the measured PVM over time.

Methods

This was a phase 2b prospective, open label study (NIH, NCT03095391) observational study conducted at two sites: the University of Alabama at Birmingham and the Clinical Research Organization ICON (San Antonio, TX, USA). The study protocol and informed consent forms were approved by Western IRB in Puyallup, WA, USA. All patients received and completed an informed consent form prior to being enrolled in the study. Four cohorts (of 8 participants each) were enrolled between June 13, 2017, and August 30, 2017. All participants provided written informed consent, and the study adhered to the Declaration of Helsinki. Eligible participants were 18–75 years old, with body mass index ≥18 and ≤40, and nonsterile participants agreed to use medically acceptable methods of contraception.

Demographics, medical and surgical history (including concomitant medication use), height, weight, vital signs, and physical examination findings were documented. Laboratory tests included chemistry, hematology, hepatic function panel, follicular stimulating hormone (females only), creatinine phosphokinase, and HIV, hepatitis C and B serologies, as well as urine pregnancy tests and drug screens. 12-lead electrocardiograms were obtained. The estimated GFR (eGFR) was calculated using the CKD-EPI formula [21].

All studies were done in fasting patients in a clinical research unit. Subjects were provided a low-protein breakfast prior to the administration of the VFI and had free access to water throughout the study. All received a VFI that consisted of 12 mg of a 150-kDa carboxy-methylated dextran, conjugated to a rhodamine dye (PVM), and 35 mg of a 5-kDa carboxy-methylated dextran, conjugated to fluorescein (RCM), in a total volume of 3.0 mL. VFI was infused intravenously over 30 s. Subjects received a light, low-protein snack 5 h after dosing. All patients underwent PV determination within 21 days of screening.

Cohorts 1 and 2 consisted of healthy volunteers. Cohort 1 received a single VFI dose and measurement followed by a 350 mL 5% albumin in normal saline 30-min infusion beginning at 120 min, with plasma taken 5 min after the end of the infusion for determination of the change in volume. Cohort 2 resided overnight in the clinical research unit, receiving 2 VFI doses 24 h apart, to determine the variability in the determinations using a paired Student's t test. They were fed a low-protein diet during their stay. Cohorts 3 and 4, representing chronic kidney disease (CKD) stage 3 ($30 \leq$ eGFR <60 mL/min/1.73 m^2) and 4 ($15 \leq$ eGFR <30 mL/min/1.73 m^2), respectively, received one VFI dose.

In all cohorts, 3.5 mL of blood was drawn prior to dosing, at 15, 30, 60, 120, 170, 310, 370, 480 min, and again at 12 and 24 h. While only the 15-min blood draw was used to determine PV, samples at the other routine time points were needed for determination of GFR by the FAST BioMedical technique (60 and 170 min) and iohexol technique (all 6 blood draws) as reported previously [19]. Additional blood draws varied by cohort in order to meet the specific experimental procedures prescribed by the protocol. In cohort 1, 350 mL of a 5% albumin solution in normal saline was administered over 30 min beginning at 130 min into the study, and additional blood samples were obtained at 165, 195, and 205 min to allow additional PV measurements after volume expansion. In cohort 2, the standard study was repeated a day later when a second-dose VFI was administered. The long-term pharmacokinetics of the PVM were determined in cohorts 2, 3, and 4, necessitating additional blood draws on days 1, 3, 7, 14, and 20 after the last VFI dose. All samples were collected in K2EDTA 3 mL tubes, from the opposite arm that VFI was administered. Samples underwent 1,500 g centrifugation for 15 min, after which 250 μL of plasma was pipetted and combined with a fluorescence-enhancing reagent (FAST BioMedical, Carmel, IN, USA) to total a volume of 2.250 mL. PVM and RCM
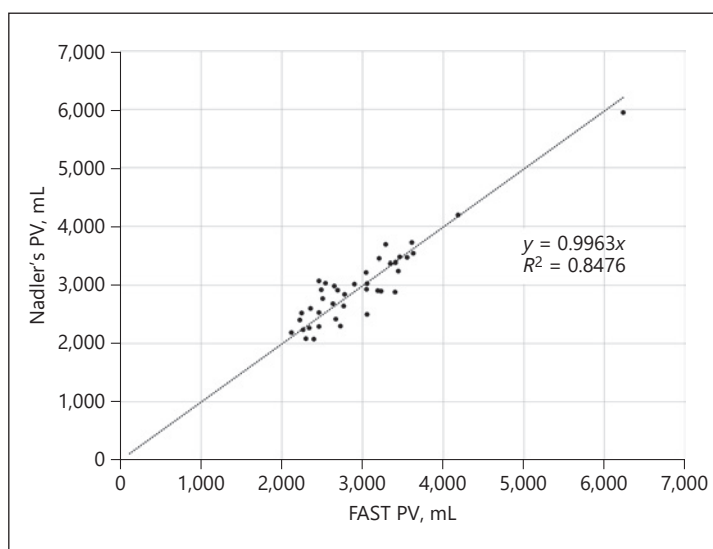
Molitoris et al.: A Novel Fluorescent Clinical Method to Rapidly Quantify PV

