Augmentation of ECG QRS Complexes after Fluid Removal via a Mechanical Ultrafiltration Pump in Patients with Congestive Heart Failure

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Background: Augmentation of the amplitude of ECG QRS complexes, correlating with loss of weight or fluid volume removed, has been documented in patients with congestive heart failure (CHF).

Methods: We investigated the effect of an ultrafiltration (UF) pump on the fluid removal and the amplitude of ECG QRS complexes in patients with CHF. Nine patients aged 48.3 ± 10.4 years with CHF were treated with an UF system, and weights, fluid removed, and sums of the amplitude of QRS complexes (Σ QRS), were inter-correlated.

Results: UF resulted in removal of 4.62 ± 1.82 L of fluid, $5.0 \pm 2.9\%$ decrease in the weights ($P = 0.002$) and $18.1 \pm 16.8\%$ increase in the Σ QRS ($P = 0.012$). There was a moderate correlation of % increase in the Σ QRS and net fluid volume losses (UF + urine – oral intake), ($r = 0.67$, $P = 0.0471$), and a poor correlation between % increase in the Σ QRS and % decrease in weights ($r = 0.11$, $P = 0.77$). Correlations of the change in weights after UF with the fluid removed by UF, or with the volume of total fluid loss (including insensible losses) were moderate but barely statistically significant ($r = 0.65$, $P = 0.0559$), and ($r = 0.65$, $P = 0.0577$), correspondingly.

Conclusion: Augmentation of the amplitude of QRS complexes correlates well with net fluid loss in response to UF in patients with CHF, and can be employed as an index of effectiveness of therapy. Also, a model of fluid losses in patients treated for CHF is being proposed.

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attenuation of QRS voltage; congestive heart failure; peripheral edema; ultrafiltration for congestive heart failure; body volume conductor; electrical impedance

In previous reports,^{1–4} encompassing 26 patients, it was shown that alleviation of peripheral edema in response to diuresis in patients with congestive heart failure (CHF) resulted in augmentation of the ECG QRS complexes; this ECG change correlated with the net volume of fluid loss,³ or was associated with reduction of the patients' weight.^{1,2,4} Those patients were treated in the hospital employing conventional management consisting of the use of routine drugs for CHF, which included a combination of oral and intravenous diuresis, over the course of several days.^{1,2,4} In one of the reports cited above,³ intravenous furosemide was used over the course of 40 ± 23 hours. The present report describes the first experience with ECG voltage augmentation observed in patients with CHF treated in the hospital

with an ultrafiltration (UF) pump, similar to the one used in recent studies.^{5,6}

METHODS

Study Patients

Ten patients admitted to the Detroit Receiving Hospital with CHF exacerbation were treated with a single session of UF; one of them, initially thought to be in CHF exacerbation, was later found to have constrictive pericarditis and was excluded from the analysis. The nine analyzable patients (seven male and two female) aged 48.3 ± 10.4 , 28–66-years old, had ischemic cardiomyopathy ($n = 2$), nonischemic cardiomyopathy ($n = 6$), and right-sided heart failure due to primary pulmonary hypertension

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without left ventricular failure ($n = 1$). Ejection fraction visually estimated by an experienced reader on two dimensional echocardiography, performed within 6 months of the index admission, was 24.4 ± 17.8 (range 10–60%). The cause for exacerbation of CHF in these patients was noncompliance with the drug regimen, with subsequent failure to respond to diuresis ($n = 1$), being only on methyldopa for hypertension ($n = 1$), and unresponsiveness to an appropriate drug regimen for CHF including an angiotensin converting enzyme (ACE)-inhibitor and furosemide at a mean dose of 80 mg a day ($n = 6$); four patients were taking a beta-blocker, one patient was on a combination of hydralazine and isosorbide dinitrate, instead of an angiotensin converting enzyme (ACE)-inhibitor, and one patient was taking spironolactone. On discharge, four more patients were started on a beta-blocker, and two on spironolactone. The decision to use UF was made by the treating physician based upon clinical criteria (fluid overload and/or resistance to diuretics); this explains the reason for not being able to recruit more than 10 patients in the present study. The exclusion criteria were allergy to heparin, systolic blood pressure below 90 mm Hg, and serum creatinine above 2 mg/dL. None of the patients had a cardiac emergency like pulmonary edema or cardiogenic shock, and none required intravenous vasoactive drugs or endotracheal intubation. All were in chronic CHF NYHA III-IV with signs of either biventricular or right ventricular failure. There were no blood transfusions given before, during, or after UF.

