

BMJ Open Soluble CD146 in the detection and grading of intravascular and tissue congestion in patients with acute dyspnoea: analysis of the prospective observational Lithuanian Echocardiography Study of Dyspnoea in Acute Settings (LEDA) cohort

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ABSTRACT

Objectives To evaluate the potential of soluble cluster of differentiation 146 (sCD146) in the detection and grading of congestion in patients with acute dyspnoea.

Design Subanalysis of the prospective observational Lithuanian Echocardiography Study of Dyspnoea in Acute Settings (LEDA) cohort.

Setting Two Lithuanian university centres.

Participants Adult patients with acute dyspnoea admitted to the emergency department.

Methods Congestion was assessed using clinical and sonographic parameters. All patients underwent sCD146 and N-terminal pro-B-type natriuretic peptide (NT-proBNP) testing.

Results The median value of sCD146 concentration in the study cohort (n=437) was 405 (IQR 315–509) ng/mL. sCD146 was higher in patients with peripheral oedema than in those without (median (IQR) 472 (373–535) vs 400 (304–501) ng/mL, p=0.009) and with pulmonary rales than in those without (439 (335–528) vs 394 (296–484) ng/mL, p=0.001). We found a parallel increase of estimated right atrial pressure (eRAP) and sCD146 concentration: sCD146 was 337 (300–425), 404 (290–489) and 477 (363–572) ng/mL in patients with normal, moderately elevated and high eRAP, respectively (p=0.001). In patients with low NT-proBNP, high sCD146 distinguished a subgroup with a higher prevalence of oedema as compared with patients with low levels of both biomarkers (76.0% vs 41.0%, p=0.010). Moreover, high sCD146 indicated a higher prevalence of elevated eRAP, irrespective of NT-proBNP concentration (p<0.05).

Conclusion sCD146 concentration reflects the degree of intravascular and tissue congestion assessed by clinical and echocardiographic indices, with this association

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study investigated important relationships between circulating soluble cluster of differentiation 146 (sCD146) and clinical and echocardiographic markers of tissue, intravascular and intracardiac congestion, in the context of a prospective observational study cohort.
- ⇒ The sample size is limited as it was not always possible to perform a high-quality echocardiography study on admission.
- ⇒ When assessing the association between blood biomarkers and congestion, we relied on clinical and echo-derived markers of volume overload, instead of invasively measured intracardiac filling pressures.
- ⇒ We were also unable to test how fast sCD146 level decreases after diuretic administration and, more importantly, we did not assess whether sCD146-guided decongestion could improve clinical outcome.

maintained in patients with low NT-proBNP. Our data support the notion that NT-proBNP might represent heart stretch while sCD146 rather represents peripheral venous congestion.

INTRODUCTION

Assessment of clinical congestion is challenging, particularly in an acute setting as it can be present in the vascular system (intravascular congestion) or the interstitium (tissue congestion), although the majority

of patients will have a mix of both.¹ Endothelial soluble cluster of differentiation 146 (sCD146) is a cell adhesion molecule that is secreted in the intercellular junction of endothelial cells mediating interaction with other cells or extracellular matrix.² sCD146 is involved in the control of vessel integrity, while its release is potentially dependent on endothelial cell stretch.³ This makes sCD146 a potential marker for congestion.⁴

This study was designed to examine the levels of sCD146 in a cohort of patients with acute dyspnoea due to multiple causes and its relationship with clinical signs and sonographic markers of congestion as well as cardiac morphology and function.

METHODS

Study design

This is a subanalysis of the Lithuanian Echocardiography Study of Dyspnoea in Acute Settings (LEDA, NCT03048032). LEDA was a prospective observational multicentre study performed in two Lithuanian university centres in collaboration with a research protocol of the international Global Research on Acute Conditions Team network. The enrolment period, inclusion/exclusion criteria, data collection and diagnosis adjudication have been previously described.⁵ Briefly, adult patients with acute dyspnoea admitted to the emergency department at two Lithuanian university centres were enrolled; patients with acute coronary syndrome (ACS) occurring during the first 4 hours of admission were excluded. Demographic data, baseline medication, comorbidities, clinical signs and laboratory parameters at admission were recorded. Clinical signs of congestion included peripheral oedema and pulmonary rales.

The main cause of acute dyspnoea was adjudicated by three cardiologists in their respective centres. Final diagnoses were classified as acute heart failure (AHF) or non-AHF; the latter included chronic obstructive pulmonary disease (COPD)/asthma exacerbation, pulmonary embolism, pulmonary/non-pulmonary infections, cancer, ACS (which occurred later in the admission) and others.

This analysis includes a subgroup of patients who had their sCD146 levels measured at admission and cardiac ultrasound performed within 48 hours of admission.

Ultrasound examination

Echocardiographic measurements of cardiac chambers, ventricular systolic and diastolic function and inferior vena cava (IVC) diameters were obtained by experienced operators using System Vivid 4 (GE Healthcare, Israel), System Vivid 7 and 9 machines (GE Healthcare, Norway) and Philips EPIQ 7 (Koninklijke Philips, the Netherlands) according to the guidelines for cardiac chamber quantification.⁶ Right atrial pressure (RAP) was estimated based on the IVC size and collapsibility: normal–IVC diameter <2.1 cm and collapsing $\geq 50\%$, moderately elevated–IVC diameter ≥ 2.1 cm and collapsing $\geq 50\%$ or IVC diameter

<2.1 cm and collapsing <50%, high–IVC diameter ≥ 2.1 cm and collapsing <50%.

Focused right-sided parameters, including right ventricular (RV) basal diameter, tricuspid annular plane systolic excursion (TAPSE), RV fractional area change and peak systolic velocity of tricuspid annulus were obtained when feasible. Furthermore, images for the RV deformation assessment were obtained from apical four-chamber view as described by Rudski *et al.*⁷ Offline speckle tracking analysis was performed by the two-dimensional strain software in the EchoPac (V.110.1.2 GE Healthcare, Norway) and QLAB (V.9.0, Koninklijke Philips, the Netherlands). Both the entire RV strain (including basal, mid, and apical segments of the RV free wall and interventricular septum) and RV free wall strain (excluding septal segments) were calculated. Left-sided parameters related to intracardiac congestion included E/e' ratio, left atrial volume index (LAVI) and left ventricular diastolic diameter (LVDD). Lung ultrasound was performed with a phased array transducer scanning in four chest sites bilaterally.⁸ The total number of B-lines was recorded as the final result.

