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Approach to decongestion therapy in patients with acute decompensated heart failure: the echocardiography guided strategy

Goal	The E/(Ea×Sa) index is an echocardiographic parameter to determine a patient's left ventricular filling pressure. This study aims to determine the safety and efficacy of the echocardiographic E/(Ea×Sa) index guided diuretic therapy compared to urine output (conventional) guided diuretic treatment.
Material and Methods	In this cross-sectional study, patients with heart failure with reduced ejection fraction (HFrEF) who were hospitalized due to acute decompensation episode were consecutively allocated in a 1:1 ratio to monitoring arms. The diuretic dose, which provided 20% reduction in the E/(Ea×Sa) index value compared to initial value, was determined as adequate dose in echocardiography guided monitoring group. The estimated glomerular filtration rate (eGFR), change in weight, NT pro-BNP level and dyspnea assessment on visual analogue scale (VAS) were analyzed at the end of the monitoring.
Results	Although the similar doses of diuretics were used in both groups, the patients with E/(Ea×Sa) index guided strategy had the substantial lower NT pro-BNP level within 72 hours after diuretic administration (2172 vs.2514 pg/mL, p= 0.036). VAS score on dyspnea assessment was significantly better in the patients with E/(Ea×Sa) index guided strategy (52 vs. 65; p= 0.04). And, in term of body weight loss (4.93 vs.5.21 kg, p= 0.87) and e-GFR (54.58±8.6 vs. 52.65±9.1 mL/min/1.73 m²p=0.74) in both groups are associated with similar outcomes. In both groups, there was no worsening renal function and electrolyte imbalance that required stopping or decreasing loop diuretic dosing.
Conclusions	The E/(Ea×Sa) index guidance might be a safe strategy for more effective diuretic response that deserves consideration for selected a subgroup of acute decomposed HFrEF patients.
Keywords	Heart failure; decongestive therapy; diuretic therapy; the combined systolic-diastolic index; left ventricular filling pressure
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Introduction

Acute decompensation episodes are the most common reason of hospital admission in patients with heart failure (HF) and a potentially life-threatening condition which predominantly requiring managing fluid overload and hemodynamic compromise [1, 2]. Herewith, volume regulation and assessment are central to management of HF and diuretic agents are the mainstays of therapy [3]. In fact, current guidelines with regard to both the mode of administration and the dosing of diuretic agents are primarily based on expert opinion [4, 5]. As a result, there is uncertainty about dosing and the optimal mode of administration. Determining the individual diuretic dose in a patient is influenced by numerous factors, including previous HF treatment, degree of volume overload and renal function. Nevertheless, more effective use of diuretics is fundamental to improve the clinical outcomes of patients with HF.

There is an increasing number of studies underway to develop more effective strategies for managing volume overload in HF [6–8]. Increased left ventricular (LV) filling pressure as an integrated result of the cardiac systolic and diastolic function causes congestive symptoms and signs regardless of the etiology of HF [9]. Remarkably, changes in congestion state with therapy usually conclude parallel changes in left-sided filling pressure. Moreover, several hemodynamic studies have determined that intravenously furosemide lowered cardiac filling pressures usually with a reduction in cardiac output over 24 hours [10, 11].

The gold standard for diagnosing congestion in HF is cardiac catheterization with direct measurement of right atrial pressure and pulmonary capillary wedge pressure. But these techniques have limitations for routine usage in clinical practice due to the invasive nature. Echocardiographic parameters can be easily used to estimate right- and left-sided filling pressures [12, 13].

In the last years, a number of research have demonstrated the prognostic value of the echocardiographic E/(Ea×Sa)

index in order to assess the LV filling pressure with a good sensitivity and specificity [14, 15]. The ability to determine the LV filling pressure makes the E/(Ea×Sa) index a candidate parameter to guide to decongestive therapy. Furthermore, physiologically this seems like an attractive approach to decongestion therapy.

Therefore, the objective of the present study establishes to the safety and efficacy of the echocardiographic E/(Ea×Sa) index guided diuretic therapy compared to urine output (conventional) guided diuretic treatment in patients with heart failure with reduced ejection fraction (HFrEF) who were hospitalized due to acute decompensation episode.

