

## Original Research

# Continuous Infusion of Furosemide Combined with Low-Dose Dopamine Compared to Intermittent Boluses in Acutely Decompensated Heart Failure is Less Nephrotoxic and Carries a Lower Readmission at Thirty Days

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**Introduction:** Furosemide is a potent loop diuretic that is widely used in the management of heart failure. Several reports have suggested that continuous intravenous administration of loop diuretics may be superior to intermittent administration. In addition the effect of low-dose dopamine to improve renal perfusion might be of benefit to this patient cohort.

**Methods:** We retrospectively evaluated 116 consecutive cardiac care unit patients, who were admitted with acute decompensated heart failure and were divided into two equal groups according to diuretic protocol. Group A patients received furosemide by continuous infusion combined with low-dose dopamine infusion. Group B patients received bolus therapy of intravenous furosemide. The effect on renal function and readmission rate was recorded.

**Results:** Among 116 patients (60% males, average age 71, range 46-96 years) 41% had ischemic cardiomyopathy, NYHA functional Class was  $3.5 \pm 0.5$  and average EF was  $21\% \pm 7\%$ . On admission, patients in Group A had creatinine (Cr)  $2.3 \pm 0.2$  mg/dL, blood urea nitrogen (BUN)  $49.2 \pm 25$  mg/100 ml and median b-type natriuretic peptide (BNP) 1340 pg/mL, compared to group B patients with Cr  $1.7 \pm 1.2$  mg/dL, BUN  $32 \pm 22$  mg/100 ml and median BNP 1106 pg/mL. The average furosemide dose in group A was  $7.9 \pm 3.5$  mg/hr compared to  $7.6 \pm 2.7$  mg/hr for group B ( $p=NS$ ). At the end of the study, patients in group A had lower Cr  $1.8 \pm 0.9$  ( $p=0.0001$ ), lower BUN  $43.6 \pm 22.9$  ( $p=NS$ ), an increase in estimated glomerular filtration rate  $57.4 \pm 27.4$ , a shorter hospital stay ( $p=0.015$ ) and lower readmission rates at 30 days ( $p=0.0003$ ).

**Conclusions:** Continuous infusion of furosemide in addition to low-dose dopamine is safe, effective and less nephrotoxic than intermittent boluses in patients admitted with acute decompensated heart failure and portends a shorter hospital stay and lower readmission rates at 30 days.

**A**cute decompensated heart failure (ADHF) constitutes one of the major causes for hospitalization in the United States, representing an important epidemiological and economic burden for the healthcare system with an annual

age-adjusted incidence of 29 cases per 1000 person-years.<sup>1</sup> In 2008, the estimated total cost of heart failure (HF) in the United States was \$37.2 billion.<sup>2</sup> An important objective in HF management is to optimize therapy for stabilization and a shorter hos-

pital stay with lower rates of complications and readmission using evidence-based pharmacological and device therapy.<sup>3,4</sup> The presence of volume overload with a positive fluid balance constitutes an important prognostic factor that is usually associated with poor outcomes.<sup>5-8</sup> Thus, intravenous diuretic administration has become the mainstay of therapy for the volume overload associated with ADHF.

A vast amount of evidence is available showing the clear benefit of diuretics, especially loop diuretics such as furosemide, in the setting of ADHF accompanied by volume overload. In patients with pulmonary edema, fluid restriction and diuretic therapy has been shown to promote a faster resolution of symptoms and clinical improvement, and has also been associated with a decrease in intubation time and intensive care unit (ICU) stay.<sup>9,10</sup> For volume resolution, different protocols of diuretic therapy in HF have been used, with the two main strategies including continuous infusions and boluses. Results have demonstrated that both therapies are effective when trying to achieve a negative fluid balance in patients with volume overload, with some data indicating superiority of furosemide infusion over boluses; however, the differences in safety and side effects between the two protocols have been described to be minimal and statistically insignificant. Nevertheless, to date it is not known which is the preferred protocol in terms of renal function preservation or whether the use of low doses of dopamine could carry an additional beneficial effect. Therefore, the aim of this study was to evaluate retrospectively the effect of continuous infusion of furosemide in addition to low doses of dopamine infusion in terms of safety and effectiveness, compared to the standardized use of intermittent furosemide boluses, as defined by nephrotoxicity and 30-day readmission rates.

