European Journal of Heart Failure (2017) doi:10.1002/ejhf.748



# The effects of short-term omission of daily medication on the pathophysiology of heart failure

## Silviu Dovancescu<sup>1,2,4†</sup>\*, Pierpaolo Pellicori<sup>1†</sup>, Thato Mabote<sup>1</sup>, Azam Torabi<sup>1</sup>, Andrew L. Clark<sup>1</sup>, and John G.F. Cleland<sup>1,3</sup>\*

<sup>1</sup>Department of Cardiology, Hull York Medical School, Hull and East Yorkshire Medical Research and Teaching Centre, Castle Hill Hospital, Cottingham, Kingston upon Hull, UK; <sup>2</sup>Philips Research, Eindhoven, The Netherlands; <sup>3</sup>National Heart & Lung Institute and National Institute of Health Research, Cardiovascular Biomedical Research Unit, Royal Brompton & Harefield Hospitals, Imperial College, London, UK; and <sup>4</sup>Department of Electrical Engineering, Eindhoven University of Technology, Eindhoven, The Netherlands *Received 10 June 2016; revised 14 December 2016; accepted 15 December 2016* 

| Aims                   | Pharmacological therapies for heart failure (HF) aim to improve congestion, symptoms, and prognosis. Failing to take medication is a potential cause of worsening HF. Characterizing the effects of short-term medication omission could inform the development of better technologies and strategies to detect and interpret the reasons for worsening HF. We examined the effect of planned HF medication omission for 48 h on weight, echocardiograms, transthoracic bio-impedance, and plasma concentrations of NT-proBNP.  |
|------------------------|---|
| Methods<br>and results | Outpatients with stable HF and an LVEF <45% were assigned to take or omit their HF medication for 48 h in a random-<br>ized, crossover trial. Twenty patients (16 men, LVEF $32 \pm 9\%$ , median NT-proBNP 962 ng/L) were included. Compared<br>with regular medication, omission led to an increase in NT-proBNP by 99% (from 962 to 1883 ng/L, $P < 0.001$ ), sys-<br>tolic blood pressure by 16% (from 131 to 152 mmHg, $P < 0.001$ ), and left atrial volume by 21% (from 69 to 80 mL,<br>$P = 0.001$ ), and reductions in transthoracic bio-impedance by 10% (from 33 to $30\Sigma$ , $P = 0.001$ ) and serum creatinine<br>by 8% (from 135 to 118 µmol/L, $P = 0.012$ ). No significant changes in body weight, heart rate, or LVEF were observed. |
| Conclusions            | The characteristic pattern of response to short-term medication omission is of increasing congestion but, in contrast to the pattern reported for disease progression, with a rise in blood pressure and improved renal function. In stable HF, weight is not a sensitive marker of short-term diuretic omission.   |
| Keywords               | Heart failure • Medication omission • Congestion • Cardiac ultrasound • Telemonitoring • Transthoracic bio-impedance  |

## Introduction

For patients with heart failure (HF), worsening congestion is a common reason for hospitalizations that might be avoided if the causes can be identified and treated. Up to one in four people in the general population do not take their medication as prescribed,<sup>1</sup> while studies of patients with HF report rates of medication adherence ranging from 10% to 98%, depending on the definition applied and the instrument used.<sup>2,3</sup> Low adherence to medications may lead to worsening HF and disease progression, resulting in hospital admission, increased healthcare costs, and death.<sup>3–5</sup> Several methods have been developed to assess adherence to medication.<sup>6</sup> Although measurement of the blood level of a medicine is a robust and objective method, it is not currently practical for routine clinical use.<sup>3</sup> On the other hand, indirect methods of adherence (patient question-naires, self-reports, pill counts, electronic medication monitors,

\*Corresponding authors. Brompton and Harefield NHS Foundation Trust, Cardiovascular Research Unit, London, UB9 6JH, UK. Tel/Fax: +44 1895 453 895, Email: j.cleland@imperial.ac.uk Department of Electrical Engineering, Eindhoven University of Technology, Den Dolech 2, 5612 AZ, Eindhoven, The Netherlands, Email: s.dovancescu@tue.nl

<sup>†</sup>These authors contributed equally to this work.

© 2017 The Authors. European Journal of Heart Failure published by John Wiley & Sons Ltd on behalf of European Society of Cardiology. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made. and patient diaries) are often subjective and may be inaccurate. The aim of this study was to investigate changes in cardiovascular and renal function following the omission of treatments for HF for 48 h, in order to provide a clinical model for the study of new technologies and strategies for the detection and management of congestion.

## Methods

### **Study population**

Outpatients on stable, guideline-indicated therapy for HF, including a loop diuretic ( $\geq$ 40 mg/day of furosemide or  $\geq$ 1 mg/day of bumetanide), in sinus rhythm with an LVEF <45% on echocardiography and a plasma concentration of NT-proBNP >200 ng/L were enrolled. Patients with breathlessness or chest pain at rest or on minimal exertion and those with implanted pacemakers or defibrillators (that might be incompatible with the bio-impedance technology) or severe valve disease were not eligible for the study.

## Study design

The HeartCycle Heart Failure Trials Programme of the European Commission was an observational trial with randomized components investigating the ability of next-generation home telemonitoring (HTM) to improve the management of patients with HF. One of its aims was to investigate how HTM might be used to improve medication adherence.

Patients were requested to attend on two occasions, on a similar diet for the 3 days prior to each visit. No other specific dietary restriction was imposed. Each patient was asked to take their medication as usual prior to one visit (medication taken) and to omit their HF medications (diuretic, ACE inhibitors, beta-blockers, and aldosterone antagonists) for 48 h prior to the other (medication omitted). The visits were scheduled ~1 week apart. The order of the visits was randomized. Patients were phoned the day before the study to ensure that omission of therapy had not caused any problems. Patients were advised to contact the research staff and/or take their medication as usual if they felt any worsening of their condition or gained >2 kg (4.5 lb).

The study was conducted in accordance with guidelines for clinical trials and the Declaration of Helsinki. The protocol was approved by all relevant ethics committees and the hospital research and development department. Patients provided written informed consent.

## **Data collection**

## Conventional telemonitoring measurements and biochemical data

After voiding urine, patients were weighed (Tanita MC 180MA Class III) while wearing a light gown. Blood pressure and heart rate were measured with an automated sphygmomanometer (Microlife AG, Switzerland). Blood samples were collected for haematology and biochemistry profiles including the assessment of plasma NT-proBNP.

#### **Bio-impedance measurements**

Whole-body bio-impedance was measured in parallel to body weight with a commercial body composition analyser (Tanita MC 180MA Class III) which uses the palms and soles of the subject as electrical contact areas. The device applies predictive modelling to estimate body composition including total body water from bio-impedance data measured at four frequencies (5, 50, 250, and 500 kHz) and subject characteristics, e.g. sex, age, weight, and height.

Transthoracic bio-impedance was measured with a wearable bio-impedance monitor (BIM) designed to enable patient self-assessment (*Figure 1*). The BIM is an investigational device which includes an electronic module and an adjustable vest with four textile electrode pads arranged pair-wise on either side of the rib cage, at the base of the lungs. The BIM measures bio-impedance at 16 different frequencies distributed logarithmically from 10 kHz to 1 MHz. The multifrequency BIM data are used to fit the Cole–Cole model ( $Z = R_{\infty} - \frac{R_{\infty} - R_E}{1 + (j\frac{E}{k})^{\alpha}}$ ),<sup>7,8</sup> which provides information about tissue characteristics. The model parameters reflect extracellular fluid ( $R_E$ ), intracellular fluid ( $R_{\infty}$ ), tissue relaxation ( $f_c$ ), and tissue heterogeneity ( $\alpha$ ). Intrathoracic fluid accumulation due to worsening HF directly affects the value of  $R_E$ , which should decrease.<sup>9,10</sup> BIM measurements were determined over 3 min in the sitting position.

#### **Echocardiographic measurements**

Echocardiography was performed by an experienced operator using a Vivid Nine (GE Healthcare, UK) system operating at 3.4 MHz. Doppler tracings and two-dimensional images were obtained from parasternal long- and short-axis, apical, and subcostal views. Echocardiograms were stored and retrospectively reviewed using an EchoPAC station (GE Healthcare, UK) by a single operator (P.P.) blinded to randomization. The LVEF was measured using Simpson's biplane method. Left atrial (LA) maximum, the frame just before mitral valve opening, and LA minimum, the frame just after mitral valve closure, volumes were measured in four-chamber view. The LA endocardial border was traced manually. The anterior border was at the mitral annular plane and the posterior border at the ostia of the pulmonary veins. The LA emptying function (LAEF) was measured using the formula:  $LAV_{max} - LAV_{min}/LAV_{max}$ . Peak early velocity (e') was measured by using tissue Doppler imaging at the lateral (e'<sub>lat</sub>) and septal (e'<sub>sep</sub>) border of the mitral valve annulus. Right ventricular (RV) systolic function was assessed using tricuspid annular plane systolic excursion (TAPSE). With the patient in the supine position, the maximum inferior vena cava (IVC) diameter during the respiratory cycle was measured  $\sim$ 3 cm before it merged with the right atrium.

### Data analysis and statistics

Categorical data are presented as percentages; normally distributed continuous data as mean  $\pm$  standard deviation (SD), and non-normally distributed variables as median and interquartile range. Effects of medication omission were studied in the overall study population and in subgroups above and below the median NT-proBNP value. Relative changes in measures between the visit medication taken and medication omitted were determined using the formula: Omitted – Taken/Taken. The statistical significance of relative and absolute changes was assessed using the *t*-test for normally distributed variables and Wilcoxon signed rank test otherwise. A *P*-value <0.05 was considered statistically significant.