Material and Methods

Study Population

Patients with HFrEF who were acutely decompensated within the previous 24 hours (at least they had one sign or symptom of congestion including dyspnea, orthopnea, rales, ascites, pedal edema, lung congestion on chest radiography) and need for hospitalization and iv diuretic therapy were eligible for enrollment [2, 16]. HFrEF was diagnosed using European Society of Cardiology (ESC) and American College of Cardiology (ACC) guidelines [4, 5]. Alleviating signs and symptoms of fluid overload was the main reason of the IV diuretic usage. Baseline characteristics of the study population were presented in Table 1.

Exclusion criteria were:
- (1) Patients with newly arisen («de novo») acute HF;
- (2) Patients with acute coronary syndrome within the last 1 month;
- (3) Patients with hemodynamic instability (defined as need for inotropic support);
- (4) Patients with electrolyte imbalances (hyponatremia was defined as sodium level <135 mEq/L, hypokalemia – as serum potassium <3.5 mEq/L, hypernatremia – as sodium level >145 mEq/L, hyperkalemia – as serum potassium >5.1 mEq/L.);
- (5) Patients with chronic renal failure (defined as creatinine level >1.3 g/d and persisting for 3 months or more, irrespective of the cause);
- (6) Patients with hypoalbuminemia (defined as albumin level <2 g/dL);
- (7) Patients with previous history of diuretic resistance (defined as failure to achieve the therapeutically desired reduction in edema even when a maximal dose of diuretic is employed [17]);
- (8) Patients with implantable cardioverter defibrillator or pacemaker;
- (9) Patients with valvulopathy which is more than mild;
- (10) Patients with atrial fibrillation.

Study Design

This cross-sectional study conducted at Bursa City Hospital (Bursa, Turkey) and collaborated with Besni State Hospital (Adıyaman, Turkey) for study design and data analysis. The study protocol was approved by the Hospital Ethics Committee.

Participants were consecutively allocated in a 1:1 ratio to echocardiography (E/(Ea×Sa) index) guided monitoring arm or urine output (conventional) guided monitoring arm to allow balance between the two monitoring arms. The monitoring strategy, was continued for up to 72 hours in not order to ignore safety and tolerability concerns and also, at 72 hours, the treating physician had the option of changing the diuretic strategy on the basis of the clinical response [16, 18]. All concomitant medications and clinical adverse events were also recorded during the monitoring, hospitalization and follow up period. Echocardiography measurements were performed by cardiologists specialized in cardiovascular imaging, who were not the investigators of the study and were blind to group allocation to avoid bias.

Urine Output Guided Strategy (Group 1): Monitoring was done on the basis of routine urine output volume. Urine output was measured 24 hours intervals [11, 19]. If there was not seen an adequate response to initial dose which means <150 ml/h, diuretic dose increased to double the previous dose. In cases where adequate response was obtained, the same dose was continued. Maximum repeat up dose was determined as 300 mg furosemide. The E/(Ea×Sa) index was also measured at 24-hours intervals.

Echocardiography Guided Strategy (Group 2): Monitoring was done on the basis of the combined systole diastolic (E/(Ea×Sa)) index. The index will be measured with 24-hour intervals [11]. The diuretic dose, which provided 20% reduction in the E/(Ea×Sa) index value compared to initial value, was determined as adequate dose [14, 20, 21]. At 24-hour intervals, if the rate of decrease in the index was less than 20% according to the initial value, the diuretic dose was increased to double the previous dose. When the adequate dose was obtained, the same dose was continued throughout the monitoring. Maximum repeat up dose was determined as 300 mg furosemide. The urine output was also measured at 24-hours intervals.

The Echocardiographic Evaluation

The mitral flow velocities were recorded from the apical four-chamber view by Pulsed Wave Doppler with the 5-mm sample volume placed at the level of the mitral valve tips. Peak early (E) and late (A) mitral entry velocities were recorded. Tissue Doppler imaging recordings, Sa, Ea, and Aa values were recorded from the lateral and medial annulus in an apical four-chamber view and taken average of at least

3 cardiac cycles. E/(Ea×Sa) index value was calculated as the arithmetic mean of the medial and lateral Ea and Sa velocities.

LV Ejection fraction was calculated according to the modified biplane Simpson method. All transthoracic echocardiography examinations were performed by using GE Vivid S60 system with 2.5 MHz transducer (GE Vingmed Ultrasound AS, Horten, Norway).

Treatment Considerations

Loop diuretic (furosemide for all patients) dosing was determined on the basis the current guidelines [4, 5].

