

# Improved cardiac and venous pressures during hospital stay in patients with acute heart failure: an echocardiography and biomarkers study

Eiichi Akiyama<sup>1,2†</sup>, Raphaël Cinotti<sup>1,3†</sup>, Kamilė Čerlinskaitė<sup>1,4†</sup>, Lucas N.L. Van Aelst<sup>1,5,6</sup>, Mattia Arrigo<sup>1,7,8</sup>, Rui Placido<sup>9</sup>, Tahar Chouihed<sup>1,10</sup>, Nicolas Girerd<sup>11,12</sup>, Faiez Zannad<sup>11,12</sup>, Patrick Rossignol<sup>11,12</sup>, Marc Badoz<sup>13</sup>, Jean-Marie Launay<sup>1,14,15</sup>, Etienne Gayat<sup>1,7,12,16</sup>, Alain Cohen-Solal<sup>1,5,16</sup>, Carolyn S.P. Lam<sup>17,18</sup>, Jeffrey Testani<sup>19</sup>, Wilfried Mullens<sup>20,21</sup>, Gad Cotter<sup>22</sup>, Marie-France Seronde<sup>1,13†</sup> and Alexandre Mebazaa<sup>1,7,12,16\*†</sup>

<sup>1</sup>Inserm UMR-S 942, Paris, France; <sup>2</sup>Division of Cardiology, Yokohama City University Medical Center, Yokohama, Japan; <sup>3</sup>Department of Anesthesia and Critical care, Hôtel Dieu, University hospital of Nantes, Nantes, France; <sup>4</sup>Clinic of Cardiac and Vascular Diseases, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania; <sup>5</sup>Department of Cardiology, Hôpitaux Universitaires Saint Louis-Lariboisière, Assistance Publique des Hôpitaux de Paris, Paris, France; <sup>6</sup>Department of Cardiovascular Sciences, KU Leuven, Leuven, Belgium; <sup>7</sup>Department of Anesthesiology and Critical Care, Hôpitaux Universitaires Saint Louis-Lariboisière, Assistance Publique des Hôpitaux de Paris, Paris, France; <sup>8</sup>Department of Cardiology, University Heart Center, University Hospital Zurich, Zurich, Switzerland; <sup>9</sup>Cardiology Department, Santa Maria University Hospital (CHLN), Lisbon Academic Medical Centre, and Centro Cardiovascular da Universidade de Lisboa, Faculdade de Medicina, Lisbon, Portugal; <sup>10</sup>Emergency Department, University Hospital of Nancy; University of Lorraine, INSERM U1116, Nancy, France; University Paris Diderot, Paris, France; <sup>11</sup>INSERM Centre d'Investigations Cliniques Plurithématique 1433, Université de Lorraine, CHRU de Nancy, INSERM U1116, Nancy, France; <sup>12</sup>F-CRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists), Nancy, France; <sup>13</sup>Department of Cardiology, University Hospital Jean Minjoz, Besançon, France; <sup>14</sup>Department of Medical Biochemistry and Molecular Biology, Hôpital Lariboisière, Paris, France; <sup>15</sup>Center for Biological Resources BB-033-00064, Hôpital Lariboisière, Paris, France; <sup>16</sup>University Paris Diderot, Sorbonne Paris Cité, Paris, France; <sup>17</sup>National Heart Centre Singapore and Duke-National University of Singapore, Singapore, Singapore; <sup>18</sup>University Medical Centre Groningen, Groningen, Netherlands; <sup>19</sup>Section of Cardiovascular Medicine, Yale University School of Medicine, New Haven, CT 06510, USA; <sup>20</sup>Department of Cardiology, Ziekenhuis Oost-Limburg, Genk, Belgium; <sup>21</sup>Biomedical Research Institute, Faculty of Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium; <sup>22</sup>Momentum Research Inc., Durham, NC 27707, USA

## Abstract

**Aims** Changes in echocardiographic parameters and biomarkers of cardiac and venous pressures or estimated plasma volume during hospitalization associated with decongestive treatments in acute heart failure (AHF) patients with either preserved left ventricular ejection fraction (LVEF) (HFPEF) or reduced LVEF (HFREF) are poorly assessed.

**Methods and results** From the metabolic road to diastolic heart failure: diastolic heart failure (MEDIA-DHF) study, 111 patients were included in this substudy: 77 AHF (43 HFPEF and 34 HFREF) and 34 non-cardiac dyspnea patients. Echocardiographic measurements and blood samples were obtained within 4 h of presentation at the emergency department and before hospital discharge. In AHF patients, echocardiographic indices of cardiac and venous pressures, including inferior vena cava diameter [from 22 (16–24) mm to 13 (11–18) mm,  $P = 0.009$ ], its respiratory variability [from 32 (8–44) % to 43 (29–70) %,  $P = 0.04$ ], medial E/e' [from 21.1 (15.8–29.6) to 16.6 (11.7–24.3),  $P = 0.004$ ], and E wave deceleration time [from 129 (105–156) ms to 166 (128–203) ms,  $P = 0.003$ ], improved during hospitalization, similarly in HFPEF and HFREF patients. By contrast, no changes were seen in non-cardiac dyspnea patients. In AHF patients, all plasma biomarkers of cardiac and venous pressures, namely B-type natriuretic peptide [from 935 (514–2037) pg/mL to 308 (183–609) pg/mL,  $P < 0.001$ ], mid-regional pro-atrial natriuretic peptide [from 449 (274–653) pmol/L to 366 (242–549) pmol/L,  $P < 0.001$ ], and soluble CD-146 levels [from 528 (406–654) ng/mL to 450 (374–529) ng/mL,  $P = 0.003$ ], significantly decreased during hospitalization, similarly in HFPEF and HFREF patients. Echocardiographic parameters of cardiac chamber dimensions [left ventricular end-diastolic volume: from 120 (76–140) mL to 118 (95–176) mL,  $P = 0.23$ ] and cardiac index [from 2.1 (1.6–2.6) mL/min/m<sup>2</sup> to 1.9 (1.4–2.4) mL/min/m<sup>2</sup>,  $P = 0.55$ ] were unchanged in AHF patients, except tricuspid annular plane systolic excursion (TAPSE) that improved during hospitalization [from 16 (15–19) mm to 19 (17–21) mm,  $P = 0.04$ ]. Estimated plasma volume increased in both AHF [from 4.8 (4.2–5.6) to 5.1 (4.4–5.8),  $P = 0.03$ ] and non-cardiac dyspnea patients ( $P = 0.01$ ). Serum creatinine [from 1.18 (0.90–1.53) to 1.19 (0.86–1.70) mg/dL,  $P = 0.89$ ] and creatinine-based estimated glomerular filtration rate [from 59 (40–75) mL/min/1.73m<sup>2</sup> to 56 (38–73) mL/min/1.73m<sup>2</sup>,  $P = 0.09$ ] were similar, while plasma cystatin C [from 1.50 (1.20–2.27) mg/L to 1.78 (1.33–2.59) mg/L,  $P < 0.001$ ] and neutrophil gelatinase associated lipocalin (NGAL) [from 127 (95–260) ng/mL to 167 (104–263) ng/mL,  $P = 0.004$ ] increased during hospitalization in AHF.