Table 1. Patient characteristics, measured GFR, PV, and BV

Cohort	Hematocrit, %	CKD EPI eGFR, mL/min/1.73 m^2	FAST PV, mL	Nadler PV, mL	FAST BV
Cohort 1, healthy subjects; volume challenge	38	133	2,115	2,186	3,411
	46	71	3,050	2,931	5,616
	48	83	3,187	2,904	6,094
	37	120	3,443	3,244	5,457
	36	89	2,775	2,840	4,356
	43	101	3,057	2,502	5,317
	32	135	2,649	2,989	3,901
	33	108	2,667	2,420	3,998
Cohort 2, healthy subjects; repeat dose					
Day 1	45	119	2,632	2,683	4,820
Day 2	46	119	2,765	2,644	5,139
Day 1	39	89	2,294	2,081	3,743
Day 2	39	89	2,395	2,074	3,920
Day 1	40	101	3,226	2,899	5,376
Day 2	40	101	3,399	2,884	5,694
Day 1	43	87	2,487	2,921	4,379
Day 2	43	87	2,691	2,911	4,754
Day 1	35	95	2,457	2,289	3,797
Day 2	35	95	2,724	2,296	4,198
Day 1	36	101	2,462	3,071	3,816
Day 2	36	101	2,540	3,033	3,987
Day 1	38	80	2,335	2,266	3,753
Day 2	39	80	2,264	2,237	3,688
Day 1	42	103	2,457	2,529	4,235
Day 2	40	103	2,353	2,603	3,941
Cohort 3, 30< eGFR <60	45	51	3,609	3,718	6,562
	36	58	2,247	2,521	3,511
	38	59	3,288	3,690	5,303
	41	57	2,224	2,405	3,770
	31	49	4,181	4,189	6,060
	36	34	2,505	2,774	3,914
	42	46	3,347	3,366	5,741
	44	46	3,458	3,470	6,209
Cohort 4, 30> eGFR >15	37	26	3,631	3,540	5,763
	26	20	6,234	5,946	8,424
	32	29	3,042	3,222	4,473
	27	20	3,204	3,446	4,389
	35	23	3,057	3,022	4,704
	37	21	3,556	3,463	5,644
	39	28	2,899	3,017	4,752
	34	25	3,409	3,383	5,165

dye concentration determinations were performed on a Turner Trilogy filter fluorimeter (Turner Designs, San Jose, CA, USA).

Pharmacokinetic parameters were calculated from the measured PVM and RCM plasma concentration data using noncompartmental methods (Phoenix WinNonlin, Version 6.3 or later, Pharsight Corporation, St. Louis, MO, USA) and actual sampling times. Using the 15-min time point, PV was determined by dividing the measured PVM concentration, in µg/mL, by the total dose given (12,000 µg). A measured hematocrit, taken prior to dosing on the same day of VFI dosing, was used to calculate BV by the following formula: BV = total PV/(1 – hematocrit) [22]. Nadler's estimated BV was converted to PV by subtracting the volume occupied by the cells from the BV determination [21].

CardioRenal Medicine

Cardiorenal Med 2019;9:168–179

DOI: 10.1159/000496480 | © 2019 S. Karger AG, Basel
www.karger.com/crm

172

Molitoris et al.: A Novel Fluorescent Clinical Method to Rapidly Quantify PV

Fig. 1. Linear correlation of FAST-measured PV compared to Nadler's estimated PV. All 32 subjects studied are reported, and one group that was studied for repeatability of measurements was reported twice. If the highest PV is removed from the correlation determination, the R^2 value is 0.71.

Subjects were followed for 21 (±1) days from last VFI injection and were assessed for adverse and serious adverse events at each encounter. Long-term monitoring was performed by blood sampling and pharmacokinetic analysis, with the median decay rate used to calculate PV >1 h post-VFI injection. The correction used was determined by an equation: Adjusted PV = measured PV – ((measured PV × decay rate (0.0053)) × time).

Statistics

Correlation analysis was done by comparing the measured PV to that estimated by Nadler's formula for each cohort, using the Pearson product-moment correlation coefficient. Data are presented as Bland-Altman graphs and comparative graphs.