## Results

Twenty patients (80% men, mean LVEF  $32 \pm 9\%$ , median NT-proBNP 962 ng/L) were enrolled in the study. Most patients



Figure 1 Bio-impedance monitor consisting of an adjustable vest with integrated textile electrodes and a slim electronics case.

had mild symptoms (16 in NYHA class II). Patient characteristics and treatment at baseline are presented in *Table 1*. All patients were treated with loop diuretics and beta-blockers, mainly carvedilol, 18 received either an ACE inhibitor or ARB, but only 7 (35%) received a mineralocorticoid receptor antagonist, although this was consistent with guidelines for patients with predominantly NYHA class II HF at the time the study was conducted.

Measurements made during visits with medication taken or omitted, and the relative changes in each variable are listed in Table 2, for the overall study group and for patients above and below the median plasma NT-proBNP. With omission of HF therapies for 48 h, six patients (30%) reported an increase in exertional breathlessness with a deterioration in NYHA class by one rank. Omission of medications was associated with an increase in systolic blood pressure (from 131 to 152 mmHg, P < 0.001) and plasma NT-proBNP, which almost doubled (from 962 to 1883 ng/L, P < 0.001), and a fall in serum creatinine (from 135 to  $118 \mu mol/L$ , P = 0.012). Weight, despite omission of diuretics, and heart rate, despite omission of beta-blockers, did not change. Amongst echocardiographic measurements, LV and LA volumes and IVC diameter increased [LV end-diastolic volume (LVEDV), +11%, P=0.008; LAV<sub>max</sub>, +21%, P<0.001; IVC diameter, +18%, P = 0.004]. The transmitral peak E velocity increased (E, +23%, P = 0.001), indicating a reduction in LAEF. However, LVEF and E/e' did not change significantly. Transthoracic BIM decreased ( $R_{\rm F}$ , -10%, P = 0.001), as did total body impedance (Z, -5%, P < 0.001). Changes in renal function [estimated glomerular filtration rate (eGFR), +12%, P=0.015) were mostly driven by improvements in the subgroup with lower NT-proBNP, while the behaviour of other measurements was similar regardless of NT-proBNP subgroup.

## Table 1 Demographic, clinical, and pharmacological treatment data for the study population

| Characteristics         | Total cohort (n = 20) |
|-------------------------|-----------------------|
| Age, years              | 71 (62, 77)           |
| Women                   | 4 (20)                |
| Aetiology               |                       |
| Ischaemic heart disease | 16 (80)               |
| Height, cm              | 167 (161, 170)        |
| Weight, kg              | 75 (68, 91)           |
| BMI, kg/m <sup>2</sup>  | 28 (24, 32)           |
| NYHA class              |                       |
| I                       | 4 (20)                |
| Ш                       | 16 (80)               |
| Co-morbidities          |                       |
| Hypertension            | 13 (65)               |
| Diabetes mellitus       | 5 (25)                |
| Sinus rhythm            | 20 (100)              |
| LVEF, %                 | 35 (27, 39)           |
| Treatments              |                       |
| ACE inhibitors or ARBs  | 18 (90)               |
| Beta-blockers           | 20 (100)              |
| Loop diuretics          | 20 (100)              |
| MRA                     | 7 (35)                |
| Digoxin                 | 1 (5)                 |

Data are expressed as median (interquartile range) or absolute number (%). BMI, body mass index; MRA, mineralocorticoid receptor antagonist.

## Discussion

This study shows that withholding medication for 48 h, including loop diuretics, results in increases in several measures of congestion including a rise in plasma NT-proBNP, increases in atrial and

Table 2 Effects of medication omission in the overall study population and in subgroups with NT-proBNP above and below median values (all patients were in cinus rhuthm) for the visit when medication was taken