Table 1. Baseline characteristics of the study population

Laboratory values	Patients with Urine Output Guided Strategy (n=34, 49.2%)	Patients with Echocardiography Guided Strategy (n=35, 50.8%)	p, value
Demographics, Age (years)	51.5±7.9	53.2±9.1	0.54
Females (n, %)	10 (29.4%)	11 (31.4%)	0.53
Clinical Parameters			
NYHA (3/4)	47/53%	48/52%	0.33
Trace pedal edema	63%	66%	0.71
In-office body weight (kg)	81±19	80±18	0.65
(BMI) (kg/m²)	28.3±7.1	27.9±7.9	0.31
Heart rate, beats/min	68 (13)	69 (11)	0.51
Systolic BP, mmHg	116 (14)	119 (16)	0.66
Comorbidities, %			
HT	11 (32.3%)	10 (28.5%)	0.88
DM	3 (8.8%)	3 (8.5%)	0.96
PAD	2 (5.8%)	3 (8.5%)	0.09
Medication for heart failure			
ACEi/ARBs/ARNI	34 (100%)	35 (100%)	
Beta Blockers	34 (100%)	35 (100%)	
MRAs	24 (70.5%)	23 (65.7%)	0.71
Ivabradine	12 (35.2%)	13 (37.1%)	0.56
Ischemic heart disease	14 (41.1%)	15 (42.8%)	0.63
Time since heart failure diagnosis (years)	4.2 (1-8)	4.3 (1-8)	0.11
Electrocardiographic Data			
LBBB	4 (11.7%)	4 (11.4%)	0.76
QRS Duration	109±4	108±27	0.51

Data are presented as mean±standard deviation, number and percentage (in brackets), or median and interquartile deviation. NYHA; New York Heart Association, BMI; Body Mass Index, BP; Blood Pressure, HT; Hypertension, DM; Diabetes mellitus, PAD; Peripheral artery disease, ACEi: Angiotensin converting enzyme inhibitor, ARBs: Angiotensin receptor blockers, ARNI: Angiotensin receptor neprilysin inhibitor, MRA: Mineralocorticoid receptor antagonists, LBBB: Left bundle branch block.

For patients on long-term loop diuretic agents, initial IV dosing was determined as 2 x of outpatient dose. For patients not receiving long-term loop diuretics agents, initial IV dosing was determined 40 mg BID of furosemide as empiric starting dose. The dose had maintained for 24 hours.

Patients were provided with a limited NaCl diet (2 gr.) daily by the hospital nutrition and dietetics department during the study. The other drugs indicated for use in HF were not removed from the treatment.

Worsening renal function was defined as increase in plasma creatinine >0.3 mg/dl at 72 hours.

Study Endpoints

The patient's global assessment of dyspnea symptoms on visual analogue scale (VAS Score of 0=the patient's subjective feeling of "best breathing" and score of 100=subjective feeling of "worst breathing") and change in N-terminal-pro hormone B-type natriuretic peptide (NT-proBNP) levels were determined as the primary endpoints of the study for efficacy [18]. Change in the estimated glomerular filtration rate (eGFR, Modification in Diet in Renal Disease-MDRD-4 formula) was determined as primary safety index. Change in weight, worsening renal function and electrolyte imbalance were secondary end points [18].

Statistical Analysis

According to the Shapiro–Wilk normality test, continuous variables were presented as mean±standard deviation, or median and interquartile deviation. Student's T test was used when the assumption of normal distribution was met, and Mann–Whitney U test was used when the normal distribution was not obtained. Categorical variables were compared by using the Chi-square test and the results were presented as percentages. For the primary outcomes, the differences in eGFR, NT-pro-BNP values, VAS Score and weight were evaluated with the chi-squared test, Fisher's exact test, T-test, or Wilcoxon rank sum test, as appropriate. Repeated measures ANOVA was used in terms of furosemide dose, urine volume and E/(Ea×Sa) index for each group. P-value of <0.05 was considered significant. SPSS 26.0 statistical package software was used to perform all data analyses.

