Early urine electrolyte patterns in patients with acute heart failure

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Abstract

Aims We conducted a prospective study of emergency department (ED) patients with acute heart failure (AHF) to determine if worsening HF (WHF) could be predicted based on urinary electrolytes during the first 1–2 h of ED care. Loop diuretics are standard therapy for AHF patients. A subset of patients hospitalized for AHF will develop a blunted natriuretic response to loop diuretics, termed diuretic resistance, which often leads to WHF. Early detection of diuretic resistance could facilitate escalation of therapy and prevention of WHF.

Methods and results Patients were eligible if they had an ED AHF diagnosis, had not yet received intravenous diuretics, had a systolic blood pressure > 90 mmHg, and were not on dialysis. Urine electrolytes and urine output were collected at 1, 2, 4, and 6 h after diuretic administration. Worsening HF was defined as clinically persistent or WHF requiring escalation of diuretics or administration of intravenous vasoactives after the ED stay. Of the 61 patients who qualified in this pilot study, there were 10 (16.3%) patients who fulfilled our definition of WHF. At 1 h after diuretic administration, patients who developed WHF were more likely to have low urinary sodium (9.5 vs. 43.0 mmol; \( P < 0.001 \)) and decreased urine sodium concentration (48 vs. 80 mmol/L; \( P = 0.004 \)) than patients without WHF. All patients with WHF had a total urine sodium of <35.4 mmol at 1 h (100% sensitivity and 60% specificity).

Conclusions One hour after diuretic administration, a urine sodium excretion of <35.4 mmol was highly suggestive of the development of WHF. These relationships require further testing to determine if early intervention with alternative agents can prevent WHF.

Keywords Acute heart failure; Emergency department; Worsening heart failure; Diuretic resistance; Urine electrolytes

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Introduction

Most patients hospitalized with acute heart failure (AHF) respond to intravenous (IV) loop diuretic therapy resulting in symptom improvement and discharge from the hospital after a 3–5 day stay.¹ However, up to 20% have a poor response to IV loop diuretics and are found to be ‘diuretic resistant’.² The treatment pathway for this patient cohort is unclear, and in part because of unchecked fluid and sodium retention, worsening heart failure (WHF) occurs during their inpatient stay and requires intensification of AHF therapy.³–⁵ Additionally, patients who develop WHF experience prolonged hospital lengths of stay and increased mortality.⁶,⁷ There are a number of proposed definitions of diuretic responsiveness, but no definition allows early identification of this in the emergency department (ED) or shortly after hospital admission.⁶–¹⁰ It would be valuable to be able to identify diuretic non-responders in the first 2 or 3 h to escalate therapy in
order to relieve symptoms, avoid WHF, and potentially reduce length of hospital stay.

Previous studies in the inpatient and outpatient setting suggest spot urine sodium may be predictive of subsequent HF-related events over 30 and 180 days. However, its association with near-term and inpatient events was less clear. A protocol to determine diuretic responsiveness based on urinary sodium measurements in the first 6 h after diuretic administration was recently reported. This study was conducted in the inpatient setting, where subjects were enrolled up to 4 days after admission. This is a novel concept and suggests diuretic resistance could be identified within 1–2 h of diuretic administration, but this concept has not been studied after the first dose of diuretic upon ED presentation. We propose a similar protocol to identify patients who develop WHF using urine electrolyte values 1 h after the initial dose of IV loop diuretic in the ED. If successful, diuretic resistance could be identified often within 3 h of presentation to the ED, and early measures could be taken to improve response to therapy.

Effective diuretic response is produced by natriuresis, measured by increased total urinary sodium excretion and urinary volume. Patients with continued low urinary sodium despite IV diuretic administration may be at risk for WHF. Our goal was to prospectively study urinary electrolyte excretion and determine the associations of these patterns with the development of in-hospital WHF. We hypothesized we could identify patients very early in their ED or hospital stay who would eventually meet clinical criteria for WHF by evaluating their urine sodium and potassium concentration, cumulative urine sodium, and urine output within the first 6 h after an initial dose of IV loop diuretic.