|  | Vertelle         Talen         Ornitadi         P-value         Main         Ornitadi         Main         Solution         Main  |  | Overall study po   | Overall study population $(n = 20)$                                |               |             |                              | NT-proBNP <         | NT-proBNP <962 ng/L ( $n = 10$ )                 | (c                              |             |                          | NT-proBNP >962 ng/L ( $n = 10$ )                                    | 962 ng/L (n = 10)        |                |                      |                         |
|--|---|--|--|--|---------------|-------------|------------------------------|---------------------|--|---------------------------------|-------------|--------------------------|---|--------------------------|----------------|----------------------|-------------------------|
| Tech data         1  | $ \begin{array}{c c c c c c c c c c c c c c c c c c c $   | Variable   | Taken  | Omitted  |               | ∆%          | P-value                      | Taken               | Omitted  | P-value                         | : 1         | P-value                  | Taken   | • 1                      | P-value        | %⊽                   | P-value                 |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$  | $ \begin{array}{cccccccccccccccccccccccccccccccccccc$   | YHA class, n (%)   |  |  |               |             |                              |                     |  |                                 |             |                          |   |                          |                |                      |                         |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$  | $ \begin{array}{cccccccccccccccccccccccccccccccccccc$   |  | 4 (20%)<br>16 (80%)  | 3 (15%)<br>12 (60%)  |               |             |                              | 3 (30%)<br>7 (70%)  | 2 (20%)<br>5 (50%)                               |                                 |             |                          | 1 (10%)<br>9 (90%)  | 1 (10%)<br>7 (70%)       |                |                      |                         |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$  | $ \begin{array}{cccccccccccccccccccccccccccccccccccc$   | _  | 0 (0%)   | 5 (25%)  |               |             |                              | 0 (0%)              | 3 (30%)  |                                 |             |                          | 0 (0%)  | 2 (20%)                  |                |                      |                         |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$  | $ \begin{array}{c} Princhial determinational determination and the form of $  | VYHA class, 'average'  | 1.8  | 2.1  | 0.010         |             |                              | 1.7                 | 2.1  | 0.037                           |             |                          | 1.9   | 2.1                      | 0.168          |                      |                         |
| Wert wert for the first of the  | Weight, Q         No.10         State 1         State 1         State 3         No.10         NV.1.1.1.1.         NO.10         NV.1.1.1.1.         NO.10         NV.1.1.1.1.         NO.10         NV.1.1.1.1.         NO.10         NV.1.1.1.1.         NO.10         NV.1.1.1.1.         NV.1.1.1.1.         NV.1.1.1.1.1.         NV.1.1.1.1.1.1.         NV.1.1.1.1.1.1.1.         NV.1.1.1.1.1.1.1.1.         NV.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1  | onventional telemonitor  | ing measurements   |  | 0000          | 0           |                              |                     |  | 107.0                           |             |                          |   |                          |                | 10.0                 | 0000                    |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$  | Be mindle Table The form the the form of  | Veight, kg   | 79.6 ± 16.8  |  | 0.089         | <1%         | 0.076                        | $79.7 \pm 16.2$     | $80.0 \pm 16.1$                                  | 0.435                           | <1%         | 0.433                    | $79.6 \pm 18.3$   | $80.2 \pm 17.9$          | 0.106          | <1%                  | 0.090                   |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$  | By Entropy and the set of the se   | BP, mmHg   | $131 \pm 20$   |  | <0.001        | 16%         | <0.001                       | $132 \pm 19$        | $154 \pm 28$                                     | 0.006                           | 17%         | 0.005                    | $131 \pm 22$  | $150 \pm 26$             | 0.010          | 15%                  | 0.015                   |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$  | The parties interaction of the target of  | )BP, mmHg  | $78 \pm 17$  |  | 0.054         | 12%         | 0.029                        | $75 \pm 18$         | $83 \pm 10$                                      | 0.221                           | 16%         | 0.118                    | $82 \pm 16$   | $87 \pm 18$              | 0.103          | 8%                   | 0.098                   |
| $ \begin{array}{c} \matrix matrix $   | $ \begin{array}{cccccccccccccccccccccccccccccccccccc$   | IR, b.p.m.   | $66 \pm 14$  |  | 0.883         | 3%          | 0.533                        | $65 \pm 18$         | $69 \pm 16$                                      | 0.115                           | 8%          | 0.102                    | $67 \pm 10$   | $65 \pm 19$              | 0.748          | -1%                  | 0.913                   |
| $ \begin{array}{c} (76-151) \\ \text{remains}, \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \$  | $ \begin{array}{cccccccccccccccccccccccccccccccccccc$   | ocriemical data<br>JT-proBNP, ng/L   | 962 (600-1486)   |  | <0.001        | %66         | <0.001                       | 601 (374–790)       | 926  | 0.005                           | %06         | 0.001                    | 1486  | 3139                     | 0.001          | 107                  | 0.003                   |
| The standard fragmer of the standard s  | lamoglobing gld. 114±15 132±16 012 -2% 0165 125±12 126±11 0154 -2% 0166 145±15 circle for the   | 0  |  |  |               |             |                              |                     | (776-1512)                                       |                                 |             |                          | (1212-1824)   | (2667–3454)              |                |                      |                         |
| GFR multiminity         33:2:40         111±-40         0013         13:2:40         111±-44         0.133         -6:2:7         0.003         15:2:40         111±-44         0.133         -6:2:7         0.033         5:2:7         0.033         0.5:2:7         0.033         0.5:2         0.033         0.5:2         0.033         0.5:2         0.033         0.5:2         0.033         0.5:2         0.033         0.5:2         0.033         0.5:2         0.033         0.5:2         0.033         0.5:2         0.033         0.5:2         0.033         0.5:2         0.033 <th0.033< th="">         &lt;</th0.033<>  | Terentine, molul, 173 ± 60 118 ± 40 0012 - 8% 0008 142 ± 62 57 ± 17 0007 17% 0033 66 ± 27 becarrentine, multi-line) 55 ± 22 59 ± 19 0023 124 ± 60 57 ± 17 0007 17% 0033 66 ± 27 becarrenting product data 55 ± 21 0006 172 ± 60 becarrentine, molti-line) 176 007 17% 0033 66 ± 27 becarrenting product data 186 ± 70 0017 13% 0008 141 ± 23 0049 14% 0047 286 0038 172 ± 73 0007 136 0018 11% 0015 59 ± 19 0013 33 ± 10 0047 13% 0007 13% 0008 141 ± 23 0007 15% 0005 172 ± 73 0077 15% 0005 172 ± 73 0071 136 ± 70 0012 0018 11% 0013 59 ± 19 0013 0014 001 0014 001 0014 001 0014 001 001  | łaemoglobin, g/dL  | $13.4 \pm 1.5$   |  | 0.128         | -2%         | 0.165                        | $12.9 \pm 1.2$      | 12.6 ± 1.1                                       | 0.154                           | -2%         | 0.166                    | $14.0 \pm 1.5$  | $13.8 \pm 1.5$           | 0.429          | -2%                  | 0.507                   |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$  | Tells, multimit 17.3m <sup>3</sup> 5.±22 39±19 0.025 12% 0.015 51±16 57±17 0.007 17% 0.033 6.±27 0.054 12.54 0.47 2.025 6.54 0.47 2.025 0.47 2.027 1% 0.25 0.54 0.47 2.027 1% 0.25 0.54 0.47 2.027 1% 0.25 0.54 0.47 2.027 1% 0.25 0.54 0.47 2.027 1% 0.25 0.54 0.47 2.027 1% 0.25 0.54 0.47 2.027 1% 0.25 0.54 0.47 2.027 1% 0.25 0.54 0.47 2.027 1% 0.25 0.54 0.47 2.027 1% 0.25 0.54 0.47 2.027 1% 0.25 0.54 0.47 2.027 1% 0.25 0.05 0.41 2.24 0.007 11% 0.008 1.41 0.2 0.001 0.55 0.010 0.57 1.5% 0.057 0.54 0.49 0.051 0.52 0.05 0.012 0.07 0.012 0.07 0.015 0.011 0.55 0.010 0.57 0.011 0.55 0.012 0.070 0.01 0.55 0.010 0.57 0.01 0.57 0.013 0.52 0.02 0.01 0.52 0.01 0.54 0.02 0.01 0.57 0.012 0.014 0.01 0.55 0.01 0.57 0.010 0.54 0.02 0.01 0.54 0.01 0.54 0.01 0.54 0.01 0.54 0.02 0.01 0.54 0.01 0.52 0.54 0.54 0.54 0.52 0.54 0.54 0.52 0.54 0.54 0.52 0.54 0.54 0.52 0.54 0.54 0.54 0.54 0.54 0.54 0.54 0.54  | Creatinine, μmol/L   | $135 \pm 60$   |  | 0.012         | -8%         | 0.008                        | $142\pm 62$         | $120 \pm 38$                                     | 0.042                           | -13%        | 0.006                    | $127 \pm 60$  | $117 \pm 44$             | 0.153          | -4%                  | 0.407                   |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$  | WEDC, mm. 133 ± 67 ± 10 0.064 3% 0.058 57 ± 6 57 ± 7 ± 7 0.572 1% 0.526 65 ± 8 VEDC, mm. 136 ± 70 200 ± 65 + 0.007 11% 0.003 14 ± 2.3 106 ± 2.3 0.057 15% 0.038 172 ± 73 VEDC, mm. 136 ± 70 200 ± 65 + 0.007 13% 0.038 172 ± 73 0.057 13% 0.038 172 \pm 73 0.071 0.056 \pm 0.071 0.057 0.013 0.057 0.013 0.071 0.05 0.031 0.071 0.05 0.013 0.071 0.05 0.031 0.072 0.015 0.014 0.01 0.071 0.012 0.012 0.071 0.012 0.012 0.071 0.012 0.071 0.012 0.014 0.01 0.071 0.012 0.014 0.01 0.011 0.015 0.013 0.014 0.01 0.017 0.013 0.014 0.01 0.017 0.012 0.014 0.01 0.017 0.012 0.014 0.01 0.011 0.014 0.01 0.015 0.01 0.012 0.014 0.01 0.017 0.012 0.014 0.01 0.011 0.014 0.01 0.011 0.014 0.01 0.01  | GFR, mL/min/1.73 m <sup>2</sup>  | $55 \pm 22$  |  | 0.025         | 12%         | 0.015                        | $51 \pm 16$         | $57 \pm 17$                                      | 0.007                           | 17%         | 0.033                    | $60 \pm 27$   | $60 \pm 22$              | 0.778          | %9                   | 0.273                   |
| The contrast of the set of the s  | Constraint         161 ± 70         0.015         11%         0.006         141 ± 30         151 ± 39         0.047         15%         0.037         13%         0.037         0.14         0.035         0.17         0.035         0.37 ± 10         0.11         13%         0.037         0.13         0.037         0.037         0.037         0.037         0.037         0.037         0.037         0.035         0.037         0.037         0.036         0.037         0.035         0.037         0.037         0.037         0.037         0.037         0.037         0.037         0.035         0.037         0.035         0.037         0.036         0.037         0.035         0.037         0.036         0.037         0.036 </td <td>NeDD mm</td> <td>61 + R</td> <td>63 + 10</td> <td>0.064</td> <td>%۲</td> <td>0.058</td> <td>57 + 6</td> <td>57+7</td> <td>0572</td> <td>1%</td> <td>0576</td> <td>65 ± 8</td> <td>68 + 10</td> <td>0.077</td> <td>76%</td> <td>0.075</td>  | NeDD mm  | 61 + R   | 63 + 10  | 0.064         | %۲          | 0.058                        | 57 + 6              | 57+7   | 0572                            | 1%          | 0576                     | 65 ± 8  | 68 + 10                  | 0.077          | 76%                  | 0.075                   |
| The second seco  | Constraint         Total To   | VEDV ml  | 01 ± 0<br>186 + 70   | 01 ± 69  | 0.007         | 11%         | 800.0                        | J/ ± 0<br>141 + 73  | 0, ⊥, 1<br>161 + 39                              | 7/C'O                           | 14%         | 0.047                    | 03 ± 0<br>230 + 75  | 00 ± 10<br>242 + 69      | 0.079          | %D                   | 0.086                   |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$  | With 55±15 66±12 0:120 12% 0.038 55±10 58±19 0:116 12% 0.073 56±19 0:16 12% 0.073 56±19 0:16 12% 0.073 56±19 0:16 12% 0.073 56±19 0:16 12% 0.073 56±19 0:16 12% 0.073 56±19 0:16 12% 0.073 56±19 0:16 12% 0.073 0:14 0:22 0:70±012 0:70±013 0:70±014 0:70 0:70±014 0:70 0:70±014 0:70 0:70±012 0:70±014 0:7   | VESV. ml   | $130 \pm 67$   |  | 0.018         | 11%         | 0.015                        | 89+19               | $101 \pm 33$<br>103 + 33                         | 0.057                           | 15%         | 0.058                    | 170 ± 73  | 2-12 ± 07<br>181 + 72    | 0.196          | %9                   | 0.139                   |
| Eff. No. $32\pm9$ $32\pm9$ $32\pm10$ $039$ $13^{\circ}$ $037$ $27\pm9$ $27\pm10$ $077$ $68$ $035$ $037$ $0366$ $036$ <td>(F)         <math>32\pm9</math> <math>32\pm10</math> <math>3</math></td> <td>&lt;, mL</td> <td><math>55 \pm 15</math></td> <td></td> <td>0.120</td> <td>12%</td> <td>0.028</td> <td><math>53 \pm 10</math></td> <td><math>58 \pm 19</math></td> <td>0.116</td> <td>12%</td> <td>0.075</td> <td><math>58 \pm 19</math></td> <td>61 ± 10</td> <td>0.495</td> <td>11%</td> <td>0.193</td>  | (F) $32\pm9$ $32\pm10$ $3$  | <, mL  | $55 \pm 15$  |  | 0.120         | 12%         | 0.028                        | $53 \pm 10$         | $58 \pm 19$                                      | 0.116                           | 12%         | 0.075                    | $58 \pm 19$   | 61 ± 10                  | 0.495          | 11%                  | 0.193                   |