Biomarkers

Blood samples were taken within 4 hours of presentation, frozen at -80°C and sent to the INSERM UMR942 institute (Paris, France) for centralised measurements of sCD146 (BioCytex, Marseille, France), N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitive troponin-T (hs-TnT) (Roche Diagnostics, Mannheim, Germany).

Statistical analysis

Values were expressed as counts and frequencies for qualitative variables and as means and SDs or medians with IQR for quantitative variables, depending on the distribution.

All study parameters were compared between two groups based on the sCD146 median value for a more detailed description of the biomarker in the acute dyspnoea cohort. To assess the relationship between sCD146 and cardiac morphology and function, sCD146 concentration was compared between the groups based on terciles of echocardiographic parameters.

The possible value of combining sCD146 and NT-proBNP in assessing congestion was examined by dividing the patients into four subgroups on the basis of the median values of the biomarkers: (1) both biomarkers below the median, (2) only NT-proBNP above the median, (3) only sCD146 above the median and (4) both biomarkers above the median. Congestion parameters (presence of peripheral oedema and estimated RAP (eRAP)) were compared between the groups.

The χ^2 test was used to compare categories. We used adjusted residuals with the Bonferroni correction for post hoc tests following the χ^2 test. The means of continuous non-parametric variables were compared using the Mann-Whitney U or Kruskal-Wallis H test when appropriate.

For group comparison, Dunn's tests with the Bonferroni correction were performed.

Performance of sCD146 and NT-proBNP in the prediction of IVC dilation and reduced collapsibility, B-lines and cardiac abnormalities were assessed conducting a receiver operating characteristic (ROC) analysis using the area under the ROC curve (AUC). Change in two AUCs was tested by DeLong *et al.*⁹

The analysis was carried out using IBM SPSS Statistics for Windows, V.23.0 (IBM Corp) and MedCalc for Windows, V.14.8 (MedCalc software). All tests were two sided and a p value of <0.05 was considered significant.

Patient and public involvement

None.

RESULTS

Study population

sCD146 measurements were available for 437 out of 1455 LEDA participants (30%). There were some differences in the baseline characteristics among patients included in the present subanalysis and the entire LEDA population (online supplemental table 1). The included patients were more likely to be dyspnoeic because of AHF and ACS, had higher plasma NT-proBNP and hs-TnT concentration and were more often on diuretics.

The baseline characteristics of the study population are shown in table 1. The patients were elderly (median age 70 (61–78) years) and 270 (68.1%) were male patients. AHF was the dominant cause of acute dyspnoea. The frequency of cardiovascular and non-cardiovascular comorbidities was high.

sCD146 in the study population

The median value of sCD146 concentration in the study cohort was 405 (315–509) ng/mL. The comparison of patients with plasma sCD146 concentration above and below the median is shown in table 1. Patients with sCD146 levels above the median were older and more frequently diagnosed with chronic heart failure, atrial fibrillation, valvular heart disease and anaemia before admission. Pulmonary rales at admission and chronic diuretic treatment were more common in patients with elevated sCD146: 58.9% vs 48.2% (p=0.036) and 53.0% vs 43.1% (p=0.044), respectively. Likewise, patients with sCD146 levels above the median had a higher plasma concentration of NT-proBNP, hs-TnT and creatinine (p<0.001 for all, see table 1). Regarding the cause of acute dyspnoea, the highest median value of sCD146 was found in patients with AHF: 441 (344–541) ng/mL, while the lowest was measured in patients diagnosed with COPD/asthma: 271 (220–363) ng/mL (online supplemental table 2).

sCD146 and clinical signs of congestion

sCD146 concentration was higher in patients with oedema, as compared with those without oedema (472 (373–535) vs 400 (304–501) ng/mL, p=0.009) (documented data

about the presence or absence of peripheral oedema were available for 161 (37%) patients). Of note, the median sCD146 concentration in patients without a documented oedema status (394 (306–498)) was like the concentration measured in patients with no oedema on admission (p=0.93).

Likewise, sCD146 concentration was higher in patients with pulmonary rales than in those without rales (439 (335–528) and 394 (296–484) ng/mL, p=0.001, data about the presence or absence of rales were available for 404 (92%) patients). Again, the median sCD146 concentration in patients without a documented rales status (384 (273–480)) was similar to the concentration detected in patients with no rales (p=0.79). Echocardiographic parameters in the total study population and the subgroups with sCD146 levels higher or lower than the median are presented in online supplemental table 3.

sCD146 and echocardiographic parameters

We revealed a significant association between the concentration of sCD146 and several functional and structural ultrasound markers, including signs of intravascular and intracardiac congestion.

First, the association with a dilated IVC and respiratory variations in IVC was observed (complete data on the size and collapsibility of IVC were available for 276 (63%) patients). As for terciles of IVC diameter at expiration and IVC collapsibility, the more IVC was dilated and the less collapsible, the higher was the concentration of sCD146 (see figure 1A,B and online supplemental table 4). We also found a parallel increase in eRAP and plasma sCD146 concentration: sCD146 was 337 (300–425), 404 (290–489) and 477 (363–572) ng/mL in patients with normal, moderately elevated and high eRAP, respectively (p=0.001, figure 1C).

Furthermore, the sCD146 level was significantly related to the average E/e' ratio—a marker of left ventricular diastolic filling (n=202 (46%)) (see figure 2A and online supplemental table 4). A parallel rise, though non-significant, was observed in sCD146 concentration with the increasing number of B-lines (n=77 (18%)) (figure 2B and online supplemental table 4), (p=0.06). The sCD146 concentration proportionally increased with the larger values of LVDD (figure 2C) and LAVI (figure 2D) (p<0.001 for both).

In addition, the sCD146 concentration corresponded to the markers of left and right ventricular function. Figure 2E,F shows an incremental increase of sCD146 levels in terciles of left ventricular ejection fraction (LVEF) and TAPSE. Similarly, the sCD146 concentration paralleled the decrease in the RV strain, both the free wall and the entire right ventricle (figure 2G,H).

sCD146 and NT-proBNP

In patients with high NT-proBNP, oedema was equally present in both high and low sCD146 subgroups (p=0.99). However, in patients with low NT-proBNP, high sCD146 distinguished a subgroup of patients with a significantly

Table 1 Baseline characteristics of the study population stratified by the median concentration of sCD146

