

Daily home monitoring of potassium, creatinine, and estimated plasma volume in heart failure post-discharge

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Abstract

Aims Congestive status, serum potassium, and renal function are major determinants of outcomes as well as critical elements for adjusting drug therapy in heart failure (HF) patients. This study aimed at describing the daily variations in estimated plasma volume (ePV, a surrogate of congestion computed from haemoglobin and haematocrit), blood potassium, and estimated glomerular filtration rate during 2 months post-hospitalization for decompensated HF with reduced ejection fraction.

Methods and results The study was conducted in a single tertiary referral centre. Capillary blood samples were drawn by study nurses at home (7–12 am), and haematocrit, blood haemoglobin, creatinine, and potassium were measured using an approved home-based device (ABOTT i-STAT) (ClinicalTrials.gov: NCT01655134). Among the 15 home-monitored patients, two patients died (one suddenly), and one was readmitted for ischaemic acute pulmonary oedema, with a subsequent acute coronary syndrome, and did not have a complete 2-month follow-up. The 5-day-a-week biological home monitoring revealed an ePV >5.5 mL/g Hb, suggestive of undiagnosed residual congestion at discharge in 3 out of the 15 patients. It was possible to document a number of episodes of hyperkalaemia (>5: mean \pm standard deviation: 2.2 ± 2.2 or $5.5: 1.7 \pm 1.6$ mmol/L), hypokalaemia (<4: 1.9 ± 2.4 or $3.5: 0.5 \pm 1.2$ mmol/L), worsening renal function (drop in estimated glomerular filtration rate-20%: 1.3 ± 1.8 or 30%: 0.7 ± 1.2) and reaccumulation (ePV rise above 10%: 1.4 ± 1.5 , 15%: 2.3 ± 2.4 , 5.5 mL/g Hb: 1.8 ± 2.6) episodes indicative of clinically relevant and potentially actionable cardiorenal and electrolytic patterns.

Conclusions Our findings demonstrate that a 5-day-a-week home monitoring combining haemoglobin/haematocrit, potassium, and creatinine measurements was able to capture a substantial number of clinically relevant cardiorenal and electrolyte events which are frequently overlooked and potentially actionable. Whether acting on these events may help optimizing renin angiotensin aldosterone system inhibitors and diuretic therapy warrants further dedicated testing. The ongoing HERMES HF study (NCT04050904) is assessing the short-term feasibility and safety of such a monitoring strategy, complemented by a decision support system, and generating recommendations based on ESC clinical guidelines in patients discharged after an episode of worsening heart failure with reduced ejection fraction.

Keywords Hypokalaemia; Hyperkalaemia; Estimated plasma volume; Kidney function; Heart failure with reduced ejection fraction; Monitoring

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Background

After discharge from heart failure (HF) hospitalization, patients are at an unacceptably high risk of death and recurrent hospitalization for HF. Patients with chronic HF and reduced ejection fraction (HFrEF) should receive renin angiotensin aldosterone

system inhibitors (RAASi) to improve survival and diuretic therapy to alleviate congestion-related symptoms. However, in daily practice, patients receive suboptimal doses of RAASi mostly due to concerns of worsening renal function (WRF) and hyperkalaemia.¹ In addition, undiagnosed residual congestion is a major driver of post-discharge early readmission.²

