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

Silviu Dovancescu[1,2,3†]*, Pierpaolo Pellicori[1†], Thato Mabote[1], Azam Torabi[1], Andrew L. Clark[1], and John G.F. Cleland[1,4]*

[1]Department of Cardiology, Hull York Medical School, Hull and East Yorkshire Medical Research and Teaching Centre, Castle Hill Hospital, Cottingham, Kingston upon Hull, UK; [2]Philips Research, Eindhoven, The Netherlands; [3]Department of Electrical Engineering, Eindhoven University of Technology, Eindhoven, The Netherlands; and [4]National Heart & Lung Institute and National Institute of Health Research, Cardiovascular Biomedical Research Unit, Royal Brompton & Harefield Hospitals, Imperial College, London, UK

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 and results	Outpatients with stable HF and an LVEF <45% were assigned to take or omit their HF medication for 48 h in a randomized, crossover trial. Twenty patients (16 men, LVEF 32 ± 9%, median NT-proBNP 962 ng/L) were included. Compared with regular medication, omission led to an increase in NT-proBNP by 99% (from 962 to 1883 ng/L, $P < 0.001$), systolic blood pressure by 16% (from 131 to 152 mmHg, $P < 0.001$), and left atrial volume by 21% (from 69 to 80 mL, $P = 0.001$), and reductions in transthoracic bio-impedance by 10% (from 33 to 30 Σ, $P = 0.001$) and serum creatinine 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,[1] 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.[2,3] Low adherence to medications may lead to worsening HF and disease progression, resulting in hospital admission, increased healthcare costs, and death.[3–5] Several methods have been developed to assess adherence to medication.[6] Although measurement of the blood level of a medicine is a robust and objective method, it is not currently practical for routine clinical use.[3] On the other hand, indirect methods of adherence (patient questionnaires, 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
†These authors contributed equally to this work.

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 ($Z = R_\infty - \frac{R_\infty - R_E}{1 + \left(j \frac{f}{f_c}\right)^\alpha}$),[7,8] which provides information about tissue characteristics. The model parameters reflect extracellular fluid (R_E), intracellular fluid (R_∞), tissue relaxation (f_c), and tissue heterogeneity (α). Intrathoracic fluid accumulation due to worsening HF directly affects the value of R_E, which should decrease.[9,10] 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'$_{lat}$) and septal (e'$_{sep}$) 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 ~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
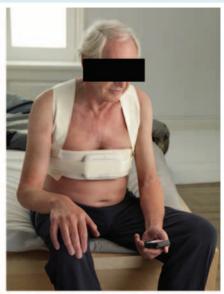
Figure 1 Bio-impedance monitor consisting of an adjustable vest with integrated textile electrodes and a slim electronics case.

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 μmol/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_{max}, +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_E, −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^2	28 (24, 32)
NYHA class	
I	4 (20)
II	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 sinus rhythm) for the visit when medication was taken

