Response of the ECG to Short-Term Diuresis in Patients with Heart Failure

John E. Madias, M.D.,* Jessica Song, Pharm.D.,† C. Michael White, Pharm.D.,† James S. Kalus, Pharm.D.,† and Jeffrey Kluger, M.D.†

From the *Mount Sinai School of Medicine, Division of Cardiology, Elmhurst Hospital Center, Elmhurst, NY and †Hartford Hospital and the University of Connecticut Schools of Pharmacy and Medicine, Hartford, CT

Background: Increase in the amplitude of electrocardiogram (ECG) QRS complexes has been observed in patients treated for heart failure (HF), but the underlying mechanism has not been delineated. Also, correlation of augmentation of the QRS potentials with loss of weight has been noted in patients recovering from anasarca of varying etiology, or after hemodialysis. We assessed the effect of diuresis-based fluid loss in patients treated for HF on the amplitude of ECG QRS complexes.

Methods: This is a cohort study based on ECG and other data from a previously published investigation of patients with HF conducted at a university affiliated hospital, which used new measurements and analysis, performed by a totally blinded investigator based at another institution. Twenty-one patients (10 men) aged 70.5 ± 12.7 years, 13 with ischemic, and 8 with nonischemic cardiomyopathy, were admitted to the hospital for management of exacerbated HF and were observed for 48 hours. The patients received diuresis, and had routine laboratory testing, documentation of the net fluid lost, and recording of ECGs prior to the initiation of therapy and at 24 and 48 hours. Percent change ($\%\Delta$) over the course of observation in the sums of the amplitude of QRS complexes from 12 leads (ΣQRS_{12}), 6-limb leads (ΣQRS_6), and leads 1 + 2 (ΣQRS_2) in mm of standard ECGs were correlated with net fluid loss corrected for admission weight in mL/kg.

Results: Fluid loss amounted to 3204.9 ± 1399.5 mL in the course of 40 ± 23 hours of diuresis. ΣQRS_{12} was 160.9 ± 42.3 mm before and 170.0 ± 50.7 mm after diuresis ($P = 0.024$). Percent change in ΣQRS_{12} , ΣQRS_6 , and ΣQRS_2 correlated well with the net fluid loss ($r = -0.70, -0.82, -0.61$, and $P = 0.002, 0.0005, 0.001$) correspondingly.

Conclusion: Changes in sums of the amplitude of QRS complexes of the standard ECG correlates well with net fluid loss in response to short-term diuresis in patients with HF. Change in the ΣQRS_{12} , ΣQRS_6 , and ΣQRS_2 from ECGs before and after diuresis can be used as an easily obtainable and universally available bedside index of the net fluid loss experienced by bedridden patients with HF undergoing therapy.

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anasarca; congestive heart failure; diuresis; QRS complex amplitude; tissue electrical resistance; body volume conductor

Management of patients with heart failure (HF) associated with anasarca peripheral edema (AN) results in augmentation of the amplitude of QRS complexes (AUG-QRS) in their electrocardiogram (ECG); such patients lose substantial amounts of fluid, experiencing over the course of several days, large weight reduction (9.2–29.0 lbs, and 8.6–19.7% of their admission weight).^{1,2} This experience was based on routinely obtained weights and ECGs,¹ or weights obtained by the investigators and routine ECGs.² The unreliability of the weights obtained in the hospital is well appreciated; also rou-

tine recording of ECGs is associated with marked variation in the thoracic landmarks from which V_1 – V_6 leads are obtained.³ Thus carefully measured weights,² meticulously kept fluid intake and output records, and comparable serial ECGs are prerequisites for meaningful correlations of the ECG and the diuresis-based loss of weight/fluid in patients treated for HF. The previous work^{1–3} used weights and ECGs, and thus the prospect of using careful records of fluid intake and output is appealing. Also, no data have been published heretofore about the effect on the ECG of modest

diuresis over the course of the initial 2 days after admission in patients with HF. We have not seen any consistent effect early in the course of therapy, suggesting that the ECG may be insensitive to modest diuresis in patients with HF.^{1,2} Also, in patients developing AN (i.e., the reverse pathophysiology to that of diuresis in HF), the early fluid accumulation and weight gain did not produce detectable attenuation in the amplitude of QRS complexes (ATT-QRS), while further weight gain led to such clear-cut changes.⁴ No data exist on the relationship of changes in the amplitude of ECG QRS complexes and net fluid loss in patients with HF. Also, patients developing AN reveal in their ECGs additional changes to the ATT-QRS, e.g., shortening of QRS complex duration (QRSd);⁵ QRSd has been shown to change in patients with HF,⁶⁻⁹ and it has been used recently in decisions regarding suitability of patients with HF for cardiac resynchronization therapy.⁶⁻⁹ Thus, it would be important to examine the response of QRSd to diuresis in patients treated for HF. Some other prognostic indices that have been used for follow-up of patients with dilated cardiomyopathy or HF are the heart rate, PR-interval, AV conduction, QT- and QTc-intervals, frontal P wave and QRS complex axis, and P wave duration.¹⁰⁻¹⁵ Perhaps, alterations in these HF long-term parameters could occur during intense short-term diuresis, and thus it would be of interest to evaluate them in a cohort where changes in the QRS amplitudes and QRSd are studied.