Table 1 Baseline characteristics

Characteristics	N	Mean ± SD or n (%)	Median (Q1–Q3)	Range
Demography				
Age (years)	15	71 ± 10	71 (68–76)	38–84
Male gender	15	11 (73%)		
Physical examination				
BMI (kg/m ²)	15	28.3 ± 5.7	28.1 (24.4–33.0)	17.6–36.7
Blood pressure				
systolic (mmHg)	15	117 ± 14	117 (107–126)	95–145
diastolic (mmHg)	15	70 ± 11	67 (63–81)	51–89
MAP (mmHg)	15	86 ± 11	85 (78–95)	66–108
Cardiac examination				
LVEF (%)	15	31 ± 9	30 (25–35)	10–45
Sinus rhythm	15	7 (47%)		
Pacing	15	2 (13%)		
ICD	15	5 (33%)		
NYHA class				
I	15	1 (7%)		
II	15	6 (40%)		
III	15	7 (47%)		
IV	15	1 (7%)		
Acute coronary syndrome				
Previous history				
Ischaemic cardiopathy	15	7 (47%)		
Hypertension	15	7 (47%)		
COPD	15	2 (13%)		
Neoplasia	15	5 (33%)		
Risk factors				
Smoker (past or current)	15	6 (40%)		
Dyslipidaemia	15	6 (40%)		
Diabetes	15	8 (53%)		
Biochemistry				
Kalaemia (mmol/L)	15	4.5 ± 0.6	4.4 (3.9–4.9)	3.8–5.8
eGFR (mL/min/1.73 m ²)	15	60 ± 17	61 (47–78)	27–87
ePV (mL/g Hb)	15	4.6 ± 1.3	4.4 (3.5–5.0)	2.8–7.9
Myocardial stretch biomarker				
BNP (pg/mL)	15	588 ± 405	432 (258–994)	94–1286

BMI, body mass index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate (CKD-EPI formula); ePV, estimated plasma volume; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; NYHA, New York Heart Association.

N: count; SD: standard deviation; Q1–Q3: 1st and 3rd quartiles.

Table 2 Individual clinical characteristics

Patient	Gender	Age (years)	Sinus rhythm	PM Y/N	ICD Y/N	Baseline values		Blood level ranges during follow-up		
						SBP/DBP (mmHg)	EF (%)	eGFR (mL/min/1.73 m ²)	K+ (mmol/L)	ePV (mL/g Hb)
01	M	68	Y	N	N	133/86	10	49–83	4.1–5.4	2.9–4.4
02	M	68	N	Y	N	117/70	30	27–56	4.8–6.2	3.5–7.2
03	M	60	N	Y	Y	112/64	35	47–92	3.1–7.0	4.2–6.0
04	M	88	N	N	N	114/67	25	62–92	4.4–6.7	3.7–5.0
05	M	78	Y	N	N	126/63	30	33–87	4.1–6.8	5.3–9.9
06	M	66	Y	N	Y	95/63	25	56–92	3.9–7.4	2.6–4.6
07	W	38	Y	N	Y	125/86	45	64–123	3.9–5.4	2.9–4.7
08	W	79	Y	N	N	114/61	33	36–82	3.7–5.7	3.6–5.3
09	M	72	Y	N	N	107/74	35	67–101	4.0–5.4	2.5–3.7
10	M	71	N	N	Y	125/69	30	40–60	4.0–5.6	3.8–5.3
12	M	76	Y	N	Y	125/67	35	38–53	4.4–5.7	3.7–4.6
13	W	75	Y	N	N	145/89	20	25–62	3.9–6.0	3.0–4.6
15	M	79	Y	N	N	96/51	40	40–63	3.6–6.0	5.0–7.6
16	M	68	Y	N	N	MD	40	33–62	3.8–4.9	4.6–6.0
18	W	84	MD	N	N	124/81	30	20–34	3.0–5.6	3.9–6.1

EF, ejection fraction; eGFR, estimated glomerular filtration rate; ePV, estimated plasma volume; ICD, implanted cardioverter defibrillator; MD, missing data; N, no; PM, pacemaker; SBP/DBP, systolic/diastolic blood pressure; Y, yes.

Instantaneous plasma volume estimated from haemoglobin/haematocrit^{3,4} and its changes⁵ are indicative of congestion status^{6,7} and are associated with prognosis in acute or chronic HF.^{8–10} We hypothesized that daily post-discharge home monitoring of plasma volume, blood potassium, and estimated glomerular filtration rate (eGFR) could identify electrolyte and cardiorenal changes that could benefit outpatient optimization of diuretic and RAASi therapy.