Study Variables

Parameters included in the study were systolic and diastolic blood pressure, heart rate, volume of fluid removed by the UF, volume of fluids drank by the patients (oral intake), volume of urine passed during UF, net volume of fluid removed, estimated fluid insensible losses (body weight in Kg $\times 10 \times$ duration of UF in hours/24),⁷ volume of total fluid losses, electrolytes, BUN, creatinine, hemoglobin, and hematocrit, brain natriuretic peptide (BNP) before and after UF, weight (before and after UF), height, body mass index, body surface area, duration of UF, rate of fluid removal by UF, and a 12 lead ECG before and after UF. All the above fluid data were also adjusted by the patients' weight prior to UF, and were used as study variables. Under typical for urban life sedentary conditions,

and with comfortable indoor ambient temperatures daily insensible losses of a healthy adult amount to 10 mL/kg body weight;⁷ however for a patient with CHF and at varying degrees of stress (physical and psychological) this value may underestimate the insensible fluid losses, and this may be reflected in our calculated fluid volumes lost. The ECGs were hard copies recorded at 25 mm/sec and at 10 mm = 1.0 mV standardization, using a GE Marquette 12 SL electrocardiograph. ECG automated measurements included heart rates, QRS duration, QTc, frontal axis of the P waves, QRS complexes, and T waves, and P-R interval. Manual measurements were made by one of us (JEM) at Elmhurst Hospital, where the set of 18 hard copies of the ECGs (two per patient) were forwarded without any identifying information (the upper part of the ECG records with the identifying information and the automated ECG measurements had been cut off), to ensure measurement and calculations on ECG QRS complexes under blinded conditions. The QRS complexes were measured to the nearest 0.5 mm, from their zenith to nadir, using hand-held calipers and with the aid of a magnifying glass under strong overhead light, and the sum of these measurements from the 12 ECG leads (Σ QRS)⁸ were calculated. A table with the calculated values of Σ QRS was sent to the investigator at the Detroit VA hospital (MEG), and following this, the study data were freely exchanged between the two investigators, and the analysis of data commenced.

Ultrafiltration Procedure

The UF was done with the Aquadex system, (an FDA approved device, manufactured by CHF Solutions, Inc., Brooklyn Park, MN), employed previously,^{5,6} using either central venous (if the catheter was already in place for other reasons) or peripheral venous access (16 gauge catheter for withdrawal and 18 gauge catheter for return), with the patients fully heparinized. The system does not need monitoring and central venous access, and has a pump, which creates the pressure gradient, and a filter, which allows the smallest molecules like water, sodium, or potassium to go through. Consequently, the concentration of electrolytes in the ultrafiltrate is the same as in the blood, and unlike high doses of furosemide or hemodialysis, UF does not cause electrolyte imbalance. Larger particles like proteins, creatinine, glucose, etc. do not fit through the pores and thus do not get removed.

Figure 1. ECG changes before (A) and after (B) ultrafiltration in a 66-year-old woman with congestive heart failure (CHF); 6.3 L of fluid were removed, the patient lost 3.1 kg of weight (2.8% decrease), which led to a 25.6% increase in the Σ QRS.

The duration of treatment was not decided in advance, but it lasted until it was felt that the clinical condition had improved. The rate of fluid removal was 200–400 cc/hour and was adjusted based on patients' symptoms and blood pressure. We did not have to discontinue UF due to side effects in any of our patients. None of the patients was given diuretics during the UF or between the end of the procedure and the recording of the second ECG. Since UF lasted for several hours there were other gains and losses of fluid during the procedure (oral intake, urine output, insensible fluid losses).