Results

Of the 69 patients, 34 were assigned to the urine output-guided monitoring group and 35 to the echocardiography guided monitoring group. Four (11.7%) patients in urine output-guided group and 5 (14.2%) patients in echocardiography guided group had not used diuretics before. No patient was excluded from the study due to clinical adverse events and safety concern. Treatment-related laboratory outcomes of patients are presented in
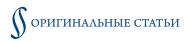
Table 2. Laboratory values of the study population

Laboratory values	Patients with Urine Output Guided Strategy (n=34, 49.2%)	Patients with Echocardio-graphy Guided Strategy (n=35, 50.8%)	p, value*
Creatinine (mg/dl) Baseline 72th hour p**	 1.06±0.3 1.05±0.3 0.17	 1.11±0.3 1.06±0.4 0.36	 0.23 0.27
Na (mmol/L) Baseline 72th hour P**	 136±6.5 138±9.3 0.11	 138±8.4 137±9.6 0.16	 0.32 0.13
K (mmol/L) Baseline 72th hour p**	 4.7±0.6 4.3±1.2 0.56	 4.6± 0.5 4.5± 0.5 0.71	 0.42 0.33
AST (U/L) Baseline 72th hour p**	 37 (14) 31 (12) **0.03**	 39 (16) 28 (9) **0.01**	 0.78 0.64
ALT (U/L) Baseline 72th hour P**	 34±9 27±11 **0.03**	 36±8 30±13 **0.03**	 0.43 0.39
Albumin (mg/dl) Baseline 72th hour p**	 3.1±0.9 3.0±1.1 0.91	 3.2±0.8 3.1±1 0.87	 0.69 0.71
Hemoglobin (g/dl) Baseline 72th hour P**	 13.2 (2.4) 13.7 (3.6) 0.64	 13.9 (3.6) 14.1 (4.2) 0.32	 0.61 0.55
Hematocrit (%) Baseline 72th hour p**	 39.7 (3.7) 41.4 (4.1) 0.54	 40.6 (3.9) 42.5 (4.4) 0.27	 0.75 0.24

Data are presented as mean±standard deviation, number and percentage (in brackets), or median and interquartile deviation. Na: Sodium, K: Potassium, AST: aspartate aminotransferase. ALT: alanine aminotransferase, Hs-CRP: Highly sensitive C reactive protein, TSH: Thyroid-stimulating hormone. * p-value of the comparative analysis between groups, ** p-value of the comparative analysis between pretreatment and posttreatment.

Table 3. Comparison of baseline echocardiographic parameters of the study patients

Variables	Patients with Urine Output Guided Strategy (Group 1, n=34, 49.2%)	Patients with Echocardio-graphy Guided Strategy (Group 2, n=35, 50.8%)	p, value
LVEDD (mm)	59.14±8.5	58.76±7.41	0.65
LVESD (mm)	42.35±4.3	41.94±4.12	0.71
IVSD (mm)	9 (1.3)	9 (1.6)	0.88
LVPWT (mm)	10±1.5	10±1.7	0.76
LVEF (%)	33.11±5.4	32.48±6.5	0.52
LA dimension (mm)	39.3 (6.1)	38.11 (7.1)	0.93
LA volume index (ml/m²)	49.4± 17	48.7±21	0.11
Mitral E vel. (cm/s)	86.12±21.39	89.54±21.67	0.23
Mitral A vel. (cm/s)	78.32±15.57	83.12±17.11	0.09
Mitral E/A	1.15±0.6	1.12±0.6	0.12
Mitral Ea vel. (cm/s)	7.14±2.5	7.08±2.9	0.32
Mitral Aa vel. (cm/s)	8.23±2.7	8.21±2.6.	0.42
Mitral Sa vel. (cm/s)	6.09±2.1	6.13±2.5	0.31
LV E/Ea	11.9±4.3	12.7±4.7	0.27
Decelerating time (ms)	244.07 (83)	229.07 (75)	0.55
Isovolumic relaxation time (ms)	119.61±54	117.43±61	0.64

Data are presented as mean±standard deviation, number and percentage (in brackets), or median and interquartile deviation. LVEDD: Left ventricle end diastolic diameter, LVESD: Left ventricle end systolic diameter, IVSD: Interventricular septum dimension, LVPWT: Left ventricle posterior wall thickness, LV EF: Left ventricle ejection fraction, Vel.: Velocity.

Table 2. The detailed echocardiographic examination of the population is listed in table 3.

The comparison of endpoints is shown in table 4. In brief, patients who monitored with echocardiography-guided strategy had significantly lower NT pro-BNP levels and lower VAS score (better breathing feeling) compared to patients who monitored with urine output-guided strategy. The absolute change in weight did not significantly differ between two groups. There was no statistically significant difference in term of eGFR in both groups as a safety index.

On the day 1, adequate diuretic response (determined as mean urine volume <150 ml/h according to the study design) could not be obtained in 14 of 34 (42%) patients in the urine output-guided group and the diuretic dose was

increased to double. At the same period, adequate diuretic response (determined as 20% reduction in the E/[Ea×Sa] index value compared to initial value according to the study design) could not be obtained in 19 of 35 (54%) patients of the echocardiography guided group and the diuretic dose was increased to double.