Variables	Total, n=437	sCD146 below the median, n=218	sCD146 above the median, n=219	P value
Demographics				
Age, years	70 (61–78)	68 (60–77)	72 (62–79)	0.037
≥65 years	281 (64.3)	129 (59.2)	152 (69.4)	0.028
Male	270 (61.8)	135 (61.9)	135 (61.6)	1
Adjudicated diagnosis				
AHF	281 (64.3)	112 (51.4)	169 (77.2)	<0.001
COPD/asthma	18 (4.1)	15 (6.9)	3 (1.4)	0.004
Pulmonary embolism	37 (8.5)	27 (12.4)	10 (4.6)	0.003
Infection	18 (4.1)	12 (5.5)	6 (2.7)	0.158
ACS	42 (9.6)	26 (11.9)	16 (7.3)	0.107
Other	25 (5.7)	18 (8.3)	7 (3.2)	0.024
Examination				
Heart rate, BPM	88 (74–102)	86 (74–101)	90 (72–103)	0.675
SBP, mm Hg	135 (120–152)	137 (120–152)	135 (116–152)	0.256
DBP, mm Hg	80 (70–90)	80 (70–90)	80 (70–90)	0.503
BMI, kg/m ²	29.4 (25.7–34.2)	29.4 (25.8–34.5)	29.5 (25.7–43.1)	0.887
Pulmonary rales	217 (58.4)	95 (48.2)	122 (58.9)	0.036
Peripheral oedema	94 (53.7)	37 (51.4)	57 (64.0)	0.111
Respiratory rate, breaths/minute	20 (17–24)	20 (17–24)	20 (17–24)	0.372
Axillary temperature, °C	36.7±0.5	36.7±0.5	36.8±0.5	0.015
Oxygen saturation, %	93 (90–96)	94 (89–96)	93 (90–96)	0.686
Medical history				
CHF	301 (69.2)	131 (60.6)	170 (77.6)	<0.001
Hypertension	340 (78.2)	170 (78.7)	170 (77.6)	0.817
CAD	183 (42.1)	84 (38.9)	99 (45.2)	0.207
Severe VHD/previous valvular surgery	94 (21.6)	33 (15.3)	61 (27.9)	0.002
Atrial fibrillation/flutter	200 (46.0)	76 (35.2)	124 (56.6)	<0.001
Pacemaker	48 (11.0)	21 (9.7)	27 (12.3)	0.445
Stroke	36 (8.3)	16 (7.4)	20 (9.1)	0.603
Diabetes	98 (22.5)	44 (20.4)	54 (24.7)	0.303
Dyslipidaemia	128 (29.4)	70 (32.4)	58 (26.5)	0.207
Active/recent cancer	48 (11.0)	29 (13.4)	19 (8.7)	0.127
Asthma/COPD	72 (16.6)	39 (18.1)	33 (15.1)	0.377
Anaemia	120 (27.5)	50 (23.1)	70 (32.0)	0.042
Medication before admission				
ACE inhibitors or ARB	191 (43.9)	95 (44.0)	96 (43.8)	0.976
Beta-blocker	216 (49.7)	100 (46.3)	116 (53.0)	0.18
Aldosterone antagonist	83 (19.1)	37 (17.1)	46 (21.0)	0.33
Loop diuretic	209 (47.8)	93 (43.1)	116 (53.0)	0.044
Statin	54 (12.4)	31 (14.4)	23 (10.5)	0.246
Antiplatelet	109 (24.9)	55 (25.5)	54 (24.7)	0.912
Anticoagulant	116 (26.7)	38 (17.6)	78 (35.6)	<0.001
CCB	70 (16.1)	42 (19.4)	28 (12.8)	0.068
None of the above	89 (20.5)	53 (24.5)	36 (16.4)	0.043
Biomarkers				
NT-proBNP (ng/L)	2547 (737–6669)	1361 (381–3898)	4558 (1596–9817)	<0.001
Troponin T (ng/L)	30 (20–60)	24 (13–40)	40 (20–70)	<0.001
CRP (mg/L)	9.1 (3.5–27.7)	9.2 (3.5–30.0)	9.0 (3.5–23.8)	0.975

Continued

Table 1 Continued

Variables	Total, n=437	sCD146 below the median, n=218	sCD146 above the median, n=219	P value
Hb (g/L)	132 (117–144)	134 (118–146)	130 (116–144)	0.122
K (mmol/L)	4.3 (4.0–4.7)	4.3 (3.9–4.6)	4.4 (4.0–4.8)	0.013
Na (mmol/L)	139 (136–141)	139 (136–141)	139 (137–142)	0.248
Creatinine (μmol/L)	95 (77–127)	87 (72–116)	103 (83–135)	<0.001

Values are expressed as n, median (IQR), mean±SD or n (%), unless otherwise stated.

Significant p values (<0.05) are presented in bold.

ACS, acute coronary syndrome; AHF, acute heart failure; ARB, angiotensin receptor blocker; BMI, body mass index; BPM, beats per minute; CAD, coronary artery disease; CCB, calcium-channel blocker; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; CRP, C reactive protein; DBP, diastolic blood pressure; Hb, haemoglobin; K, potassium; n, number of subjects with available data; Na, sodium; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure; sCD146, soluble cluster of differentiation 146; VHD, valvular heart disease.

higher prevalence of oedema, as compared with patients with low levels of both biomarkers (76% vs 41%, $p=0.010$) (figure 3A). Furthermore, high sCD146 indicated a higher prevalence of elevated eRAP, irrespective of NT-proBNP concentration ($p<0.05$, figure 3B).

We also compared the value of sCD146 and NT-proBNP and the combination of both biomarkers in predicting the presence of congestion and cardiac dysfunction. AUCs for sCD146 and NT-proBNP were similar for IVC diameter, IVC collapse and the number of B-lines ($p>0.05$, figure 4 and online supplemental table 5). However, sCD146 better predicted the presence of peripheral oedema than NT-proBNP (AUC 0.63 (0.51–0.70) vs 0.51 (0.43–0.59), $p=0.009$), whereas NT-proBNP was a better predictor of LVEF and rales than sCD146 (AUC 0.76 (0.71–0.80) vs 0.63 (0.58–0.68), $p<0.001$ and AUC 0.66 (0.61–0.70) vs 0.60 (0.55–0.64), $p=0.049$, respectively). The AUC values for echocardiographic parameters are detailed in online supplemental table 5.

DISCUSSION

The present study reveals an important relationship between circulating sCD146 and clinical and echocardiographic markers of tissue, intravascular and intracardiac congestion, which is maintained in patients even with lower NT-proBNP.