Statistical Analysis

Continuous data are presented as mean $\pm$ SD; the paired *t* test was used for the analyses of such data corresponding to the first and second ECGs. Regression analyses were carried out considering the

weights, volume of fluid removed by UF, net volume of fluid removed (UF + urine – fluids drunk), total volume losses (UF + urine passed + insensible losses – fluids drunk) and Σ QRS, as independent or dependent variables, as appropriate.^{9,10} All statistical operations were 2-tailed. The SPSS/PC+ 4.0.1 statistical package was used,¹⁰ and a *P* < 0.05 was taken as statistically significant.

RESULTS

UF led to removal of 4.62 ± 1.82 L of fluid, $5.0 \pm 2.9\%$ decrease in the patients' weight (*P* = 0.002), and an $18.1 \pm 16.8\%$ increase in the Σ QRS (*P* = 0.012) (Fig. 1 and Tables 1 and 2). Additional fluid volume data are shown on Table 2. Other ECG-derived parameters, clinical, laboratory, and other study variables did not change significantly

Table 1. ECG and Laboratory Data Tabulated According to the Timing of the Recording of the 2 ECG Tracings in Patients Treated for Heart Failure (n = 9).

Variable	ECG1	ECG2	P value
ΣQRS (mm)	167.1 ± 56.6	197.2 ± 72.9	0.01
QRS duration (ms)	108.2 ± 2	106.2 ± 11.1	0.29
QRS frontal axis (°)	-2.3 ± 59.3	-6.1 ± 53.2	0.33
QTc (ms)	465.6 ± 43.0	462.0 ± 34.9	0.82
PR interval (ms)	173.8 ± 22.5	173.0 ± 26.3	0.90
P-wave frontal axis (°)	57.0 ± 14.6	52.8 ± 14.2	0.52
Heart rate (beats/min)	89.7 ± 8.6	85.9 ± 11.3	0.40
T-wave frontal axis (°)	83.1 ± 47.4	89.4 ± 46.0	0.56
BNP (mg/m)	1,353.6 ± 1,525.2	709.2 ± 504.1	0.114
Hemoglobin (g/dL)	12.3 ± 1.7	12.7 ± 1.6	0.178
Hematocrit (%)	37.8 ± 5.0	38.0 ± 3.9	0.877
K ⁺ (mEq/L)	4.0 ± 0.7	4.1 ± 0.6	0.177
Mg ⁺⁺ (mg/dL)	1.7 ± 0.2	1.8 ± 0.3	0.290
BUN	24.1 ± 8.2	24.4 ± 7.6	0.780
Creatinine (mg/dL)	1.4 ± 0.3	1.5 ± 0.5	0.325

Abbreviations: ECG1 reflects variables prior to ultrafiltration; ECG2 reflects variables after hemofiltration; data are n = 9, except for P-wave frontal axis and PR interval (n = 8) due to atrial fibrillation.

during UF (Table 1). Correlations of % increase in the ΣQRS, and % decrease in weight with the UF volumes or the various composite volumes measured during UF are shown on Table 3 and Figure 2. Interestingly, the mean ±SD values of

the parameters of fluid volume removed by UF, net fluid volume removed (UF + urine – oral intake), and total fluid losses (UF + urine + insensible losses – oral intake) adjusted for the patients' weights prior to UF were identical at 0.05 ± 0.02

Table 2. ECG and Laboratory Data Tabulated According to the Timing of the Recording of the 2 ECG Tracings in Patients Treated for Heart Failure (n = 9).