On the day 2, adequate diuretic response could not be obtained in 10 of 34 (29%) patients in the urine output-guided group and the diuretic dose was increased to double. At the same period, adequate diuretic response could not be obtained in 5 of 35 (14%) patient echocardiography guided group and the diuretic dose was increased to double.

At the end of the 72 hours, adequate diuretic response could be obtained in 25 of 34 (73%) patients in the urine

output-guided group and 29 of 35 (83%) patients in the echocardiography guided group. Detailed comparison of study patients regarding furosemide dose, urine volume and E/(Ea×Sa) index during monitoring is presented in Table 5.

Discussion

Insufficient data are available to determine euvolemia or the optimal dosing and stopping point for decongestive therapy in HF. This study conducted to more definitively inform these questions.

The principal finding of this study is that echocardiographic data (The E/(Ea×Sa) index) can be monitored and used to determine the response to changes in diuretics in patients with HFrEF. And, this approach mainly focuses on early and enhancer dosing in diuretic therapy based on alterations in LV hemodynamic.

Although the similar doses of diuretics were used in both groups, the patients with echocardiography guided strategy had the substantial lower NT pro-BNP level and significantly better VAS score on dyspnea assessment within 72 hours. Additionally, there was no worsening renal function and electrolyte imbalance that required stopping or decreasing loop diuretic dosing in both groups.

The patients in both groups received similar cumulative furosemide dose during their hospitalization. However, there was significant heterogeneity in the peak dose of loop diuretic in days (Table 5). 54% of patients in echocardiography guided strategy group needed increased diuretic dose after the first 24 hours while this ratio was 42% in patients with urine output guided strategy at the end of the first 24 hours. In contrast, the ratio of patient who need increased dose of diuretic was higher in urine output guided strategy group than to echocardiography guided strategy group at the end of 48 hours (29% vs. 14%). Remarkably, this strategy potentially might have advantage to determine loop diuretic response in a systematic and timely fashion, potentially allowing for more timely adjustments in therapy. These can be also supported by pharmacodynamic view. The loop diuretics have the log-linear increase in the dose effect, meaning that there is little natriuretic response until a threshold is achieved [22, 23]. In this approach, early evaluation of the diuretic response with LV hemodynamic will allow for the early dose enhancing in patients with a poor diuretic response. And, once diuretic response has been achieved, loop diuretic therapy would be continued at the same dose that it can maintain euvolemia.

In fact, similar urine output was seen in both groups. But, weight loss and excessive urine output during hospitalization are not necessarily associated with optimal result for decongestive therapy [24, 25]. Additionally, it is well

Table 4. Comparaison of the end points between study groups

Variables	Patients with Urine Output Guided Strategy (Group 1, n=34, 49.2%)	Patients with Echocardio-graphy Guided Strategy (Group 2, n=35, 50.8%)	p value*
VAS Score Baseline 72th hour p**	78±18 65±23 **0.04**	81±14 52±12 **0.03**	0.65 **0.04**
NT-proBNP Baseline 72th hour p**	4675±1207 2514±756 **0.01**	4855±1364 2172±914 **0.01**	0.88 **0.036**
E-GFR Baseline 72th hour p**	51.84±9.3 54.58±8.6 0.08	49.17±7.3 52.65±9.1 0.14	0.91 0.74
Change in weight (kg)	4.93 (1.4)	5.21 (1.9)	0.87

Data are presented as mean±standard deviation, or median and interquartile deviation. VAS: Visual analogue scale (0–100). NT-proBNP : N Terminal prohormone brain natriuretic peptide (pg/mL), E-GFR : Estimated glomerular filtration rate (MDRD-4 Formula, ml/min/1.73 m2), * p-value of the comparative analysis between groups, ** p- value of the comparative analysis between pretreatment and posttreatment.