## Methods

### *Patient population*

One hundred fifty patients consecutively admitted with the diagnosis of ADHF with volume overload to the cardiac care unit (CCU) were retrospectively screened for this study. Their medical records were reviewed for data, including initial labs (b-type natriuretic peptide, potassium, and complete blood cell count), initial electrocardiogram, the reason for their screening in the CCU, admission weight, as well as daily weights, follow-up labs and detailed urine out-

put. Of the initial total, 116 patients had complete records and were included in the final analysis. For this analysis, patients were divided into two groups according to the diuretic protocol utilized by the admitting team. Group A included patients receiving furosemide by continuous infusion combined with low-dose dopamine infusion. Group B included patients who received bolus therapy of intravenous furosemide. Exclusion criteria were thrombocytopenia; allergy or contraindications to the use of dopamine and/or furosemide; terminal conditions, such as cancer with poor prognosis of survival at 1 year; severe electrolyte abnormalities, such as potassium >5.5 mmol/L or <2.5 mmol/L, or sodium on admission >150 mmol/L or <120 mmol/L; severe hypotension; the need for the use of vasopressors or positive inotropic agents other than low doses of dopamine; and the use of other diuretics in combination to furosemide.

### *Diuretic protocols*

The selection of the diuretic protocol employed for each patient was based on the clinical practice in our CCU and depended on the severity of the disease and the degree of renal function as determined by creatinine levels. Patients in group A were often sicker and had on average higher creatinine levels on admission; they received furosemide infusion starting at 0.2-0.4 mg/kg/hr in combination with dopamine infusion at doses of 1-2 µg/kg/min. Furosemide doses were titrated according to the clinical response to diuresis and to signs of volume overload. Patients requiring higher doses of dopamine for blood pressure support were excluded from the study.

Group B patients were treated with boluses of IV furosemide based on the novel heart failure pathway utilized at our institution;<sup>11</sup> boluses were titrated based on diuresis and clinical response. In those individuals taking oral furosemide in the outpatient settings, the conversion from the oral to the intravenous dose used the algorithm of our pathway.<sup>12</sup>

### *Endpoints*

The co-primary endpoints in our study included nephrotoxicity, determined by the rise in blood urea nitrogen and creatinine levels, and readmission rates for heart failure decompensation at a 30-day follow up. Secondary endpoints were the effect on delta weight change, length of hospital stay, and all cause mortality at 90 days.

### Statistical analysis

Statistical analysis was performed using a standard statistical software package (SPSS for Windows, version 17; SPSS; Chicago, IL, USA). Continuous variables are expressed as mean  $\pm$  SD. Normally distributed variables were compared by ANOVA. Categorical variables were expressed as a percentage of the total sample and compared using the chi-square test or Fisher's exact test, as appropriate. The baseline predictors of the primary outcome were selected using stepwise variable selection. Comparison of the two study groups with respect to the change from baseline to secondary endpoints was performed using Wilcoxon rank sum tests. The log-rank test was used to compare the two study groups statistically with respect to the time until the first occurrence of either component of the secondary composite endpoint. Relative risks were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs) and were calculated using the Cox proportional hazards model.<sup>13</sup> A p-value  $<0.05$  was considered statistically significant.

### Results

Demographic parameters are shown in Table 1. Among the 116 patients, 60% were males; the mean age was 71 years. Forty-one percent of the patients had ischemic cardiomyopathy. The New York Heart Association (NYHA) functional class was  $3.5 \pm 0.5$ , and the average ejection fraction was  $21 \pm 7\%$ . Laboratory values on admission from all patients included an average admission sodium of  $139 \pm 5.2$  mEq/L, potassium  $4.7 \pm 0.8$  mEq/L, blood urea nitrogen (BUN)  $44 \pm 27$  mg/dL, creatinine  $1.9 \pm 1$  mg/dL and b-type natriuretic peptide (BNP)  $1589 \pm 1160$  pg/mL. The two treatment groups each included 58 patients; baseline variables are reported in Table 1. When compared to group B, group A had worse kidney function (creatinine on admission  $2.3 \pm 0.2$  vs.  $1.7 \pm 1.2$  mg/dL,  $p=0.072$ ), and significantly lower estimated glomerular filtration rate (eGFR) ( $40 \pm 15$  vs.  $63 \pm 33$  mL/min per  $1.73$  m<sup>2</sup>,  $p=0.00001$ ), with higher admission potassium ( $4.7 \pm 0.8$  vs.  $4.3 \pm 0.5$  mmol/L,  $p=0.004$ ). Group A also had elevated troponin ( $1.9$