Variable	ECG1	ECG2	P Value
Fluid removed between			
ECG1 and ECG2 (L)	4.62 ± 1.82*		
Urine volume passed (L)	0.58 ± 0.26*		
Oral fluid intake (L)	0.67 ± 0.31*		
Calculated insensible losses (L)	0.71 ± 0.34*		
Total fluid loss (L)	5.20 ± 2.03*		
Weights (kg)	99.3 ± 23.0	94.5 ± 22.7	0.002
Decrease in weight between			
ECG1 and ECG2 (kg)	4.8 ± 3.2*		
Height (m)	1.81 ± 0.14		
Body mass index (kg/m ²)	30.7 ± 7.9		
Body surface area (m ²)	2.22 ± 0.29		
Duration of ultrafiltration (hours)	16.9 ± 7.3		
Fluid volume removed/			
Admission weight (L/kg)	0.05 ± 0.02		
Net fluid volume removed/			
Admission weight (L/kg)	0.05 ± 0.02		
Total fluid volume losses/			
Admission weight (L/kg)	0.05 ± 0.02		
Fluid volume removed/			
Admission body surface area (L/m ²)	0.05 ± 0.02		
Rate of fluid removal (L/hours)	0.29 ± 0.08		

Abbreviations: Data values under "ECG1" and "ECG2" reflect variables measured before and after ultrafiltration, respectively; *, reflects data values of the changes of the various fluid volumes measured during the course of ultrafiltration.

Table 3. Correlations of Various Fluid Volume Variables with Changes in ECG and Weight in Patients Treated for Heart Failure (n = 9)

Variables	r value	P Value
% increase in Σ QRS versus UF volume + urine – oral intake, adjusted to admission weight	0.67	0.0471
% increase in Σ QRS versus UF volume, adjusted to admission weight	0.66	0.0542
% increase in Σ QRS versus UF volume + urine + insensible losses – oral intake, adjusted to admission weight	0.62	0.0771
% increase in the Σ QRS versus % decrease in weight	0.11	0.77
% decrease in weight versus UF volume	0.65	0.0559
% decrease in weight versus UF volume + urine + insensible losses – oral intake, adjusted to admission weight	0.65	0.0577
% decrease in weight versus UF volume + urine – oral intake, adjusted to admission weight	0.40	0.29

Abbreviations, as in the text.

(Table 1), reflecting the variation in the volumes of fluid removed by UF, urine, oral intake, and insensible losses in these patients.

DISCUSSION

What is novel about this report is the augmentation of the Σ QRS in conjunction with the employment of UF in patients with CHF, and the correlation of such ECG alteration with the fluid volume lost. In addition, the design of this study is proposed as a model for studies of patients with CHF, particularly in reference to the variables of net fluid volume removed, with inclusion of volumes of urine, oral fluid intake, insensible losses, adjusted to the initial weight, and duration of therapies. This comprehensive approach has not been employed heretofore, and its application may lead to more accurate assessment of patients with CHF treated with various therapeutic modalities. This also underscores the importance of meticulous collection of fluid volume intake and output data, and particularly weights before and after the procedure, which often are obtained without attention to details (same scale, patient wearing the same garments, with same handling of monitoring wires and cables, or other tubes, and attachments to the patients. The P values showing borderline statistical significance for some fluid volume variables in our study most probably represent a type 2 error related to the small number of patients. We started using the Aquadex in 2004, at first as a part of the UNLOAD trial, and then also for clinical purposes. Patients included herein were the first in

whom the UF was used for treatment purposes; however physicians still view UF as a last resort for the management of their patients with decompensated CHF. Presently, UF remains a novel treatment modality, and its niche in the spectrum of therapies for CHF is still to be established. The electrolytes and hematocrit remained unchanged in our patients (Table 1), corroborating previous reports.^{5,6} Also, the stability in the QRS duration, QTc and frontal axes of the P wave, QRS complexes, and the T waves (Table 1) suggested that no significant alterations in the patients' electrophysiology took place during CHF (vide infra), but only the amplitude of the QRS complexes increased with the procedure.