Variable	Overall study population (n = 20)					NT-proBNP <962 ng/L (n = 10)					NT-proBNP >962 ng/L (n = 10)				
	Taken	Omitted	P-value	Δ%	P-value	Taken	Omitted	P-value	Δ%	P-value	Taken	Omitted	P-value	Δ%	P-value
NYHA class, n (%)															
I	4 (20%)	3 (15%)				3 (30%)	2 (20%)				1 (10%)	1 (10%)			
II	16 (80%)	12 (60%)				7 (70%)	5 (50%)				9 (90%)	7 (70%)			
III	0 (0%)	5 (25%)				0 (0%)	3 (30%)				0 (0%)	2 (20%)			
NYHA class, 'average'	1.8	2.1	0.010			1.7	2.1	0.037			1.9	2.1	0.168		
Conventional telemonitoring measurements															
Weight, kg	79.6 ± 16.8	80.1 ± 16.6	0.089	<1%	0.076	79.7 ± 16.2	80.0 ± 16.1	0.435	<1%	0.433	79.6 ± 18.3	80.2 ± 17.9	0.106	<1%	0.090
SBP, mmHg	131 ± 20	152 ± 26	<0.001	16%	<0.001	132 ± 19	154 ± 28	0.006	17%	0.005	131 ± 22	150 ± 26	0.010	15%	0.015
DBP, mmHg	78 ± 17	85 ± 15	0.054	12%	0.029	75 ± 18	83 ± 10	0.221	16%	0.118	82 ± 16	87 ± 18	0.103	8%	0.098
HR, b.p.m.	66 ± 14	67 ± 17	0.883	3%	0.533	65 ± 16	69 ± 16	0.115	8%	0.102	67 ± 10	65 ± 19	0.748	−1%	0.913
Biochemical data															
NT-proBNP, ng/L	962 (600–1486)	1883 (926–3138)	<0.001	99%	<0.001	601 (374–790)	926 (776–1512)	0.005	90%	0.005	1486 (1212–1824)	3139 (2667–3454)	0.001	107	0.003
Haemoglobin, g/dL	13.4 ± 1.5	13.2 ± 1.4	0.128	−2%	0.165	12.9 ± 1.2	12.6 ± 1.1	0.154	−2%	0.166	14.0 ± 1.5	13.8 ± 1.5	0.429	−2%	0.507
Creatinine, μmol/L	135 ± 60	118 ± 40	0.012	−8%	0.008	142 ± 62	120 ± 38	0.042	−13%	0.006	127 ± 60	117 ± 44	0.153	−4%	0.407
eGFR, mL/min/1.73 m²	55 ± 22	59 ± 19	0.025	12%	0.015	51 ± 16	57 ± 17	0.007	17%	0.033	60 ± 27	60 ± 22	0.778	6%	0.273
Echocardiographic data															
LVEDD, mm	61 ± 8	63 ± 10	0.064	3%	0.058	57 ± 6	57 ± 7	0.572	1%	0.526	65 ± 8	68 ± 10	0.077	6%	0.075
LVEDV, mL	186 ± 70	202 ± 69	0.007	11%	0.008	141 ± 23	161 ± 39	0.049	14%	0.047	230 ± 75	242 ± 69	0.079	7%	0.086
LVESV, mL	130 ± 67	142 ± 68	0.018	11%	0.015	89 ± 19	103 ± 33	0.057	15%	0.058	172 ± 73	181 ± 72	0.196	6%	0.139
SV, mL	55 ± 15	60 ± 12	0.120	12%	0.028	53 ± 10	58 ± 19	0.116	12%	0.075	58 ± 19	61 ± 10	0.495	11%	0.193
LVEF, %	32 ± 9	32 ± 10	0.998	1%	0.763	38 ± 6	37 ± 7	0.655	−2%	0.579	27 ± 9	27 ± 10	0.797	4%	0.560
E, m/s	0.59 ± 0.19	0.70 ± 0.19	0.001	23%	0.001	0.57 ± 0.14	0.64 ± 0.14	0.020	13%	0.023	0.61 ± 0.25	0.76 ± 0.23	0.011	32%	0.008
A, m/s	0.70 ± 0.22	0.74 ± 0.28	0.279	6%	0.352	0.79 ± 0.20	0.87 ± 0.23	0.142	12%	0.198	0.62 ± 0.22	0.62 ± 0.28	0.964	0%	0.982
E/A ratio	0.96 ± 0.55	1.13 ± 0.70	0.056	20%	0.013	0.74 ± 0.22	0.73 ± 0.11	0.816	2%	0.794	1.15 ± 0.69	1.49 ± 0.82	0.031	37%	0.006
e'$_{sep}$, m/s	0.04 ± 0.01	0.05 ± 0.01	0.121	15%	0.102	0.04 ± 0.01	0.05 ± 0.01	0.093	15%	0.087	0.04 ± 0.01	0.04 ± 0.02	0.462	15%	0.379
e'$_{lat}$, m/s	0.06 ± 0.02	0.06 ± 0.02	0.524	20%	0.176	0.06 ± 0.02	0.07 ± 0.02	0.204	32%	0.198	0.05 ± 0.02	0.05 ± 0.02	0.708	9%	0.640
E/e'^{sep}	15 ± 5	17 ± 10	0.262	20%	0.102	14 ± 3	14 ± 4	0.957	3%	0.736	16 ± 6	21 ± 13	0.258	37%	0.109
E/e'$_{lat}$	13 ± 10	13 ± 7	0.749	24%	0.081	11 ± 6	10 ± 4	0.483	−1%	0.955	15 ± 14	17 ± 8	0.468	49%	0.052
LA diameter, mm	40 ± 6	42 ± 5	0.011	6%	0.010	37 ± 6	39 ± 5	0.127	6%	0.120	43 ± 5	46 ± 4	0.053	7%	0.049
LAV$_{max}$, mL	69 ± 28	80 ± 26	0.001	21%	0.001	57 ± 25	68 ± 24	0.015	24%	0.016	80 ± 27	92 ± 24	0.037	18%	0.041
LAV$_{min}$, mL	39 ± 20	50 ± 20	<0.001	37%	<0.001	31 ± 17	41 ± 15	0.004	41%	0.001	48 ± 21	60 ± 21	0.016	34%	0.013
LAEF, %	45 ± 9	37 ± 13	0.003	−17%	0.004	47 ± 8	39 ± 16	0.066	−18%	0.086	42 ± 10	36 ± 11	0.012	−16%	0.010
TAPSE, mm	19 ± 4	20 ± 4	0.602	5%	0.357	19 ± 4	21 ± 5	0.242	9%	0.238	19 ± 4	19 ± 3	0.700	1%	0.920
IVC diameter*, cm	1.8 ± 0.3	2.1 ± 0.4	0.003	18%	0.004	1.7 ± 0.4	2.0 ± 0.4	0.072	23%	0.080	1.9 ± 0.3	2.2 ± 0.4	0.045	14%	0.033
Bio-impedance data															
BCA – Z, Ω	597 ± 86	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
BCA – TBW, L	38.3 ± 7.1	39.4 ± 7.0	<0.001	3%	<0.001	37.7 ± 6.6	38.6 ± 6.4	0.046	3%	0.040	38.9 ± 7.8	40.2 ± 7.9	0.001	4%	0.001
BCA – TBW, %	48.6 ± 5.1	49.7 ± 5.5	<0.001	2%	<0.001	47.8 ± 5.1	48.8 ± 5.5	0.010	2%	0.009	49 ± 5.3	50.6 ± 5.6	0.002	3%	0.001
BIM – R$_E$, Ω	33 ± 8	30 ± 8	0.002	−10%	<0.001	35 ± 9	31 ± 9	0.066	−9%	0.053	32 ± 8	29 ± 8	0.013	−11%	0.007