| mis         059±019         071±019         071±019         071±019         071±019         071±019         071±013         0  | mis         0.59±019         0.70±019         0.001         23%         0.001         0.57±0.10         0.64±0.14         0.020         1.13         0.023         0.61±0.22           intis         0.70±0.12         0.74±0.28         0.73±0.10         0.64±0.14         0.023         0.61±0.22         0.77±0.18         0.023         0.61±0.22         0.77±0.18         0.024±0.01         0.03±0.01         0.03±0.01         0.03±0.01         0.03±0.01         0.03±0.01         0.03±0.01         0.03±0.01         0.03±0.01         0.03±0.01         0.03±0.01         0.03±0.01         0.03±0.01         0.04±0.01         0.03±0.01         0.04±0.01         0.03±0.01         0.04±0.01         0.03±0.01         0.04±0.01         0.03±0.01         0.04±0.01         0.03±0.01         0.04±0.01         0.03±0.01         0.04±0.01         0.03±0.01         0.04±0.01         0.03±0.01         0.04±0.01         0.04±0.01         0.04±0.01         0.04±0.01         0.03±0.01         0.04±0.01         0.03±0.01         0.04±0.01         0.04±0.01         0.04±0.01         0.04±0.01         0.04±0.01         0.04±0.01         0.04±0.01         0.04±0.01         0.04±0.01         0.04±0.01         0.04±0.01         0.04±0.01         0.04±0.01         0.04±0.01         0.04±0.01         0.04±0.01         0.04±0.01         <   | /EF, %   | $32 \pm 9$   |  | 0.998         | 1%          | 0.763                        | 38±6                | $37 \pm 7$                                       | 0.655                           | -2%         | 0.579                    | $27 \pm 9$  | $27 \pm 10$              | 0.797          | 4%                   | 0.560                   |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$  | $ \begin{array}{llllllllllllllllllllllllllllllllllll$   | , m/s  | $0.59 \pm 0.19$  | 19   |               | 23%         | 0.001                        | $0.57 \pm 0.10$     | $0.64 \pm 0.14$                                  | 0.020                           | 13%         | 0.023                    | $0.61 \pm 0.25$   | $0.76 \pm 0.23$          | 0.011          | 32%                  | 0.008                   |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$  | A ratio         0.96 ± 0.55         1.13 ± 0.70         0.056         20%         0.013         0.74 \pm 0.22         0.73 \pm 0.11         0.816         2%         0.793         1.15 \pm 0.69         0.055 ± 0.01         0.1121         15%         0.064 ± 0.01         0.015 ± 0.03         0.055 ± 0.03         0.014 ± 0.01         0.055 ± 0.01         0.1121         15%         0.064 ± 0.01         0.015 ± 0.03         0.064 ± 0.01         0.055 ± 0.03         0.014 ± 0.01         0.035 ± 0.03         0.044 ± 0.01         0.055 ± 0.03         0.061 ± 0.02         0.064 ± 0.01         0.055 ± 0.03         0.044 ± 0.01         0.055 ± 0.03         0.045 ± 0.03         0.065 ± 0.03         0.055 ± 0.03         0.055 ± 0.03         0.055 ± 0.03         0.055 ± 0.03         0.055 ± 0.03         0.055 ± 0.03         0.055 ± 0.03         0.055 ± 0.03         0.055 ± 0.03         0.055 ± 0.03         0.012 ± 0.64         0.055 ± 0.03         0.012 ± 0.64         0.012 ± 0  | , m/s  | $0.70 \pm 0.22$  |  |               | %9          | 0.352                        | $0.79 \pm 0.20$     | $0.87 \pm 0.23$                                  | 0.142                           | 12%         | 0.198                    | $0.62 \pm 0.22$   | $0.62 \pm 0.28$          | 0.964          | %0                   | 0.982                   |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$  | weak         0.04 \pm 0.01         0.05 \pm 0.01         0.05 \pm 0.01         0.033         15%         0.087         0.044 \pm 0.01           ist, m/s         0.06 \pm 0.02         0.05 \pm 0.02         0.05 \pm 0.01         0.05 \pm 0.01         0.07 \pm 0.01         0.04 \pm 0.01         0.05 \pm 0.02         0.037         0.044 \pm 0.01           ist, m/s         0.06 \pm 0.02         0.06 \pm 0.02         0.05 \pm 0.02         0.522         20%         0.117         0.06 \pm 0.02         0.024         32%         0.336         15 \pm 5         0.336         15 \pm 6         0.335         15 \pm 6         0.335         15 \pm 6         0.335         15 \pm 5         0.101         37 \pm 5         0.011         5%         0.015         24%         0.016         37 \pm 5         0.011         6%         0.127         6%         0.127         6%         0.126         0.326         17 \pm 6         0.312         45 \pm 5         0.116         6%         0.127         6%         0.126         0.326         0.126         0.326         0.127         6%         0.127         6%         0.120         0.326         0.326         0.326         0.326         0.326         0.326         0.326         0.326         0.326         0.326         0.326         0.326         0.326   | /A ratio   | $0.96 \pm 0.55$  |  |               | 20%         | 0.013                        | $0.74 \pm 0.22$     | $0.73 \pm 0.11$                                  | 0.816                           | 2%          | 0.794                    | $1.15 \pm 0.69$   | $1.49 \pm 0.82$          | 0.031          | 37%                  | 0.006                   |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$  |   | sep, m/s   | $0.04 \pm 0.01$  |  |               | 15%         | 0.102                        | $0.04 \pm 0.01$     | $0.05 \pm 0.01$                                  | 0.093                           | 15%         | 0.087                    | $0.04 \pm 0.01$   | $0.04 \pm 0.02$          | 0.462          | 15%                  | 0.379                   |
| $e_{ix}^{(u)}$ 15 ±5 17 ±10 0.252 20% 0.102 14±3 14±4 0.957 3% 0.736 15±16 21±13 0.258 37% 0.109 e_{ix}^{(u)} 15 ±5 17 ±16 0.246 49% 0.022 e_{ix}^{(u)} 15 ±5 17 ±16 0.246 49% 0.023 7% 0.041 $e_{ix}^{(u)}$ 13 ±10 13 ±17 0.248 0.011 5% 0.001 37 ± 5 0.242 9% 0.015 0.455 15 ± 14 17 ± 8 0.033 7% 0.043 $e_{ix}^{(u)}$ 13 ± 10 12 ± 1 ± 0.016 0.012 21% 0.013 7% 0.001 27 ± 5 0.013 7% 0.001 20 ± 16% 0.010 $e_{ix}^{(u)}$ 13 ± 1 0 0.011 21% 0.001 37 ± 5 0.012 0.41 $e_{ix}^{(u)}$ 13 ± 1 0.015 34% 0.013 $e_{ix}^{(u)}$ 13 ± 1 0.015 34% 0.013 $e_{ix}^{(u)}$ 19 ± 4 0.013 75 ± 10 0.016 12 1% 0.001 27 ± 6 0.012 11% 0.013 $e_{ix}^{(u)}$ 19 ± 4 0.013 75 ± 10 0.010 21 ± 16% 0.010 $e_{ix}^{(u)}$ 19 ± 4 0.013 25 ± 10 0.012 - 16% 0.010 $e_{ix}^{(u)}$ 19 ± 4 0.013 25 ± 10 0.012 - 16% 0.010 $e_{ix}^{(u)}$ 19 ± 4 0.013 25 ± 10 0.012 - 16% 0.010 $e_{ix}^{(u)}$ 19 ± 4 0.013 25 ± 0.001 19 ± 4 0.012 - 16% 0.010 $e_{ix}^{(u)}$ 10 $e_{ix}^{(u)}$ 11 $e_{ix}^{(u)}$ 10 $e_{ix}^{(u)}$ 11 $e_{ix}^{(u)}$ 10 $e_{ix}^{(u)}$ 11 $e_{ix}^{(u)}$ 11 $e_{ix}^{(u)}$ 10 $e_{ix}^{(u)}$ 10 $e_{ix}^{(u)}$ 11  |   | lat, m/s   | $0.06 \pm 0.02$  | 02   | 0.524         | 20%         | 0.176                        | $0.06 \pm 0.02$     | $0.07 \pm 0.02$                                  | 0.204                           | 32%         | 0.198                    | $0.05 \pm 0.03$   | $0.05 \pm 0.02$          | 0.708          | %6                   | 0.640                   |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$  | $le_{i_{i_{i_{i_{i_{i_{i_{i_{i_{i_{i_{i_{i_$  | /e' <sub>sep</sub>   | $15 \pm 5$   |  | 0.262         | 20%         | 0.102                        | 14±3                | $14\pm4$   | 0.957                           | 3%          | 0.736                    | <b>16±6</b>   | $21 \pm 13$              | 0.258          | 37%                  | 0.109                   |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$  | A diameter, mm $40\pm 6$ $42\pm 5$ 0.001 21% 0.001 37 $\pm 6$ 39 $\pm 5$ 0.127 6% 0.120 83 $\pm 5$ 0.120 43 $\pm 5$ 0.120 43 $\pm 5$ 0.120 43 $\pm 5$ 0.120 43 $\pm 5$ 0.121 45 0.001 48 $\pm 21$ 450, mm, mL 39 $\pm 20$ 59 $\pm 20$ 59 $\pm 20$ 50.001 37 $\times$ 0.001 31 $\pm 17$ 41 $\pm 15$ 0.004 41 $\times$ 0.001 88 $\pm 21$ 450, mm 19 $\pm 4$ 55, mm 19 $\pm 4$ 25.1 0.003 19 $\pm 4$ 0.001 37 $\times$ 0.001 47 $\pm 8$ 21 $\pm 5$ 0.004 41 $\pm 8$ 0.001 88 $\pm 21$ 0.001 48 $\pm 21$ APS, mm 19 $\pm 4$ 25.1 0.003 19 $\pm 4$ 0.001 37 $\times$ 0.004 17 $\pm 6$ 0.016 -18% 0.086 42\pm 10 0.056 -18% 0.086 42\pm 10 0.056 mm 19\pm 4 20 $\pm 4$ 2.0 20.0 19\pm 4 0.001 37 $\times$ 0.001 17 $\pm 0.4$ 2.0 $\pm 0.012$ 2.3% 0.080 1.9 \pm 0.3 -impedance data 5.7 3 2.1 $\pm 0.4$ 0.003 18% 0.004 1.7 \pm 0.4 2.0 \pm 0.012 2.3% 0.080 1.9 \pm 0.3 -impedance data 5.1 394 $\pm 7.0$ 0.001 37 $\times$ 0.001 37 $\times$ 1.4 0.4 2.0 \pm 0.012 2.3% 0.080 1.9 \pm 0.3 CA - TBW, L 383 $\pm 7.1$ 39.4 $\pm 7.0$ 0.001 3% 0.001 47.8 \pm 5.1 48.8 \pm 5.5 0.010 2.3% 0.080 49\pm 7.8 CA - TBW, $\%$ 48.6 $\pm 5.1$ 49.7 $\pm 5.3$ 2.001 3% 0.001 37.7 \pm 6.6 38.6 \pm 6.4 0.012 2\% 0.009 601 $\pm 105$ CA - TBW, $\%$ 48.6 $\pm 5.1$ 49.7 $\pm 5.3$ 2.4 0.001 2\% 0.001 37.7 \pm 6.6 38.6 \pm 6.4 0.010 2\% 0.003 49 \pm 5.3 MI - $R_{\rm c}$ .03 33 $\pm 8$ 3.0 $\pm 8$ 0.001 2\% 0.001 3% 0.001 3.7.7 \pm 6.6 38.6 \pm 6.4 0.010 2\% 0.003 49 \pm 5.3 MI - $R_{\rm c}$ .03 33 $\pm 8$ 0.002 -10% 0.001 3% 0.001 3.7.7 \pm 6.6 38.6 $\pm 6.4$ 0.010 2\% 0.003 49 \pm 5.3 MI - $R_{\rm c}$ .0 33 $\pm 8$ 0.001 2\% 0.001 3% 0.001 3.7.7 \pm 6.6 38.6 $\pm 6.4$ 0.010 2\% 0.003 49 \pm 5.3 MI - $R_{\rm c}$ .0 33 $\pm 8$ 0.003 2.10 $\pm 0.001$ 2% 0.0001 2\% 0.006 -9\% 0.053 3.2 \pm 8 MI - $R_{\rm c}$ .0 33 $\pm 0.6$ 0.002 -10% 0.001 35 \pm 9 31 $\pm 9$ 0.006 -9\% 0.053 3.2 \pm 8 muts are reported as percentage of the respective subgroup. Transmitral past atrial flow velocity metal and usci 1.4 \pm 10.4 mutus $\epsilon^{\rm exp}$ past atrial flow velocity metal and 0.0002 -10\% 0.0001 35 \pm 9 31 $\pm 9$ 0.006 -9\% 0.005 -9\% 0.005 3.2 \pm 8 mutus $\epsilon^{\rm exp}$ the septentian flow velocity metal and the septentian flow velocity metal and 0.0001 2\% 0.0000 1000000000000000000000000000000                                       | /e <sup>'lat</sup>   | $13 \pm 10$  |  | 0.749         | 24%         | 0.081                        | $11 \pm 6$          | $10 \pm 4$                                       | 0.483                           | -1%         | 0.955                    | $15 \pm 14$   | 17±8                     | 0.468          | 49%                  | 0.052                   |
| $ \begin{split} \mathcal{W}^{max}, mL = 69\pm 26  0.001  21\%  0.001  21\%  0.001  21\%  0.001  21\pm 5  0.001  80\pm 21  0.015  24\%  0.001  80\pm 21  0.021  10\%  0.001  34\%  0.001  34\%  0.001  34\%  0.001  34\%  0.001  34\%  0.001  34\%  0.001  34\%  0.001  34\%  0.001  34\%  0.001  34\%  0.001  34\%  0.001  34\%  0.001  34\%  0.001  34\%  0.001  34\%  0.001  34\%  0.001  34\%  0.001  34\%  0.001  35\pm 11  0.012  -16\%  0.000  35\pm 11  0.012  -16\%  0.000  35\pm 11  0.012  -16\%  0.001  25\%  0.004  1.7\pm 0.4  2.0\pm 0.4  0.002  25\%  0.001  13\%  0.000  19\pm 0.3  2.2\pm 0.4  0.045  36\%  0.001  -6\%  0.001 $   | Mmax, mL $69\pm 28$ $80\pm 2.6$ $0.001$ $21\%$ $0.001$ $31\pm 17$ $41\pm 15$ $0.015$ $24\%$ $0.016$ $80\pm 2.1$ $M_{min}$ , mL $39\pm 20$ $50\pm 20$ $6.0001$ $31\pm 17$ $41\pm 15$ $0.015$ $24\%$ $0.001$ $80\pm 2.1$ $M_{min}$ , mL $39\pm 20$ $50\pm 20$ $<0.001$ $31\pm 17$ $41\pm 15$ $0.005$ $42\pm 10$ $MPSE$ , mm $19\pm 4$ $0.023$ $=17\%$ $0.004$ $47\pm 8$ $39\pm 16$ $0.001$ $48\pm 21$ $APSE$ , mm $19\pm 4$ $0.023$ $=17\%$ $0.004$ $47\pm 8$ $0.016$ $41\%$ $0.001$ $48\pm 21$ $APSE$ , mm $19\pm 4$ $0.023$ $=17\%$ $0.004$ $41\pm 8$ $0.001$ $48\pm 21$ $APSE$ , mm $18\%$ $0.001$ $57\pm 66$ $564\pm 48$ $0.013$ $42\pm 10$ $C = TBW, L         383\pm 7.1 39\pm 4\pm 7.0 0.001 37.7\pm 6.6 564\pm 48 0.013 59\pm 7.8 C = TBW, $  | A diameter, mm   | $40\pm 6$  |  | 0.011         |             | 0.010                        | $37 \pm 6$          | 39±5   | 0.127                           | %9          | 0.120                    | $43 \pm 5$  | 46±4<br>55 51            | 0.053          | %/                   | 0.049                   |
| $ \begin{array}{llllllllllllllllllllllllllllllllllll$  | Wrini, mL $37\pm 20$ $50\pm 20$ $50\pm 20$ $50\pm 20$ $50\pm 20$ $50\pm 20$ $41\pm 15$ $0.004$ $41\%$ $20\pm 4$ $20\pm 1$ $48\pm 1$ AEF, % $45\pm 9$ $37\pm 13$ $0.003$ $-17\%$ $0.004$ $47\pm 8$ $39\pm 16$ $0.006$ $-13\%$ $0.003$ $19\pm 4$ $22\pm 4$ $20\pm 4$ $0.233$ $19\pm 4$ $21\pm 5$ $0.022$ $5\%$ $0.003$ $11\% - 0.4$ $2.0\pm 6$ $56\pm 4$ $0.072$ $2\%$ $0.003$ $19\pm 4$ $2.0\pm 0.4$ $0.072$ $2\%$ $0.003$ $19\pm 4$ $2.1\pm 0.3$ $2.0\pm 0.3$ $2.0\pm$   | AV <sub>max</sub> , mL   | $69 \pm 28$  |  | 1.00.0        |             | 1.00.0                       | 57 ± 75             | 68±24  | 61.0.0<br>2000                  | 24%         | 0.016                    | $80 \pm 2/$   | 92±24                    | 0.03/          | %8L                  | 0.041                   |