Clinical congestion is a result of a complex pathophysiological process which in the case of heart failure starts with a gradual increase in filling pressures and culminates

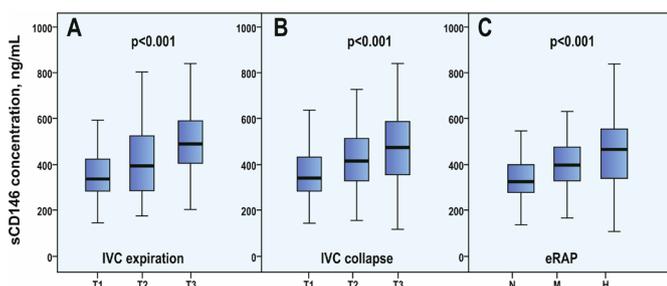


Figure 1 sCD146 concentration in tertiles of IVC diameter at expiration (A), IVC collapse (B) and eRAP subgroups (C). eRAP, estimated right atrial pressure; IVC, inferior vena cava; sCD146, soluble cluster of differentiation 146.

with extravascular fluid accumulation.¹⁰ Yet, congestion is the main reason for hospitalisation in an AHF setting, as the majority of patients show up with signs and symptoms of volume overload.¹⁰ It is however difficult to assess the level of congestion, and accurate detection and grading are therefore crucial for optimal medical care.

Along with a significant reduction in the length of AHF-related inpatient stays, the readmission rate remained unchanged during the past four decades,¹¹ meaning that a large proportion of patients with AHF are readmitted for acute decompensation within a year.¹² The deleterious effect of congestion in decompensated heart failure on outcome has been identified in other clinical scenarios, including end-stage renal disease,¹³ COPD¹⁴ and COVID-19 infection.¹⁵ Lung ultrasound is being increasingly recognised as a useful tool to assess pulmonary congestion and pleural effusion in acute dyspnoea,^{15–18} but may not be accessible in all facilities. Despite obvious harm, congestion management often remains suboptimal.

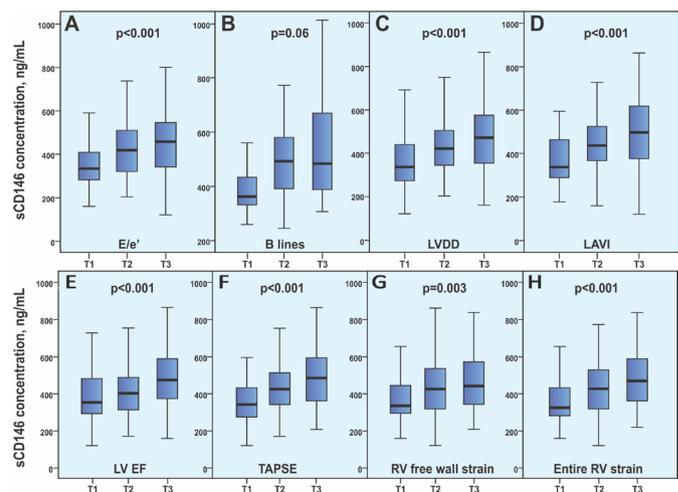


Figure 2 sCD146 concentration in tertiles of ultrasound parameters: (A) average E/e' ratio, (B) B-lines, (C) LVDD, (D) LAVI, (E) LVEF, (F) TAPSE, (G) RV free wall strain and (H) entire RV strain. LAVI, left atrial volume index; LVDD, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; RV, right ventricular; sCD146, soluble cluster of differentiation 146; TAPSE, tricuspid annular plane systolic excursion.

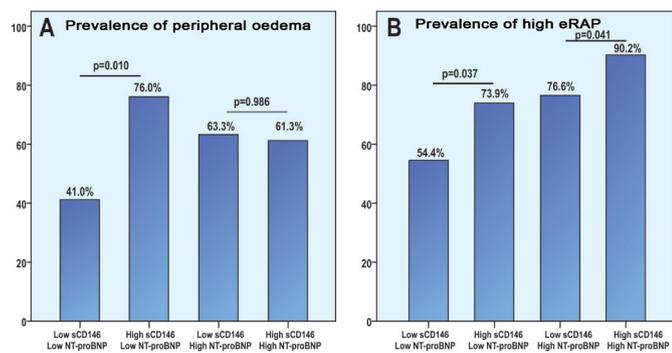


Figure 3 Frequency of peripheral oedema in patients stratified according to the median values of sCD146 and NT-proBNP (A) and prevalence of elevated eRAP in patients stratified according to the median values sCD146 and NT-proBNP (B). eRAP, estimated right atrial pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sCD146, soluble cluster of differentiation 146.

This means that many patients remain wet and possibly experience overhydration-related events.

This difficulty is prevalent in the setting of acute dyspnoea, given often similar clinical presentations

despite a diverse spectrum of aetiologies.^{19–21} Delayed identification leads to delays in initiation of decongestive therapies in acute dyspnoea, although early diuretic administration has been related to a better outcome in AHF.²²

Recently, sCD146—a promising blood biomarker for congestion—has been introduced. Initially, sCD146 was identified as a marker for tumour progression and metastasis formation in human melanoma.²³ Later, it was discovered that sCD146 is involved in the control of vessel integrity and angiogenesis,^{24–27} especially in different tumour pathogenesis, including paediatric leukaemia,²⁸ breast cancer,^{29–31} melanoma³² and other types of cancer.^{33–34} Later on, Gayat *et al* showed that sCD146 concentration correlates well with weight gain and the size of IVC in patients with AHF.³⁵ The relationship between venous stretch and sCD146 was demonstrated in an elegant experimental study by Arrigo *et al*.³ The authors measured the level of sCD146 in patients with heart failure at baseline and after 90 min of unilateral forearm venous congestion, and documented a rapid release of sCD146 in response to congestion-mediated venous stretch that may reflect systemic congestion in chronic heart failure. Another study revealed a relationship between sCD146 and pulmonary congestion in the

