

# Ultrasound evaluation of the inferior vena cava collapsibility index in congestive heart failure patients treated with intravenous diuretics: new insights about its relationship with renal function: An observational study

*Intravenöz diüretikle tedavi edilen doğuştan kalp yetmezliği olan hastalarda inferiyör vena cava kollapsibilite indeksinin ultrason değerlendirmesi: Böbrek fonksiyonu ile olan ilişkisi hakkında yeni anlayışlar-gözlemsel bir çalışma*

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## ABSTRACT

**Objective:** In chronic heart failure (CHF), collapsibility index of the inferior vena cava (IVCCI) is used for noninvasive ultrasonographic appraisal of central venous pressure, but it also may be related both to estimated glomerular filtration rate (eGFR) and renal outcome.

**Methods:** On the basis of retrospective observational cohort study, we analyzed 49 patients with right or biventricular CHF in III NYHA class, who had undergone intravenous intensive treatment with furosemide. Aggravated renal dysfunction (ARD) was defined by serum creatinine (Cr) increase of  $\geq 0.3$  mg/dL from baseline. IVCCI was categorized in three layers (IVCCI  $\leq 15\%$ , IVCCI 16-40% and IVCCI  $>40\%$ ). The predictors of ARD were searched for as well as any relation between basal IVCCI and both eGFR at admission and occurrence of ARD.

**Results:** Overall, 15 cases and 34 controls were compared. Multivariate predictors of ARD were a lower basal eGFR (HR: 0.82 CI: 0.72-0.94  $p=0.0045$ ) and intravenous furosemide daily mean dose  $>80$  mg (HR: 48.62 CI: 1.62-3841.5  $p=0.0430$ ). A very significant positive correlation was found between IVCCI at admission  $\leq 15\%$  and basal eGFR ( $r=0.96$   $p<0.0001$ ), while a negative correlation with eGFR was detected in the IVCCI highest ( $>40\%$ ) range ( $r=-0.696$   $p=0.0013$ ). Furthermore, the category with basal IVCCI  $>40\%$  showed a higher rate of ARD compared to that with basal IVCCI 16-40% ( $p<0.05$ ).

**Conclusion:** On the basis of the demonstrated u-shaped relationship between IVCCI and eGFR both the stratum with the highest ( $>40\%$ ) and the one with the lowest ( $\leq 15\%$ ) basal IVCCI may be associated with increased risk of ARD. (*Anadolu Kardiyol Derg* 2012; 12: 391-400)

**Key words:** Heart failure, ultrasound monitoring, inferior vena cava, diuretics, acute kidney injury, regression analysis

## ÖZET

**Amaç:** Kronik kalp yetersizliğinde (KKY), inferiyör vena kavanın kollapsibilite indeksi santral venöz basıncın noninvaziv ultrasonografik değerlendirilmesi için kullanılır, fakat bu hem tahmini glomerüler filtrasyon hızı (tGFH) ve hem de böbreğin akibeti ile ilgili olabilir.

**Yöntemler:** Retrospektif gözlemsel Kohort çalışmanın temelinde, furosemidle intravenöz yoğun tedaviye alınan NYHA 3 sınıfta sağ ya da biventriküler KKY'li 49 hastayı analiz ettik. Böbrek fonksiyon bozukluğunun kötüleşmesi (ABFB) başlangıcından itibaren  $\geq 0.3$  mg/dL serum kreatinin (SK) yükselmesi olarak tanımlandı. Inferiyör vena cava kollapsibilite indeksi (İVKÇİ) üç katta kategorize edildi (IVCCI  $\leq 15\%$ , IVCCI %16-40 ve IVCCI  $>40\%$ ). ABFB öngördürücüleri yataışta ve ABFB meydana geldiğinde, bazal İVKÇİ ve hem tGFH arasında herhangi bir ilişki varlığı araştırıldı.

**Bulgular:** On beş olgu ve 34 kontrol karşılaştırıldı. ABFB'nin multivaryant öngördürücüleri düşük bazal tGFH (HR: 0.82 CI: 0.72-0.94  $p=0.0045$ ) ve günlük intravenöz furosemid ortalama  $>80$  mg dozudur (HR: 48.62 CI: 1.62-3841.5  $p=0.0430$ ). İVKÇİ'nin en yüksek ( $>40\%$ ) oranında ( $r=-0.696$

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$p=0.0013$ ) tGFH ile negatif korelasyon bulunmuşken, yatışta İVKÇİ  $\leq\%15$  ve bazal tGFH ( $r=0.96$   $p<0.0001$ ) arasında çok önemli bir pozitif korelasyon bulundu. Ayrıca, İVKÇİ'li  $>\%40$  kategorisi bazal İVKÇİ  $\%16-40$  ile karşılaştırılmasında en yüksek ABFB gösterdi ( $p<0.05$ ).

**Sonuç:** İVKÇİ ve tGFH arasında U-şeklinde bir ilişki gösterildiğinden bazal en düşük ( $\leq\%15$ ) ile en yüksek ( $>\%40$ ) İVKÇİ katmanı ABFB riskinde yükselme ile alakalı olabilir. (*Anadolu Kardiyol Derg 2012; 12: 391-400*)

**Anahtar kelimeler:** Kalp yetersizliği, ultrason görüntüleme, inferiyör vena kava, diüretik, akut böbrek hasarı, regresyon analizi

## Introduction

It is known that absence of physical or radiographic signs of congestion (jugular venous distension, peripheral edema, rales, radiological signs of pulmonary congestion etc) does not ensure normal values of neither right atrial nor pulmonary capillary wedge pressure (PCWP) and may lead to inaccurate diagnosis and inadequate therapy (1). On the other hand, although pulmonary artery catheters (PACs) have been used to guide therapy in multiple settings, several studies have raised concerns that PACs may lead to increased mortality in hospitalized patients (2, 3). Thus, considerable attention has recently been focused on specific noninvasive diagnostic strategies able to yield more careful assessment and grading of the congestion (4) without entailing the harmful side effects inherent in PACs, especially infective or traumatic catheter-related complications (2). Besides, invasive monitoring of central venous pressure (CVP), while an accepted gold standard, might be seen as too 'aggressive' for many of the elderly subjects commonly presenting with heart failure syndromes (5).