Methods

Study design and setting

From August 2016 to June 2017, we conducted a pilot single-centre prospective observational study (Trial Registration: NCT02751242) of a convenience sample of ED patients over 18 years of age whose primary ED admission diagnosis was AHF. Patients were enrolled at a tertiary care academic hospital in the southeastern United States. The study and all associated procedures were approved by the local Institutional Review Board. Informed consent for study participation was obtained from each patient or an acting surrogate.

Participants

The inclusion criterion was a clinical diagnosis of AHF in the ED by the treating provider. ED providers established a diagnosis of AHF using history, physical exam, chest radiography, and natriuretic peptide levels. Patients who had a systolic blood pressure < 90 mmHg, received IV diuretic administration prior to enrolment, had an allergy to furosemide or bumetanide, were currently receiving any form of dialysis, had no AHF diagnosis based on subsequent chart review, or did not receive the study recommended diuretic dose were excluded. Those who were subsequently discharged home from the ED prior to completion of 6 h of data collection were excluded from the final analysis. To confirm the ED diagnosis of AHF, all enrolled patients had their AHF diagnoses independently confirmed by two physician reviewers blinded to each other and urine electrolyte results. They reviewed the ED and inpatient medical records to confirm an AHF diagnosis (yes/no) using standard chart review techniques. This included a standard data abstraction form and independent data abstraction by each reviewer using the ED and inpatient medical record. When the two abstractors could not agree on whether the case in question was AHF, a third abstractor adjudicated. Those subjects with confirmed AHF after chart review comprised the final study cohort.

Definition of worsening heart failure

We defined WHF as (i) persistent (symptoms not improving despite initial therapy) or worsening AHF symptoms during the first 5 days of hospitalization after ED management and (ii) an intensification of AHF therapy, which could include pharmacologic (additional diuretics, uptitration of diuretics, or IV vasodilators) or initiation of mechanical measures such as non-invasive ventilation, intubation, or a mechanical assist device. Our definition of WHF was determined by two physician reviewers who were blinded to each other and to the urinary electrolytes. The physician reviewers determined if WHF was present using the ED history and physical examination, daily inpatient physician notes, urine output, laboratory and radiographic testing, medications administered, procedures performed, and discharge summaries. Only in the case of disagreements were the cases discussed by the two physician reviewers and an additional third physician reviewer to come to a consensus determination of WHF.

Study procedures

Prior to diuretic dosing, patients were asked to empty their bladder. The study did not mandate use of a Foley catheter. Per study protocol, patients were given two times their daily dose of furosemide up to a maximum of 200 mg IV. For example, a patient on 80 mg of oral furosemide twice daily would receive 160 mg IV as their ED dose. If a patient...
remained in the ED for 12 h, they would receive another two times their home dose (i.e. 160 mg IV furosemide in the aforementioned example). Patient underwent a continuous urine collection for 6 h, which documented urine output and collected a spot urine sample at baseline, and at 1, 2, 4, and 6 h after the first dose of IV diuretic, terminating with a forced void at hour 6. The urine was processed, stored, and sent to the clinical lab to quantify urine sodium, potassium, and creatinine concentrations at the individual time points as well as over the entire 6 h period. Patients were followed up throughout the remainder of their hospital stay to document changes in weight, total urinary output, hospital length of stay (LOS), and adverse events. The clinical teams determined subsequent diuretic therapies, including the need for escalating doses of diuretics and other AHF therapies. Patients had a chart review performed and were phoned 30 days after enrolment to determine if they experienced any subsequent adverse events after discharge, including ED revisits, hospital readmission, or cardiovascular death.

### Results

#### Participant characteristics

We enrolled 75 patients and subsequently excluded eight patients who did not have AHF based on physician chart review, four patients who were discharged from the ED prior to 6 h of data collection, one patient who withdrew, and one patient who did not receive the protocol mandated dose of diuretic. Figure 1 shows the study cohort of the 61 patients. The median age was 63 years (IQR 54–77), 46% were female, and 30% were African American (Table 1). Median (IQR) left ventricular ejection fraction was 50% (30–55%), median ED initial systolic blood pressure was 142 mmHg (IQR 123–167 mmHg), median estimated glomerular filtration rate (eGFR) was 48 mL/min/1.73 m² (IQR 31–60 mL/min.1.73 m²), and median b-type natriuretic peptide level was 879 pg/mL (IQR 474–1501 pg/mL). The kappa between reviewers for the definition of WHF was 0.74 [95% confidence interval (CI) = 0.50–0.98].