Table 5. Detailed comparison of furosemide dose, urine volume and E/ (Ea x Sa) index of study patients during monitoring
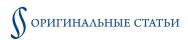
Variables	Patients with Urine output guided monitoring group (Group 1, n=34, 49.2%)	Patients with Echocardio-graphy guided monitoring group (Group 2, n=35, 50.8%)	p* value
Furosemide dose#			
Day 1	72.4	70.8	0.69
Day 2	102.2	107.8	0.08
Day 3	130.5	121.1	0.02
p** value	**0.01**[a,b,c]	**0.01**[a,b,c]	
Cumulative dose	305.1	299.7	0.61
Urine volume (mL/h)			
Day 1	2648	2532	0.17
Day 2	3444	4008	0.03
Day 3	3653	3816	0.04
p** value	**0.01**[a,b]	**0.01**[a,b]	
Cumulative volume	9745	10356	0.03
E/ (Ea x Sa) index			
Baseline	2.14±0.42	2.26±0.71	0.14
Day 1	1.94±0.51	1.95±0.64	0.71
Day 2	1.85±0.43	1.71±0.39	0.02
Day 3	1.77±0.33	1.67±0.52	0.03
p** value	**0.01**[a,b]	**0.01**[a,b,c]	

#;(intravenously, mg), *; p values; Independent Samples-T Test or Mann–Whitney U test,
**; p values; repeated measures ANOVA test.
[a]: p<0.05: Day 1 vs. Day 2; [b]: p<0.05: Day 1 vs. Day 3;
[c]: p<0.05: Day 2 vs. Day 3.

recognized that volume overload is not the only mechanism to explain congestion of HF. Redistribution of volume is also the other reason, which contributing to the development of congestion. Therefore, ESC guidelines for HF management recommend to distinguish acute fluid redistribution from true volume overload in patients with congestion [4, 26]. LV filling pressure will increase as an integrated result of the effective circulating volume regardless of volume overload or redistribution.

Previous studies demonstrated that hemodynamic data can be monitored over time and used to determine the response to changes in diuretics [27, 28]. A decrease in central venous pressure was observed (from 15.5±5.3 mmHg at baseline to 12.8±4.8mmHg) at the end of the Reprieve therapy (implantable monitor) [29]. In another study, reductions in pulmonary wedge pressure (– 30%) with furosemide were described [11]. So, it seems physiologically reasonable to assess LV filling pressure to adjust diuretic intensity.

The E/Ea ratio is widely used to assess LV filling pressure in clinical practice. Recently, Ohman et al. investigated the changes in cardiac filling pressures, with the resolution of pulmonary congestion among treatment. They divided the study population into two groups according to whether resolution of pulmonary congestion during their hospitalization period (responders and non-responders). They found that a rapid decline in E/Ea (>15%) occurred among responders by as early as the first 12 hours of treatment, predicting resolution of pulmonary congestion. And very little decline in cardiac filling pressures and in E/Ea occurred in non-responders. They reported that E/Ea seemed to be the fastest and useful objective marker for monitoring early treatment response, predicting prognostically relevant resolution of congestion [20].

The E/(Ea×Sa) is considered as E/Ea adjusted for contractility (Sa) based on its formula. Mornos C. et al. reported a strong linear correlation between the E/(Ea×Sa) index (an index combined systolic and diastolic Doppler parameters) and LV filling pressure [14, 30]. And several prominent validation studies have confirmed the correlation of this ratio with LV filling pressure [14, 21]. Additionally, previous studies showed that the E/(Ea×Sa) index had superior predictive ability to E/Ea alone [31]. In collaboration these data, a 20% reduction in the E/(Ea×Sa) index was accepted as a cut-off value to predict a favorable treatment throughout the hospitalization.

As a result, serving as an index for congestion and responding to changes in congestion status rapidly makes the E/(Ea×Sa) index a reliable candidate to guide to decongestive therapy. The echocardiography guided strategy has advantage of being easy to measure. Another potential advantage of echocardiographic hemodynamic monitoring is that changes in pressure is recognized before they clinical decompensation and provide a positive control to detect subclinical congestion. However, this hypothesis should be tested in a larger trial.

There are limitations that must be considered when interpreting these results. First, this analysis is exploratory and should be interpreted as hypothesis generating. Secondly, treatment was not blinded to the physician in charge of the patient because of the study nature. Third, there is need for larger and multi-center studies which involve the E/(Ea×Sa) index-guided decongestive therapy powered for improvement in clinical outcome. Fourth, this analysis was restricted to furosemide and this pilot study does not permit any general conclusions to all diuretics. Furthermore, it is a pioneer call for further investigation into which patients may benefit from echocardiography guided (serial LV filling pressure monitoring) diuretic therapy.

Conclusion

The findings of this study emphasize that the E/(Ea×Sa) index guidance might be a safe strategy for more effective diuretic response that deserves consideration for selected a subgroup of acute decomposed HFrEF patients.

Informed consent

The study protocol was approved with registration number of 2020–5/4 by the Bursa City Hospital ethics committee.

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