| No.         17.4         0.003         17.4         0.357         17.4         0.357         19.4         0.002         17.6         0.001         17.6         0.001         17.6         0.001         17.6         0.001         17.6         0.001         17.6         0.001         17.6         0.001         17.6         0.001         17.6         0.001         17.6         0.001         17.6         0.001         17.6         0.001         17.6         0.001         17.6         0.001         17.6         0.001         17.7         0.66         17.4         0.012         23.8         0.036         19.4.3         0.001         17.6         0.001         17.6         0.001         17.7         6.6         544.48         0.012         23.8         0.001         17.8         0.001         17.9         0.001         17.6         0.001         17.6         0.001         17.6         0.001         17.9         0.001         18.8         0.001         18.8         0.001         25.6         0.001         25.6         0.001         27.6         0.001         27.6         0.001         27.6         0.001         28.8         0.001         28.8         0.001         28.6         0.001         28.6 <t< td=""><td>APSE, mm <math>73\pm7</math> <math>37\pm13</math> <math>3023</math> <math>-11/5</math> <math>0.000</math> <math>-11/5</math> <math>0.004</math> <math>1.7\pm0</math> <math>37\pm10</math> <math>0.006</math> <math>-105</math> <math>0.000</math> <math>1.9\pm0</math><br/>APSE, mm <math>19\pm4</math> <math>20\pm4</math> <math>20\pm4</math> <math>0.602</math> <math>5\%</math> <math>0.303</math> <math>11\%</math> <math>0.04</math> <math>1.7\pm0.4</math> <math>2.0\pm0.4</math> <math>0.072</math> <math>2\%</math> <math>0.080</math> <math>1.9\pm0.3</math> <math>-106</math> <math>0.006</math> <math>1.9\pm0.3</math> <math>-106</math> <math>0.013</math> <math>-1\%</math> <math>0.007</math> <math>23\%</math> <math>0.000</math> <math>1.9\pm0.3</math> <math>-106</math> <math>-10\%</math> <math>0.001</math> <math>3.9\pm7.8</math> <math>-10.2</math> <math>-10.2</math></td><td>AV<sub>min</sub>, mL</td><td>39 ± 20<br/>4E · 0</td><td>50 ± 20</td><td>&lt;0.000</td><td>31%</td><td>&lt;0.001</td><td>31±1/<br/>47 0</td><td>21 ± 14</td><td>0.004</td><td>41%</td><td>0.00</td><td>48 ± 2 1</td><td>60±21<br/>34 11</td><td>0.016</td><td>34%</td><td>0.013</td></t<> | APSE, mm $73\pm7$ $37\pm13$ $3023$ $-11/5$ $0.000$ $-11/5$ $0.004$ $1.7\pm0$ $37\pm10$ $0.006$ $-105$ $0.000$ $1.9\pm0$<br>APSE, mm $19\pm4$ $20\pm4$ $20\pm4$ $0.602$ $5\%$ $0.303$ $11\%$ $0.04$ $1.7\pm0.4$ $2.0\pm0.4$ $0.072$ $2\%$ $0.080$ $1.9\pm0.3$ $-106$ $0.006$ $1.9\pm0.3$ $-106$ $0.013$ $-1\%$ $0.007$ $23\%$ $0.000$ $1.9\pm0.3$ $-106$ $-10\%$ $0.001$ $3.9\pm7.8$ $-10.2$   | AV <sub>min</sub> , mL   | 39 ± 20<br>4E · 0  | 50 ± 20  | <0.000        | 31%         | <0.001                       | 31±1/<br>47 0       | 21 ± 14  | 0.004                           | 41%         | 0.00                     | 48 ± 2 1  | 60±21<br>34 11           | 0.016          | 34%                  | 0.013                   |
| The formation is the formation. The formation is the for  | The constraint is the set of the   | ACT, %   | 10 ± 7   | 5/ ± 15  | c 007 0       | - 1/ %      | 0.007                        | 4/ ± 0<br>10 - 1    | 01 H C   |                                 | - 10%       | 000.0                    | 10 - 1<br>10 - 1  | 10 ± 01                  | 70020          | - 10%                |                         |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$  | $ \begin{array}{c} Comparison of the contrast of the co$  | /C diamater* cm  | 12±13  | 21±04  | 2000          | ۵.c<br>18%  | 7000                         | 17±04               | 5 T T T T  | 242.0                           | %čC         | 0 000                    | 10+03   | 17 ± 3                   | 0.045          | 14%                  | 074.0                   |
| CA - Z.0.         597 ± 66         564 ± 73         <0.001         -5%         <0.001         592 ± 66         564 ± 48         0.013         -4%         0.009         601 ± 105         564 ± 95         <0.001         -6%         <0.001           CA - TBW, L         38.3 ± 7.1         39.4 ± 7.0         <0.001  | $ \begin{array}{cccccccccccccccccccccccccccccccccccc$   | o-impedance data   |  |  | 600.0         | 200         | - 00.0                       |                     |  | 4 10.0                          | 22          | 0000                     |   | 1.0 - 1.1                | 200            | 2                    | 0.000                   |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$  | $ \begin{array}{cccccccccccccccccccccccccccccccccccc$   | $CA - Z, \Omega$   | 597 <u>+</u> 86  | $564 \pm 73$   | <0.001        | -5%         | <0.001                       | $592 \pm 66$        | $564 \pm 48$                                     | 0.013                           | -4%         | 0.009                    | 601 <u>±</u> 105  | $564 \pm 95$             | <0.001         | ~9~                  | <0.001                  |
| $ CA - TBW, \\ A.6. 45.1  49.7 \pm 5.5 \\ A.0.01  2\%  <0.001  2\%  <0.001  2\%  <0.001  2\%  <0.001  2\%  <0.002  3\%  0.001 \\ IM - R_{E}, \Omega  33 \pm 8  30 \pm 8  0.013  2.1\%  <0.003  3.1 \pm 9  0.066  -9\%  0.053  3.2 \pm 8  0.013  -11\%  0.007 \\ at a re expressed as mean \pm SD if the variable is normally distributed, and median (interquartile range) otherwise. \\ at a re expressed as mean \pm SD if the variable is normally distributed, and median (interquartile range) otherwise. \\ at are expressed as mean \pm SD if the variable is normally distributed, and median (interquartile range) otherwise. \\ transmiral peak arrial flow velocity: BCA, body composition analyser: BIM, bio-impedance monitor: BMI, body mass index: DBR, distolic blood pressure; E, transmiral peak early flow velocity: elax, peak early velocity measured with tissue Doppler imaging at th earl and unset. DECM, different and under the end-diastolic dameter: LVEDV, left ventricle end-systolic volume: (LA'_{min}, minimum left arrial volume: (LYCD) left ventricle end-diastolic dameter: LVEDV, left ventricle end-systolic volume: (LA'_{max}, traile month, for total body vareer; SV, whole body impedance monitors: DNT, end the end vareary is the ventricle end-diastolic dameter: LVEDV, left ventricle end-systolic volume: (LA'_{max}, month, minimum left arrial volume: (LA'_{max}, minimum left arrial volume: (LYCD) left ventricle end-systolic volume: (LE) (eff varial volume: SR, vertoke volume: TASN) (eff ventricle end-systolic volume: (LYCD) left ventricle end-systolic volume: TASN) (eff ventricle end-systolic volume: CD) (eff varial is concerved) and the overved volume: (LYCD) left ventricle end-systolic volume: (LYCD) (eff ventricle end-systolic volume: CD) (eff ventricle end-diastolic volume) (eff) (eff volume: CD) ($  | $ CA - TBW, \& 48.6 \pm 5.1  49.7 \pm 5.5 \\ CA - TBW, \& 48.6 \pm 5.1  49.7 \pm 5.5 \\ CA - TBW, \& 48.6 \pm 5.1  49.7 \pm 5.5 \\ M - R_{E}, \Omega & 33 \pm 8 \\ 30 \pm 8 & 0.002 & -10\% & <0.001 & 2\% & 0.006 & -9\% & 0.053 & 32 \pm 8 \\ M - R_{E}, \Omega & 33 \pm 8 & 0.056 & -9\% & 0.053 & 32 \pm 8 \\ M - R_{E}, \Omega & 31 \pm 9 & 0.066 & -9\% & 0.053 & 32 \pm 8 \\ M - R_{E}, \Omega & 0.066 & -9\% & 0.053 & 32 \pm 8 \\ M - R_{E}, \Omega & 0.066 & -9\% & 0.053 & 32 \pm 8 \\ M - R_{E}, \Omega & 0.066 & -9\% & 0.053 & 32 \pm 8 \\ M - R_{E}, \Omega & 0.066 & -9\% & 0.053 & 32 \pm 8 \\ M - R_{E}, \Omega & 0.066 & -9\% & 0.053 & 32 \pm 8 \\ M - R_{E}, \Omega & 0.066 & -9\% & 0.053 & 32 \pm 8 \\ M - R_{E}, \Omega & 0.066 & -9\% & 0.053 & 32 \pm 8 \\ M - R_{E}, \Omega & 0.066 & -9\% & 0.056 & -9\% & 0.053 & 32 \pm 8 \\ M - R_{E}, \Omega & 0.066 & -9\% & 0.053 & 32 \pm 8 \\ M - R_{E}, \Omega & 0.066 & -9\% & 0.056 & -9\% & 0.053 & 32 \pm 8 \\ M - R_{E}, \Omega & 0.066 & -9\% & 0.053 & 32 \pm 8 \\ M - R_{E}, \Omega & 0.066 & -9\% & 0.056 & -9\% & 0.056 & -9\% & 0.056 \\ M - R_{E}, \Omega & 0.066 & -9\% & 0.056 & -9\% & 0.056 & -9\% & 0.056 & -9\% & 0.056 & -7\% & 0.056 & -9\% & 0.056 $ | CA – TBW, L  | $38.3 \pm 7.1$   | $39.4 \pm 7.0$   | <0.001        | 3%          | <0.001                       | 37.7±6.6            | $38.6 \pm 6.4$                                   | 0.046                           | 3%          | 0.040                    | $38.9 \pm 7.8$  | $40.2 \pm 7.9$           | 0.001          | 4%                   | 0.001                   |
| I/M - R <sub>E</sub> , Ω       33±8       30±8       0.002       -10%       <0.001   | I/M - R <sub>E</sub> , Ω 33 ± 8 30 ± 8 0.002 - 10% <0.001 35 ± 9 31 ± 9 0.066 -9% 0.053 32 ± 8 tat are expressed as mean ± SD if the variable is normally distributed, and median (interquartile range) otherwise. The are expressed as mean ± SD if the variable is normally distributed, and median (interquartile range) otherwise. The are expressed as mean ± SD if the variable is normally distributed, and median (interquartile range) otherwise. The are expressed as mean ± SD if the variable is normally distributed, and median (interquartile range) otherwise. The are expressed as mean ± SD if the variable is normally distributed, and median (interquartile range) otherwise. The are exported as percentage of the respective subgroup. The area interaction and set (interquartile range) otherwise. The area interaction range (interceraction range) for area (  | CA – TBW, %  | $48.6 \pm 5.1$   | $49.7 \pm 5.5$   |               | 2%          | <0.001                       | $47.8 \pm 5.1$      | $48.8 \pm 5.5$                                   | 0.010                           | 2%          | 0.009                    | $49 \pm 5.3$  | $50.6 \pm 5.6$           | 0.002          | 3%                   | 0.001                   |
| ata are expressed as mean ±SD if the variable is normally distributed, and median (interquartile range) otherwise.<br>ounts are reported as percentage of the respective subgroup.<br>arrentage changes (Δ% = Omitted - Taken/Taken) are expressed as means.<br>transmitral peak acrial flow velocity, BCA, body composition analyser; BIM, bio-impedance monitor; BMI, body mass index; DBP, diastolic blood pressure; E, transmitral peak early flow velocity, relact velocity measured with tissue Doppler imaging at th<br>transmitral peak early velocity measured with tissue Doppler imaging at the septal mitral annulus; eGFR, estimated giomerular filtration rate; HR, heart rate; IVC, inferior vena cava; LA, left atrial emptying fraction; LA/ <sub>max</sub> , maximut<br>frartial kunnei: mirmun mitra ania volume; LYEDD, left ventricle end-diastolic volume; LVEDV, left ventricle end-systolic volume; R <sub>e</sub> , extracellular resistance; SBP, systolic blood pressure; TAPSI<br>fractial annulure peak excision; TBV, tocal body mass. Z. whole body impedance monitors.   | ata are expressed as mean ±SD if the variable is normally distributed, and median (interquartile range) otherwise.<br>ounts are reported as percentage of the respective subgroup.<br>arrentage changes (∆% = Omitted - Taken/Taken) are expressed as means.<br>, transmitral peak artial flow velocity: BCA, body composition analyser; BIM, bio-impedance monitor; BMI, body mass index; DBP, diastolic blood pressure; E, transmitral peak early flow velocity; e <sup>l</sup> <sub>int</sub> , peal<br>, transmitral peak artial flow velocity measured with tissue Doppler imaging at the set and muluus; eGFR, estimated glomerular filtration rate, IR, heart rate; IVC, infenior rena cava; IA, left<br>frantal volume: IAX minimum inter arrial volume: IVFDD left vontricle and-distrolic diameter: UFDV left ventrice and version rate, IR, heart rate; IVC, infenior era cava: IA, et frantal volume: IV, ETX, left ventricle and versions.   | $SIM - R_E, \Omega$  | $33 \pm 8$   | $30 \pm 8$   | 0.002         | -10%        | <0.001                       | $35 \pm 9$          | $31 \pm 9$                                       | 0.066                           | ~6~         | 0.053                    | $32\pm 8$   | $29\pm 8$                | 0.013          | -11%                 | 0.007                   |
| A transmisser from the first of   | A transmired from the control of the  | Data are expressed as mean <u>-</u><br>Counts are reported as perce<br>Percentae changes (A% <u>-</u> Or | SD if the variable is n<br>ntage of the respectiv<br>oitted – Taken/Taken) | iormally distributed, and<br>e subgroup.<br>are extressed as means | median (in    | quartile ra | Inge) otherw                 | rise.               |  |                                 |             |                          |   |                          |                |                      |                         |
| rest and solution is the second of the second s   | of a state when a state of the   | v, transmitral peak atrial flow  | v velocity; BCA, body  | composition analyser; Bl   | M, bio-imped  | ance mon    | itor; BMI, bo<br>mitral annu | ody mass index; DB  | P, diastolic blood pre<br>d elomerular filtratio | ssure; E, tran:<br>n rate: HR h | smitral pea | k early flow             | velocity; e' <sub>lat</sub> , peak ear<br>vena cava: I A left atria | -ly velocity measured v  | with tissue D  | oppler im:<br>n: IAV | aging at the<br>maximum |
| icuspid anular plane systolic excursion; TBVV, total body water; Z, whole body impedance modulus.  |   | ft atrial volume; LAV <sub>min</sub> , mi  | nimum left atrial volum  | he; LVEDD, left ventricle  | end-diastolic | diameter;   | LVEDV, left v                | entricle end-diasto | lic volume; ; LVESV, le                          | aft ventricle ei                | rd-systolic | volume; R <sub>E</sub> , | extracellular resistance;   | ; SBP, systolic blood pi | ressure; SV, s | troke volu           | me; TAPSE               |
|  | icuspid anular plane systolic excursion; TBVV, total body water; Z, whole body impedance modulus.   | icuspid annular plane systoli  | c excursion; TBW, tot  | al body water; Z, whole  | body impedar  | nce modul   | us.                          |                     |  |                                 |             |                          |   |                          |                |                      |                         |