**Conclusions** Echocardiographic parameters and plasma biomarkers of cardiac and venous pressures improved during AHF hospitalization in both acute HFPEF and HFREF patients, while cardiac chamber dimensions, cardiac output, and estimated plasma volume showed minimal changes.

**Keywords** Acute heart failure; Congestion; Biomarker; Echocardiography; Heart failure with preserved ejection fraction; Heart failure with reduced ejection fraction

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\*Correspondence to: Alexandre Mebazaa, MD PhD, Department of Anesthesia and Critical Care, Hôpitaux Universitaires Saint Louis-Lariboisière, 2 Rue Ambroise-Paré 75010 Paris, France. Tel.: +33149956565. Email: alexandre.mebazaa@aphp.fr

†E.A., R.C., and K. Č contributed equally to this manuscript.

‡M.F.S. and A.M. contributed equally to this manuscript.

## Introduction

In his landmark paper, WC Little and his group showed that patients admitted with cardiogenic pulmonary edema and high blood pressure had preserved left ventricular (LV) ejection fraction (EF) and increased LV filling pressure, and improvement in clinical and radiological signs of pulmonary edema during hospital stay was associated with improved LV filling pressure but no change in LVEF.<sup>1</sup> This was the first demonstration that pulmonary congestion in acute heart failure (AHF) is related to afterload mismatch.<sup>2</sup> However, WC Little's paper did not explore right heart function nor effects of 'decongestive' therapies on cardiac parameters or plasma volume during hospital stay. Several novel biomarkers were identified in recent years, including natriuretic peptides<sup>3</sup> and endothelial soluble CD146,<sup>4</sup> which are associated with cardiac and/or venous pressures. To this day, changes in cardiac function, plasma biomarkers, and plasma volume during hospital stay associated with decongestive therapy in AHF still remain elusive.

Therefore, in the present study, we sought to assess changes in echocardiographic parameters, plasma biomarkers of cardiac and venous pressures, and estimated plasma volume during hospital stay in AHF patients, with special attention to differences between acute HFPEF, HFREF, and patients with non-cardiac dyspnea.

## Methods

### Study population

The study population consisted of a subset of patients included in the metabolic road to diastolic heart failure: diastolic heart failure (MEDIA-DHF study, Clinical Trials.gov, NCT02446327). MEDIA-DHF enrolled patients with acute dyspnea of non-cardiac origin, AHF, and chronic HF. For this specific substudy, patients who were admitted for acute dyspnea of cardiac and non-cardiac origin as the main symptom at two university hospitals in France (Hôpital Lariboisière, Paris and Hôpital Universitaire Jean Minjot,

Besançon) and who were 18 years or older, were included between February 2011 and April 2014. Exclusion criteria were shown elsewhere.<sup>5</sup> Adjudication of the final diagnosis (AHF or non-cardiac dyspnea, using clinical exams, echocardiography, and natriuretic peptides) was performed independently by two cardiologists blinded from patients' management. When the two evaluators disagreed regarding the final diagnosis, a third physician adjudicated the final diagnosis.<sup>6</sup> AHF patients were divided into two subgroups based on their LVEF on admission: HFREF (defined as LVEF < 40%) and HFPEF (defined as LVEF ≥ 40%). Data on AHF with LVEF ≥ 50% were also investigated. For the purposes of this study, we included patients whose echocardiographic parameters or plasma biomarkers were available within 4 h of presentation for dyspnea in the emergency department and before hospital discharge [at median (interquartile range) 6 (5–8) days after hospital admission].

Total intravenous furosemide dose during hospital stay was collected from the medical record in AHF patients. Forty milligrammes of furosemide was considered equivalent to 1 mg of bumetanide. AHF patients were divided into two groups (high and low) using median value of total intravenous furosemide dose during hospital stay.

The study protocol complied with the Declaration of Helsinki and was approved by the ethical committee of the participating institutions (Commission Nationale de l'Informatique et des Libertés 910198; Comité d'Évaluation de l'Éthique des projets de Recherche Biomedicale 10–017). All patients provided written informed consent.

### Echocardiography

Echocardiographic measurements of cardiac chamber, cardiac systolic and diastolic functions, and inferior vena cava (IVC) diameters were obtained according to the guidelines by experienced cardiologists (RP and MFS) within 4 h of presentation for dyspnea at the emergency department and before hospital discharge, using Philips CX50® or Philips iE33® ultrasound systems.<sup>7</sup> Investigators involved in image acquisition were blinded to plasma biomarker values or patients'

management and were not involved in further statistical data analysis.