Thus, in some institutions several surrogate techniques have been introduced in the recent years aimed to noninvasively evaluate the volume status without employing the central venous catheters (6-10). Among these, ultrasound assessment of inferior vena cava collapsibility index has recently gained ground as a dynamic parameter able to monitor volume unloading during hemodialysis (11-13) -to better recognize patients at risk of intra-dialytic hypotension- as well as during intensive intravenous (IV) diuretic administration in chronic heart failure (CHF) patients with extreme fluid retention (14, 15) - for more careful assessment of hemodynamic congestion so as to avoid intravascular dangerous volume depletion, related to overzealous or too prolonged IV unloading diuretic therapy.

Our search was prompted by observations of other authors, who broached the issue of the repercussions upon renal hemodynamics caused by systemic venous congestion measured by thermoludion catheter (16) or by forearm compression sonography (9). Among them, Damman et al. (16) investigated the cardiorenal interactions in a retrospective manner across the entire spectrum of cardiovascular diseases with or without overt picture of heart failure, while Uthoff et al. (9) explored the impact of the hemodynamic congestion on renal function in the setting of the acute decompensated heart failure requiring hospitalization. Besides, our search was influenced also by interesting insights ensued from some studies by Mullens et al. (17, 18) which would suggest that the presence of venous congestion may be the strongest hemodynamic determinant for the development of worsened renal function. Overall these studies would corroborate the concept that impact of systemic and renal

venous congestion overcomes even that exerted by low cardiac output as regards the genesis and/or aggravation of renal dysfunction in CHF patients.

## Objectives

The main objective of our study was to search for an association between some clinical and hematochemical variables and development of renal impairment during diuretic intensive therapy. Furthermore, the relations between IVCCI - used as a surrogate index of central venous pressure - and some measures of renal function -particularly estimated glomerular filtration rate (eGFR) - measured at admission and at the end of IV diuretic treatment were explored to verify whether any IVCCI basal values may have the property of reliably predicting aggravated renal dysfunction sometimes occurring after intensive diuretic treatment; moreover, it was investigated whether a biphasic relation might be detected between eGFR and IVCCI, consistent with that already demonstrated between eGFR and central venous pressure when invasively measured (16).

## Methods

### Study design

An observational retrospective study was conducted by enrolling patients from two Centers (C.U. E. d'A. and N.R. S.M.d P). For enrollment, the following inclusion criteria were applied: evidence of right or bi-ventricular chronic heart failure in III NYHA class; resistance to oral diuretic therapy, as proven by recent occurrence of oliguria (urine output  $<20$  mL per hour during 12 hours at least) despite oral furosemide therapy at dose  $\geq 125$  mg per day; ascertained administration-during day hospital or ordinary hospital stay-of one course or more of IV unloading intensive therapy with loop diuretic (furosemide in all cases).

Exclusion criteria were as following: patients with pacemaker or treated by cardiac resynchronization therapy;- myocardial infarction within 30 days, arrhythmia-related syncope, major cardiac surgery, unstable angina, uncontrollable hypertension, cor pulmonale, advanced pulmonary disease, major neurologic disease or cerebrovascular disease, suspected renal artery stenosis, advanced renal failure (i.e. serum creatinine  $>2.5$  mg/dL at baseline), other life-threatening diseases.

Retrospective chart review was performed to analyze characteristics of all eligible patients. For each patient, date of birth, sex, race, and weight and height were noted. Comorbid conditions, including diabetes, dyslipidemia, nicotine abuse, hypertension, ischemic heart disease, preexisting diabetic nephropathy or other chronic renal disease in addition to medical treatment at the time of unloading IV diuretic treatment also were extracted for each patient.

### IVCCI assessment

IVCCI was defined as the difference between maximum expiratory diameter and minimum inspiratory diameter divided by the maximum expiratory diameter. IVCCI measurements were obtained 1 to 2 cm below the level of the hepatic veins, using a two-dimensional echographic sector (Vivid 7 ultrasound machine, GE Healthcare Systems, Milwaukee, WI). The IVC diameter recording was made on M-mode approximately 3 cm from the right atrium with patients in a 45° recumbent position. Subcostal or subxiphoid windows were used based on available views, patient habitus, presence of external impediments (e.g., drains, surgical dressings), and preference of the sonologist.

According to the customary approach applied at the two Centers for refractory oliguria treated with IV loop diuretics in CHF patients, repeated measurements of IVCCI were performed (at least two examinations in each patient) in order to obtain a noninvasive assessment of the right atrial pressure. Although a first IVCCI measurement was acquired at admission in all of the patients recruited in the study, it is to be remarked that diuretic therapy was usually not driven by IVCCI measurements through the first 48 hours of the course of IV loop diuretic infusions, the diuretic dosing being rather determined on the basis of the signs and symptoms of clinical congestion (presence and grade of peripheral edema, fall in urine output, jugular venous distension, pulmonary rales, orthopnea) as well as of the systolic blood pressure profile.

For non-invasive appraisal of systemic venous pressure in our clinical scenario (patients with right only or biventricular chronic heart failure undergoing IV loop diuretic infusions), it was stated that echographic criteria should have complied with those previously adopted by other authors (19-21). Therefore, IVCCI was stratified by 3 layers: IVCCI  $\leq 15\%$ , IVCCI 16-40% and IVCCI  $>40\%$ . Among these, first and third layers were assumed to indicate the presence of systemic venous congestive status or of likely intravascular depletion, respectively; whereas an IVCCI in the intermediate range (0.16 to 0.40) was considered not helpful in discriminating CVP.

### Renal function assessment

Estimated glomerular filtration rate obtained with four-variable modification of diet in renal disease (MDRD) equation (22) was adopted for evaluating renal function. In accordance with several previous studies (23, 24), we defined new onset or aggravated renal dysfunction (ARD) as an increase in serum creatinine of  $\geq 0.3$  mg/dL (26.5 mmol/L) at any time point during hospitalization.

### Study protocol

The study protocol established that every patient, who was demonstrated to have accomplished the course of therapy with IV furosemide for the prescribed time duration (6-8 days), was to be enrolled as a case, if he had exhibited a rise in serum creatinine of  $\geq 0.3$  mg/dL compared to basal value (measured before the onset of IV diuretic therapy), so as to fulfill the definition of ARD as previously stated. As a general rule applied during diuretic unloading therapy at each of two Centers, the IV furose-

mid doses for every patient were considered appropriate and were maintained in case they were shown to be associated with a daily urine output of 2 liters at least; whereas, in case this target were not attained, the IV furosemide dosage was enhanced since the second day of therapy by daily graded increases until the agreed target (24-hour diuresis of 2 liters or more) had been gained. Moreover, during the IV furosemide treatment, the daily dietary water intake was not more than 1000 mL, with a sodium intake of 120 mEq daily (normosodic diet) in all patients; likewise, in the absence of remarkable and/or harmful side-effects, the IV intensive furosemide therapy was maintained from 6 to a maximum of 8 days, according to the protocol usually adopted by the two Centers.