ventricular volumes, and a reduction in transthoracic BIM and, for some patients, a deterioration in NYHA functional class. Weight, a commonly used measure of fluid retention and congestion, did not change significantly. In patients with worsening congestion due to disease progression, a decline in blood pressure and renal function would be expected. In contrast, we observed a substantial increase in systolic blood pressure and improvement in renal function. Thus, the clinical profiles of congestion due to medication omission and disease progression appear to differ.

Early identification of congestion, its likely cause, and appropriate intervention might decrease the need for admission.<sup>11</sup> Increases in heart rate, and changes in heart rhythm and temperature might be useful in the diagnosis of alternative reasons for worsening congestion such as arrhythmias or infection. However, medication non-adherence may be a common problem among patients with HF; either because they are told to stop (i.e. the patient is told to withhold medication prior to a procedure), intentional (i.e. a patient chooses not to take some or several medications after weighing the risk and benefits against adverse effects, such as the frequent need to urinate), or unintentional, because the patient is careless or forgetful about prescribed therapy.<sup>3</sup> This analysis suggests that short-term omission of HF medications does not cause marked deterioration in symptoms in patients with mild to moderate HF, although the study is too small to assess safety fully. However, an increase in congestion was observed and extension of the period of omission would most probably lead to overt deterioration in symptoms and signs. Reports from studies that pre-date modern diagnostic standards indicated that a large proportion of patients with HF could stop their diuretic indefinitely, but this may be because these patients did not have, or had only mild, HF.<sup>12-14</sup>