## Biomarkers

During initial presentation at the emergency department and before hospital discharge, blood samples were collected in plastic tubes containing ethylenediaminetetra-acetic acid. Aliquots of plasma samples were stored at  $-80^{\circ}\text{C}$  for further analysis. Several plasma biomarkers were assessed as indicators of cardiac filling pressures [B-type natriuretic peptide (BNP; Abbott), mid-regional pro-atrial natriuretic peptide (MR-proANP; BRAHMS AG–ThermoFisher)], venous pressures [the endothelial soluble cluster of differentiation 146 (sCD146; Biocytex)], or renal function [NGAL (Abbott) and cystatin C (Abbott)]. Other biomarkers of myocardial ischemia [high sensitive troponin I (hsTnI; Roche Diagnostics)], cardiovascular [soluble suppression of tumorigenicity-2 (sST-2; Critical Diagnostics)], and systemic inflammation [C-reactive protein (CRP; Siemens) and procalcitonin (BRAHMS AG–ThermoFisher)] are also measured. Estimated glomerular filtration rate (eGFR) was calculated from creatinine values using the modified diet in renal disease formula. Relative changes in estimated plasma volume (estimated plasma volume) between at admission and before discharge were calculated using the Straus formula: estimated plasma volume =  $100 * [(haemoglobin\ at\ admission) / (haemoglobin\ at\ discharge)] * [(1-haematocrit\ at\ discharge) / (1-haematocrit\ at\ admission)]$ .<sup>8,9</sup> Because estimated plasma volume was thought to be proportional to this value, the instantaneous estimated plasma volume was defined using this formula as previously described: estimated plasma volume =  $(1-haematocrit) / haemoglobin\ (g/dL) * 0.01$ .<sup>10</sup>

## Primary and secondary outcome

The primary outcome of the present study was changes in echocardiographic parameters and plasma biomarkers of cardiac and venous pressures during hospital stay in acute HFPEF, HFREF, and non-cardiac dyspnea patients. The secondary outcomes were (i) changes in echocardiographic parameters of cardiac chamber dimensions and function, (ii) estimated plasma volume, and (iii) changes in plasma renal biomarkers during hospital stay in acute HFPEF, HFREF, and non-cardiac dyspnea patients.

## Statistical analysis

Continuous variables were summarized as the median (interquartile range). Comparisons of changes within group were performed using Wilcoxon signed-rank test and changes between group were Mann–Whitney *U*-test.

Analyses were performed with PASW Statistics 18 (SPSS Japan Inc., an IBM company, Tokyo, Japan). A *P* value  $<0.05$  was considered statistically significant.

## Results

### Study population

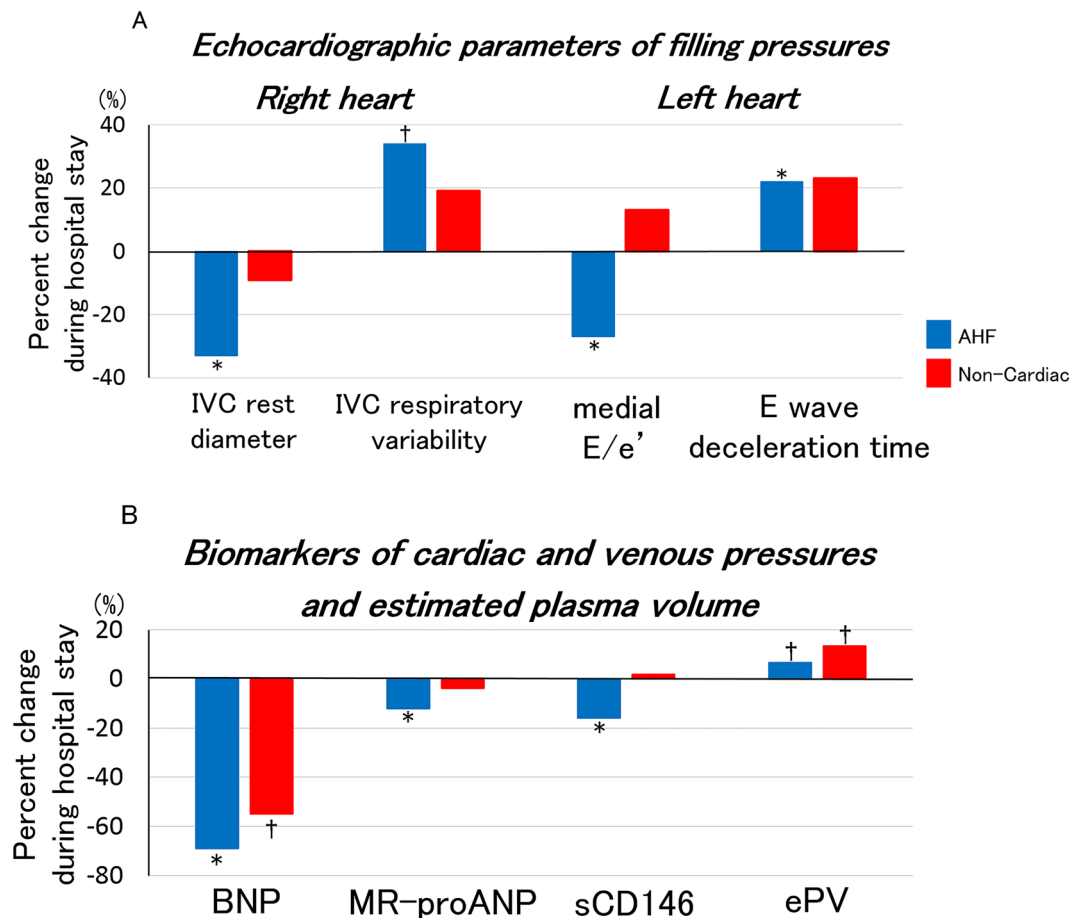
Of 146 patients in the MEDIA-DHF cohort, 111 patients fulfilled the inclusion criteria and were analysed in this substudy comprised of 43 HFPEF [age 83 (76–89) years, LVEF 50 (40–60) %, BNP 732 (380–1183) pg/mL, systolic blood pressure (SBP) at admission 149 (134–181) mmHg], 34 HFREF [age 63 (57–76) years, LVEF 27 (20–31) %, BNP 1027 (874–2781) pg/mL, SBP 132 (116–159) mmHg], and 34 non-cardiac dyspnea [age 76 (55–86) years, LVEF 60 (54–65) %, BNP 137 (29–254) pg/mL, SBP 143 (124–162) mmHg] patients. Dyspnea improved in all patients, and they all left the hospital alive.