The occurrence of ARD across the three IVCCI clusters was investigated. Besides, both individual eGFR and IVCCI values at admission were acquired in order to compare the distribution of the respective eGFR values across the entire spectrum of the possible basal IVCCI values as found in our CHF patients at admission (before starting unloading diuretic therapy). Mean IV diuretic dosage was calculated in both patients with and without ARD development in order to detect any possible significant difference. Moreover, individual values of systolic blood pressure (SBP) measured at admission were grouped by IVCCI basal values, for identifying any possible inter-range difference. According to the customary approach applied at the two Centers, in every patient undergoing unloading diuretic therapy two IVCCI measurements at least were achieved, including a first determination at admission and a subsequent measurement made at the end of the planned course of IV diuretic infusions (namely after 6-8 days of daily administration of IV furosemide). On this basis, in every patient, a comparison was made between the basal and the last IVCCI measurement, the latter being usually made at the end of the IV treatment. Similarly, in every patient, basal and post-treatment eGFR values were compared.

### Statistical analysis

We used the Statistical Package of Social Sciences (SPSS Version 14, SPSS Inc, Chicago, IL, USA) and Excel® (Microsoft Office Excel® release 2007, Microsoft Inc, Seattle, USA) to perform the analysis. Baseline demographics, physical examination, and laboratory findings were compared between patients with and without ARD. The Chi-square test and the unpaired t-test were respectively applied for comparison of dichotomous or continuous variables. Correlations among continuous variables were assessed by the Spearman rank correlation coefficient drawn from the linear regression analysis. One-way analysis of variance (ANOVA) and Student-Newman-Keuls test for all pairwise comparisons were used for multiple comparisons. D'Agostino Pearson test for normal distribution was used. Paired samples t-test was used for comparing basal data to the post-treatment data. For comparison of data with asymmetric distribution, Wilcoxon sign ranked test for paired samples and Kruskal-Wallis test were also employed. For identifying the predictors of occurrence of ARD during the planned course of IV furosemide infusion, univariate and multivariate Cox propor-

tional hazards regression analyses were used. The following variables were entered into the model as exposure variables:

- History of repeated previous episodes (two at least) of oliguria (less than 20 ml of urine per hour over 12 hours at least)
- e-GFR (ml/min /1.73 m<sup>2</sup>)-continuous variable
- basal e-GFR >60 mL/ min /1.73 m<sup>2</sup>
- Dose of IV furosemide >80 mg per day
- IVCCI >40%
- IVCCI ≤15%
- Left ventricular ejection fraction (LVEF)-continuous variable
- SBP - continuous variable
- SBP <105 mmHg

Besides, the Kaplan- Meier curve was set up to compare the respective risks of developing renal worsening across the three layers of IVCCI values.

Furthermore, receiver operating characteristic (ROC) curve was built for the dose of IV loop diuretic (furosemide) and the prediction of the aggravated renal dysfunction, i.e. in order to ascertain the dose provided with the most reliable cut-off value for predicting the occurrence of renal worsening at the end of the prescribed course of IV diuretic infusion.

## Results

### Baseline characteristics of the patients

A total of 49 patients were retrospectively enrolled, by drawing them from the charts of all CHF patients admitted for day-hospital stay between June 2009 and June 2010 at the two Centers. This group consisted of 26 women and 23 men, with mean age of 76.5±9.5 years. Their basal clinical and hematochemical characteristics are depicted in Table 1. By comparing patients with and without WRF, a significant difference was found relative to the following exposure variables: *basal* estimated GFR (p<0.0001), mean dose of oral furosemide prior to IV loop diuretic therapy (p=0.0030), mean dose of IV furosemide during intensive unloading therapy (mg/day) (p=0.0001), intravenous furosemide mean dose >80 mg per day (p<0.0001) and SBP (mmHg) (p=0.0216).

### Risk factors for worsening renal function (WRF)

Table 2 shows the results of the multivariate Cox proportional hazards regression analysis including 9 covariates entered in the model. Multivariate predictors of WRF were a lower basal eGFR (HR 0.8242 95% CI: 0.72 to 0.94 p=0.0045) and use of IV furosemide mean dose >80 mg per day (HR 48.62 95%CI: 1.62 to 3841.5 p=0.0430). Low (≤105 mm Hg) blood systolic pressure was significantly associated with worsened renal function at univariate analysis but this association was lost at multivariate analysis after adjustment for several covariates, a trend only (p=0.0556) towards more frequent renal worsening being observed in patients with lower systolic blood pressure. LVEF was not associated with ARD neither in univariate, nor in multivariate Cox regression analysis.

**Table 1. Baseline hematochemical and clinical characteristics of patients who developed a new or aggravated renal dysfunction with iv diuretics and in controls who did not**

Worsening renal failure	Yes (n=15)	No (n=34)	*p
Age, years	78±6	75±8	0.2009
Male, n	8	15	0.7755
Mean duration of symptoms of heart failure, months	8±3	7±3	0.2877
LVEF, %	46±6	47±7	0.6333
<b>History of co-morbidities</b>			
Diabetes, n	4	7	0.9215
Dyslipidemia, n	3	6	0.8382
Nicotine abuse, n	7	15	0.8837
Hypertension, n	12	24	0.7273
Ischemic heart disease, n	11	26	0.9005
History of preexisting diabetic nephropathy or other chronic renal disease, n	3	5	0.687
<b>Preexistent pharmacotherapy</b>			
Digitalis, n	3	7	0.7358
Beta-blockers, n (carvedilol or bisoprolol)	11	26	0.47
ACE-inhibitor/angiotensin receptor blocker, n	12	27	0.7358
Aldosterone receptor antagonist, n	12	31	0.353301
Nitrate, n	4	9	0.7363
Mean dose of oral furosemide prior to iv loop diuretic therapy, mg/day	166±24	150±12	0.0030
Mean dose of iv furosemide during intensive unloading therapy, mg/day	94±21	67±21	0.0001
Intravenous furosemide mean dose >80 mg per day, n	14	6	<0.0001
<b>Clinical parameters</b>			
SBP, mmHg	102±10	111±17	0.0216
Heart rate, beats/min	91±25	83±20	0.2384
Body mass index, kg/m <sup>2</sup>	27.8±5.6	26.9±5.8	0.6154
<b>Laboratory and echographic variables</b>			
IVCCI, %	34.8±20.8	25.27±14	0.0657
Hemoglobin, mg/dL	13±1.7	12.5±2.2	0.4384
Estimated GFR mL/min/1.73 m <sup>2</sup>	44±12	65±12	<0.0001
Urea, mg/dL	95±15	80±12	0.0005
Serum Na <sup>+</sup> , mmol/L	138.2±4.7	139.2±5.2	0.5265
Serum K <sup>+</sup> , mmol/L	4.3±0.5	4.6±0.8	0.1876
BNP, pg/mL	1310±216	1344±245	0.6453
Data are presented as mean±SD and numbers			
*Chi-square and unpaired t-test			
ACE - angiotensin converting enzyme, BNP - brain natriuretic peptide, GFR - glomerular filtration rate, IVCCI - inferior vena cava collapsibility index, LVEF - left ventricular ejection fraction, SBP - systolic blood pressure			