Results

Table 1 shows the results in all 32 subjects studied under equilibrium conditions. Measured PV varied from a low of 2,115 mL to a high of 6,234 mL, with concomitant BV of 3,411 and 8,424 mL, respectively, in those 2 subjects. When adjusted for body weight, the ranges in PV and BV were 28.6–41.9 and 44.4–69.8 mL/kg, respectively. In healthy volunteers (cohorts 1 and 2), 6/16 (37.5%) were male, 8 (50%) Latino, 7 (43.7%) white, and 1 (6.2%) African-American, with a mean (± SD) weight of 79.7 ± 11.6 kg. Their mean plasma creatinine was 0.76 ± 0.17 mg/dL, and the mean eGFR was 99.6 ± 16 mL/min/1.73 m². The mean measured PV was 2,706 ± 370 mL and weight-adjusted PV was 36.2 ± 3.5 mL/kg, and for Nadler's estimate the corresponding values were 2,672 ± 341 mL and 35.7 ± 2.7 mL/kg. The median measured PV was 2,640.3 mL versus that estimated by Nadler's formula of 2,761.5 mL. In CKD patients (cohorts 3 and 4), 8 (50%) were male, 50% African-American, 7 white (43.7%), and 1 Hispanic (6.2%), with a mean (±SD) weight of 96 ± 18 kg. Their mean (±SD) plasma creatinine levels were 1.41 ± 0.30 and 2.75 ± 0.55 mg/dL, and mean (±SD) eGFRs were 50 ± 7.8 and 24 ± 3.3 mL/min/1.73 m² for cohorts 3 and 4, respectively. The mean measured PV was 3,368 ± 895 mL and weight-adjusted PV was 35.0 ± 4.5 mL/kg, and corresponding Nadler's estimates were 3,448 ± 781 mL and 36.0 ± 3.5 mL/kg. The median measured total PV was 3,317 mL versus Nadler's formula estimation of 3,448 mL. One patient in this group had a measured PV of 6,234 mL, making the standard deviation of the mean for this group very high. However, the weight-adjusted PV in mL/kg was similar to other subjects (Table 1).
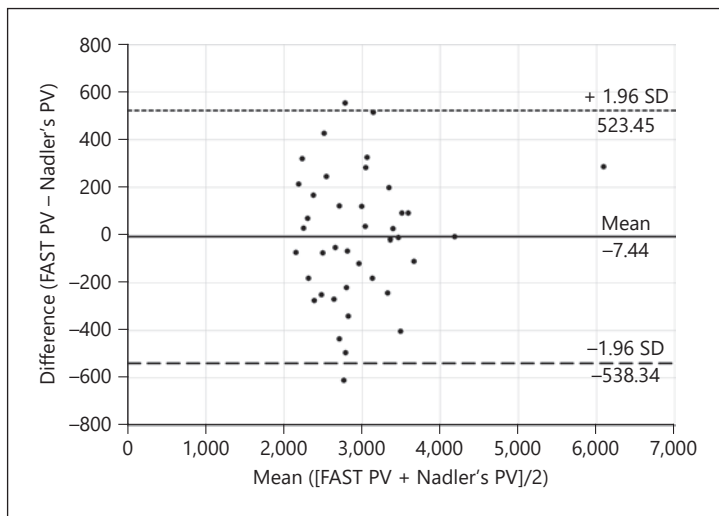
CardioRenal Medicine