METHODS

Study Participants

Data on which the present communication was based are from a previous study of 21 patients with decompensated HF, who were treated with diuresis following admission to the HF unit of Hartford Hospital.¹⁵ Briefly, the patients were included in that study if they did not have atrial flutter or fibrillation, or an implanted pacemaker, or were not treated with sodium nitroprusside. There were 10 men and 11 women aged 70.5 ± 12.7 years with HF, 13 with ischemic and 8 with non-ischemic cardiomyopathy. They were treated with intravenous furosemide (N-19), while 7 received additional oral diuresis with spironolactone, furosemide, metolazone, and bumetanide. Two patients received only oral aldactazide and hydrochlorothiazide.

Study Design

Net fluid lost over the course of diuresis was calculated as fluid lost – fluid administered, and it amounted to 3204.9 ± 1399.5 mL; the patients were weighed on admission and their observation extended to 40 ± 23 hours; insensible fluid losses were not considered, but since such losses would depend on body weights and the net fluid lost was adjusted for admission weights, it was felt that the latter will suffice as a measure for net fluid lost. The patients had three standard 12-lead ECGs (ECG1, ECG2, and ECG3) recorded just before commencement of diuresis, in ~ 12 hours, and at the conclusion of therapy, respectively. Electrodes for the recording of the precordial leads were affixed on the chest of the patients for the entire duration of the study, to ensure comparability of the serial ECG tracings. Calibration of the ECG recordings was 10 mm = 1.0 mV (1 ECG was calibrated at 5 mm = 1.0 mV), and the paper speed was 25 mm/s. ECG measurements were carried out prior to any other evaluation of data, as follows: for the purposes of the present communication, and as per study design, copies of the ECGs ($n = 62$) (one tracing of the database was missing), bearing only a serial number (#1-#63) for identification, were sent to one of us (JEM) for measurements and data tabulation, thus ensuring blinded and unbiased evaluation. The sum of QRS complexes measured to the nearest 0.5 mm from peak to nadir of the deflection in the 12 leads in mm (ΣQRS_{12}), using a magnified glass and calipers, was measured under strong overhead light. The intra-observer variability of measurements of ΣQRS_{12} in 10 randomly used ECGs was $0.41 \pm 3.34\%$ in a previous study.⁴ Since the 6-limb ECG leads are not influenced by variable positioning of the thoracic sites for the recording of precordial leads, and most ECG-machines record only leads 1 and 2, and calculate the remaining 4-limb leads in real time as per available formulas, we hypothesized that using merely the sum of amplitudes of QRS of the 6-limb leads (ΣQRS_6) and leads 1 and 2 (ΣQRS_2) will provide us with two additional ECG parameters, which can substitute for the entire array of 12 leads;^{2,16} this was not necessary for the present study in which the precordial leads were recorded from fixed landmarks; however, since routine ECGs are not obtained with such diligence, employment of the ΣQRS_6 and ΣQRS_2 would enhance the generalizability of our

conclusions. Data included absolute values of all ECG parameters, % change of $\sum QRS_{12}$, $\sum QRS_6$, and $\sum QRS_2$ from ECG1 to ECG2 and from ECG1 to ECG3. Values for other parameters (than $\sum QRS_{12}$, $\sum QRS_6$, and $\sum QRS_2$) were obtained from the ECG automated measurement and interpretation reports of the previous study.¹⁵ Also, weights, net fluid volumes lost, corresponding to ECG2 and ECG3, electrolytes, creatinine, hemoglobin, and hematocrit obtained before and after diuresis were obtained from the database of the previous study.¹⁵ Since AUG-QRS has been observed with increases in heart rate (albeit large ones),¹⁷⁻¹⁹ this parameter was considered when analyzing the ECG changes imparted by diuresis.

Statistical Analysis

Continuous data are presented as mean $\pm$ SD. Absolute values of $\sum QRS_{12}$, $\sum QRS_6$, and $\sum QRS_2$ weights, of all other ECG parameters; net volume of fluid lost; and electrolytes, hemoglobin/hematocrit, and creatinine were used as variables. Also, % change (% Δ) in $\sum QRS_{12}$, $\sum QRS_6$, and $\sum QRS_2$, and volume of net fluid lost during diuresis, adjusted for

admission weights, between the time of ECG1 and ECG2, and the ECG1 and ECG3 were used as variables. The analysis for data obtained at ECG2 level was used for evaluating a "dose-response" effect on the influence of variables; also, these data as per the original study¹⁵ "was not designed to be powered for a three-group comparison." Two-tailed paired *t*-testing and Pearson regression analysis (taking net fluid lost as the independent and % Δ in $\sum QRS_{12}$, $\sum QRS_6$, and $\sum QRS_2$ as the dependent variables) were used in the statistical evaluations.^{20,21} P values < 0.05 was taken as indicative of a statistically significant result.