### Curvilinear relationship between IVCCI and eGFR

IVCCI at presentation was  $28.18 \pm 16.75\%$ . It was not significantly associated with eGFR ( $r=0.0086$   $p=0.9529$ ), when taken as a continuous variable.

However, when stratified by 3 IVCCI layers (IVCCI  $\leq 15\%$ , IVCCI 16-40% and IVCCI  $>40\%$ ), the relation with eGFR was modified as follows: -eGFR showed a sharp increase when IVCCI increased from 1 to 15%; this finding resulted in a strong correlation of  $r=0.9645$ ,  $p<0.0001$  in patients ( $n=12$ ) with IVCCI  $\leq 15\%$ ;

-no significant correlation was seen in the range IVCCI 16-40% (19 patients;  $r=-0.0760$ ,  $p=0.7570$ );

- a significant negative correlation was found in the IVCCI upper range (IVCCI  $>40\%$ , 18 patients  $r=-0.6960$   $p=0.0013$ ).

Of note, a curvilinear regression was detected by relating the eGFR values to the IVCCI values as drawn from the entire sample of 47 subjects. In this manner, a U-shaped curve, parabola-like, was built, as represented in Fig. 1. The pattern was judged to be consistent with the hypothesis of a bimodal expression of the relation linking the IVCCI to the glomerular filtration. Actually, estimated GFR showed an evident increase when IVCCI increased from 1 to 15% ( $r=0.9645$ ,  $p<0.0001$ ). However, in IVCCI values  $>40\%$ , a steep decrease in eGFR was observed with increasing IVCCI values ( $r=-0.6960$ ,  $p=0.0013$ ). Instead, on a continuous scale, eGFR was not significantly associated with IVCCI ( $r=0.0086$ ,  $p=0.9529$ ).

### Distribution of renal worsening among the IVCCI layers

Figure 2 shows the distribution (%) of the cases (15 on the whole) of aggravated renal dysfunction among the 3 IVCCI layers during intensive loop diuretic treatment. It documents that in the IVCCI  $>40\%$  group, occurrence of ARD was higher than in IVCCI=16-40% group (10 cases in the former compared to one case in the latter):  $p$  (Kruskal -Wallis)  $<0.05$ . Kaplan- Meier curve was

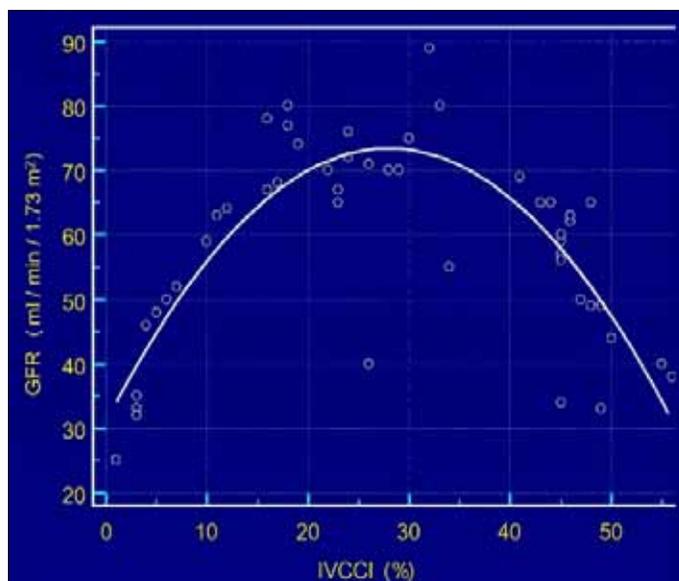


Figure 1. Distribution of IVCCI and curvilinear relationship between IVCCI and eGFR in the study population. The curvilinear model had the following individual polynomial components:  $Y = a + b_1X + b_2X^2$   
IVCCI - inferior vena collapsibility index, eGFR - estimated glomerular filtration rate

built to compare the respective risks of developing WRF across the three classes of IVCCI values. The category with IVCCI  $>40\%$  was demonstrated to have the highest risk of WRF-  $p=0.0089$ - (see Fig. 3). Indeed, this reflects univariate Cox proportional-hazards regression (Table 2a) which would indicate IVCCI  $>40\%$  as a predictor of post-infusional ARD (HR 3.8805; 95% CI: 1.3316 - 11.3087  $p=0.013$ ); but subsequent multivariable analysis failed to confirm a significant predictive role of this parameter (Table 2b).

### Relation between basal IVCCI layer and eGFR

The values of eGFR at admission were also compared. As represented in Figure 4, in IVCCI=16-40% range, eGFR mean value was significantly higher compared to IVCCI  $>40\%$  and IVCCI  $\leq 15\%$  ranges:  $70.7 \pm 13$  ml/min versus  $53.2 \pm 4$  and  $47.5 \pm 13.6$  ml/min/ $1.73$  m<sup>2</sup>;  $p$  (Student-Newman-Keuls test for all pairwise comparisons) $<0.05$  for both.

### Relation between basal IVCCI layer and SBP

The relation between systolic blood pressure (SBP) and IVCCI at admission was also investigated. In the IVCCI=16-40% patients, SBP was significantly higher than in those with IVCCI  $>40\%$ - ( $115.6 \pm 19$  versus  $99.83 \pm 11$  mm Hg;  $p$  (ANOVA)=0.007). Nevertheless, on the basis of the linear regression analysis a well definite relationship between IVCCI and systolic blood pressure could not be demonstrated (correlation coefficient  $r=-0.3078$ ;  $p=0.2140$ ).