#### Urinary characteristics in patients with and without worsening heart failure

There were 10 (16.4%) patients who fulfilled our definition of WHF (Table 2). Of the 10 who had WHF, eight had their diuretic regimens intensified without IV vasoactives, while two had both their diuretic regimen intensified and IV vasoactives initiated. They were more likely to have a lower eGFR at the time of enrollment and on the day of discharge than those who did not fulfill the WHF definition. The overall median dose of IV diuretic administered was 80 (IQR 40–120) mg furosemide equivalents (where 1 mg bumetanide = 40 mg furosemide). Those with WHF received 120 (IQR 50–200) mg furosemide equivalents and those who were not found to have WHF received 80 (IQR 40–100) mg furosemide equivalents. At 1 and 2 h after diuretic administration, patients with WHF had lower total urine sodium excretion (first hour: 9.5 mmol [8.3–17.0] vs. 43.0 mmol [22.3–65.9]; second hour: 50.8 mmol [9.2–75.3] vs. 82.3 mmol [61.4–126.3]) and lower urine output (first hour: 162 mL [19–299] vs. 500 mL [335–750]; second hour: 200 mL [60–425] vs. 500 mL [338–700]) compared with those without WHF (Figure 2A and B). Patients with WHF also had significantly lower urine sodium concentration (48 mmol/L [36–54] vs. 80 mmol/L [58–108]) (Figure 2C) and a decreased urine sodium/potassium ratio (1.8 [1.3–7.0] vs. 8.0 [4.8–10.1]) (Figure 2D) at 1 h after initial ED diuretic compared with those without WHF.

Amongst the urinary biomarkers, the overall diagnostic accuracy based on the AUC of the receiver operating characteristic curves throughout the 6 h of data collection suggests 1 h urine sodium concentration (AUC = 0.83, 066–0.99), 1 h total

### Laboratory measurement

Laboratory chemistries were measured by the Vanderbilt University Medical Center clinical laboratory using Clinical Laboratory Improvement Amendments-approved methods. Urine sodium and potassium were determined by ion-selective electrode diluted (indirect) via Integrated Chip Technology, and urine creatinine was determined by Kinetic Alkaline Picrate (Abbott Architect System, Abbott Park, IL, USA).

### Statistical analysis

Simple descriptive statistics were used to describe the study population overall and across our clinical definition of WHF including median [interquartile range (IQR)] and counts (proportions), as appropriate using Wilcoxon rank sum and Pearson $\chi^2$ tests. During the first 6 h after IV diuretic administration, we compared patients who fulfilled our definition of WHF with those who did not by comparing the following: (i) urinary sodium concentration, (ii) urinary sodium output, (iii) urinary output, and (iv) urinary sodium to potassium ratio.

The diagnostic accuracy of urine sodium concentration, absolute urine sodium output, urinary output, and urinary sodium/potassium ratio was each assessed using area under the curve (AUC) calculated from receiver operating characteristic curves. We also explored the association of LOS with both (i) WHF and (ii) urinary electrolyte and urinary output cutpoints. Because this was a pilot study, no formal power calculations were performed.

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Figure 1  Patient identification and enrolment. AHF, acute heart failure; BP, blood pressure; ED, emergency department.