### Changes in echocardiographic parameters during hospital stay in acute dyspneic patients

Concerning LV filling pressures, medial *E/e'* decreased from 21.1 (15.8–29.6) at admission to 16.6 (11.7–24.3) at discharge ( $P = 0.004$ ), and *E* wave deceleration time increased during hospitalization in AHF patients from 129 (105–156) ms at admission to 166 (128–203) ms at discharge ( $P = 0.003$ ), suggesting improved LV filling pressures (Figure 1A and Supporting Information, Table S1). By contrast, most left heart chamber dimensions and parameters of LV systolic function, including left atrial areas, LV end-diastolic volume, LVEF, and cardiac index, were similar during hospital stay (Figure 2A, 2B and Table S1). Echocardiographic indices of right heart showed marked decrease in venous pressures during hospitalization: IVC diameter at rest decreased from 22 (16–24) mm at admission to 13 (11–18) mm at discharge ( $P = 0.009$ ) and respiratory variability of IVC diameter increased from 32 (8–44) % at admission to 43 (29–70) % at discharge ( $P = 0.04$ ), an improvement of TAPSE that increased [from 16 (15–19) mm at admission to 19 (17–21) mm at discharge,  $P = 0.04$ ], and no changes in right atrial area (Figures 1A, 2A, 2B and Table S1).

Echocardiographic changes during hospital stay were similar in HFPEF and HFREF (Table 1). Echocardiographic findings of AHF with LVEF  $\geq 50\%$  were similar to those with LVEF  $\geq 40\%$  (Table S2). Echocardiographic changes were also similar (i) between AHF patients receiving high ( $>$ median cumulative dose of 280 mg during hospital stay) and low ( $\leq 280$  mg) total intravenous furosemide dose and (ii) between those receiving intravenous furosemide alone and those receiving the

**Figure 1** Percent changes in echocardiographic parameters and plasma biomarkers of cardiac and venous pressures and estimated plasma volume during hospital stay for AHF. Figure 1(A) shows median values of percent changes in echocardiographic parameters of right and left cardiac filling pressures (IVC rest diameter, IVC respiratory variability, medial E/e', and E wave deceleration time) during hospital stay in AHF. Figure 1(B) shows median values of percent changes in plasma biomarkers of cardiac and venous pressures (BNP, MR-proANP, and sCD146) and estimated plasma volume during hospital stay in AHF. \* $P < 0.01$ , † $P < 0.05$ . AHF, acute heart failure; BNP, B-type natriuretic peptide; ePV, estimated plasma volume; IVC, inferior vena cava; MR-proANP, mid-regional pro-atrial natriuretic peptide; sCD146, soluble cluster of differentiation 146.



combination of intravenous furosemide and vasodilators during hospital stay (Tables S3 and S4).

In patients with non-cardiac dyspnea, echocardiographic parameters were normal at admission and unaltered during hospitalization (Figures 1A, 2A, 2B and Table S1).

### Changes in plasma cardiovascular biomarkers and estimated plasma volume during hospital stay in acute dyspneic patients

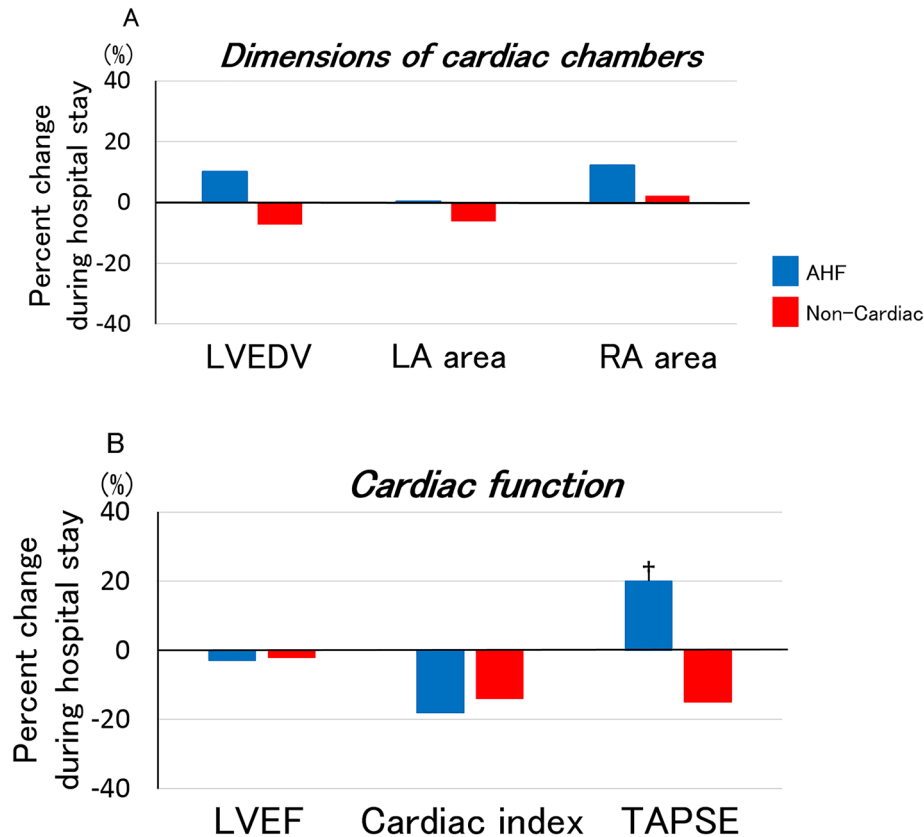
All plasma biomarkers of cardiac and venous pressures improved during hospitalization in AHF patients: BNP decreased from 935 (514–2037) pg/mL at admission to 308 (183–609) pg/mL at discharge ( $P < 0.001$ ), MR-proANP decreased from 449 (274–653) pmol/L at admission to 366 (242–549) pmol/L at discharge ( $P < 0.001$ ), sCD146 decreased from 528 (406–