Attenuated voltage of the QRS complexes in patients with CHF was noted 50 years ago with augmentation in patients who had improved clinically.¹¹ Also hypertensive patients with previous ECG evidence of left ventricular hypertrophy showed attenuated QRS voltage after multiple episodes of CHF, as also noted by us in patients with peripheral edema of varying etiology.¹² Augmentation of the magnitude of spatial maximal QRS vector and decrease in the heart size was observed in patients with CHF clinically improved over the course of a mean of 10 days by Ishikawa et al. in 1971, but the correlation of these two variables was poor, and the authors were at loss as to the underlying mechanism;¹³ they had hypothesized that the alleviation of cardiomegaly was influencing the surface ECG potentials, but they concluded that "other factors" must be at play, since their findings contradicted the so-called Brody effect,¹⁴ according to

Figure 2. Plots of the % change in weight (A), ultrafiltration (UF) fluid volume removed (B), net fluid volume removed (C), and total fluid losses (D), the last three adjusted for admission weights, all in the vertical axis, with % change in the Σ QRS from all 12 ECG leads, in the horizontal axis: the numeral “1” in the plots denote individual cases (n = 9).

which reduced cardiac volumes with therapy of CHF should have led to attenuated (and not augmented as they have found) QRS complexes. An alternative explanation has been advanced for the attenuation of QRS potentials in patients with decompensated CHF and augmentation with clinical improvement,¹⁵ and it is based on the effects exerted by the body volume conductor surrounding the heart,^{16,17} whose electrical properties change with the level of compensation of CHF. Accordingly, decompensation results in fluid overload with resultant electrical short-circuiting, due to reduced electrical impedance leading to attenuated QRS potentials; the opposite (augmented QRS potentials) takes place with improved compensation as was noted in this, and previous studies.^{2-4,18} Such increase in the body volume conductor impedance with UF is due to the decrease in fluid content,

which imparts increase in resistivity, and consequently increased QRS voltage. In fact increased electrical impedance of the body was found by actual measurements using a special device in a patient treated for CHF,² and after hemodialysis.¹⁸ It is also conceivable that intrinsic cardiac influences could be totally or partially responsible for the augmentation of the QRS potentials noted with UF. However limited experience with intracardiac electrograms obtained in patients with massive peripheral edema of varying etiology undergoing UF, by which they lost large amounts of fluid, revealed stability of such recordings before and after UF, while massive voltage augmentation of the corresponding surface ECGs was documented;⁸ this suggests that augmentation of the surface QRS potentials resulting from UF are in all probability extracardiac in nature.

The number of patients recruited ($n = 10$) represents a limitation of the present study. However, we were able to study only patients who were referred to us by their physicians, and only when in their judgment, conventional means of managing the patients have proven ineffective. Also, we could not study retrospectively patients who had been recruited in therapeutic trials of UF, because they lack properly timed ECGs before and after implementation of UF. The primary objective of this study was to evaluate the response of the 12 lead ECG to UF, and this was accomplished with the nine evaluable patients. In addition, the objective of our work was to propose a model for a detailed qualitative assessment of fluid intake and losses experienced by patients with CHF undergoing therapy.

Presently, patients with CHF constitute a large portion of the pool of subjects cared for by physicians in both the inpatient and outpatient settings. Such patients have frequent ECGs recorded, and it appears from studies of patients who were managed with diuretics^{2-4,13} or UF (as in this study) that the associated attenuation/augmentation of the QRS voltage may be an untapped diagnostic aid, beyond what the ECG traditionally offers in monitoring patients with CHF. Qualitatively "eyeballing" serial ECGs from patients undergoing treatment for CHF, may suffice for monitoring their body fluid volume status; however actual manual or automation-derived measurements of QRS complexes provides a quantitative variable akin to a specific laboratory test value (e.g., BNP). Adoption of such a clinical parameter by physicians may induce the ECG manufacturers to provide automation-based calculation of Σ QRS, as part of the panel of measurements provided in routine ECG recordings. Such an addition would enhance the clinician's armamentarium of diagnostic tools employed in monitoring acute and chronic management of patients with CHF.

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