**Table 1.** Patient demographics and baseline findings.

Parameter	Group A (n=58)	Group B (n=58)	p
Demographics:			
Age, yrs	71 $\pm$ 15	71 $\pm$ 13	0.953
Sex, men (%)	39 (67)	29 (50)	0.062
Hypertension (%)	54 (93)	49 (85)	0.115
Diabetes mellitus (%)	33 (57)	27 (46)	0.227
Smoking (%)	27 (46)	35 (60)	0.523
Body mass index, kg/m <sup>2</sup>	30 $\pm$ 8	27 $\pm$ 7	0.068
Hyperlipidemia (%)	14 (24)	23 (40)	0.073
Heart failure indices:			
NYHA Class	3.2 $\pm$ 0.5	3.1 $\pm$ 0.5	0.853
LVEF, %	19.5 $\pm$ 7	22.5 $\pm$ 7	0.551
Ischemic etiology (%)	29 (50)	18 (31)	0.293
Median BNP, pg/mL	1340	1106	0.193
Excess weight on admission, kg	5.2 $\pm$ 3.2	6.3 $\pm$ 3.8	0.107
Kidney function:			
Creatinine, mg/dL	2.3 $\pm$ 0.2	1.7 $\pm$ 1.2	0.072
Blood urea nitrogen, mg/dL	49 $\pm$ 25	32 $\pm$ 22	0.0002
eGFR, mL/min/1.73 m <sup>2</sup>	40 $\pm$ 15	63 $\pm$ 33	0.00001
Admission laboratory values:			
Sodium, mmol/L	139 $\pm$ 6	139 $\pm$ 4	0.951
Potassium, mmol/L	4.7 $\pm$ 0.8	4.3 $\pm$ 0.5	0.004
Chloride, mmol/L	103 $\pm$ 6	104 $\pm$ 5	0.836
Troponin, ng/mL	1.9 $\pm$ 5.6	0.08 $\pm$ 0.1	0.026
Creatine kinase (CK-MB), ng/mL	15 $\pm$ 18	3.8 $\pm$ 2.7	0.002
Home medications:			
Hydrochlorothiazide (%)	1 (1.7)	3 (5.2)	0.313
Furosemide (%)	19 (32)	14 (24)	0.307
Spirinolactone (%)	4 (7)	0 (0)	0.044

BNP – B-type natriuretic peptide; eGFR – estimated glomerular filtration rate; LVEF – left ventricular ejection fraction; NYHA – New York Heart Association.

$\pm 5.6$  vs.  $0.08 \pm 0.1$ ,  $p=0.026$ ) and higher creatine kinase-MB, ( $15 \pm 18$  vs.  $3.8 \pm 2.7$  ng/mL,  $p=0.002$ ). The average furosemide dose in-group A was  $7.9 \pm 3.5$  mg/hr compared to  $7.6 \pm 2.7$  mg/hr for group B ( $p=0.77$ ). Patients in group B received higher initial doses of furosemide than group A ( $71 \pm 13$  mg vs.  $42 \pm 28$  mg,  $p=0.035$ ). Hourly urinary output was significantly higher in group A than group B ( $147 \pm 72$  ml/hr vs.  $91 \pm 27$  ml/hr,  $p<0.00001$ ).

### Primary endpoints

Patients in group A had lower creatinine ( $p=0.006$ ), lower BNP levels ( $p<0.015$ ) and higher eGFR ( $p<0.0006$ ) when compared to patients in group B (Table 2). The delta change in creatinine values from admission to discharge was more favorable for group A ( $-0.45$ ) when compared to group B ( $+0.87$ ,  $p=0.00001$ ), as was the delta change in BUN for group A ( $-5.66$ ) vs. group B ( $+10.31$ ,  $p=0.0001$ ) and the delta change in eGFR ( $+17.4$  for group A and  $-21.8$  for group B,  $p<0.00001$ ; Figure 1). These results are particularly significant considering that patients in group A had evidence of worse renal function on admission. Importantly, group A patients had a greater delta change in admission weight when compared to group B ( $7.3$  kg versus  $4.0$  kg,  $p<0.0001$ ). Group A patients also had significantly lower readmission rates when followed for a 30-day period ( $17.2\%$  vs.  $48.3\%$ ,  $p=0.0003$ ; Figure 2), with HR 0.45 (95% CI: 0.22 to 0.90,  $p=0.023$ ) as shown by a Kaplan-Meier curve (Figure 3).