Our study shows that withholding HF medicines for 48 h is associated with an increase in LA volumes and worsening atrial contraction. The increase in LA volume was mirrored by an increase in IVC diameter, suggesting a concordant rise in both right and LA pressure. LV volumes changed less than LA volumes perhaps because volume measures are less accurate for the ventricle compared with the atrium or because the LV wall thickness is greater and therefore less likely to be deformed by modest, short-term increases in pressure. A measure thought to reflect LA pressure, E/e', did not change significantly despite a substantial and consistent increase in E-wave velocity. We did not measure atrial pressures directly and therefore can only speculate about the accuracy of E/e' as a measure of atrial pressure or diastolic dysfunction. Unfortunately, a large proportion of patients did not have enough tricuspid regurgitation to measure changes in pulmonary artery pressure that would be expected to accompany congestion.

Our results show that renal function improved after medication omission. ACE inhibitors, ARBs, beta-blockers, mineralocorticoid receptor antagonists, and diuretics all conspire to reduce the GFR and do so either by reducing net arterio-venous renal perfusion pressure or by complex effects on intraglomerular haemodynamics; therefore, this result is not surprising.<sup>15</sup> It is remarkable that so many agents that improve prognosis cause renal function to decline; renal dysfunction may also limit their use.<sup>16</sup> Interestingly, it was only patients with lower NT-proBNP whose renal function appeared to benefit from medication omission, suggesting that these patients might be relatively dehydrated and that more aggressive diuresis, in an attempt to reduce NT-proBNP further, might have adverse consequences in such patients.

Increased pressures and wall stress will increase secretion of natriuretic peptides, leading to a rise in plasma NT-proBNP despite improved renal function and therefore presumably increased renal clearance of NT-proBNP. Natriuretic peptides are a natural defence against congestion, which is useful diagnostically; they are also powerful markers of prognosis.<sup>17–19</sup> Plasma concentrations of NT-proBNP almost doubled after interrupting treatment for 48 h before any obvious change in weight and before most patients had noticed any change in symptoms. Frequent home testing by a finger-stick test has recently been shown to be feasible and might be a useful monitoring strategy.<sup>20</sup> However, natriuretic peptides are influenced by other factors including renal function and heart rhythm, which may make interpretation difficult when measured in isolation.

Although echocardiography requires a good acoustic window and an experienced operator, the increasing availability and low cost of pocket-size ultrasound devices is likely to increase their use by health professionals in the home and outpatient settings.<sup>21–23</sup> The usefulness of these hand-held devices in identifying early signs of deterioration, including IVC distension, the presence of lung comets, or evidence of pleural effusion, has recently been reported and is being assessed in several prospective clinical studies.

Measurements of bio-impedance using suitably enabled weighing scales (e.g. the Tanita body composition analyser) can be used in combination with predictive models to assess body composition including total body water. However, this approach may have a decreased sensitivity to detect changes in thoracic fluid because the trunk accounts for a disproportionately small fraction of the whole-body bio-impedance (5-12%) compared with body weight ( $\sim$ 50%). This may limit the accuracy in certain clinical populations where small changes in thoracic fluid play an important role. Early stages of worsening HF are often characterized by an increase in pulmonary pressures in the absence of weight gain, suggesting that pulmonary volume overload might be predominantly due to fluid redistribution rather than fluid retention.<sup>24,25</sup> Our results suggest that transthoracic bio-impedance can measure localized volume overload in the absence of a substantial gain in weight. Furthermore, haematocrit did not change, suggesting that no substantial change in plasma volume had occurred.

Taken together, these data suggest the following sequence of events. Medication omission, perhaps especially of diuretics, results in net fluid retention, vasoconstriction, a rise in arterial and ventricular filling pressures and, consequently, natriuretic peptides. The rise in natriuretic peptides, blood pressure, and glomerular filtration serves to limit, at least temporarily, the tendency to overall salt and water retention. However, vulnerable vascular beds, such as the lung, are still prone to an increase in tissue fluid prior to developing overt oedema.

Although transthoracic bio-impedance is mainly determined by fluid content in tissue, it is also affected by physical characteristics, e.g. chest geometry. So far, there are no reliable normalization techniques that enable the definition of an absolute cut-off to discriminate between patients with and without congestion. However, serial measurements, as obtained daily through HTM, may indicate deviations of transthoracic bio-impedance from a patient's personalized normal range.<sup>26</sup> Novel sensors such as the BIM could be easily incorporated into a HTM system tailored for patients with HE.<sup>27,28</sup>

A recent alternative to bio-impedance is remote dielectric sensing (ReDS) which measures lung fluid using low-power electromagnetic radiation.<sup>29,30</sup> However, this technique is unable to distinguish between intravascular and parenchymal fluid, and thus may predominantly measure pulmonary venous distension.