Table 1  Clinical characteristics of patients stratified by WHF

|                          | No WHF | WHF  | Combined |
|--------------------------|--------|------|----------|
|                          | $N = 51$ | $N = 10$ | $N = 61$ |
| Age                      | 61     | 65 (54, 78) | 62 (57, 68) | 63 (54, 77) |
| Sex                      | 61     | 0.47 (24) | 0.40 (4) | 0.46 (28) |
| Female                   | 61     | 0.53 (27) | 0.60 (6) | 0.54 (33) |
| Race (self-report)       | 61     | 0.00 (0) | 0.00 (0) | 0.00 (0) |
| American Indian or Alaska Native | 61 | 0.00 (0) | 0.00 (0) | 0.00 (0) |
| Asian                    | 61     | 0.29 (15) | 0.30 (3) | 0.30 (18) |
| Black or African American | 61    | 0.00 (0) | 0.00 (0) | 0.00 (0) |
| Native Hawaiian or Other Pacific Islander | 61 | 0.00 (0) | 0.00 (0) | 0.00 (0) |
| White or Caucasian       | 61     | 0.71 (36) | 0.70 (7) | 0.70 (43) |
| Median IV diuretic dose on Day 0 (IQR) (mg) | 61 | 80 (40, 100) | 120 (50, 200) | 80 (40, 120) |
| eGFR value (MDRD method) | 61     | 50 (34, 66) | 34 (23, 50) | 48 (31, 60) |
| Median serum creatinine (IQR) (mg/dL) | 61 | 1.19 (0.93, 1.85) | 1.96 (1.54, 2.58) | 1.24 (0.97, 1.97) |
| Median systolic BP (IQR) (mmHg) | 61 | 142 (129, 166) | 134 (110, 163) | 142 (123, 167) |
| Median diastolic BP (IQR) (mmHg) | 61 | 79 (66, 92) | 76 (64, 102) | 79 (64, 92) |
| Median EF (IQR) (%) in the last 6 months | 57 | 30 (25, 30) | 30 (25, 50) | 50 (30, 55) |
| Median BNP (IQR) (units)  | 57     | 20.0 (0.0, 140.0) | 24.0 (0.5, 140.0) | 20.0 (0.0, 40.0) |

BP, blood pressure; EF, ejection fraction; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MDRD, Modification of Diet in Renal Disease; WHF, worsening heart failure.

$N$ is the number of non-missing values. Numbers after proportions are frequencies.
Table 2: Markers of worsening heart failure (WHF) at 1 and 2 h after diuretic administration

|                          | No WHF   | WHF      | Combined | P-value |
|--------------------------|----------|----------|----------|---------|
|                          | N = 51   | N = 10   | N = 61   |         |
| **Observed urine output**|          |          |          |         |
| Hour 0–1 (mL)            | 500 (335, 750) | 162 (19, 299) | 450 (250, 700) | <0.001  |
| Hours 1–2 (mL)           | 500 (338, 700) | 200 (60, 425) | 460 (285, 700) | 0.009   |
| **Observed sodium output**|          |          |          |         |
| Hour 1 (mmol)            | 82.3 (61.4, 126.3) | 50.8 (9.2, 75.3) | 75.0 (57.2, 123.7) | 0.053   |
| Hours 0–2 (mmol)         | 82.3 (61.4, 126.3) | 50.8 (9.2, 75.3) | 75.0 (57.2, 123.7) | 0.001   |
| **Urine sodium**         |          |          |          |         |
| Hour 1 (mmol/L)          | 80 (58, 108) | 48 (36, 54) | 71 (56, 106) | 0.004   |
| Hour 2 (mmol/L)          | 77 (60, 112) | 57 (34, 94) | 75 (60, 109) | 0.14    |
| **Urine Na/K**           |          |          |          |         |
| Hour 1                   | 8.0 (4.8, 10.1) | 1.8 (1.3, 7.0) | 7.8 (4.0, 9.7) | 0.01    |
| Hour 2                   | 9.67 (7.53, 12.45) | 5.94 (0.88, 10.70) | 9.37 (7.20, 12.34) | 0.12    |
| **FeNa**                 |          |          |          |         |
| Hour 1                   | 6.4 (3.8, 10.6) | 2.8 (1.1, 4.7) | 6.0 (3.3, 10.1) | 0.01    |
| Hour 2                   | 12.2 (8.7, 42.6) | 7.5 (1.5, 13.1) | 11.8 (8.2, 41.5) | 0.12    |
| **Urine sodium: Hours 2–1** | -1.0 (–8.0, 7.0) | 0.0 (–7.0, 7.0) | –0.5 (–8.0, 7.0) | 0.75    |
| Na/K: Hours 2–1          | 1.57 (0.13, 3.66) | 1.63 (0.0093, 4.16) | 1.60 (0.048, 3.96) | 0.86    |

Figure 2: Urinary measures of natriuresis and diuresis in patients without and with worsening heart failure (WHF): (A) urine sodium output, (B) urine output, (C) urine sodium concentration, and (D) urine sodium/potassium ratio.
urine output (AUC = 0.86, 0.76–0.96), 1 h total urine sodium excretion (AUC = 0.88, 0.77–1.0), and 1 h sodium/potassium ratio (AUC = 0.80, 0.62–0.97) were the most accurate markers of WHF (Figure 3). In this population, a total urine sodium of <35.4 mmol 1 h after diuretic administration was 100% sensitive (95% CI = 0.0–35.4%) and 60.4% specific (95% CI = 46.3–73.0%) for WHF. Total urinary output of <480 mL 1 h after diuretic administration was 100% sensitive (95% CI = 0.0–27.8%) and 54.9% specific (95% CI = 41.4–67.7%).