### Comparison of basal and post- treatment eGFR and IVCCI values

Mean eGFR measured after completing the course of unloading diuretic treatment was significantly lower compared to basal mean value-determined before the onset of diuretic IV infusions:  $54.4 \pm 18$  versus  $58.6 \pm 15.1$  mL/min/ $1.73$  m<sup>2</sup>;  $p$  (paired

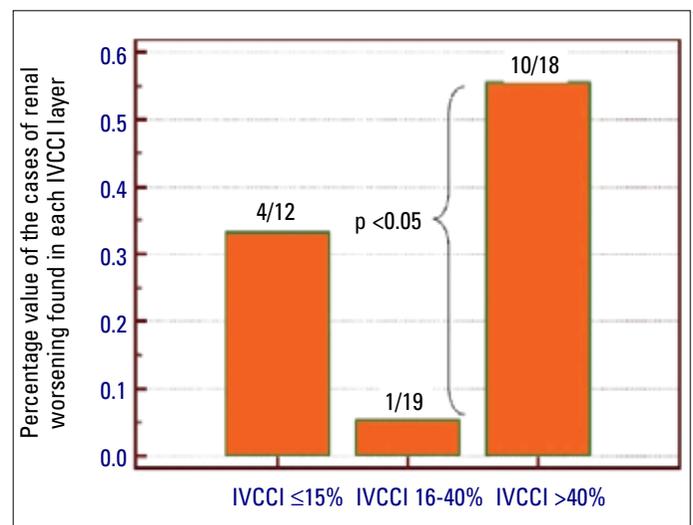
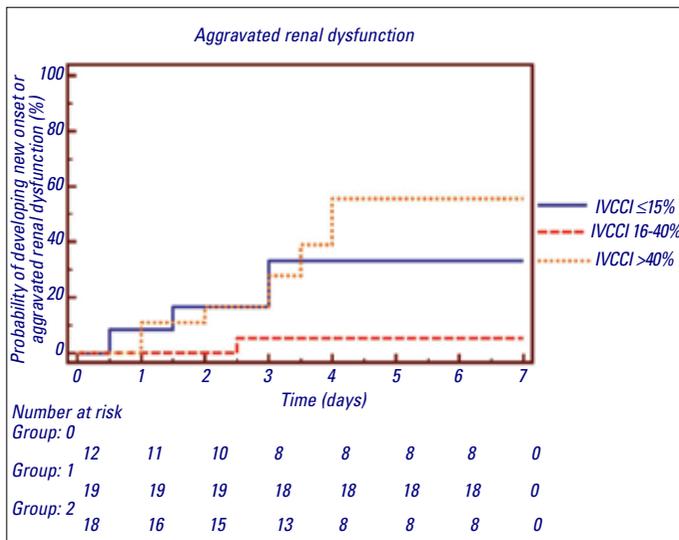


Figure 2. Renal worsening during intensive diuretic therapy (15 cases found in the case-record of 49 pts undergone unloading diuretic therapy). In the IVCCI  $>40\%$  group, occurrence of ARD was higher than in IVCCI=16-40% group - 10 cases in the former compared to one case in the latter:  $p$  (Kruskal Wallis test)  $<0.05$

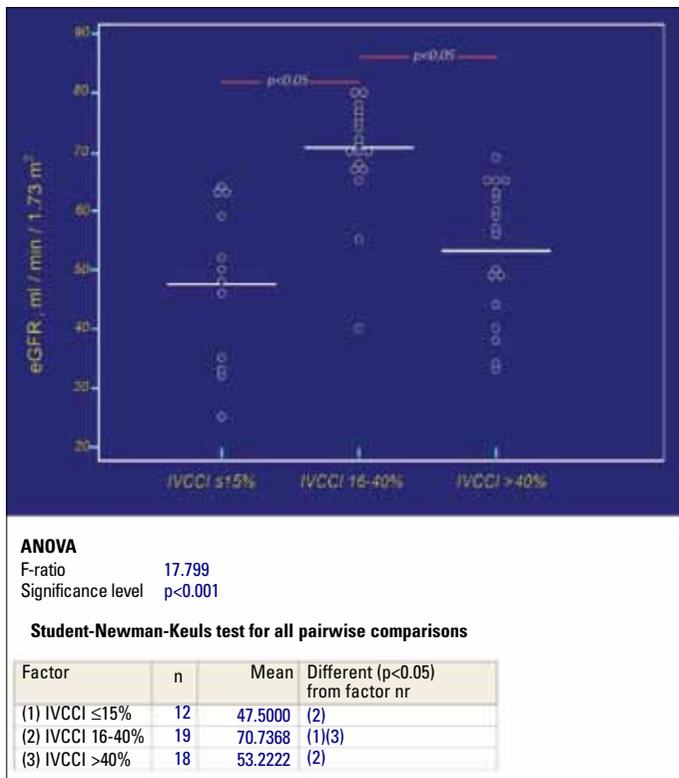
ARD - aggravated renal dysfunction, IVCCI - inferior vena collapsibility index



**Figure 3.** Kaplan-Meier curve is used to compare the respective risks of developing aggravated renal dysfunction (ARD) across the three classes of IVCCI values. The category with IVCCI >40% is shown to have the highest risk of ARD

p (Log rank test)=0.0089

IVCCI - inferior vena cava collapsibility index



**Figure 4.** Individual values of eGFR (ml/min/1.73m<sup>2</sup>) within each IVCCI range. In the IVCCI=16-40% range, eGFR was significantly higher than in the other two intervals

eGFR - estimated glomerular filtration rate, IVCCI - inferior vena cava collapsibility index

samples t-test)= 0.0007. On the contrary, no difference was detected by comparing IVCCI basal and post-infusion mean values: 28.2±16.7 versus 30±12%; p (paired samples t-test)= 0.2260. In this regard, more information could be provided by

**Table 2.** Univariate and multivariate clinical and hematochemical predictors of worsening renal function in CHF patients who underwent unloading treatment with IV diuretics: COX proportional regression analysis