### Secondary endpoints

Forty-three (37%) patients reached the secondary outcome of combined readmission at 30 days and mortality at 90 days, with the majority occurring in group B (48% versus 25%,  $p=0.012$ ; HR 0.50 95% CI: 0.27 to 0.94,  $p=0.031$ ; Figure 4). Not surprisingly, patients treated with furosemide and dopamine infusion had a shorter duration of hospital stay ( $6.8$  vs.  $9.41$  days,  $p=0.0001$ ). There was a trend toward lower all-cause mortality at the end of the follow-up period ( $6\%$  vs.  $14\%$ ,  $p=0.08$ ). Based on a logistic regression module for predictors of endpoints, diabetics (HR 2.2, 95% CI: 0.89 to 5.35,  $p=0.08$ ) and group B patients who had diuretics boluses (HR 4.7, 95% CI: 1.87 to 11.71,  $p=0.0009$ ) were more likely to have worse outcomes.

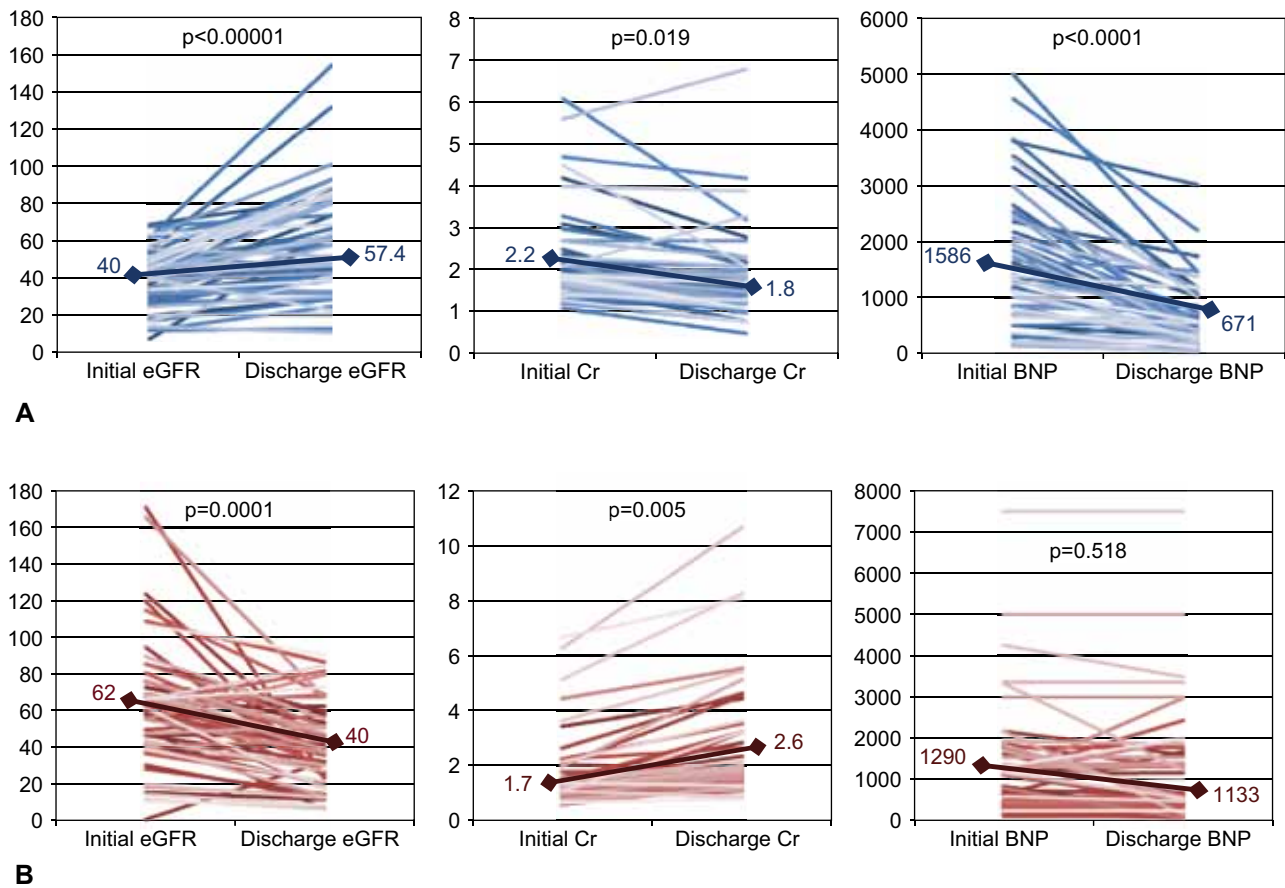
### Discussion

Heart failure incidence has increased in the last decades, with an estimated 5.3 million patients in the United States suffering from this condition and about half a million patients newly diagnosed every year.<sup>2</sup> Similarly, ADHF is one of the leading causes for hospitalization in the USA and contributes in great percentage to the economic burden of public health.<sup>14,15</sup> During acute decompensation, these patients present with volume overload requiring diuretic therapy routinely at high doses. Thus, the prompt identification of patients admitted with a positive fluid balance who will benefit from diuretic administration is a key point

**Table 2.** Treatment plans. Differences between groups regarding the effects on the predetermined endpoints before hospital discharge.

	Group A (n=58)	Group B (n=58)	p
Treatment plans:			
Initial furosemide bolus (mg, iv)	42.4 $\pm$ 28.1	70.6 $\pm$ 13.3	0.035
Mean furosemide dose (mg/hr)	7.9 $\pm$ 3.5	7.6 $\pm$ 2.7	0.776