Association of urinary markers of diuretic responsiveness and worsening heart failure with hospital length of stay

Patients with WHF had significantly longer hospital LOS than those without WHF (9.4 days [7.7–10.9] vs. 2.8 days [1.9–4.5]; P < 0.001). Patients with urinary sodium of <35.4 mmol 1 h after diuretic administration tended to have a longer hospital LOS than those with urinary sodium of >35.4 mmol (median: 4.02 days [2.80–9.14] vs. 2.84 days [1.90–4.83]; P = 0.053). Total urine output of <480 mL at 1 h after diuretic was associated with a similar trend of increased hospital LOS compared with those with urine output of >480 mL (median: 4.03 days [1.92–7.99] vs. 2.84 days [2.07–4.84]; P = 0.20).

Discussion

We have completed the first prospective study evaluating diuretic responsiveness in ED patients with AHF who receive a protocolized dose of diuretics. In contrast to prior studies that were conducted in the inpatient setting after admission and initial therapy, we followed up patients in the ED and documented urine output in the first 6 h as a measure of acute diuretic response. Our study has two important findings. First, markers of natriuresis were easily quantified and associated with WHF 1 h following the first IV loop diuretic.

Figure 3  Receiver operating characteristic curves for (A) urine sodium concentration, (B) urine sodium output, (C) urine output, and (D) predicted urine sodium concentration at 6 h, during the first hour after diuretic administration to discriminate between patients with and without worsening heart failure. AUC, area under the curve.
A low 1 h urine sodium concentration, low total urine sodium, or a low sodium to potassium ratio was all associated with development of WHF. Specifically, urine sodium output at 1 h <35.4 mmol was 100% sensitive for predicting WHF. Second, those who developed WHF during hospitalization had low 1 h urine sodium excretion and low 1 h urinary output and tended to have a longer LOS than those who did not develop WHF. These findings, if confirmed in a larger cohort, could have important clinical implications for the care of patients with AHF. Our previous study also suggested a relationship between urinary sodium and hospital LOS. Evaluating natriuresis and diuresis within 1 h of diuretic administration could identify patients within 2–3 h of ED presentation who may need early treatment intensification. Other markers of response to diuretic therapy, such as weight loss and fluid excretion, have been used and have been inconsistent markers of decongestion and treatment endpoints. Importantly, up to 50% of patients have no weight loss during hospitalization, and even those who do experience weight loss are still at risk for readmission. A reproducible, objective marker of response to therapy, with an intervention that can influence the marker, is a critical unmet need. Urine sodium is easily measurable and readily available in most hospital EDs, and its dynamic changes could be followed after up titration of diuretic therapy.

Commonly applied interventions in patients with low natriuresis include escalation of diuretics, but the ideal strategy to treat diuretic resistance is unknown. The addition of thiazide diuretics, acetazolamide, or mineralocorticoid receptor antagonists could be considered. Thiazides would reduce sodium reabsorption in the distal tubule while acetazolamide has been shown to prevent proximal sodium reabsorption and may act synergistically with the initial loop diuretic. Recent studies demonstrate a primary role of distal sodium reabsorption as a reason for diuretic resistance. Thus, specifically targeting this segment with a mineralocorticoid receptor antagonist or epithelial sodium channel inhibitor could be a more effective alternative. Patients given SGLTII inhibitors have also shown increased diuresis and natriuresis. Depending on the associated blood pressure, the addition of early vasodilators might be considered. The most intriguing possibility is that the evaluation of all of these measures could be carried out very rapidly using the urinary sodium. The timing of response to each of these possible interventions will need to be considered, but conceivably multiple strategies might be evaluated in a 12 to 24 h period.