COX univariate analysis					
Covariate	β	SE	p	HR	95% CI of HR
GFR continuous	-0.09971	0.02213	<0.0001	0.9051	0.8669 to 0.9450
GFR >60 mL/min	-1.9031	0.6471	0.0033	0.1491	0.0422 to 0.5266
Oliguria	1.6587	0.5487	0.0025	5.2527	1.8019 to 15.3118
LVEF	-0.01098	0.03673	0.7649	0.9891	0.9207 to 1.0625
SBP ≤105	1.5788	0.6462	0.0146	4.8489	1.3753 to 17.0954
SBP continuous	-0.02410	0.01425	0.0908	0.9762	0.9494 to 1.0037
IVCCI >40%	1.3560	0.5485	0.0134	3.8805	1.3316 to 11.3087
IVCCI ≤15%	0.2230	0.5842	0.7027	1.2498	0.4000 to 3.9047
Furosemide >80mg	3.3870	1.0375	0.0011	29.5764	3.9116 to 223.6354
COX multivariate analysis					
Covariate	β	SE	p	HR	95% CI of HR
GFR_continuous	-0.1934	0.06800	0.0045	0.8242	0.7218 to 0.9410
GFR >60 mL/min	1.2845	1.7301	0.4578	3.6130	0.1238 to 105.4511
SBP ≤105 mmHg	0.6888	1.1257	0.5406	1.9914	0.2217 to 17.8862
SBP continuous	-0.1038	0.05422	0.0556	0.9014	0.8110 to 1.0019
Oliguria	-0.2251	0.6857	0.7428	0.7985	0.2097 to 3.0408
LVEF	-0.06788	0.05648	0.2294	0.9344	0.8369 to 1.0432
IVCCI >40%	-0.3172	2.0364	0.8762	0.7282	0.0137 to 38.6221
IVCCI ≤15%	-1.9420	2.1834	0.3738	0.1434	0.0020 to 10.1311
Furosemide >80mg	3.8840	2.2409	0.0430	48.6170	1.6153 to 3841.565

β - regression coefficient, BNP - brain natriuretic peptide, CI - confidence interval, GFR - glomerular filtration rate, HR - hazard ratio, IVCCI - inferior vena cava collapsibility index, LVEF - left ventricular ejection fraction, SBP - systolic blood pressure, SE - standard error of β

separate analysis of the eGFR and IVCCI values in each of the three IVCCI layers, measured before and after IV diuretic treatment; in this manner, it would be evident that the unloading treatment produces an increased IVC wall motility in the low (≤15%) and intermediate (16-40%) IVCCI categories, while it is strikingly associated with post-infusion reduction in respiratory collapsibility when the analysis is restricted to patients with the highest basal venous collapse values (>40%). The net consequence of this pattern is the lack of significant changes, diuretic treatment -related, in IVCCI mean value, i.e. when considering the IVCCI data population overall.

**Intravenous diuretic dose and renal function**

Receiver operating characteristic (ROC) curve was also set up for the daily dose of intravenous furosemide and the prediction of acute renal dysfunction. ROC curve analysis indicated that 80 mg per day was the most reliable cut-off value for predicting aggravated renal dysfunction, this dose being provided with a sensitivity of 93.3%, specificity of 82.35%, positive predictive value of 70% and negative predictive value of 96.6% (Fig. 5). Besides, the IV diuretic mean dose was significantly higher (Fig. 6) in patients with eGFR ≤40 mL/min/1.73 m<sup>2</sup>, i.e. the patients with the lowest

eGFR values, compared to both the cluster with eGFR ranging from 41 to 59 mL/min/1.73 m<sup>2</sup> and the one with eGFR relatively preserved (i.e. eGFR ≥60 mL/min/1.73 m<sup>2</sup>).

## Discussion

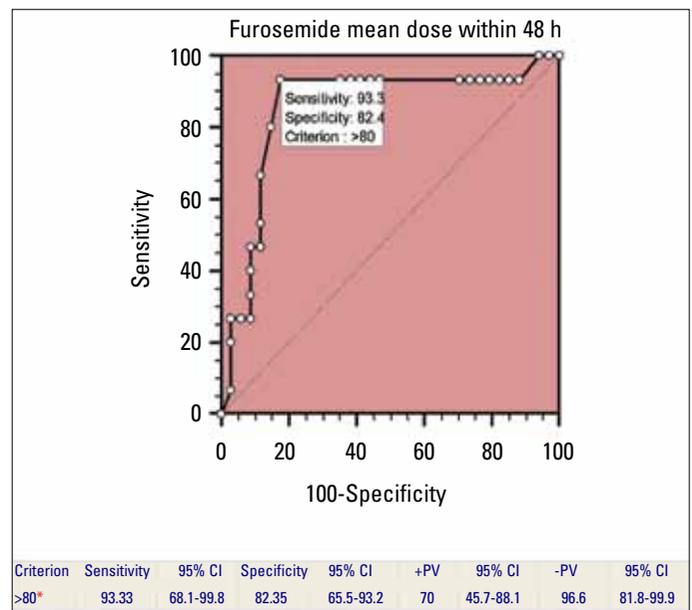
In our study, a basally reduced renal function and an IV furosemide mean dose >80 mg per day predicted the occurrence of renal worsening at the end of a course of unloading IV diuretic infusion. Furthermore, a curvilinear relationship was detected between basal IVCCI and eGFR values in the study population. Besides, among the three IVCCI layers arbitrarily defined (≤15%, 16-40% and >40%), the one with the IVCCI highest value exhibited increased probability of developing WRF compared to the other two clusters.

### IVCCI as a tool for monitoring of intravascular volume in CHF patients: pathophysiologic basis and literature data

Ultrasound assessment of IVC respiratory fluctuations has been proposed from a long while as a possible diagnostic tool for achieving noninvasive reliable estimation of volume status and/or right atrial pressure in CHF patients (25). In effect, in spontaneously breathing subjects, intrathoracic pressure decreases during inspiration, thereby increasing venous return and inducing collapse of the IVC. Inversely, during expiration, venous return decreases, so causing an increase in the diameter of the IVC (25). High right atrial pressures dilate the IVC and impair this normal IVC collapsibility. Therefore, small, collapsible IVCs as visualized by echocardiography represent low right atrial pressures, whereas large, non-collapsible IVCs reflect high right atrial pressures. In the presence of marked volume overload, the respiratory cycle leads to minimal change in diameter of IVC, regardless of its absolute diameter (26). This depends on the peculiar non-linear pressure-diameter relationship of the IVC so that, above a threshold pressure (i.e., CVP >20 mmHg), no further increase in IVC diameter can be observed (27, 28). This has been confirmed by a recent study in which an IVCCI ≤15% was highly sensitive and specific for the diagnosis of acute decompensated heart failure, whereas the absolute diameter of the IVC in itself was non-diagnostic (28). Moreover, Stawicki et al. (21) noticed that IVCCI appears to correlate best with CVP in the setting of low (<0.20) and high (>0.60) collapsibility ranges. Of note, Blehar et al. (28) noted in turn that receiver operating characteristic (ROC) curve analysis showed good diagnostic accuracy for the diagnosis of right CHF (area under curve=0.96; sensitivity =92% ; specificity: 84%) when a cutoff of ≤15% variation in IVC diameter was adopted.