Mean dopamine dose ( $\mu$ g/kg/hr)	2.48 $\pm$ 0.89	0	0.00001
Concomitant medical therapy:			
Hydrochlorothiazide (%)	14 (24)	6 (10)	0.061
Spirolactone (%)	5 (7)	7 (12)	0.546
Hydralazine (%)	6 (10)	8 (14)	0.572
Effects of treatment:			
Average urine output, ml/hr	147 $\pm$ 72	91 $\pm$ 27	0.00001
Creatinine, mg/dl	1.8 $\pm$ 0.9	2.6 $\pm$ 1.9	0.006
Blood urea nitrogen, mg/dl	44 $\pm$ 23	43 $\pm$ 24	0.796
eGFR, ml/min/1.73 m <sup>2</sup>	57 $\pm$ 27	41 $\pm$ 23	0.0006
BNP, pg/ml	670 $\pm$ 565	1133 $\pm$ 1307	0.012
Delta change in weight, kg	7.3 $\pm$ 4.0	4.0 $\pm$ 4.5	0.0001

Abbreviations as in Table 1.



**Figure 1.** Observed effects on estimated glomerular filtration rate (eGFR), creatinine (Cr), and b-type natriuretic peptide (BNP) in relation to the treatment plans studied. A. Continuous furosemide infusion in addition to low dose dopamine. B. Furosemide boluses.

of management and might influence outcomes, as we have previously demonstrated.<sup>16</sup> The beneficial effect of diuretic therapy in HF is well known, especially in acute settings such as post myocardial infarction patients and patients with volume overload.<sup>17</sup> Furosemide, a loop diuretic that acts on the  $\text{Na}^+ \text{-K}^+ \text{-2Cl}^-$  co-transporter in the thick ascending limb of the loop of Henle to inhibit sodium and chloride reabsorption, exerts its major effect during acute pulmonary edema by achieving a potent diuretic action.<sup>18</sup> However, its efficacy goes beyond its renal action, as manifested by its hemodynamic effects in improving vascular congestion. Dikshit et al demonstrated that the immediate action in relieving pulmonary congestion in congestive heart failure starts by relieving ventricular filling pressures and by changing venous capacitance, even before causing changes in natriuresis or free water clearance.<sup>19</sup>