Cardiorenal Med 2019;9:168–179

DOI: 10.1159/000496480 | © 2019 S. Karger AG, Basel
www.karger.com/crm

Molitoris et al.: A Novel Fluorescent Clinical Method to Rapidly Quantify PV

173

Fig. 2. Bland-Altman plot of all patient data, FAST-measured PV in mL compared to Nadler's estimated PV.
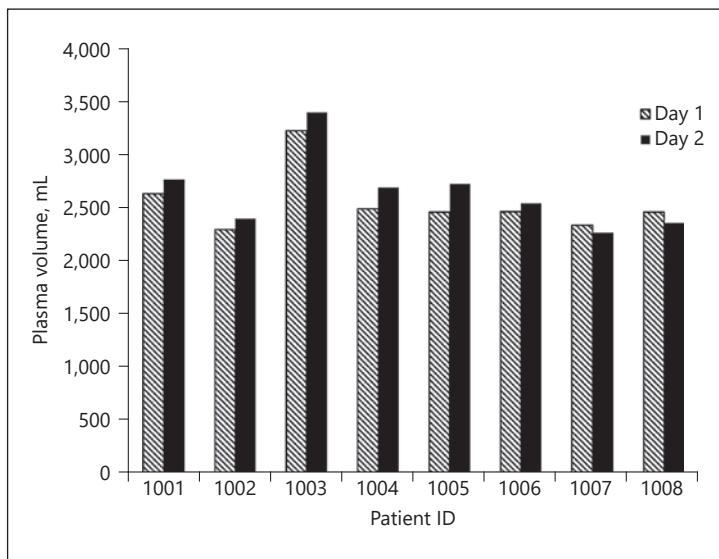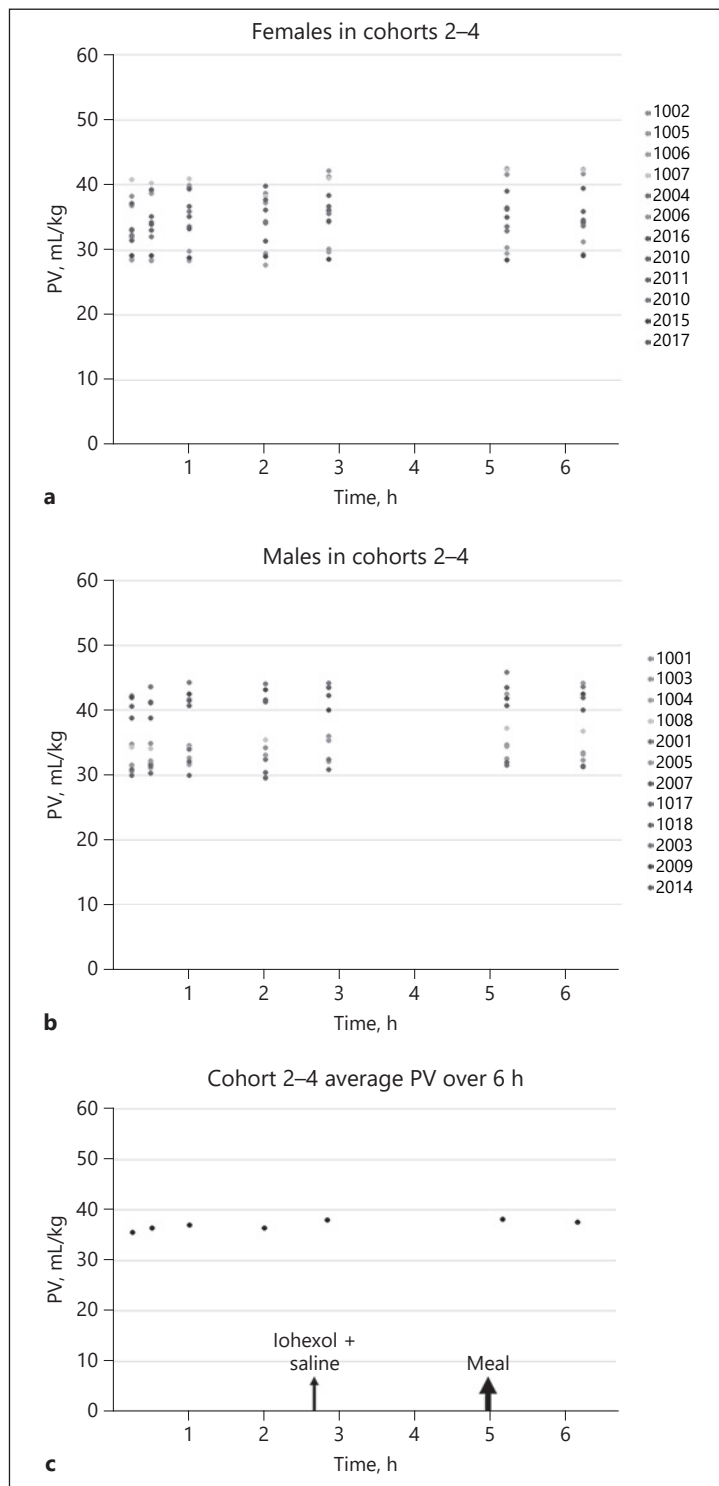

Fig. 3. Plasma volume measurement repeat analysis (24-h separation of doses). In normal subjects, a repeat PV was determined 24 h after the first dose. The remaining background 150 kDa signal was taken as the new background level to not interfere in the new measurement.

Comparisons of the measured PV to Nadler's PV estimating equation are shown in Figure 1, with an R^2 correlation coefficient of 0.85. If the highest PV patient is not included in the analysis, R^2 is 0.71 (suppl. Fig. 1; see www.karger.com/doi/10.1159/000496480 for all online suppl. material). A Bland-Altman analysis (Fig. 2) showed a symmetrical distribution around the mean. However, values as high as 555 mL above and 609 mL below Nadler's equation estimated values were measured. This suggests that Nadler's formula was up to 7.1 mL/kg (23.7%) above or 6.8 mL/kg (18.2%) below the FAST-measured PV.

Patients with consecutive-day PV measurements (cohort 2) had results that were stable (Fig. 3). The mean difference from day 1 to 2 was 98 ± 121 mL ($p = 0.05$), representing a mean change of 3.8%. In cohort 2–4 patients, followed for 21 days, the mean plasma half-life of the 150 kDa PVM was 95.3 ± 38.6, 99.1 ± 23.8, and 106.2 ± 22.5 h, respectively, suggesting that the presence of CKD did not alter metabolic elimination of the 150 kDa PVM.

Figure 4 shows the mean measured PV in mL/kg body weight for 24 patients (cohorts 2–4) over 6 h. Female and male subjects were separated into Figure 4a and b, respectively. Figure 4c shows the mean of all 24 patients over time. PVs were stable over time for individual

CardioRenal Medicine

Cardiorenal Med 2019;9:168–179

DOI: 10.1159/000496480 | © 2019 S. Karger AG, Basel
www.karger.com/crm

174

Molitoris et al.: A Novel Fluorescent Clinical Method to Rapidly Quantify PV

Fig. 4. Change in PV over 6 h. Plasma volume was measured in 12 females (**a**) and 12 males (**b**) as individual determinations over 6 h. The mean PV in mL/kg for all 24 subjects is shown in **c**. Subjects received 5 mL iohexol and 5 mL normal saline i.v. at 160 min (thin arrow) and were fed a light meal beginning at 300 min (thick arrow) into the study. The mean standard deviation for individual patients was 1.04 mL/kg and is not shown, as it was smaller than the filled circle used to show the value.