Aims

The aim of this study is to assess the daily variations in estimated plasma volume (ePV), blood potassium, and eGFR

after discharge from hospitalization for decompensated heart failure, using a home-based finger capillary blood measurement 5 days a week during 2 months post-discharge and an approved bioassay device (ABOTT i-STAT) (ClinicalTrials.gov: NCT01655134).

Methods

The study was performed in a single tertiary referral centre, sponsored and funded by the University Hospital (CHRU) of Nancy, France. The protocol was approved by the Comité de Protection de Personnes Est-III prior to study initiation. All patients provided written informed consent before

Table 3 Individual treatments and events

Patient	Baseline medications and daily doses (mg)					Drug changes	Clinical event
01	Ramipril 5	Bisoprolol 2.5	Furosemide 120	Eplerenone 12.5	None	D13: Biso 3.75 D29: Biso 5 D30: Eple 25 D45: Eple 50	None
02	Ramipril 10	Celiprolol 200	Furosemide 125	Eplerenone 25	Diffu-K 600	None	D40: sudden death
03	Ramipril 10	Bisoprolol 10	Furosemide 375	Spiro. 25	Diffu-K 4200	D07: Furo 500 D16: K+ 5400 D17: K+ 4200 D21: K+ decrease D28: K+ 3600 D30: K+ 3000 D42: Furo 625	None
04	Candesartan 8	Bisoprolol 1.25	Furosemide 40	None	None	None	D13: septic shock D24: death
05	Perindopril 5	Bisoprolol 5	Furosemide 40	None	Diffu-K 1200	None	D27: bladder infection D28: raised creatinine
06	Candesartan 8	—	Furosemide 250	Eplerenone 50	Diffu-K 7200	None	None
07	Perindopril 10	Bisoprolol 2.5	Furosemide 40	Spiro. 25	None	None	D21: chest pain
08	Perindopril 7.5	Bisoprolol 2.5	Furosemide 40	Spiro. 25	None	D01: Diffu-K 600 D20: stop Diffu-K D20: Spiro 12.5 D29: Perin 2.5 D29: Biso 1.25 D29: Spir 25	D48: viral infection of upper respiratorytract
09	Ramipril 5	Bisoprolol 7.5	Furosemide 375	None	Diffu-K 5400	D03: Diffu-K 3600 D03: Biso 10 D03: Furo 125	None
10	Fosinopril 20	Bisoprolol 10	Furosemide 125	None	Diffu-K 1800	D21: Furo 120 D34: Furo 140	None
12	Ramipril 10	Bisoprolol 10	Furosemide 40	Eplerenone 50	None	None	None
13	Fosinopril 20	-	Furosemide 120	Spiro. 25	None	None	D45: stent (planned) D52: dry cough
15	Ramipril 2.5	Bisoprolol 3.75	Furosemide 60	None	Diffu-K 1800	None	None
16	Perindopril 5	Bisoprolol 10	Furosemide 375	Eplerenone 12.5	Diffu-K 1800	D32: Diffu-K 3000 D32: Rami 10	D22: ischemic acute pulmonary edema D42: severe chest pain
18	Yes	Yes	Yes	None	None	D05: Diffu-K 600 D39: Bumetan. 2 D54: Fosi. 10	D36: dehydration D41: nausea

Yes: drug intake, no other specification.

participating in the study. Assuming 8% of nonanalysable observations, a sample size of 20 patients was required to ensure a 0.5 SD accuracy for daily measurements and a corresponding 0.2 mmol/L accuracy for serum potassium.⁵

The capillary blood samples were drawn by study nurses at home (7–12 am). No data were communicated to the treating physician except in instances where blood potassium was ≥ 5.8 mmol/L. Haematocrit was determined using conductometry by i-STAT, which provides a calculated haemoglobin result as follows:

haemoglobin (g/dL) = haematocrit (%) \times 0.34, which was shown to be well correlated with the reference methods over a broad range of values between 6 and 16 g/dL.¹¹