Several reports have evaluated the efficacy of a continuous infusion of intravenous furosemide versus

intermittent boluses, based on questions raised from evidence showing a wide dose-response curve of this pharmacological agent.<sup>20</sup> It has been proposed that the rate of furosemide delivery to the kidney tissue, both renal corpuscle and tubules, is a main factor influencing diuretic response. This was demonstrated in healthy individuals, in whom furosemide infusion was associated with higher total urinary volume, natriuresis and kaliuresis.<sup>21,22</sup> Dormans et al reported similar results favoring continuous infusion over boluses for treatment of severe heart failure.<sup>23</sup> Conversely, a study done in patients post cardiac surgery showed no significant pharmacodynamic differences when comparing infusion versus boluses. These data, however, came from a study that neither used a crossover design nor employed a loading dose of diuretic in order to avoid confounding factors.<sup>24</sup> Similarly, a recent paper reported no difference between the two modalities, although a higher furosemide dose requirement was found in the group of patients receiving boluses.

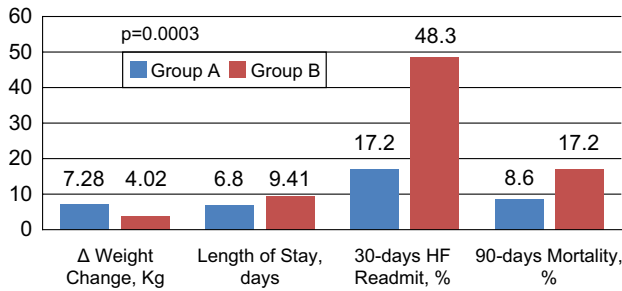


Figure 2. Primary and secondary outcomes.

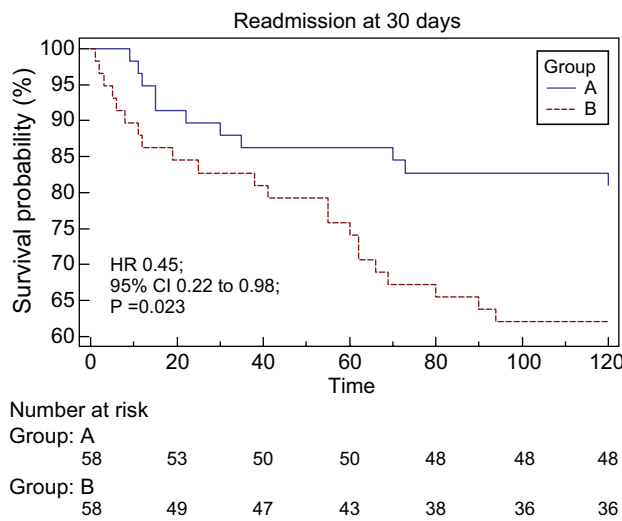


Figure 3. Kaplan-Meier curve for time to readmission as a function of treatment plans.

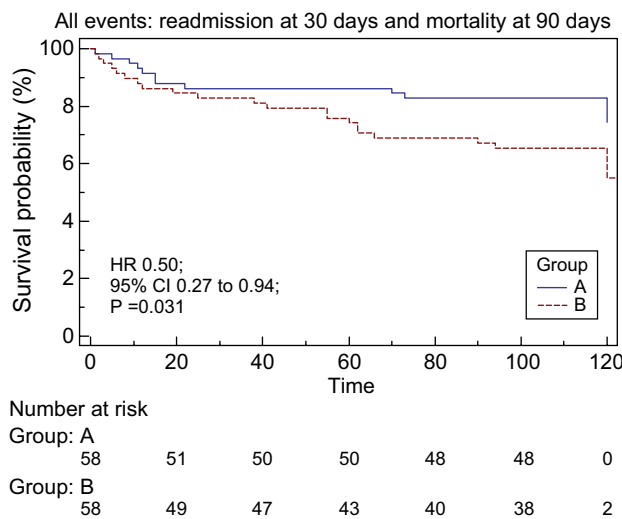


Figure 4. Kaplan-Meier survival curve for all events (readmission and mortality) as a function of treatment plans.