patients and overall, but varied between patients. There was a tendency to see a rise in PV after the iohexol injection at 160 min, and the subjects received a small meal at 300 min. Subjects in cohort 1 were excluded due to the volume challenge administered and the subsequent alteration of PV during the 6 h.
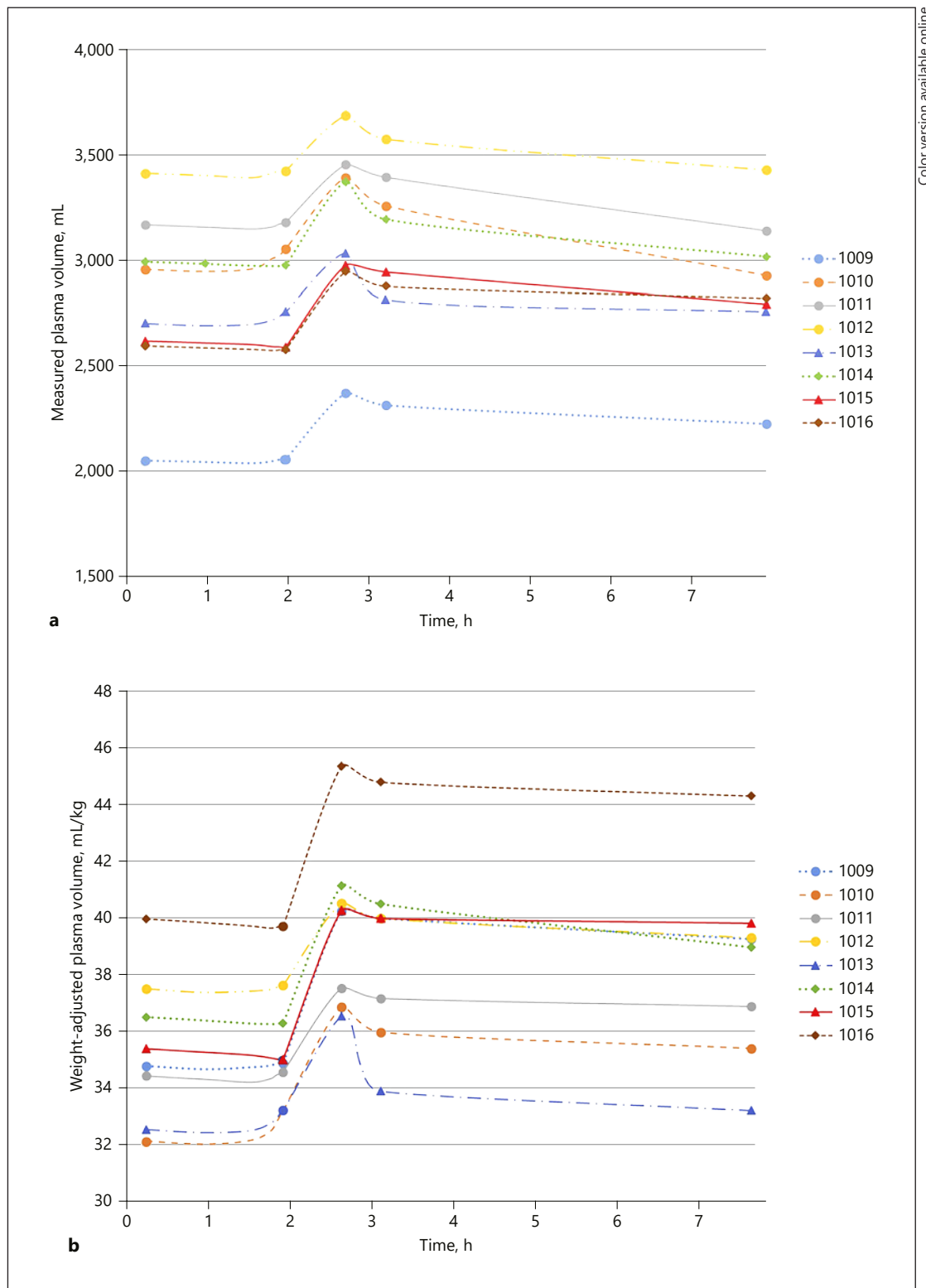
Molitoris et al.: A Novel Fluorescent Clinical Method to Rapidly Quantify PV

Fig. 5. PV change (mL/kg) during 350 mL volume challenge. 350 mL of 5% albumin solution in normal saline was given over 30 min beginning at 120 min of the study. Measured PV in mL (**a**) and weight-adjusted PV in mL/kg (**b**) prior to and over time following the volume challenge for individual subjects.