Estimated plasma volume¹² and its changes⁵ were computed as previously described. A threshold of 5.5 mL/g Hb at discharge was deemed clinically relevant since associated with both congestion features and poor clinical outcomes.⁹

Estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula.¹³

Biological events are described as episodes (mean number of separate sequences with values persistently above or below a given threshold, i.e., hyperkalaemia >5.5 mmol/L or >5 mmol/L, hypokalaemia <4 or 3.5 mmol/L, WRF (drop in eGFR) $>20\%$ or 30%, ePV increase $>10\%$ or 15% or above 5.5 mL/g Hb) and mean number of measurements per episode.

Results

Among the 15 home-monitored patients, two patients died (one suddenly), and one was readmitted for ischaemic acute pulmonary oedema, with a subsequent acute coronary

Figure 1 Mean kinetics in the 12 patients who completed the study. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate; PV, plasma volume.

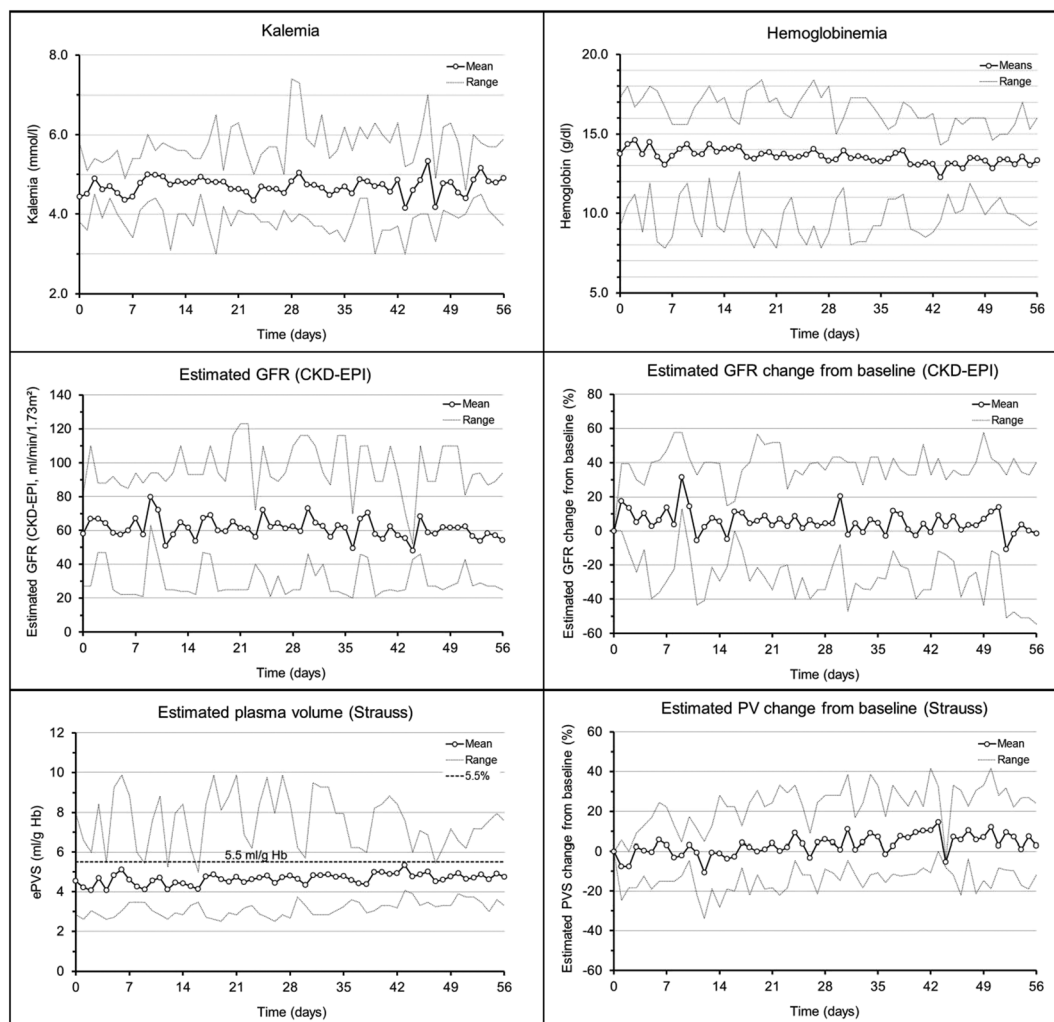


Table 4 Biological events during follow-up

Parameter	Number of ^a	Mean ± SD	Median (Q1–Q3)	Range
Potassium >5.5 mmol/L	Episodes	1.7 ± 1.6	1.5 (0.5–0.5)	0–5
	Measurements per episode	4.4 ± 6.9	1.5 (0.5–0.5)	0–22
Potassium >5.0 mmol/L	Episodes	2.2 ± 2.2	1.0 (1.0–1.0)	0–8
	Measurements per episode	9.1 ± 10.1	5.5 (2.5–2.5)	1 ^b –33
Potassium <4.0 mmol/L	Episodes	1.9 ± 2.4	1.0 (0.0–0.0)	0–6
	Measurements per episode	3.7 ± 5.7	1.0 (0.0–0.0)	0–17
Potassium <3.5 mmol/L	Episodes	0.5 ± 1.2	0.0 (0.0–0.0)	0–3
	Measurements per episode	0.7 ± 1.6	0.0 (0.0–0.0)	0–5
WRF > 20%	Episodes	1.3 ± 1.8	0.5 (0.0–0.0)	0–6