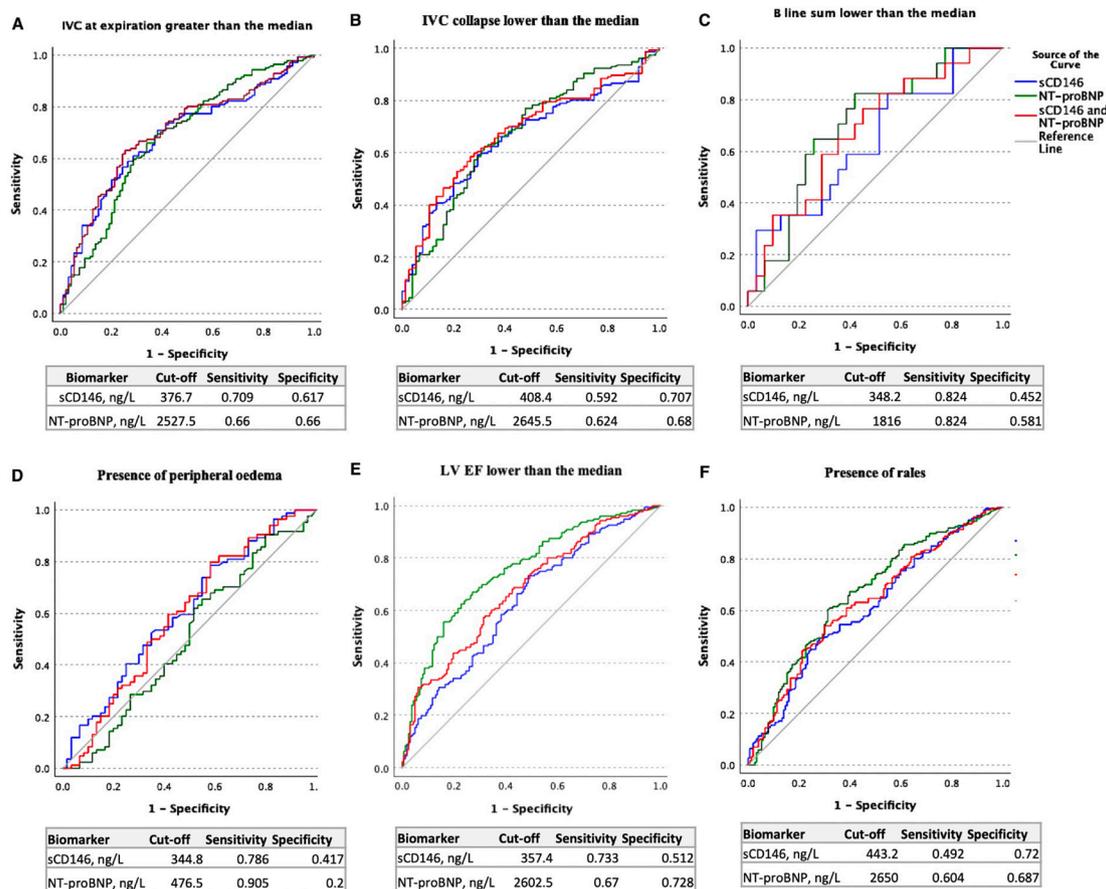


Figure 4 ROC curves of the predictive value of sCD146 and NT-proBNP and the combination of sCD146 and NT-proBNP: (A) IVCexp, (B) IVC collapse, (C) B-lines, (D) oedema, (E) LVEF, (F) rales. IVC, inferior vena cava; IVCexp, inferior vena cava at expiration; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; ROC, receiver operating characteristic; sCD146, soluble cluster of differentiation 146.

early phase of ACS, which was independent from the severity of myocardial cell necrosis.³⁶

The present study extends the accumulated data by revealing a close association between the levels of sCD146 and clinical and echocardiographic evidence of congestion as well as cardiac morphology and function in an unselected population of acute dyspnoea.

We found that median sCD146 concentration in patients with different aetiologies of acute dyspnoea differs, with patients with AHF having the highest concentrations, and patients with bronchial asthma (BA)/COPD having the lowest. Due to the modest sample size, we did not investigate this association further.

Regarding the left heart and pulmonary congestion, we were able to confirm a definite link between sCD146 concentration and the presence of pulmonary rales as well as impairment of diastolic filling reflected by elevated E/e'. We also showed that the greater the level of sCD146, the larger the left atrium and left ventricle, and the lower the LVEF. There was a parallel rise, though non-significant, in sCD146 with the increasing number of B-lines that requires further testing in a larger population.

Concerning the right ventricle and systemic congestion, the present results demonstrate a strong relationship between sCD146 concentration and clinical (peripheral oedema) as well as ultrasound signs of right-sided congestion. A stepwise increase in sCD146 concentration is demonstrated along with rising eRAP, consistent with intravascular volume overload. In addition, elevated sCD146 concentration was related to impaired RV function, as evidenced by a reduction in RV strain and TAPSE. The present findings indicate that sCD146 concentration proportionally increases not only with increasing congestion but also in parallel with decreasing biventricular function and progressing cardiac enlargement. Cardiac dysfunction is a likely cause of water retention in some cases, and sCD146 can reflect them both, that is, the cause and the consequence.

We have previously shown in dialysis patients that sCD146 rapidly follows patient hydration independently from the levels of natriuretic peptides. Most haemodialysis subjects with low BNP but high sCD146 have been shown to be overhydrated.³⁷ The present study further confirms the significant additional value of sCD146 in detecting congestion in patients with acute dyspnoea with relatively low NT-proBNP. For instance, subjects with high sCD146 and low NT-proBNP frequently had elevated eRAP. By contrast, sCD146 had a minor additional value in patients with high NT-proBNP that likely carry both prominent intracardiac and peripheral congestion. However, in patients with relatively low NT-proBNP, sCD146 was able to discern a subgroup of patients with a high prevalence of peripheral oedema. Altogether, these data support the notion that natriuretic peptides are more likely to represent cardiac stretch in the context of heart failure, while sCD146 reflects hypervolaemia and peripheral venous stretch in acute dyspnoea.

Clinical significance

The present study indicates that NT-proBNP—an established diagnostic biomarker—may not accurately reflect systemic congestion in some scenarios. This observation is in line with some previous findings showing that BNP-guided congestion management is not superior to a conventional clinical approach.³⁸ On the other hand, sCD146 presents a potential to be used as a congestion biomarker, and we hypothesise that its role in decongestion guidance might be superior to NT-proBNP, given the venous origin of its release.³ This may be particularly helpful in patients with acute dyspnoea not related to heart failure who may have hypervolaemia and may need diuretics despite low values of natriuretic peptides. These cases could potentially include patients with renal and hepatic failure, or subjects with severe malnutrition-related volume overload. The present data further suggest that the goal of diuretic treatment might be to reduce both NT-proBNP and sCD146. Our study was held in two academic facilities with immediate access to a cardiologist experienced in echocardiography, but we assume that in other settings many patients do not have or have delayed access to cardiac ultrasound. This means that sCD146 may assist emergency physicians, internists and intensivists in prompt congestion detection, leading to faster medical care. Also, this reliable congestion biomarker has a potential to fill the current gap of knowledge regarding congestion detection and grading, especially in emergency and primary care where modalities such as advanced echocardiography and lung ultrasound are often unavailable.