These authors did not report any differences in terms of mortality and changes in renal function.<sup>25</sup> Similarly, Easer et al found no difference between the diuretic effect of bolus or continuous infusion, and reported that there was no difference in the level of neurohormonal activation with either therapy, except for pro-atrial natriuretic factor, which decreased more during the initial 8 hours of bolus therapy.<sup>26</sup>

It can be argued that the type of patients included in the cohorts analyzed might explain some of the conflicting results observed between studies. For instance, some of these cohorts included patients with volume overload secondary to heart failure, renal insufficiency or both—a fact that can clearly influence the outcomes in terms of fluid balance and nephrotoxicity, as explained above. When evaluating the whole spectrum of studies performed, animal studies, for example, have reported increased diuresis and natriuresis with infusion therapy, and at the same time higher concentrations of serum creatinine when this type of therapy was employed,<sup>27</sup> while studies in healthy individuals have shown superiority of infusion over boluses.<sup>21</sup> In patients with renal failure, some authors have found that continuous intravenous infusion of furosemide had significantly better natriuretic and diuretic effects than bolus administration of the same dose of the drug in patients with advanced chronic renal insufficiency.<sup>28</sup> However, Schuller et al found that intravenous furosemide therapy by either infusion or bolus did not show any difference in terms of fluid balance goals in a cohort of patients with volume overload of cardiac and renal etiologies.<sup>29</sup>

In terms of patients with congestive heart failure, the overall evidence supports the use of continuous furosemide infusion when a gentle diuresis is desired.<sup>22,23</sup> However, few data are available in terms of side effects and complication rates, especially in those patients in which renal (low-dose) dopamine is concomitantly used with furosemide infusion in order to achieve therapeutic goals with less side effects. Therefore, we considered it important to assess whether the use of dopamine in addition to furosemide infusion had any beneficial effect in terms of nephrotoxicity and readmission rates when compared to furosemide boluses in patients with acute decompensated heart failure, as only a few studies have reported changes in creatinine levels—also with conflicting outcomes. One diuretic study found a small statistical increase in creatinine levels in the bolus group,<sup>10</sup> while another reported that furosemide infusion increases diuresis as well as creatinine levels

more than bolus therapy.<sup>30</sup> Others, however, reported no differences in creatinine levels with either modality.<sup>23,31</sup>

A major issue in patients with severe heart failure (NYHA Class III and IV) is the lack of response to furosemide, which is not uncommon in clinical practice. This is usually related to impairments in renal function, the use of concomitant medications and alterations in the metabolism of the drug secondary to altered splanchnic flow.<sup>32-36</sup> Thus, different strategies have been proposed to increase the diuretic response in patients with this resistance. For instance, Licata et al demonstrated how the concomitant use of hypertonic saline with furosemide infusion positively impacted diuresis, morbidity and mortality in patients with severe refractory heart failure.<sup>37</sup> Their findings could be explained by an increased stimulation of myocardial function and by a redistribution of the intravascular volume, as shown by other authors.<sup>38,39</sup>

Another strategy proposed is the concomitant use of inotropic agents, which are frequently used for patients in the critical care settings who need vasopressor support.<sup>40</sup> One of the agents commonly used for this purpose is dopamine. It is an endogenous catecholamine used by infusion in patients requiring hemodynamic support and acts on a variety of different receptors in the renal, splanchnic, and cardiac or vascular tissues, according to the dose employed. When infused at low rates ( $\leq 3 \mu\text{g}/\text{kg}/\text{min}$ ), it selectively stimulates receptors in the renal and splanchnic vasculature, promoting a higher blood flow in these tissues. Additionally, it provides a natriuretic effect by acting on the tubular epithelial cells independently of the changes in blood flow.<sup>41</sup> These renal effects led originally to the use of the so called "renal dose" of dopamine infusion in the past, for more than 30 years, with the purpose of preventing or reversing acute kidney injury. However, increasing evidence has led to the conclusion that the use of dopamine at these doses is actually not as effective as thought in patients with acute renal failure. The explanation is that the beneficial effects on the renal blood flow and tubular natriuresis are blunted in patients presenting with acute renal failure, especially those who are oliguric.<sup>42</sup>