654) ng/mL at admission to 450 (374–529) ng/mL at discharge ( $P = 0.003$ ) (Figure 1B and Table S5). Estimated plasma volume significantly increased during hospitalization in AHF patients from 4.8 (4.2–5.6) at admission to 5.1 (4.4–5.8) ( $P = 0.03$ ) (Figure 1B and Table S5).

High sensitive troponin I [from 36 (18–87) pg/mL at admission to 22 (11–66) pg/mL at discharge,  $P = 0.02$ ] and sT2 [from 83 (61–132) ng/mL at admission to 42 (36–59) ng/mL at discharge,  $P < 0.001$ ] significantly decreased, while CRP and procalcitonin were similar during hospitalization (Table S5).

The decrease in circulating biomarkers during hospital stay was similar (i) in HFPEF and HFREF (Table 2 and Table S6 for LVEF  $\geq 50\%$ ), (ii) in AHF patients receiving high and low dose of intravenous furosemide (Table S7), and (iii) in AHF patients receiving intravenous furosemide alone and the combination of intravenous furosemide and vasodilators (Table S8).

**Figure 2** Percent changes in cardiac chamber dimensions and function during hospitalization for AHF. Figure 2(A) shows median values of percent changes in cardiac chamber dimensions assessed by echocardiography during hospital stay in AHF. Figure 2(B) shows median values of percent changes in echocardiographic parameters of cardiac function during hospital stay in AHF. \* $P < 0.01$ , † $P < 0.05$ . AHF, acute heart failure; LA, left atrial; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; RA, right atrial; TAPSE, tricuspid annular plane systolic excursion.



Regarding patients with non-cardiac dyspnea, BNP, hsTnI, sST2, and CRP levels decreased, whereas MR-proANP and sCD146 levels were unchanged during hospitalization (Figure 1B and Table S5). Estimated plasma volume increased in patients with non-cardiac dyspnea as in AHF patients (Figure 1B and Table S5).

### Changes in renal function during hospital stay in AHF

In patients with AHF, serum creatinine and creatinine-based eGFR seemed similar during hospitalization: creatinine from 1.18 (0.90–1.53) at admission to 1.19 (0.86–1.70) mg/dL at discharge ( $P = 0.89$ ), eGFR from 59 (40–75) mL/min/1.73m<sup>2</sup> at admission to 56 (38–73) mL/min/1.73m<sup>2</sup> at discharge ( $P = 0.09$ ), while urea nitrogen increased from 8.9 (6.9–13.2) mmol/L at admission to 10.2 (7.6–16.0) mmol/L at discharge ( $P = 0.006$ ), cystatin C increased from 1.50 (1.20–2.27) mg/L at admission to 1.78 (1.33–2.59) mg/L at discharge ( $P < 0.001$ ), and plasma NGAL increased from 127

(95–260) ng/mL at admission to 167 (104–263) ng/mL at discharge ( $P = 0.004$ ) (Figure 3 and Table S5).

The results were consistent in HFPEF, HFREF, and in AHF patients receiving low or high total intravenous furosemide dose (Table 2, Table S6 for LVEF  $\geq 50\%$ , and Table 7). Serum creatinine increased, and eGFR decreased in patients receiving the combination of intravenous furosemide and vasodilators (Table S8).

In patients with non-cardiac dyspnea, most of renal parameters were similar, except that eGFR and cystatin C slightly but significantly improved during hospital stay (Figure 3 and Table S5).

## Discussion

Our study shows that AHF is a single disease, regardless of LVEF, and surrogates for right and left cardiac filling pressures as assessed by echocardiography, and circulating cardiovascular biomarkers improve in both acute HFPEF and HFREF patients during hospital stay despite minimal changes in

**Table 1** Changes of echocardiographic parameters during hospitalization in patients with acute heart failure with preserved left ventricular ejection fraction and heart failure with reduced left ventricular ejection fraction