Limitations

This study has several limitations. First of all, the sample size is limited as it was not always possible to perform a high-quality echocardiography study on admission. Also, some patients were excluded from different parts of the analysis due to missing values in the patient history, which is often the case in a real-life emergency setting. Further research is needed to determine if sCD146 could potentially help to distinguish cardiac and non-cardiac dyspnoea as well as to guide diuretic treatment in different conditions. We do not have the data of deceleration time on echocardiography, which could give additional information on diastolic function. When assessing the association between blood biomarkers and congestion, we relied on clinical and echo-derived markers of volume overload instead of invasively measured intracardiac filling pressures. Still, we do not believe that such a trial of invasive nature would have ever been carried out in an acute dyspnoea setting. We were also unable to test how fast the sCD146 level decreases after diuretic administration and, more importantly, if sCD146-guided decongestion would improve outcome.

CONCLUSION

To sum up, sCD146 concentration reflects the degree of intravascular and tissue congestion as assessed by

clinical and echocardiographic indices. This association remains present in patients with low NT-proBNP. sCD146 better represents peripheral venous congestion, while NT-proBNP might better represent cardiac stretch.

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Supplementary Table 1. Comparison of patients included in the present sub-analysis and the entire LEDA cohort					
Variables	LEDA n=1455	population	sCD146 n=437	population	p-value
Demographics					
Age, years	71 [62-79]		70 [61-78]		0,447
>=65 years	955 (65.6)		281 (64.3)		0,577
Male	824 (56.6)		270 (61.8)		0,030
Adjudicated diagnosis					
AHF	761 (52.3)		281 (64.3)		<0.001
Non-AHF	694 (47.7)		156 (35.7)		<0.001
COPD/asthma	98 (6.7)		18 (4.1)		0,029
Pulmonary embolism	96 (6.6)		37 (8.5)		0,116
Infection	121 (8.3)		18 (4.1)		0,001
ACS	88 (6.0)		42 (9.6)		0,002
Other	291 (19.9)		41 (9.4)		<0.001
Examination					
Heart rate, BPM	88 [73; 104]		88 [74; 102]		0,520
SBP, mmHg	140 [123; 160]		135 [120;152]		0,016
DBP, mmHg	80 [71; 90]		80 [70; 90]		0,611
BMI, kg/m²	29.4 [23.4; 34.4]		29.4 [25.7; 34.2]		0,860
Rales	651 (50.3)		217 (53.7)		0,166
Peripheral oedema	299 (52.5)		94 (58.4)		0,138
Respiratory rate, breaths/minute	20 [16; 22]		20 [17; 24]		0,072
Axillary temperature, °C	36.7±0.6		36.7±0.5		0,074
Oxygen saturation (SpO₂), %	94 [89; 96]		93 [90; 96]		0,354
Medical history					
CHF	877 (61.4)		301 (69.2)		0,001
Hypertension	1120 (78.4)		340 (78.2)		0,901
CAD	495 (34.6)		183 (41.9)		0,001
Severe VHD or previous valvular surgery	277 (19.4)		94 (21.6)		0,240
Atrial fibrillation/flutter	618 (43.2)		200 (46.0)		0,250
Pacemaker	169 (11.8)		48 (11.0)		0,609
PAD	90 (6.3)		32 (7.4)		0,369
Stroke	128 (9.0)		36 (8.3)		0,619
Pulmonary embolism	95 (6.6)		26 (6.0)		0,574
Diabetes	324 (22.7)		98 (22.5)		0,943
Dyslipidaemia	390 (27.3)		128 (29.4)		0,318
Active/recent cancer	204 (14.3)		48 (11.0)		0,053
Asthma/COPD	275 (19.2)		72 (16.6)		0,154

Anaemia	331 (22.7)	120 (27.6)	0,029
Chronic inflammatory disease	102 (7.0)	102 (7.6)	0,716
Medication before admission			
ACE inhibitors or ARB	650 (45.5)	191 (43.90)	0,500
Beta blocker	713 (49.9)	216 (49.7)	0,909
Aldosterone antagonist	243 (17.0)	83 (19.1)	0,252
Diuretic	615 (43.1)	209 (48.0)	0,036
Cardiac glycoside	74 (5.1)	22 (5.1)	0,907
Nitrate	106 (7.3)	34 (7.8)	0,754
Statin	184 (12.9)	54 (12.4)	0,769
Antiplatelet	335 (23.5)	109 (25.1)	0,432
Anticoagulant	390 (27.3)	116 (26.7)	0,763
CCB	212 (14.8)	70 (16.1)	0,465
Inhaled steroid	80 (5.6)	20 (4.6)	0,362
Beta2 agonist	115 (8.1)	20 (4.6)	0,008
Insulin	68 (4.7)	22 (5.1)	0,772
Antidiabetic (other than insulin)	180 (12.6)	60 (13.8)	0,455
None of the above	313 (21.9)	89 (20.5)	0,462
Biomarkers			
NT-proBNP (ng/L)	1828 [453; 5305]	2547 [737; 6669]	0,001
Troponin T (ng/L)	27 [13; 48]	30 [20; 60]	<0.001
CRP (mg/L)	10.3 [3.5; 33.8]	9.1 [3.5; 27.7]	0,098
Hb (g/L)	131 [116; 144]	132 [117; 144]	0,684
K (mmol/L)	4.3 [4.0; 4.7]	4.3 [4.0; 4.7]	0,562
Na (mmol/L)	139 [136; 141]	139 [136; 141]	0,194
Creatinine (µmol/L)	94 [75; 122]	95 [77; 127]	0,844
Values are expressed as n, median (interquartile range), mean±SD or n (%), unless otherwise stated. Significant p-values (<0.05) are presented in bold. ACE: angiotensin-converting enzyme; ACS: acute coronary syndrome; AHF: acute heart failure; ARB: angiotensin-receptor blocker; BMI: body mass index; BPM: beats per minute; CAD: coronary artery disease; CCB: calcium-channel blocker; CD146: cluster of differentiation 146; CHF: chronic heart failure; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; DBP: diastolic blood pressure; Hb: haemoglobin; K: potassium; LEDA = Lithuanian Echocardiography Study of Dyspnea in Acute Settings; n: number of subjects with available data; Na: sodium; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PAD: peripheral artery disease; SBP: systolic blood pressure; VHD: valvular heart disease.			