CardioRenal Medicine

Cardiorenal Med 2019;9:168–179

176

DOI: 10.1159/000496480 | © 2019 S. Karger AG, Basel
www.karger.com/crm

Molitoris et al.: A Novel Fluorescent Clinical Method to Rapidly Quantify PV

Table 2. Pre- and post-volume infusion measured plasma volumes

patient ID	age, years	sex	weight, kg	height, cm	before infusion		after 350 mL infusion		
					15 min	120 min	165 min	195 min	480 min
1009	19	F	59	158	2,058	2,098	2,437	2,388	2,321
1010	64	M	92	171	2,965	3,114	3,482	3,360	3,053
1011	58	M	92	176	3,177	3,242	3,545	3,501	3,274
1012	47	F	91	176	3,423	3,490	3,784	3,688	3,574
1013	69	F	83	163	2,710	2,810	3,113	2,903	2,875
1014	51	F	82	160	3,002	3,034	3,461	3,294	3,147
1015	30	F	74	171	2,627	2,641	3,057	3,038	2,912
1016	48	F	65	153	2,604	2,629	3,025	2,969	2,942
Average change (SD), mL							355.8 (50.1)		

Cohort 1 plasma volume measuring fluid challenge response

Figure 5a and Table 2 show PV changes in response to a volume-expanding albumin infusion in cohort 1 beginning at 130 min after the start of the study. Five minutes after a 30-min infusion of 350 mL 5% albumin in normal saline, there was a mean increase of 355.8 ± 50.1 mL (range 294–427 mL), followed by a slow reduction thereafter. Figure 5b shows this weight-adjusted response in mL/kg body weight with the 350 mL volume challenge for individual patients.

Discussion

The present study shows PV is accurately and reproducibly measured using a fluorescent 150 kDa PVM. We also described that the large inert PVM had a long half-life and could detect dynamic changes in PV induced by a volume challenge without re-dosing the patient for up to 6 h. Its use evaluating therapeutically induced changes, e.g. with diuretic administration or IV fluid bolus, will require additional study; however, the present study indicates it could be of significant benefit in a number of clinical situations where knowing PV and dynamic changes in PV are important.

Determination of PV and BV has been a clinical goal for over 70 years. Research studies using radioactive iodinated serum albumin (RISA) and chromium 51 erythrocyte (RBC) labeling have been used to measure PV and RBC volumes, respectively. These studies have identified many areas where measurement of PV and BV would be clinically useful including congestive HF [21, 23–26], sepsis [27], and surgical patients [28]. Research radioisotope measurements, using the indicator dilution technique have traditionally been considered the gold standard for BV and PV assessment [22, 29–32], but they are cumbersome and expensive, especially at the bedside. An FDA-approved BV measurement system (Daxor, BVA-100) has commercialized the RISA technique and utilized comparisons to the ideal BV weight method [33]. This technique uses I^{131} labeled albumin, requires multiple blood draws, is expensive, and only one BV determination is possible per injection of radioactive albumin.

The present fluorescent technique uses an inert carboxy-methylated 150-kDa dextran conjugated to a rhodamine-derived fluorescent dye as a PVM. The carboxy-methyl substitution markedly improves immunologic tolerance, as does the RCM [34]. In more than 89 subjects and 97 injections to date, there have been no serious adverse events described. Furthermore, the large size of the PVM eliminates vascular leakage resulting in a stable

CardioRenal Medicine

Cardiorenal Med 2019;9:168–179

DOI: 10.1159/000496480 | © 2019 S. Karger AG, Basel
www.karger.com/crm

177

Molitoris et al.: A Novel Fluorescent Clinical Method to Rapidly Quantify PV

plasma concentration that allows for multiple determinations following a single injection for at least 6 h.

This technique is not without limitations. Its use in bleeding subjects may be limited, as the indicator dye will be lost with the extravasated blood and thus result in a falsely high PV calculation. Also, a high vascular permeability could result in leakage of the dextran thus limiting the time the marker could be used with accuracy. Additionally, determining whether or not a particular PV measurement is abnormal, for a particular patient, is not straightforward. To address this, the International Council on Standardization in Hematology have published a recommendation [35] on the interpretation of red cell mass and PV measurements and established prediction formulae based on body surface area for red cell mass. In general, 98–99% of measurements calculated using these formulae are within 25% of the predicted norm [31, 33]. One such formula is that described by Nadler et al. [20] using body surface area, where: total BV = $(0.3669 \times height (m)3) + (0.03219 \times weight (kg)) + 0.6041$ for males, and $(0.3561 \times height (m)3) + (0.03308 \times weight (kg)) + 0.1833$ for females.

Although current approaches to volume assessment [36–38] are entrenched in our daily practice, we believe a technique capable of rapid determination of PV (instead of surrogate markers of volume status and/or tissue perfusion) would represent a significant advance in the clinical management of critically ill patients. Patients with acute and/or chronic HF [39, 40], especially when complicated by renal insufficiency, frequently present difficult volume management problems. The coexistence of both heart and renal failure makes these patients particularly difficult to manage, and a small change in intravascular volume status can lead to a large change in overall clinical condition. A direct measurement of PV, used alone or in combination with surrogates of organ perfusion and/or measurements of blood flow, would guide fluid removal more precisely. In turn, this could potentially improve clinical outcomes, the ultimate test of any clinical technique. Given this technique also measures GFR accurately when compared to a 6 h iohexol measurement [19], its use in cardiorenal patients seems an ideal opportunity, where knowledge of both actual measured PV and GFR will assist in therapeutic decisions.

Conclusion

We report the results of a novel fluorescent dye technique, capable of repeatedly measuring PV easily and accurately. The technique correlates well with Nadler's estimates of PV, but identifies outliers from the predicted value, and accurately tracks acute volume therapy. We believe this technology will prove valuable in the assessment and management of fluid therapy in hospitalized patients.