	HFPEF			HFREF			Difference in percent change between groups	
	n	Admission	Discharge	P	n	Admission	Discharge	P
<b>Cardiac geometry</b>								
LVEDD (mm)	16	51 [45-55]	49 [42-55]	0.98	14	68 [61-72]	66 [61-71]	0.21
LVEDS (mm)	16	33 [27-42]	31 [29-40]	0.95	14	56 [48-61]	55 [44-59]	0.16
LVEDV (mL)	14	88 [68-103]	93 [68-103]	0.36	15	138 [131-173]	171 [147-183]	0.51
LVESV (mL)	13	42 [36-60]	43 [31-51]	0.07	13	108 [78-126]	124 [75-147]	0.62
Left atrial area (cm <sup>2</sup> )	23	22 [18-26]	23 [19-27]	0.73	15	27 [25-34]	29 [24-34]	0.98
Right atrial area (cm <sup>2</sup> )	8	17 [12-20]	17 [16-18]	0.48	11	18 [17-23]	22 [17-27]	0.48
<b>Cardiac function</b>								
Heart rate (bpm)	22	80 [72-98]	74 [67-81]	<b>0.04</b>	16	96 [88-110]	75 [62-95]	<b>0.01</b>
LVEF (%)	23	48 [40-60]	54 [48-61]	0.17	18	30 [25-36]	29 [23-32]	0.24
Stroke volume (mL)	14	34 [29-49]	48 [37-66]	0.10	13	52 [36-61]	45 [35-58]	0.75
Cardiac index (mL/min/m <sup>2</sup> )	10	1.6 [1.4-2.2]	2.1 [1.5-2.4]	0.80	9	2.5 [2.1-3.3]	1.9 [1.4-2.4]	0.21
TAPSE (mm)	11	17 [13-20]	17 [16-19]	0.34	10	16 [15-18]	19 [18-25]	0.06
E wave (cm/s)	24	98 [80-117]	83 [69-114]	0.08	18	91 [70-131]	89 [74-111]	0.83
E wave deceleration time (ms)	22	145 [107-184]	177 [133-226]	0.09	19	121 [102-139]	159 [127-179]	<b>0.008</b>
A wave (cm/s)	13	91 [57-103]	81 [68-110]	0.53	11	31 [25-62]	46 [32-67]	0.35
E/A	12	1.03 [0.67-1.96]	1.25 [0.82-1.50]	0.64	10	2.15 [1.50-2.81]	2.17 [1.26-2.69]	0.33
Medial e'	22	4 [4-7]	6 [4-7]	0.09	12	4 [3-4]	5 [4-6]	<b>0.007</b>
Lateral e'	22	7 [5-8]	7 [5-8]	0.25	17	7 [5-8]	8 [5-11]	0.53
Medial E/e'	25	21.3 [16.0-30.5]	14.3 [11.5-24.3]	<b>0.007</b>	17	21.0 [14.0-25.5]	19.2 [12.0-22.0]	0.20
Lateral E/e'	26	15.0 [11.4-19.8]	14.0 [9.4-17.4]	0.85	22	13.0 [8.8-16.0]	13.4 [8.8-19.0]	0.71
Mean E/e'	23	19.8 [16.1-27.0]	17.4 [11.1-20.1]	0.08	16	18.0 [11.3-21.5]	18.0 [10.6-23.5]	0.44
<b>Parameters of venous congestion</b>								
IVC rest diameter (mm)	11	22 [16-24]	13 [11-18]	0.09	12	22 [18-25]	14 [12-20]	<b>0.04</b>
IVC sniff diameter (mm)	11	11 [9-22]	6 [5-11]	<b>0.04</b>	10	19 [10-24]	7 [0-13]	<b>0.03</b>
Respiratory variability of IVC diameter (%)	11	40 [9-44]	40 [31-65]	0.11	10	24 [8-43]	50 [23-100]	0.11

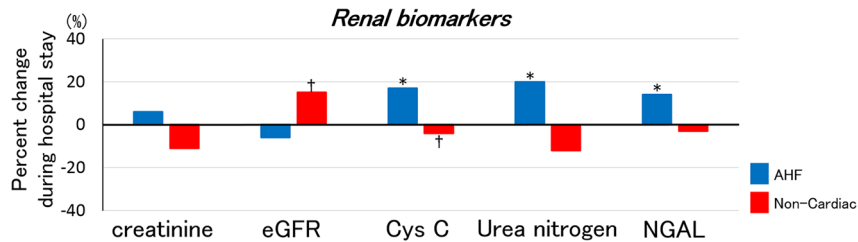
HFPEF, heart failure with preserved left ventricular ejection fraction; HFREF, heart failure with reduced left ventricular ejection fraction; IVC, inferior vena cava; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; TAPSE, tricuspid annular plane systolic excursion. Data are presented as median [interquartile range]. Bold numbers mean statistically significant.

**Table 2** Changes of biomarkers during hospitalization in patients with acute heart failure with preserved left ventricular ejection fraction and heart failure with reduced left ventricular ejection fraction