Data are expressed as mean ± SD if the variable is normally distributed, and median (interquartile range) otherwise.

Counts are reported as percentage of the respective subgroup.

Percentage changes (Δ% = Omitted − Taken/Taken) are expressed as means.

A, transmitral peak atrial 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'$_{lat}$, peak early velocity measured with tissue Doppler imaging at the lateral mitral annulus; e'$_{sep}$, peak early velocity measured with tissue Doppler imaging at the septal mitral annulus; eGFR, estimated glomerular filtration rate; HR, heart rate; IVC, inferior vena cava; LA, left atrial; LAEF, left atrial emptying fraction; LAV$_{max}$, maximum left atrial volume; LAV$_{min}$, minimum left atrial volume; LVEDD, left ventricle end-diastolic diameter; ; LVEDV, left ventricle end-diastolic volume; LVESV, left ventricle end-systolic volume; R$_E$, extracellular resistance; SBP, systolic blood pressure; SV, stroke volume; TAPSE, tricuspid annular plane systolic excursion; TBW, total body water; Z, whole body impedance modulus.

*Pairs of IVC diameters for both visits were available in only nine patients.

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.[11] 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.[3] 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.[12−14]

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.[15] It is remarkable that so many agents that improve prognosis cause renal function to decline; renal dysfunction may also limit their use.[16] 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.[17−19] 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.[20] 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.[21−23] 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 (∼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.[24,25] 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.[26] Novel sensors such as the BIM could be easily incorporated into a HTM system tailored for patients with HF.[27,28]

A recent alternative to bio-impedance is remote dielectric sensing (ReDS) which measures lung fluid using low-power electromagnetic radiation.[29,30] 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.[31] 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

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

1. DiMatteo MR. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. *Med Care* 2004;**42**:200–209.
2. van der Wal MHL, Jaarsma T. Adherence in heart failure in the elderly: problem and possible solutions. *Int J Cardiol* 2008;**125**:203–208.
3. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. *Circulation* 2009;**119**:3028–3035.
4. 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.
5. 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.
6. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005;**353**:487–497.
7. Cole KS, Cole RH. Dispersion and absorption in dielectrics I. Alternating current characteristics. *J Chem Phys* 1941;**9**:341–351.
8. 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.
9. 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.
10. 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.
11. 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.
12. 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.
13. 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.
14. 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.
15. 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.
16. 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.
17. 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.
18. 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.
19. 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.
20. 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.

21. 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.

22. 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.

23. 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.

24. 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.

25. 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.

26. 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.

27. 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.

28. 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.

29. 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.

30. Abraham WT, Amir O, Weinstein JM, Abbo A, Ben Gal T. Remote Dielectric Sensing (ReDS™)-guided patient management of ambulatory heart failure patients reduces rehospitalization rates. *J Card Fail* 2015;**21**:S77.

31. 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.

32. 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.