	Measurements per episode	5.3 ± 7.2	2.5 (0.0–0.0)	0–22
WRF > 30%	Episodes	0.7 ± 1.2	0.0 (0.0–0.0)	0–3
	Measurements per episode	2.4 ± 5.0	0.0 (0.0–0.0)	0–16
ePV >5.5 mL/g Hb	Episodes	1.8 ± 2.6	0.0 (0.0–0.5)	0–7
	Measurements per episode	6.8 ± 11.6	0.0 (0.0–12.0)	0–37
ePV increase >10%	Episodes	1.4 ± 1.5	1.0 (0.0–0.0)	0–5
	Measurements per episode	10.4 ± 9.1	12.0 (1.0–1.0)	0–30
ePV increase >15%	Episodes	2.3 ± 2.4	1.5 (0.0–0.0)	0–6
	Measurements per episode	7.7 ± 8.0	8.0 (0.0–0.0)	0–25

Note that an episode with values >x may include several shorter episodes with values y > x, and conversely for values <x and y with y < x. For instance, the mean number of episodes with ePV increases >10% (1.4 ± 1.5) was lower than for increases >15% (2.3 ± 2.4), although the mean number of measurements per episode was higher (10.4 ± 9.1 vs. 7.7 ± 8.0).

ePV, estimated plasma volume; WRF, worsening renal function from baseline.

^a12 complete observations, excluding three premature (two deaths and one hospitalization for ischaemic acute pulmonary oedema) and five consent withdrawals.

^bOne patient had only one 1-day hyperkalaemia >5.5 mmol/L.

syndrome, and thus did not have a complete 2-month follow-up (see study flowchart in online supplement).

Baseline patient characteristics are presented in *Table 1*. Individual follow-up data and post-discharge treatment changes are presented in *Tables 2* and *3*. The 5-day-a-week biological home monitoring (*Figure 1*) enabled documenting a number of hyperkalaemia, hypokalaemia, WRF and reoedemation episodes (*Table 4*).