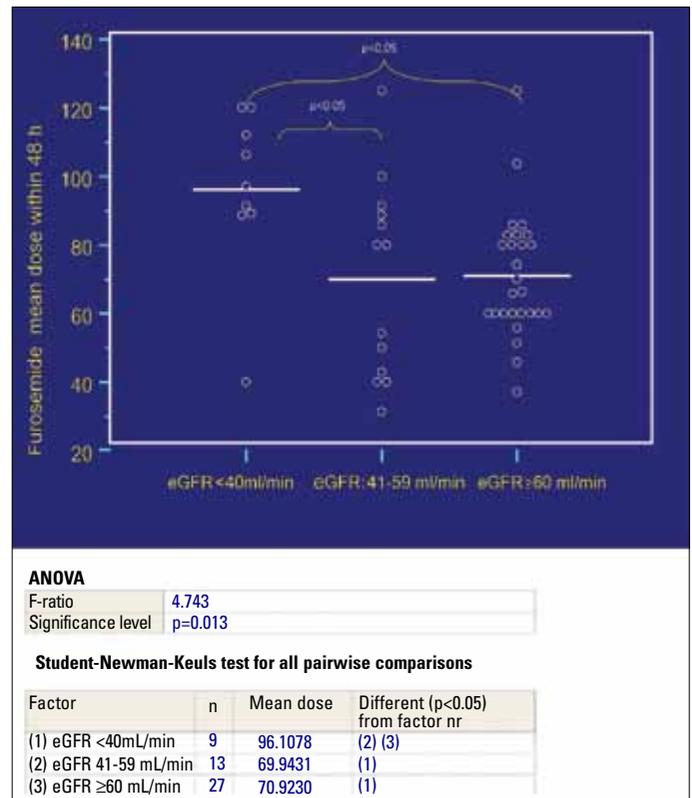
### Inferior vena cava respiratory collapsibility and severity of basal renal dysfunction: possible relationship

In our study we decided to categorize IVCCI values by grouping them in three classes: ≤15%, 16-40% and >40%. These IVCCI cut-off values were determined arbitrarily, with the intention of selecting groups with low, intermediate and high collapsibility indices.



**Figure 5. Receiver operating characteristic (ROC) curve analysis for the intravenous furosemide and the prediction of acute renal dysfunction. ROC curve analysis indicated that 80 mg per day was the most reliable cut-off value for predicting aggravated renal dysfunction, this dose being provided with a sensitivity of 93.3%, specificity of 82.35%, positive predictive value of 70% and negative predictive value of 96.6%**

AUC - area under curve, CI - confidence interval, +PV - positive predictive value, -PV - negative predictive value



**Figure 6. Comparison of daily mean dosage of IV furosemide across the three clusters of eGFR in our study. The patients belonging to the cluster with most impaired eGFR got the highest mean dose of IV furosemide during a 6-8 day course of intravenous loop diuretic treatment**

eGFR - estimated glomerular filtration rate

While planning the study, we considered that the three IVCCI ranges of our study may reflect also different levels of renal function, so as to reproduce the differences found by comparing eGFRs associated with different levels of invasively measured PVC in another previous study (16). Actually, in the IVCCI=16-40% range, eGFR was significantly higher than in the other two intervals (Fig. 4). This finding being interpreted as a favorable repercussion upon renal hemodynamics by relatively preserved central venous pressure- as proven by patient location in IVCCI intermediate range, that is the segment of all IVCCI possible values showing the closest association (21) with the physiologic CVP range: 0 - 6 mm Hg or 0-8.22 cm H<sub>2</sub>O.

In addition, in IVCCI  $\leq$ 15% (12 patients), eGFR at admission showed a sharp increase when IVCCI increased from 1 to 15%. Instead, in IVCCI >40% range eGFR at admission was shown to inversely relate to inferior vena cava respiratory collapsibility.

#### **Oral diuretic chronically high dosages and their reflexes on volume status**

It could appear striking that as many as 18 among 49 patients on the whole (36.7%) were found to exhibit a pattern of relatively high IVC collapsibility (IVCCI >40%). However, this might arise from the peculiar composition of case record: actually all of the recruited patients had diuretic resistance, as proven by failure of oral furosemide (125 mg per day or more) to retrieve normal urine output and relieve clinical signs of hydrosaline retention; thus, several patients might have developed marked decrease in effective circulating volume caused by prolonged administration of high oral doses of loop diuretic as well as by chronic heart failure per se (29).

#### **Intravenous diuretic dosing and its reflexes on renal hemodynamics and function**

Of note, the mean dosage of IV furosemide within 48 h after admission was significantly higher in patients who subsequently developed ARD. Furthermore, furosemide dosages did not significantly differ by comparing patients across the different IVCCI ranges ( $\leq$ 15, 16-40 and >40%) during the first 2 days after admission, as individual doses within the first 48 hours were exclusively established on the basis of clinical signs and symptoms. Moreover, it should be underscored that in the recent ESCAPE trial (3), renal function was worsened in the group where treatment was guided only by expert clinical assessment, whereas it did not worsen when treatment was directed at lowering invasively measured right atrial pressure. Since clinical examination has been shown to be an unreliable tool to assess CVP (30), thus in our case record, 'inappropriate' administration, e.g. intravenous diuretics to patients with high IVCCI -low CVP, may occur and might worsen renal function. It remains to be established whether a different approach, IVCCI serial determination -based, would have prevented or reduced the occurrence of ARD diuretic-related by more careful tailoring of diuretic therapy within the first 48 hours. On the basis of our results, it is also reasonable to speculate that renal impairment in CHF patients may be frequently related to subclinical condi-

tion of subtle intravascular volume depletion, whose relatively high (>40%) IVC collapsibility is a reliable marker (31). Actually in our study (Fig. 2) in the highest IVCCI range (>40%) a higher rate of renal worsening was found compared to IVCCI 16-40% range- 10 cases in the former versus one case in the latter ( $p=0.0044$ )-.