Statement of Ethics

The study protocol and informed consent forms were approved by Western IRB in Puyallup, WA, USA. All patients received and completed an informed consent form prior to being enrolled in the study.

Disclosure Statement

Bruce A. Molitoris is a co-founder, stockholder, and the Medical Director of FAST BioMedical. Erinn S. Reilly and Daniel Meier are employees of FAST BioMedical, and Ruben M. Sandoval is a paid consultant for FAST BioMedical. Patrick T. Murray, Erin Barreto, and Andrew D. Shaw are Scientific Advisory Board members, who have received compensation for consultancy. The investigators and authors did not receive any honoraria for their work on this study or authorship. FAST BioMedical, www.fastbiomedical.com, is a Delaware C-Corp. developing measured GFR and PV technology.

CardioRenal Medicine

Cardiorenal Med 2019;9:168–179	
DOI: 10.1159/000496480	© 2019 S. Karger AG, Basel
	www.karger.com/crm

178

Molitoris et al.: A Novel Fluorescent Clinical Method to Rapidly Quantify PV

Author Contributions

B.A.M., *P.T.M.*, *D.M.*, *E.S.R.*, *E.B.*, *R.M.S.*, *D.V.R.*, *A.D.S.* made substantial contributions to conception and design, or acquisition, analysis and or interpretation of data. *B.A.M.*, *A.D.S.*, *A.G.G.*, *D.M.*, *E.S.R.*, *D.V.R.*, and *W.F.P.* were involved in writing and or revising the manuscript. All authors gave final approval to the manuscript.

References

1 Dao Q, Krishnaswamy P, Kazanegra R, Harrison A, Amirnovin R, Lenert L, et al. Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting. J Am Coll Cardiol. 2001 Feb;37(2): 379–85.

2 Mard S, Nielsen FE. Positive predictive value and impact of misdiagnosis of a heart failure diagnosis in administrative registers among patients admitted to a University Hospital cardiac care unit. Clin Epidemiol. 2010 Oct;2:235–9.

3 McCullough PA, Nowak RM, McCord J, Hollander JE, Herrmann HC, Steg PG, et al. B-type natriuretic peptide and clinical judgment in emergency diagnosis of heart failure: analysis from Breathing Not Properly (BNP) Multinational Study. Circulation. 2002 Jul;106(4):416–22.

4 McHugh ML. Interrater reliability: the kappa statistic. Biochem Med (Zagreb). 2012;22(3):276–82.

5 Chaudhry A, Singer AJ, Chohan J, Russo V, Lee C. Interrater reliability of hemodynamic profiling of patients with heart failure in the ED. Am J Emerg Med. 2008 Feb;26(2):196–201.

6 Clement RP, Vos JJ, Scheeren TW. Minimally invasive cardiac output technologies in the ICU: putting it all together. Curr Opin Crit Care. 2017 Aug;23(4):302–9.

7 Lancellotti P, Price S, Edvardsen T, Cosyns B, Neskovic AN, Dulgheru R, et al. The use of echocardiography in acute cardiovascular care: recommendations of the European Association of Cardiovascular Imaging and the Acute Cardiovascular Care Association. Eur Heart J Cardiovasc Imaging. 2015 Feb;16(2):119–46.

8 Saugel B, Cecconi M, Wagner JY, Reuter DA. Noninvasive continuous cardiac output monitoring in perioperative and intensive care medicine. Br J Anaesth. 2015 Apr;114(4):562–75.

9 Vincent JL, Pelosi P, Pearse R, Payen D, Perel A, Hoeft A, et al. Perioperative cardiovascular monitoring of high-risk patients: a consensus of 12. Crit Care. 2015 May;19(1):224.

10 Monnet X, Marik PE, Teboul JL. Prediction of fluid responsiveness: an update. Ann Intensive Care. 2016 Dec; 6(1):111.

11 Yang X, Du B. Does pulse pressure variation predict fluid responsiveness in critically ill patients? A systematic review and meta-analysis. Crit Care. 2014 Nov;18(6):650.

12 Marik PE, Cavallazzi R, Vasu T, Hirani A. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. Crit Care Med. 2009 Sep;37(9):2642–7.

13 Zhang Z, Lu B, Sheng X, Jin N. Accuracy of stroke volume variation in predicting fluid responsiveness: a systematic review and meta-analysis. J Anesth. 2011 Dec;25(6):904–16.

14 Hasanin A, Mukhtar A, Nassar H. Perfusion indices revisited. J Intensive Care. 2017 Mar;5(1):24.

15 Mayer K, Trzeciak S, Puri NK. Assessment of the adequacy of oxygen delivery. Curr Opin Crit Care. 2016 Oct; 22(5):437–43.

16 Molitoris BA, Wang E, Sandoval RM, Sheridan E, Strickland JS. Quantifying glomerular filtration rates: kidney function analysis method and apparatus. Recent Pat Biomark. 2012;2(3):209–18.

17 Wang E, Meier DJ, Sandoval RM, Von Hendy-Willson VE, Pressler BM, Bunch RM, et al. A portable fiberoptic ratiometric fluorescence analyzer provides rapid point-of-care determination of glomerular filtration rate in large animals. Kidney Int. 2012 Jan;81(1):112–7.