Supplementary Table 2. The median sCD146 concentration in patients with different aetiologies of acute dyspnoea

Variables	Total (n=437)	sCD146 concentration, ng/L		
		Present	Absent	p-value
Adjudicated diagnosis				
AHF	281 (64.3%)	440.9 [344.1; 540.6]	336.7 [281.5; 434.6]	<0.001
ACS	42 (9.6%)	356.5 [304.7; 467.7]	411.0 [317.4; 514.6]	0.043
Pulmonary embolism	37 (8.5%)	330.0 [290.2; 427.5]	415.3 [322.3; 517.4]	0.002
Infection	18 (4.1%)	352.1 [246.7; 469.0]	407.7 [246.7; 469.4]	0.118
COPD/asthma	18 (4.1%)	271.1 [220.3; 362.8]	411.0 [320.9; 514.6]	<0.001
Other	41 (9.4%)	351.4 [282.6; 439.4]	410.3 [318.9; 514.6]	0.056

Values are expressed as n, median (interquartile range) or n (%). Significant p-values (<0.05) are presented in bold. ACS: acute coronary syndrome; AHF: acute heart failure; CD146: cluster of differentiation 146; COPD: chronic obstructive pulmonary disease; n: number of subjects with available data;

Supplementary table 3. Echocardiographic parameters stratified by the median concentration of sCD146

VARIABLES	n	Total	Below the median, n=218	Above the median, n=219	p-value
Intravascular Congestion parameters					
IVCexp (cm)	281	2.3 [1.8; 2.7]	2.0 [1.6; 2.4]	2.4 [2.0; 2.8]	<0.001
IVCinsp (cm)	276	1.3 [0.8; 1.9]	1.0 [0.6; 1.6]	1.6 [1.2; 2.3]	<0.001
IVC collapsibility (%)	276	39.6 [22.3; 57.7]	46.7 [31.2; 63.4]	31.6 [14.8; 50.0]	<0.001
Right heart parameters					
RV basal diameter (cm)	276	4.3 [3.8; 5.0]	4.1 [3.6; 4.7]	4.5 [3.9; 5.2]	0.001
RA area (cm ²)	254	23.7 [18.5; 29.5]	21.6 [18.0; 26.1]	27.0 [20.0; 32.0]	<0.001
TAPSE (cm)	318	1.6 [1.3; 2.0]	1.8 [1.4; 2.2]	1.5 [1.2; 1.8]	<0.001
FAC (%)	222	35.3 [27.8; 48.1]	39.0 [30.2; 49.3]	31.9 [23.4; 40.5]	<0.001
RV free wall strain, %	189	-16.9 [-22.2; -11.6]	-18.8 [-24.0; -13.3]	-15.8 [-19.0; -11.2]	0.003
Entire RV strain, %	189	-13.1 [-17.4; -9.5]	-15.8 [-18.2; -10.7]	-12.0 [-14.9; -9.1]	0.001
Estimated SPAP (mmHg)	317	45 [36; 55]	42.0 [33.5; 50.0]	48.3 [38.0; 58.0]	<0.001
Left heart parameters					
LVDD (cm)	397	5.4 [4.8; 6.2]	5.1 [4.6; 5.8]	5.7 [5.0; 6.5]	<0.001
LVMI (g/m ²)	346	115.4 [93.7; 142.0]	106.9 [84.5; 134.0]	123.0 [100.0; 147.0]	<0.001
LAVI (cm ³ /m ²)	217	57.0 [42.9; 72.7]	50.0 [39.7; 66.4]	60.0 [50.8; 77.1]	<0.001

MV regurgitation	322	1.5 [1.0; 2.0]	1.0 [1.0; 2.0]	1.5 [1.0; 2.0]	<0.001
LVEF	404	45.0 [30.0; 55.0]	50.0 [35.0; 55.0]	38.0 [25.0; 55.0]	<0.001
LV EF \geq 50%, yes	404	117 (43.8 %)	107 (54.0 %)	70 (34.0 %)	<0.001
E	310	0.8 [0.6; 1.0]	0.7 [0.5; 0.9]	0.9 [0.7; 1.1]	<0.001
E/A	220	1.1 [0.7; 1.9]	0.8 [0.7; 1.4]	1.6 [0.8; 2.2]	<0.001
Average E/e'	202	12.6 [8.5; 18.3]	10.2 [7.5; 15.5]	14.7 [10.2; 20.1]	<0.001
Estimated PCWP	202	16.9 [11.8; 23.8]	13.8 [10.5; 20.4]	19.4 [13.9; 26.1]	<0.001

Values are expressed as n, median (interquartile range) or n (%), unless otherwise stated. Significant p-values (<0.05) are presented in bold. IVC: inferior vena cava; IVCexp: inferior vena cava at expiration; IVCinsp: inferior vena cava et inspiration; FAC: Fractional Area Change; LAVI: left atrial volume index; LVDD: *left ventricular internal diameter* in end-diastole; LVEF: left ventricular ejection fraction; LVMI: left ventricular mass index; MV: mitral valve; PCWP: estimated pulmonary capillary wedge pressure $PCWP = 1.24 * (E/e') + 1.9$; $e' = (e'_{lateral} + e'_{septal}) / 2$ [39]; RA: right atrial; RV: right ventricular; RWT: relative wall thickness; SPAP: systolic pulmonary artery pressure; TA S': peak systolic velocity of tricuspid annulus ; TAPSE: tricuspid annular plane systolic excursion.

Supplementary Table 4. sCD146 concentration in terciles of echocardiographic parameters			
VARIABLES	Terciles	Cut-off points	sCD146 concentration, ng/L
IVC expiration, cm	T1	0.5; 1.91	343.4 [298.5;434.8]
	T2	1.92; 2.48	411.0 [293.9;529.2]
	T3	2.5; 4.2	490.2 [406.3;590.0]
IVC collapse, %	T1	100; 51	348.8 [298.5;437.1]
	T2	50; 29	424.1 [327.7;525.4]
	T3	28; 0	478.6 [377.4;593.8]
B-lines	T1	0; 2	363.3 [332.4;433.7]

	T2	3; 7	439.8 [392.0;582.1]
	T3	8; 31	485.1 [388.5;671.8]
TAPSE, cm	T1	4.0; 1.9	343.4 [273.8;433.2]
	T2	1.8; 1.4	425.6 [342.1;514.1]
	T3	1.36; 0.4	484.1 [360.9;593.8]
RV free wall strain, %	T1	-34.0; -24.1	363.3 [332.4;433.7]
	T2	-19.7; -14.0	439.8 [392.0;582.1]
	T3	-13.9; -2.0	485.1 [388.5;671.8]
Entire RV strain, %	T1	-25.2; -16.4	324.8 [282.0;433.2]
	T2	-16.3; -11.0	426.8 [318.6;530.5]
	T3	-10.8; -1.2	469.4 [360.9;588.9]
E/e'	T1	3.6; 9.4	334.3 [282.1;409.7]
	T2	9.5; 15.6	421.0 [321.0;510.4]
	T3	15.7; 56.7	458.6 [340.0;546.0]
LVDD, cm	T1	3.6; 4.9	336.4 [272.3;440.5]
	T2	5.0; 5.8	421.0 [343.8;506.7]
	T3	5.9; 8.4	471.7 [352.7;575.1]
LAVI, cm ³ /m ²	T1	19.7; 48.4	337.5 [287.5;464.9]
	T2	48.5; 66.4	439.4 [366.5;533.7]
	T3	66.6; 202.0	498.0 [377.4;618.6]
LV EF, %	T1	73; 55	352.8 [292.9;481.5]
	T2	54; 35	402.2 [312.1;489.8]
	T3	34; 3	473.9 [373.1;590.0]
eRAP	Categories		
	Normal		337.5 [299.6;424.8]