Advances in technology have made it possible to create HTM systems that can monitor symptoms, weight, heart rate and rhythm, and blood pressure, as well as providing medication reminders and educational material. Whether such systems can reduce hospitalizations and/or improve prognosis is controversial, although the most recent Cochrane analysis suggests that it does.<sup>31</sup> The identification of a reliable and robust method for measuring, recording, and reporting subclinical increases in congestion and its likely cause might allow the development of personalized HTM systems. A wide range of sensors are being used or considered for integration into HTM systems, including bio-impedance monitoring, acoustic cardiography or pulse wave characteristics, lung congestion, and point-of-care biomarker devices. Which, if any, will prove useful for routine clinical practice is uncertain, but early detection and control of congestion could play a key role in improving outcome for patients with HF.32

This study was a small, exploratory study and therefore not powered to observe subtle differences between study days. However, when the effects of an intervention or its withdrawal are substantial and consistent, large trials are not required, as this analysis clearly shows. Indeed, large studies may be misleading by identifying statistically significant differences that are clinically irrelevant. The study was not blinded and it is possible that patients, although they were asked not to, changed their dietary behaviour. It is possible that dietary salt and water intake was lower on diuretic-free days and this prevented a significant increase in weight. Measuring urinary sodium excretion would have resolved this, but to do this reliably requires highly compliant patients, preferably studied during admission to a metabolic ward with a carefully measured diet. We did not have the resources to do this.

## Conclusions

Increasing plasma NT-proBNP and declining transthoracic bio-impedance might be used to detect congestion, while changes in blood pressure and renal function might indicate whether this is due to omission of medications or progression of disease. The utility of this physiological pattern for the early detection of congestion and the reasons for congestion should be tested by the next generation of HTM systems.

## Funding

The work leading to these results has received funding from the European Community's Seventh Framework Programme under

grant agreement FP7-216695 (HeartCycle: Closed-loop Disease Management for HF and Coronary Heart Disease).

**Conflict of interest:** J.G.F.C. has received research support and honoraria from Philips. S.D. is an employee of Philips. All other authors have no conflicts to declare.

### References

- DiMatteo MR. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. Med Care 2004;42:200–209.
- van der Wal MHL, Jaarsma T. Adherence in heart failure in the elderly: problem and possible solutions. Int J Cardiol 2008;125:203–208.
- Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. *Circulation* 2009;119:3028-3035.
- O'Connor CM, Stough WG, Gallup DS, Hasselblad V, Gheorghiade M. Demographics, clinical characteristics, and outcomes of patients hospitalized for decompensated heart failure: observations from the IMPACT-HF registry. J Card Fail 2005;11:200–205.
- Hope CJ, Wu J, Tu W, Young J, Murray MD. Association of medication adherence, knowledge, and skills with emergency department visits by adults 50 years or older with congestive heart failure. Am J Health Syst Pharm 2004;61:2043–2049.
- Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;353:487–497.
- Cole KS, Cole RH. Dispersion and absorption in dielectrics I. Alternating current characteristics. J Chem Phys 1941;9:341–351.
- Buendia R, Gil-Pita R, Seoane F. Cole parameter estimation from the modulus of the electrical bioimpeadance for assessment of body composition. A full spectroscopy approach. J Electr Bioimpedance 2011;2:72–78.
- Weyer S, Zink MD, Wartzek T, Leicht L, Mischke K, Vollmer T, Leonhardt S. Bioelectrical impedance spectroscopy as a fluid management system in heart failure. *Physiol Meas* 2014;35:917–930.
- Dovancescu S, Torabi A, Mabote T, Caffarel J, Kelkboom E, Aarts R, Korsten E; Cleland J. Sensitivity of a wearable bioimpedance monitor to changes in the thoracic fluid content of heart failure patients. *Comput Cardiol* 2013;40:927–930.
- Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, Strickland W, Neelagaru S, Raval N, Krueger S, Weiner S, Shavelle D, Jeffries B, Yadav JS; CHAMPION Trial Study Group. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. *Lancet* 2011;**377**:658–666.
- van Kraaij DJ, Jansen RW, Sweep FC, Hoefnagels WH. Neurohormonal effects of furosemide withdrawal in elderly heart failure patients with normal systolic function. Eur J Heart Fail 2003;5:47–53.
- Grinstead WC, Francis MJ, Marks GF, Tawa CB, Zoghbi WA, Young JB. Discontinuation of chronic diuretic therapy in stable congestive heart failure secondary to coronary artery disease or to idiopathic dilated cardiomyopathy. *Am J Cardiol* 1994;**73**:881–886.
- Galve E, Mallol A, Catalan R, Palet J, Méndez S, Nieto E, Diaz A, Soler-Soler J. Clinical and neurohumoral consequences of diuretic withdrawal in patients with chronic, stabilized heart failure and systolic dysfunction. *Eur J Heart Fail* 2005;7:892–898.
- Good JM, Brady AJ, Noormohamed FH, Oakley CM, Cleland JG. Effect of intense angiotensin II suppression on the diuretic response to furosemide during chronic ACE inhibition. *Circulation* 1994;90:220–224.
- Brunner-La Rocca HP, Knackstedt C, Eurlings L, Rolny V, Krause F, Pfisterer ME, Tobler D, Rickenbacher P, Maeder MT; TIME-CHF investigators. Impact of worsening renal function related to medication in heart failure. *Eur J Heart Fail* 2015;**17**:159–168.
- Pellicori P, Carubelli V, Zhang J, Castiello T, Sherwi N, Clark AL, Cleland JG. IVC diameter in patients with chronic heart failure: relationships and prognostic significance. JACC Cardiovasc Imaging 2013;6:16–28.
- Cleland JGF, Taylor J, Freemantle N, Goode KM, Rigby AS, Tendera M. Relationship between plasma concentrations of N-terminal pro brain natriuretic peptide and the characteristics and outcome of patients with a clinical diagnosis of diastolic heart failure: a report from the PEP-CHF study. *Eur J Heart Fail* 2012;14:487–494.
- Pellicori P, Hutchinson K, Clark AL, Cleland JG. Does speckle tracking really improve diagnosis and risk stratification in patients with HF with normal EF? J Am Coll Cardiol 2014;64:1535.
- Maisel A, Barnard D, Jaski B, Frivold G, Marais J, Azer M, Miyamoto MI, Lombardo D, Kelsay D, Borden K, Iqbal N, Taub PR, Kupfer K, Clopton P, Greenberg B. Primary results of the HABIT trial (Heart Failure Assessment With BNP in the Home). J Am Coll Cardiol 2013;61:1726–1735.

- Dalen H, Gundersen GH, Skjetne K, Haug HH, Kleinau JO, Norekval TM, Graven T. Feasibility and reliability of pocket-size ultrasound examinations of the pleural cavities and vena cava inferior performed by nurses in an outpatient heart failure clinic. *Eur J Cardiovasc Nurs* 2015;14:286–293.
- Platz E, Lewis EF, Uno H, Peck J, Pivetta E, Merz AA, Hempel D, Wilson C, Frasure SE, Jhund PS, Cheng S, Solomon SD. Detection and prognostic value of pulmonary congestion by lung ultrasound in ambulatory heart failure patients. *Eur Heart J* 2016;**37**:1244–1251.
- Gundersen GH, Norekval TM, Haug HH, Skjetne K, Kleinau JO, Graven T, Dalen H. Adding point of care ultrasound to assess volume status in heart failure patients in a nurse-led outpatient clinic. A randomised study. *Heart* 2016;**102**:29–34.
- Cotter G, Metra M, Milo-Cotter O, Dittrich HC, Gheorghiade M. Fluid overload in acute heart failure: re-distribution and other mechanisms beyond fluid accumulation. *Eur J Heart Fail* 2008;10:165–169.
- Cotter G, Felker GM, Adams KF, Milo-Cotter O, O'Connor CM. The pathophysiology of acute heart failure. Is it all about fluid accumulation? Am Heart J 2008;155:9–18.
- Shochat MK, Shotan A, Blondheim DS, Kazatsker M, Dahan I, Asif A, Rozenman Y, Kleiner I, Weinstein JM, Frimerman A, Vasilenko L, Meisel SR. Non-invasive lung impedance-guided preemptive treatment in chronic heart failure patients: a randomized controlled trial (IMPEDANCE-HF Trial). J Card Fail 2016;22:713–722.

- Dovancescu S, Saczynski JS, Darling CE, Riistama J, Sert Kuniyoshi F, Meyer T, Goldberg R, McManus DD. Detecting heart failure decompensation by measuring transthoracic bioimpedance in the outpatient setting: rationale and design of the SENTINEL-HF study. JMIR Res Protoc 2015;4:e121.
- Darling CE, Dovancescu S, Riistama J, Saczynski J, Kini N, Kuniyoshi FS, Rock J, Meyer TE, Goldberg RJ, McManus DD. Abstract 19477: Transthoracic bioimpedance monitoring predicts readmission after hospitalization for heart failure: preliminary results from the SENTINEL-HF study. *Circulation* 2015;**132**(Suppl 3):A19477–A19477.
- Amir O, Rappaport D, Zafrir B, Abraham WT. A novel approach to monitoring pulmonary congestion in heart failure: initial animal and clinical experiences using remote dielectric sensing technology. *Congest Heart Fail* 2013;19:149–155.
- Abraham WT, Amir O, Weinstein JM, Abbo A, Ben Gal T. Remote Dielectric Sensing (ReDS<sup>TM</sup>)-guided patient management of ambulatory heart failure patients reduces rehospitalization rates. J Card Fail 2015;21:S77.
- Inglis SC, Clark RA, Dierckx R, Prieto-Merino D, Cleland JG. Structured telephone support or non-invasive telemonitoring for patients with heart failure. *Cochrane Database Syst Rev* 2015;10:CD007228.
- Mentz RJ, Kjeldsen K, Rossi GP, Voors AA, Cleland JG, Anker SD, Gheorghiade M, Fiuzat M, Rossignol P, Zannad F, Pitt B, O'Connor C, Felker GM. Decongestion in acute heart failure. *Eur J Heart Fail* 2014;**16**:471–482.