#### **Markers of WRF: comparison of the results with literature data**

In our study, according to the multivariate Cox proportional hazards analysis, the variables found associated with increased risk of renal impairment during a course of intravenous infusions with furosemide (duration: 6-8 days) were a lower eGFR at admission and a mean dose of intravenous furosemide >80 mg per day. Moreover, a trend towards more frequent occurrence of renal worsening was also found in patients with lower systolic blood pressure ( $p=0.0556$ ).

These results are in keeping with those of other previous studies, which have emphasized the potential for nephrotoxic and cardiotoxic effects inherent in intensive IV diuretic regimens, especially when administered to patients already involved by signs of renal insufficiency (14, 15).

Several other considerations and inferences could be derived from our study.

Firstly, it is remarkable that IV diuretic mean dose was significantly higher in patients with basal eGFR  $\leq$ 40 ml/min, i.e. the patients with the lowest eGFR values. This finding also is in line with the data of other studies (32-35), where a higher dose of diuretics is usually given to CHF patients who have a more compromised renal function at baseline. According to several Authors (36), in these patients a higher diuretic dosing may be appropriate because the delivery of furosemide to the renal tubules positively depends on renal function in CHF patients and considering that a creatinine clearance of 15 mL/min parallels a tubular secretion of furosemide five- to ten-fold lower than that in normal subjects (37). However, in our opinion, this approach, i.e. a higher daily diuretic dose to be administered to CHF patients with basal renal insufficiency, entails also a higher risk of harmful effects on renal hemodynamics, should IV diuretics be erroneously administered despite a undiagnosed condition of arterial underfilling or volume depletion.

Moreover, no correlation was found between urine output and risk of renal worsening during diuretic therapy.

#### **IVCCI during diuretic unloading therapy: a "window" with the potential for exploring the diuretic - related changes in central venous pressure?**

In our study, mean eGFR was demonstrated to decrease after unloading diuretic treatment, while IVCCI mean value was found unchanged. Such a discrepancy suggests that development of sustained detrimental drop in eGFR pointing to persistent impairment in filtration function may originate from unloading diuretic therapy and may be detectable at the end of the course of IV infusions. Instead, the effect on vena cava collapsibility index is masked by a biphasic reaction which usually occurs in patients who were basally involved by a condition of

likely marked vascular underfilling, as proven by relatively high values of IVCCI (>40%) at admission. In this category we hypothesize that inappropriate, erroneous or excessive diuretic administration is able to provoke deleterious loss of preload in some CHF patients, so as to elicit further worsening of cardiac pump performance due to insufficient ventricular diastolic filling and relaxation. This maladaptive myocardial response to the intravascular volume subtraction could be responsible for dramatic fall in stroke volume and rapid reproduction of blood stagnation in pulmonary veins and caval venous bed; thus, even though intravascular depletion, diuretic related, initially brings relief to the heart by attenuating or suppressing cardiopulmonary symptoms of congestion, it may quickly translate into a condition of venous slow-down due to pump ineffectiveness and harmful low output state. In this setting, a shift toward a condition of systemic venous hypertension can be signaled by rapid relapse of relatively poor motility of the wall of the inferior vena cava. So, paradoxically, in our sample of CHF patients, the IVCCI increased when diuretics were administered to patients with hemodynamic congestion (basal IVCCI  $\leq 15\%$ ), but it was not further augmented in patients with vascular underfilling or frank depletion (IVCCI >40% at baseline).

#### Diuretic-related WRF: interpretative theories

It is reasonable to assume that in some CHF patients (e.g. those with myocardial function critically dependent on adequate cardiac preload) a critical reduction in cardiac output may occur due to cardiac preload exaggerated fall, so as to rapidly reproduce the previous pattern of slowing down in venous return at level of inferior vena cava. Meanwhile, glomerular filtration is simultaneously damaged by a peculiar type of unfavorable vasomotor kidney reaction (14, 15) consisting in intense vasoconstriction of the afferent arteriolar bed, as elicited by macula densa chemoceptor apparatus highly sensitive to increased delivery of sodium to tubules due to diuretic administration. According to several authors (31, 38) this "vasomotor nephropathy" could be minimized using slow mechanical fluid removal by ultrafiltration. In this manner, we could avoid engaging renal excretory pathways and their inherent tubulo-glomerular feedback, whose role in nephrotoxic effect of diuretics in syndromes with reduced effective circulating volume (CHF, cirrhosis of the liver) has been focused in other studies (38, 39).

#### Study limitations

Observational retrospective design and reduced sample size are the most relevant limitations of our study. Moreover, no invasive data are available on central venous pressure, renal blood flow and true GFR in these patients. IVC measurements were not done by a single operator, so inter-observer bias cannot be excluded. In addition, we cannot exclude that tricuspid regurgitation affected IVC diameter, although this influence is less pronounced on IVCCI. Finally, due to sometimes insufficient documentation, the evaluation of relations between eGFR and IVCCI might have not enough considered preexisting undiag-

nosed or subclinical nephropathies responsible for chronic renal damage, which in these cases shouldn't be attributed to chronic heart failure per se.

#### Conclusion

In right or biventricular CHF patients undergone unloading IV furosemide therapy, high diuretic dosages and preexisting decreased renal function predicted new onset or aggravated renal dysfunction. Occurrence of renal impairment was significantly higher in patients with marked IVC respiratory collapsibility (IVCCI >40%) at admission compared to those with basal IVCCI located in the intermediate range (16-40%). Moreover, in the latter eGFR at admission was higher compared to both the cluster with basal IVCCI >40% and the one with basal IVCCI  $\leq 15\%$  ( $p < 0.05$  for both).

It remains to be established whether a different approach, IVCCI serial determination -based, would have prevented or decreased the occurrence of WRF diuretic-related by more careful tailoring of diuretic therapy within the first 48 hours. Further well designed randomized clinical trials are warranted in the future, aimed to test IVC respiratory fluctuations as a critical index in edematous CHF patients for supporting expert clinical examination and achieving more accurate volume status assessment targeted on more appropriate therapy.

**Conflict of interest:** None declared.

**Authorship contributions.** Concept - R.D.V.; Design - R.D.V.; Supervision - R.D.V.; Resource - R.D.V., A.C., C.A., C.C., G.A., E.L., F.A.; Material - C.A., A.C., R.D.V., C.C., G.A., C.S.; Data collection&/or Processing - R.D.V., A.C.; Analysis &/or interpretation - R.D.V., A.C.; Literature search - R.D.V., F.A., E.L.; Writing - R.D.V., A.C.; Critical review - R.D.V., A.C., C.S., C.A., C.C., G.A., E.L., F.A.

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