	Moderately elevated	404.4 [290.2;488.9]
	High	477.1 [363.3;572.0]
<p>Values are expressed as n, median (interquartile range) or n (%), unless otherwise stated. IVC: inferior vena cava; IVCexp: inferior vena cava at expiration; LAVI: left atrial volume index; LVDD: <i>left ventricular internal diameter</i> in end-diastole; LV EF: left ventricular ejection fraction; RV: right ventricular; TAPSE: tricuspid annular plane systolic excursion.</p>		

Supplementary Table 5. The comparison of AUCs between sCD146 and NT-proBNP for prediction of sonographic and clinical parameters

Variables	n	sCD146		NT- proBNP		p-value#	sCD146 and NT-proBNP		p-value##	P-value###
		AUC	p-value	AUC	p-value		AUC	p-value		
Peripheral oedema, yes	156 (35.7 %)	0.626 [0.545; 0.702]	0,029	0.510 [0.429; 0.591]	0,837	0,009	0.592 [0.494; 0.689]	0,065	0,236	0,022
Rales, yes	399 (91.3 %)	0.596 [0.546; 0.645]	<0.001	0.658 [0.609; 0.704]	<0.001	0,049	0.630 [0.571; 0.690]	<0.001	0,033	0,259
B-lines **	77 (17.6 %)	0.639 [0.472; 0.807]	0,103	0.704 [0.551; 0.857]	0,009	0,529	0.679 [0.520; 0.838]	0,027	0,283	0,758
IVCexp, cm **	278 (63.6 %)	0.680 [0.622; 0.734]	<0.001	0.685 [0.627; 0.739]	<0.001	0,89	0.700 [0.632; 0.867]	<0.001	0,22	0,55
IVC collapse, % *	274 (62.7 %)	0.660 [0.588; 0.731]	<0.001	0.671 [0.596; 0.746]	<0.001	0,785	0.680 [0.609; 0.750]	<0.001	0,065	0,785
RV basal diameter **	275 (62.9 %)	0.593 [0.521; 0.666]	0,012	0.683 [0.616; 0.750]	<0.001	0,023	0.637 [0.566; 0.708]	<0.001	<0.001	0,152
RA end-systolic area**	253 (57.9 %)	0.684 [0.615; 0.754]	<0.001	0.677 [0.607; 0.747]	<0.001	0,861	0.704 [0.636; 0.772]	<0.001	0,071	0,439
TAPSE*	315 (72.1 %)	0.685 [0.623; 0.747]	<0.001	0.701 [0.639; 0.762]	<0.001	0,656	0.702 [0.641; 0.763]	<0.001	0,092	0,966
RV free wall strain, %*	189 (43.2 %)	0.642 [0.558; 0.726]	0,001	0.710 [0.631; 0.789]	<0.001	0,126	0.677 [0.596; 0.758]	<0.001	0,007	0,351
Entire RV strain, %*	189 (43.2 %)	0.659 [0.576; 0.741]	<0.001	0.737 [0.661; 0.813]	<0.001	0,068	0.707 [0.628; 0.785]	<0.001	<0.001	0,372
Tricuspid regurgitation velocity, m/s **	314 (71.9 %)	0.625 [0.557; 0.693]	<0.001	0.629 [0.562; 0.696]	<0.001	0,914	0.642 [0.575; 0.709]	<0.001	0,123	0,673
high eRAP, yes	274 (62.7 %)	0.682 [0.606; 0.757]	<0.001	0.690 [0.612; 0.768]	<0.001	0,85	0.705 [0.632; 0.777]	<0.001	0,011	0,686
LVDD, cm **	393 (89.9 %)	0.656 [0.597; 0.714]	<0.001	0.682 [0.625; 0.739]	<0.001	0,412	0.674 [0.617; 0.732]	<0.001	0,024	0,769
LVMI, g/m ² **	344 (78.7 %)	0.646 [0.583; 0.708]	<0.001	0.742 [0.686; 0.799]	<0.001	0,003	0.681 [0.620; 0.742]	<0.001	<0.001	0,023
LAVI, mL/m ² **	217 (40.3 %)	0.623 [0.540; 0.706]	0,004	0.733 [0.660; 0.806]	<0.001	0,015	0.663 [0.582; 0.744]	<0.001	0,001	0,066
LV EF, % *	400 (91.5 %)	0.632 [0.583; 0.679]	<0.001	0.757 [0.712; 0.798]	<0.001	<0.001	0.678 [0.621; 0.734]	<0.001	<0.001	0,004
E wave *	307 (70.3 %)	0.641 [0.573; 0.708]	<0.001	0.660 [0.594; 0.727]	<0.001	0,59	0.656 [0.590; 0.722]	<0.001	0,12	0,855

E/e' (average) **	ratio	201 (46.0 %)	0.690 [0.613; 0.767]	<0.001	0.710 [0.637; 0.783]	<0.001	0,629	0.720 [0.646; 0.794]	<0.001	0,003	0,778
<p>* Value lower than the median, ** value greater than the median, # P for comparison between sCD146 and NT-proBNP, ## result pairs sCD146 and sCD146/NT-proBNP, ### Test result pairs NT-proBNP and sCD146/NT-proBNP. Values are expressed as n, median (interquartile range) or n (%), unless otherwise stated. Significant p-values (<0.05) are presented in bold. eRAP: estimated right atrial pressure; IVC: inferior vena cava; IVCexp: inferior vena cava at expiration; LAVI: left atrial volume index; LVDD: <i>left ventricular</i> internal <i>diameter</i> in end-diastole; LV EF: left ventricular ejection fraction; LVMI: left ventricular mass index; RA: right atrial; RV: right ventricular; TAPSE: tricuspid annular plane systolic excursion.</p>											