18 Yu W, Sandoval RM, Molitoris BA. Rapid determination of renal filtration function using an optical ratiometric imaging approach. Am J Physiol Renal Physiol. 2007 Jun;292(6):F1873–80.

19 Rizk DV, Sandoval RM, Chacana T, Reilly ES, Seegmiller JS, Denoia E, et al. A Novel Method for Rapid Bedside Determination of Measured Glomerular Filtration Rate in Healthy and Chronic Kidney Disease Subjects. J Am Soc Nephrol. Forthcoming 2018.

20 Nadler SB, Hidalgo JH, Bloch T. Prediction of blood volume in normal human adults. Surgery. 1962 Feb;51(2): 224–32.

KARGER

21   Carry BJ, Katz SD. Subclinical Volume Overload Across the Spectrum of Heart Failure: Lessons From Total Blood Volume Measurements. J Card Fail. 2018 Jul;24(7):425–7.

22   Lote C. Principles of Renal Physiology. 4th ed. Berlin: Springer; 2000. https://doi.org/10.1007/978-94-011-4086-7.

23   Androne AS, Hryniewicz K, Hudaihed A, Mancini D, Lamanca J, Katz SD. Relation of unrecognized hypervolemia in chronic heart failure to clinical status, hemodynamics, and patient outcomes. Am J Cardiol. 2004 May;93(10):1254–9.

24   Katz SD. Blood volume assessment in the diagnosis and treatment of chronic heart failure. Am J Med Sci. 2007 Jul;334(1):47–52.

25   Strobeck JE, Feldschuh J, Miller WL. Heart Failure Outcomes With Volume-Guided Management. JACC Heart Fail. 2018 Nov;6(11):940–8.

26   Tang WH, Telukuntla KS, Mayuga KA. Can Blood Volume Analysis-Guided Acute Heart Failure Therapy Improve Clinical Outcomes? JACC Heart Fail. 2018 Nov;6(11):949–50.

27   Yu M, Pei K, Moran S, Edwards KD, Domingo S, Steinemann S, et al. A prospective randomized trial using blood volume analysis in addition to pulmonary artery catheter, compared with pulmonary artery catheter alone, to guide shock resuscitation in critically ill surgical patients. Shock. 2011 Mar;35(3):220–8.

28   Takanishi DM Jr, Biuk-Aghai EN, Yu M, Lurie F, Yamauchi H, Ho HC, et al. The availability of circulating blood volume values alters fluid management in critically ill surgical patients. Am J Surg. 2009 Feb;197(2):232–7.

29   Recommended methods for measurement of red-cell and plasma volume: International Committee for Standardization in Haematology. J Nucl Med. 1980 Aug;21(8):793–800.

30   International Committee for Standardization in Haematology Expert Panel on Blood Cell Sizing. Recommendation for reference method for determination by centrifugation of packed cell volume of blood. J Clin Pathol. 1980 Jan;33(1):1–2.

31   Ertl AC, Diedrich A, Raj SR. Techniques used for the determination of blood volume. Am J Med Sci. 2007 Jul;334(1):32–6.

32   Manzone TA, Dam HQ, Soltis D, Sagar VV. Blood volume analysis: a new technique and new clinical interest reinvigorate a classic study. J Nucl Med Technol. 2007;35(2):55-63; quiz 77, 9.

33   Feldschuh J, Katz S. The importance of correct norms in blood volume measurement. Am J Med Sci. 2007 Jul;334(1):41–6.

34   Richter W. Effect of substitution on reactivity of B 512 dextran fractions with anti-B 512 dextran in heterologous passive cutaneous anaphylaxis. Int Arch Allergy Appl Immunol. 1975;48(4):505–12.

35   Pearson TC, Guthrie DL, Simpson J, Chinn S, Barosi G, Ferrant A, et al. Interpretation of measured red cell mass and plasma volume in adults: Expert Panel on Radionuclides of the International Council for Standardization in Haematology. Br J Haematol. 1995 Apr;89(4):748–56.

36   Bednarczyk JM, Fridfinnson JA, Kumar A, Blanchard L, Rabbani R, Bell D, et al. Incorporating Dynamic Assessment of Fluid Responsiveness Into Goal-Directed Therapy: A Systematic Review and Meta-Analysis. Crit Care Med. 2017 Sep;45(9):1538–45.

37   Bentzer P, Griesdale DE, Boyd J, MacLean K, Sirounis D, Ayas NT. Will This Hemodynamically Unstable Patient Respond to a Bolus of Intravenous Fluids? JAMA. 2016 Sep;316(12):1298–309.

38   Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med. 2017 Mar;43(3):304–77.

39   Adams KF Jr, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, et al.; ADHERE Scientific Advisory Committee and Investigators. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J. 2005 Feb;149(2):209–16.

40   Ronco C, Di Lullo L. Cardiorenal Syndrome in Western Countries: Epidemiology, Diagnosis and Management Approaches. Kidney Dis (Basel). 2017 Jan;2(4):151–63.