At the individual level (*Data S1*), relevant and consistent profiles (e.g. persistent and/or recurrent dyskalaemia, WRF, reoedemation, or deoedemation patterns) were easily identified. For instance, Patient #2 (who suddenly died at Day 40), Patients #6 and #13 were chronically hyperkalaemic and displayed sustained trends toward worsening renal function and reoedemation, without any recorded change in cardiovascular medications. Before being rehospitalized for an acute pulmonary oedema of ischaemic origin, Patient #16 had a decrease in ePV and became hypokalaemic, with a transient WRF. When considering congestion separately, six patients presented ePV >5.5 mL/g Hb at inclusion (Patients #05 and #15: permanently raised ePV; Patient #16: ePV oscillating at around the 5.5-threshold value), indicative of post-discharge residual congestion, and/or ePV >5.5 mL/g Hb during follow-up. Patient #02 had an ePV <5.5 at inclusion, which continued to increase steadily until sudden death, which occurred in conjunction with massive leg oedema. Patient #03 had an ePV close to the threshold, with short occasional excursions above 5.5, while Patient #18 had a slow increase in ePV during follow-up, with values oscillating around 5.5 after Day 28. Of note, this latter Patient # 18 was nevertheless documented as “clinically dehydrated” by

the treating physician at Day 36, concomitant with an obvious decrease in ePV, a WRF, and hypokalaemia.

Conclusions

To the best of our knowledge, this is the first attempt of a daily home monitoring of blood potassium, eGFR, and ePV in HFrEF patients within the vulnerable post-discharge phase. Despite its small sample size and related limitation, such home monitoring study was already able to capture a substantial number of clinically relevant cardiorenal and electrolytic changes which are otherwise undiagnosed in routine daily practice with no monitoring.^{14,15} Additionally, given that (i) undiagnosed residual congestion is a major driver of post-discharge early readmission²; (ii) excessive deoedemation and use of diuretic therapy is associated with dehydration, hypotension, WRF, and poor prognosis¹⁶; (iii) dyskalaemia is associated with poor outcome¹⁷; and hyperkalaemia and WRF are the main reasons for the underuse, underdosing and frequent discontinuation of RAASi, and mineralocorticoid antagonists¹⁸; and (iv) use of the newly available potassium binders warrants proper biological monitoring,¹⁹ we believe that concomitant monitoring of plasma volume, blood potassium, and renal function is a relevant strategy for assessing congestion and the delicate cardiorenal balance.²⁰ Plasma volume, blood potassium, and renal function are potentially the most clinically actionable variables for the dynamic optimization of diuretic therapy and of life-saving RAASi therapy.

The ongoing HERMES HF study (NCT04050904) is currently assessing the short-term feasibility and safety of such a monitoring strategy, complemented by a decision support system (“ExpHeart”), and generating recommendations based on ESC clinical guidelines (CardioRenal ExpHeart) in patients discharged after an episode of worsening HFrEF.

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Conflict of Interest

Dr. Rossignol reports grants and personal fees from AstraZeneca, Bayer, CVRx, personal fees from Fresenius, grants and personal fees from Novartis, personal fees from Grunenthal, Servier, Stealth Peptides, Vifor Fresenius Medical Care Renal Pharma, Idorsia, NovoNordisk, Ablative Solutions, G3P, Corvidia, Relypsa, outside the submitted work; and Cofounder: CardioRenal. Cofounder: CardioRenal, a company developing a telemonitoring loop in heart failure (including creatinine, potassium and Hb measurements) Nicolas Girerd: personal fees from Novartis, personal fees from Boehringer, outside the submitted work; Renaud Fay: none Faiez Zannad: Dr. Zannad reports personal fees from Janssen, personal fees

from Bayer, personal fees from Boston Scientific, personal fees from Amgen, personal fees from CVRx, personal fees from Boehringer, other from cardiorenal, personal fees from AstraZeneca, personal fees from Vifor Fresenius, personal fees from Cardior, personal fees from Cereno pharmaceutical, personal fees from Applied Therapeutics, personal fees from Merck, other from CVCT, personal fees from Novartis, outside the submitted work; Cofounder: CardioRenal, a company developing a telemonitoring loop in heart failure (including creatinine, potassium and Hb measurements)

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Supporting information

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

Data S1: Study flowchart.

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