In patients with heart failure, early reports showed a synergistic effect when dopamine was combined with furosemide infusion, since the positive effects of dopamine seem to be preserved in patients who do not have compromised renal function.<sup>43-45</sup> A study performed in a small number of patients showed that there were no added benefits when combining furosemide infusion

with low doses of dopamine in terms of sodium excretion or GFR. Nonetheless, this study included only 6 patients and did not report creatinine levels or readmission data and only reported GFR estimated by insulin clearance.<sup>46</sup> A recent publication by Elkayam evaluated the renal effects of intravenous dopamine on 13 patients with chronic heart failure. Renal blood flow was calculated from renal artery cross-sectional area measured with intravascular ultrasound and renal blood flow velocity-time integral measured by the intravascular Doppler technique. Cross-sectional area increased and was significantly higher than baseline; also the velocity-time integral was significantly higher than baseline at doses of 3 and 5  $\mu\text{g}/\text{kg}/\text{min}$ . Similarly, renal blood flow increased whereas renal vascular resistance decreased, resulting in an increase in cardiac output. However, the increase in renal blood flow appeared proportionately larger than corresponding increases in cardiac output, suggesting that low-dose dopamine is associated with an increase in renal blood flow in patients with heart failure, likely due to dilation of both the large conductance and small resistance renal blood vessels.<sup>47</sup>

In the present study we found that patients who were receiving continuous furosemide infusion in addition to low-dose dopamine demonstrated less nephrotoxicity (despite starting with worse renal function), a shorter hospital stay and lower readmission rates at 30 days when compared to patients receiving intermittent boluses. Our findings are similar to those reported by Cotter et al, who evaluated the combination of low doses of dopamine with oral or intravenous furosemide by continuous infusion versus intravenous infusion of furosemide alone in patients with refractory HF. They found that the treatment with furosemide infusion alone carried higher nephrotoxicity, manifested by creatinine levels and creatinine clearance – worse than the combination of dopamine and furosemide, either by infusion or oral route. It is notable that the group that received oral furosemide plus dopamine had a modest elevation in creatinine values and presented less incidence of hypokalemia, while diuretic effectiveness did not differ among the three groups.<sup>48</sup> In this study, however, readmission rates were not reported and a study arm receiving furosemide boluses was not included. As noted by Dormans,<sup>19</sup> a greater response to continuous infusion occurred with equal if not smaller quantities of diuretics excreted in the urine, so that the efficacy of loop diuretics may be equal if not greater with infusion than with bolus administration. This may be explained by less fluctuation in diuretic plasma levels in continuous

infusions, which results in a smoother, more constant, yet greater diuretic effect relative to the amount of drug excreted in the urine.

We found that those patients who received combined therapy had a shorter hospital stay, less nephrotoxicity and lower readmission rates at 30 days than those receiving only furosemide boluses. This may be multifactorial and related to achieving quicker therapeutic endpoints, as noted by Schuller et al,<sup>7</sup> with the better response to a steady urine output flow and the improvement in eGFR that are seen with the combination therapy. These findings are more striking when we take into account the fact that those patients who received dopamine and furosemide infusion seemed to be sicker than those who received bolus therapy, as revealed by the baseline levels of creatinine, BUN and BNP.

Our results suggest a synergistic effect from both medications when administered together, with a possible increase in renal perfusion and function.

### Limitations

The limitations of our study arise from the retrospective nature of our work, which precluded the use of a randomized design in which the inclusion of a third arm of study receiving both intermittent boluses and low-dose dopamine infusion could add valuable information. Similarly, we did not focus on outcomes for diuretic or natriuretic effectiveness according to each therapy modality. However, our objective was more towards the evaluation of the role of the renal dose of dopamine, which is not commonly used, in the setting of acute heart failure, and to address whether its combination with furosemide infusion has a significant impact on side effects and complications. We consider that, in order to resolve questions regarding effectiveness in these specific patients, it would be necessary to carry out a prospectively designed, double blind, randomized, two-by-two study with a similar population, including different combinations of bolus versus continuous infusion diuretic therapy, with or without renal dose dopamine therapy. Furosemide was used as the sole loop diuretic, so we cannot offer any information on the relative effectiveness of other loop diuretics.

### Conclusions

In a retrospectively designed study, we reported a lower rate of complications driven by less nephrotoxicity, shorter hospital stay and lower readmission rates at

30 days in patients receiving both low-dose dopamine and furosemide infusion when compared to intermittent administration of furosemide boluses. However, a complete evaluation of the combination of furosemide and dopamine in patients with congestive heart failure has yet to be made, especially in patients undergoing either infusion or boluses of furosemide. Our data merit further investigations with an accurate methodological design and an appropriate number of subjects, stratified by the degree of heart failure and by the presence or absence of renal dysfunction. This will be the proper way to answer specific questions in terms of effectiveness, safety and complications.

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