	HFPEF			HFREF			Difference in percent change between groups	
	n	Admission	Discharge	P	n	Admission	Discharge	P
<b>Markers of cardiovascular stress and congestion:</b>								
BNP (pg/mL)	19	848 [414–1577]	228 [161–520]	<0.001	19	989 [901–3039]	313 [194–598]	<0.001
MR-proANP (pmol/L)	34	386 [267–626]	362 [230–502]	0.02	25	515 [305–737]	376 [254–587]	0.003
sCD146 (ng/mL)	34	509 [379–624]	420 [320–519]	0.01	24	606 [448–705]	483 [423–590]	0.12
hsTnI (pg/mL)	34	29 [16–75]	19 [10–66]	0.03	20	45 [21–111]	31 [15–89]	0.20
<b>Markers of inflammation and fibrosis</b>								
Soluble ST2 (ng/mL)	34	81 [61–131]	50 [40–59]	<0.001	25	89 [59–133]	41 [33–53]	<0.001
CRP (mg/L)	34	11.8 [4.7–37.3]	10.7 [6.4–34.4]	0.86	24	8.0 [3.8–17.9]	4.0 [2.5–27.9]	0.14
Procalcitonin (ng/mL)	32	0.11 [0.08–0.14]	0.10 [0.07–0.14]	0.34	24	0.10 [0.08–0.17]	0.11 [0.07–0.17]	0.75
<b>Biological markers of renal function:</b>								
Creatinine (mg/dL)	34	1.05 [0.87–1.39]	1.05 [0.79–1.90]	0.17	25	1.27 [1.05–1.60]	1.34 [1.13–1.64]	0.46
eGFR (mL/min/1.73m <sup>2</sup> )	34	59 [40–74]	56 [36–74]	0.19	25	59 [45–76]	56 [41–68]	0.41
Cystatin C (mg/L)	33	1.55 [1.23–2.35]	1.92 [1.51–2.73]	0.002	24	1.40 [1.14–1.83]	1.49 [1.30–1.88]	0.002
Urea nitrogen (mmol/L)	33	8.9 [6.8–12.3]	10.2 [7.5–16.0]	0.02	24	8.5 [7.2–14.1]	10.4 [7.9–16.4]	0.16
Uric acid (μmol/L)	33	358 [331–476]	478 [343–544]	<0.001	24	449 [394–679]	481 [401–635]	0.95
NGAL (ng/mL)	32	176 [104–273]	217 [111–273]	0.02	22	107 [85–147]	132 [84–188]	0.09
<b>Markers of plasma volume:</b>								
Haemoglobin (g/dL)	27	12.2 [10.9–13.3]	11.5 [11.0–12.4]	0.10	26	13.5 [12.5–14.4]	13.1 [11.9–13.9]	0.14
Haematocrit (%)	27	37 [35–40]	35 [34–38]	0.08	26	41 [38–44]	39 [37–43]	0.12
Estimated plasma volume	27	5.2 [4.5–5.9]	5.7 [5.1–6.2]	0.12	26	4.3 [3.9–4.9]	4.7 [4.1–5.1]	0.16

AHF, acute heart failure; BNP, B-type natriuretic peptide, CRP: C-reactive protein; eGFR, estimated glomerular filtration rate; HFPEF, heart failure with preserved left ventricular ejection fraction; hsTnI, high sensitive troponin I; MR-proANP, mid-regional pro-atrial natriuretic peptide; NGAL, neutrophil gelatinase associated lipocalin; sCD146, soluble cluster of differentiation 146; ST-2, suppression of tumorigenicity-2. Data are presented as median [interquartile range]. Bold numbers mean statistically significant.

**Figure 3** Percent changes in renal biomarkers during hospital stay for AHF. It shows median values of percent changes in renal biomarkers during hospital stay in AHF. \* $P < 0.01$ , † $P < 0.05$ . AHF, acute heart failure; Cys C, cystatin C; eGFR, estimated glomerular filtration rate; NGAL, neutrophil gelatinase associated lipocalin.



cardiac chamber dimensions, cardiac output, or estimated plasma volume.

Our study confirms the concept delineated by Gandhi and Little *et al.* that excess of congestion upstream the LV, rather than acute deterioration of LV systolic function, is critical in the pathogenesis of acute pulmonary edema.<sup>1</sup> We recently showed that right cardiac function was also altered, with decreased TAPSE and increased IVC diameter, in both acute HFPEF and HFREF patients.<sup>5</sup> The present study shows a marked and parallel improvement in left and right cardiac and venous pressures during hospital stay in AHF. The marked reduction in intracardiac and central venous pressures was associated with increased estimated plasma volume during hospitalization. Similarly, Konishi *et al.* showed haemoglobin decrease associated with improvement of acute pulmonary edema following diuretic treatments.<sup>11</sup> Discrepancies between improvement in cardiac and venous pressures with minimal changes in estimated plasma volume in AHF patients suggest that venous capacitance better accommodate plasma volume during hospital stay compared with the early phase, as previously mentioned.<sup>12</sup> A better cardio-arterial coupling of both right and left ventricle may have improved venous congestion. Increased estimated plasma volume was also observed in non-cardiac dyspnea, suggesting that it might be related to uncontrolled fluid balance during hospital stay. Although the impact of “decongestive” therapies on improvement in cardiac and venous pressures seemed minimal in our study, further studies are needed.

Our study further clarifies the role of echocardiography in the management of AHF patients. Recent recommendations mention that echocardiography should be performed at admission only in case of hemodynamic instability, including cardiogenic shock or acute valvular disease.<sup>13</sup> However, there are no clear guidelines on when performing an echocardiography in the following days. Our study showed that cardiac dimensions, LV systolic indices of cardiac function, and cardiac output were roughly unchanged in the days following admission in both acute HFPEF and HFREF, suggesting that assessment of cardiac function by echocardiography could be performed during hospital stay. By contrast, elevated filling pressures of right and left ventricle as assessed by IVC

parameters, medial E/e', and E wave deceleration time were significantly improved by decongestion therapy in AHF patients, again regardless of LVEF. These results suggest that serial echocardiographic measurement of congestion could be useful for the follow-up during hospital stay.

Biomarkers of cardiac filling pressures, namely natriuretic peptides, are released by cardiac overstretch and are important tools for diagnosis and risk prediction in HF.<sup>3</sup> Our study showed a striking reduction in BNP and MR-proANP despite no changes in atrial and ventricular dimensions by echocardiography and even increase in estimated plasma volume. This is true in both acute HFPEF and acute HFREF. Our study also shows that circulating sCD146, the endothelial marker of venous pressure, decreased during hospital stay in AHF patients as previously described.<sup>4,14</sup> Our study confirms that natriuretic peptides and sCD146 are good markers of cardiac and venous pressures, independent from estimated plasma volume and may be measured at admission and during hospital stay to evaluate benefits of management on cardiac filling pressures.