In AHF, the underfill hypothesis postulates that decreased cardiac output leads to arterial underfilling and decreased renal perfusion, increased renin-angiotensin-aldosterone system activity, and increased proximal tubule sodium reabsorption. Retention of sodium and water due to inadequate natriuresis and diuresis are hallmarks of HF. Patients with HF have a markedly reduced rate of renal sodium excretion, and cumulative sodium retention has been closely correlated with an increase in body weight. When loop diuretics are effective, urinary sodium and potassium excretion increases, often resulting in hypokalaemia. Poor gut absorption of orally administered loop diuretics, decreased delivery to molecular targets, low serum albumin, renal tubular hypertrophy, and circulating organic acids inhibiting the organic anion transporter, all lead to a diminished effect of diuretics, resulting in impaired urinary sodium excretion. Even when diuretics are given intravenously, diuretic ‘braking’ can be encountered, negating intended natriuresis and contributing to diuretic resistance in patients with AHF. Thus, identifying this phenomenon early in a patient’s course, before it is clinically apparent, could result in an intervention that would prevent a cascade of untoward events.

While our study was prospectively conducted with predefined criteria for WHF and AHF, several limitations need to be considered. First, our cohort consisted of 61 patients from one academic institution and may not be representative of the broader AHF population. Second, our cohort had relatively low median eGFR at 48 mL/min/m², and this could be important when translating these findings to other cohorts with different renal function and how they may respond to initial diuretic therapy. Patients with lower eGFR were more likely to experience WHF. A larger study would need to adjust for baseline eGFR in a multivariable model to determine the independent predictive ability of urinary natriuresis. However, renal dysfunction is commonly encountered in patients with AHF, and we feel that this finding is consistent with that encountered in clinical care. Third, while there is no true gold standard for WHF, we used a clinically meaningful definition based on worsening or persistent AHF requiring intensification of therapy. Our definition of WHF also strongly predicted hospital LOS. Fourth, while we had 16% of patients who developed WHF, the total number of events (n = 10) was relatively small because of the small sample size. While this leads to wider parameter estimates in our findings, the compendium of our data suggests early markers of diuresis and natriuresis are predictive of subsequent WHF. Fifth, the urine sample prior to ED diuretic administration may provide insight into the association of natriuresis while on oral diuretics in the outpatient setting and the development of WHF. However, only ~35% of our cohort had a baseline, pre-IV diuretic sample collected. Future investigations should evaluate this relationship more extensively. Finally, inpatient teams were not blinded to the ED dose of diuretic and the diuretic response in the ED, and subsequent dosing and escalation of therapy could have been influenced by this initial dose. Further, subsequent underdosing could have slowed diuresis, causing a sudden need for an increase in diuretic and the fulfilment of our WHF definition.

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Conclusions

In our study of 61 ED patients with AHF, 16% met criteria for WHF. Urine markers of natriuresis and diuresis within 1 h of diuretic administration were significantly associated with WHF. Urine sodium excretion during the first hour after diuretic administration of <35.4 mmol was 100% sensitive for subsequent WHF. Our study establishes a proof of concept, and future studies should (i) validate these predictive thresholds, (ii) use this information to determine if triaging patients to different levels of care improves WHF rates, and (iii) compare alternative treatment strategies with standard loop diuretics to determine if this can prevent development of WHF.

Conflict of interest

S.P.C. receives grants from AHA, PCORI, NIH, AHRQ, and Novartis and is a consultant of Novartis, Vixiar and Medtronic. C.A.J. receives grants from Novartis. A.B.S. receives grants from PCORI and NIH and is a consultant of Novartis, Siemens, MCM Education, and Alere. J.H.H. receives grants from Novartis and Bristol Myers Squibb. N.J.B. receives grants from NIH and is a consultant of Novartis, Shire, and Viamet and a member of Scientific Advisory Board of Alynlam. D.L. receives grants from PCORI. J.M.L. receives grants from Novartis. C.D.M. receives grants from NIH, DOD, and VA Office of Rural Health. D.P. receives grants from Novartis. J.M.T. receives grants from NIH. J.L. receives grants from Novartis, AstraZeneca, and Boehringer Ingelheim and is a consultant of Novartis, ResMed, Relypsa, V-Wave, CVRx, AMGEN, and Cytokinetic.

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