Increased right and left filling pressures, in a context of altered endothelial properties, are major determinants of organ congestion, including lung and kidney and hospital admissions for AHF. It is, however, very difficult to assess the degree of right and left filling pressures and to follow its reduction during hospitalization.<sup>15</sup> Many AHF patients are discharged with persistent signs and symptoms of congestion,<sup>16</sup> and residual congestion has been shown to be associated with worse outcomes in hospitalized AHF patients.<sup>17–21</sup> Our study showed that repeated measures of IVC, medial E/e', E wave deceleration time, and biomarkers allow to assess improvement in cardiac and venous pressures during hospital stay for AHF and might help to decide on the optimal time point for hospital discharge, which supports the concepts of the current practical guidance of the Heart Failure Association of the European Society of Cardiology.<sup>22,23</sup>

The present study also shows that some biological markers of renal function such as serum creatinine and eGFR were similar, whereas other renal biomarkers including cystatin C and NGAL worsened during hospital stay for AHF. Recently, venous congestion has gathered increased attention in the



pathogenesis of renal dysfunction in patients with HF, especially in patients with advanced decompensated HFREF who underwent right heart catheterization.<sup>24–27</sup> By contrast, other papers showed low central venous pressure at admission,<sup>28</sup> or aggressive decongestive therapy<sup>29</sup> was associated with worsening renal function. The recent subanalysis of Renal Optimization Strategies Evaluation (ROSE)-AHF trial<sup>30</sup> showed that cystatin C levels were elevated, though renal tubular biomarkers such as urine NGAL were unchanged or slightly improved during aggressive decongestive treatment. These differences between ROSE-AHF and our study might be caused by differences in baseline renal function, follow-up duration, or prevalence of HFPEF. ROSE-AHF also reported that changes in renal tubular biomarkers were not associated with changes in urine output or body weight. Further studies are needed to clarify whether the improvements in cardiac filling pressures were associated with changes in renal function or renal tubular injury in the broad spectrum of AHF population including HFPEF.

### Study limitations

Our study has several limitations. First, the present study included only a small number of AHF patients from two French university hospitals, and AHF patients were not consecutively recruited. Moreover, our cohort has missing values of echocardiographic parameters and plasma biomarkers. Selection bias might affect the results. Those results should be confirmed by larger AHF population enrolled consecutively, though obtaining echocardiographic parameters at emergency room in consecutive AHF patients has much difficulty in both clinical and research settings. Second, echocardiographic measurement and biomarkers were available only at admission and before discharge, and early changes in those parameters could not be ascertained. Third, we lack data regarding patients' urine output, body weight, or HF signs and symptoms during hospital stay and at discharge. Our study could not assess relationships between echocardiographic parameters and plasma biomarkers of congestion and classical HF signs and symptoms. Fourth, because estimated plasma volume was calculated using haemoglobin and haematocrit, repeated blood sampling tests might affect the results of changes in estimated plasma volume.

### Conclusions

Our study showed that echocardiographic parameters and plasma biomarkers of cardiac and venous pressures improved during hospitalization for AHF in both acute HFPEF and HFREF, while echocardiographic parameters of cardiac chamber dimensions, cardiac output, and estimated plasma volume showed minimal changes. Serial assessment of cardiac

filling pressures using echocardiography and plasma biomarkers could be useful for the follow-up during hospital stay and determining benefits of management in AHF patients.

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### Conflict of interest

F.Z. has received personal fees for Steering Committee membership from Janssen, Bayer, Pfizer, Novartis, Boston Scientific, Resmed, Takeda, General Electric, and Boehringer Ingelheim, has had consultancy for Amgen, CVRx, Quantum Genomics, Relypsa, ZS Pharma, AstraZeneca, GSK, and is a founder of Cardiovascular Clinical Trialists (CVCT) and of CardioRenal. P.R. has received personal fees (consulting) from Novartis, Relypsa, AstraZeneca, Grünenthal, Idorsia, Stealth Peptides, Fresenius, Vifor Fresenius Medical Care Renal Pharma, Vifor and CTMA, lecture fees from Bayer and CVRx and is a cofounder of CardioRenal. A.C.S. has received grants or honoraria from Novartis, Servier, Daichii-Sankyo, Vifor, Menarini and Cardioentis. C.S.L. is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Boston Scientific, Bayer, Thermofisher, Medtronic, and Vifor Pharma; and has consulted for Bayer, Novartis, Takeda, Merck, AstraZeneca, Janssen Research & Development, LLC, Menarini, Boehringer Ingelheim, Abbott Diagnostics, Corvia, Stealth BioTherapeutics, Roche, and Amgen. J.T. has received consulting fees and research support from FIRE-1. W.M. has received research grants from Novartis, Vifor, Medtronic, Biotronik, Abbott and Boston Scientific. A.M. received speaker's honoraria from Abbott, Orion, Roche and Servier and fee as member of advisory board and/or Steering Committee and/or research grant from BMS, Adrenomed, Neurotronik, Roche, Sanofi, and Sphingotec.

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## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Changes of echocardiographic parameters during hospitalization in patients with AHF and non-cardiac dyspnea.

**Table S2.** Changes of echocardiographic parameters during hospitalization in patients with acute HFPEF (LVEF $\geq$ 50%) and HFREF (LVEF $<$ 40%).

**Table S3.** Changes of echocardiographic parameters during

hospitalization in AHF patients according to below or above median value of total IV furosemide dose.

**Table S4.** Changes of echocardiographic parameters during hospitalization in AHF patients receiving IV furosemide alone or IV furosemide plus vasodilators.

**Table S5.** Changes of biomarkers during hospitalization in patients with AHF and non-cardiac dyspnea.

**Table S6.** Changes of biomarkers during hospitalization in patients with acute HFPEF (LVEF $\geq$ 50%) and HFREF (LVEF $<$ 40%).

**Table S7.** Changes of biomarkers during hospitalization in AHF patients according to below or above median value of total IV furosemide dose.

**Table S8.** Changes of biomarkers during hospitalization in AHF patients receiving IV furosemide only or IV furosemide plus vasodilators.

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