RESULTS

Results are shown in Table 1, and representative ECG changes in Figure 1. ECG parameters corresponding to the recording times of ECG1, ECG2, and ECG3 were not different, save for the increase in the $\sum QRS_{12}$ between ECG1 and ECG3, and the slowing of heart rate, noted at both ECG2 and ECG3 in comparison with ECG1. When the patients who had admission weights (N = 17), and thus adjustment of the net fluid lost could be carried

Table 1. Data Tabulated According to the Timing of the Recording of the Three ECG Tracings in Patients Treated for Heart Failure (n = 21)

Variable	ECG1	ECG2	P value ^a	ECG3	P value ^b
$\sum QRS_{12}$ (mm)	160.9 $\pm$ 42.3	164.8 $\pm$ 43.6	0.68	170.0 $\pm$ 50.7	0.024
$\sum QRS_6$ (mm)	59.8 $\pm$ 22.0	61.8 $\pm$ 22.3	0.91	62.4 $\pm$ 22.4	0.21
$\sum QRS_2$ (mm)	21.0 $\pm$ 7.1	21.2 $\pm$ 7.0	0.50	22.0 $\pm$ 6.9	0.14
QRS duration (ms)	107.9 $\pm$ 20.4	104.0 $\pm$ 20.2	0.11	107.7 $\pm$ 22.6	0.87
QRS frontal axis (°)	-1.5 $\pm$ 43.8	-1.1 $\pm$ 41.4	0.53	-6.8 $\pm$ 38.3	0.35
QTc (ms)	447.8 $\pm$ 33.4	450.1 $\pm$ 45.6	0.96	452.9 $\pm$ 83.3	0.79
PR interval (ms)	175.6 $\pm$ 33.6	173.9 $\pm$ 34.7	0.95	170.7 $\pm$ 38.1	0.28
P wave frontal axis (°)	45.9 $\pm$ 23.3	52.1 $\pm$ 20.9	0.37	47.5 $\pm$ 23.8	0.76
Heart rate (beats/min)	85.0 $\pm$ 17.6	77.8 $\pm$ 14.5	0.003	74.8 $\pm$ 15.1	0.005
T wave frontal axis (°)	94.6 $\pm$ 91.5	101.6 $\pm$ 86.9	0.62	107.3 $\pm$ 71.8	0.46
Net fluid lost between ECG1 and ECG2 (mL)		1883.1 $\pm$ 1384.8			
Net fluid lost between ECG1 and ECG3 (mL)			3204.9 $\pm$ 1399.5		
Weight on admission (kg)	65.6 $\pm$ 37.1				
Hemoglobin (g/dL)	11.6 $\pm$ 1.5			11.3 $\pm$ 1.6	0.17
Hematocrit (%)	35.0 $\pm$ 3.8			33.6 $\pm$ 3.9	0.07
Na ⁺ (mEq/L)	136.9 $\pm$ 4.8			136.5 $\pm$ 3.6	0.62
K ⁺ (mEq/L)	4.4 $\pm$ 0.7			4.1 $\pm$ 0.5	0.08
Mg ²⁺ (mg/dL)	2.1 $\pm$ 0.1			2.2 $\pm$ 0.2	0.08
Creatinine (mg/dL)	1.6 $\pm$ 1.6			1.7 $\pm$ 1.9	0.20

^aThe P value reflects a comparison of data corresponding to the ECG1 and ECG2; ^bP value corresponding to the ECG1 and ECG3. For all, data are N = 21, except ECG2 (N = 20), weight (N = 17), Na⁺, K⁺, and creatinine (N = 20), hemoglobin (N = 15), hematocrit (N = 15), and Mg²⁺ (N = 4).

Increase in the amplitude of QRS complexes in patient #19 before (A) and after (B) loss of 6,250 mL of fluid

Figure 1. ECG changes before and after diuresis.

out, were analyzed, $\% \Delta \Sigma QRS_{12}$ correlated directly with fluid loss, corresponding to the time of recording of ECG3 ($N = 17$, $r = -0.70$, $P = 0.002$) (Fig. 2A); no such correlation was found corresponding to the time of recording of ECG2 ($n = 16$, $r = -0.05$, $P = 0.85$) (Fig. 2B). Similarly, $\% \Delta \Sigma QRS_6$ correlated directly with fluid loss, corresponding to the time of recording of both ECG3 ($n = 17$, $r = -0.82$, $P = 0.0005$) (Fig. 3A), and ECG2 ($n = 16$, $r = -0.69$, $P = 0.003$) (Fig. 3B). Finally, $\% \Delta \Sigma QRS_2$ correlated directly with fluid loss, corresponding to the time of recording of both ECG3 ($n = 17$, $r = -0.72$, $P = 0.001$) (Fig. 4A), and ECG2 ($n = 16$, $r = -0.61$, $P = 0.012$) (Fig. 4B). QRSd did not change during the study. There were no differences in serum sodium, potassium, magnesium, or creatinine between admission and the final day of the patients' assessment.¹⁵ Hemoglobin/hematocrit from admission and at the completion of therapy were not statistically different.

DISCUSSION

This study showed an AUG-QRS, as assessed by ΣQRS_{12} , and a relationship between this increase and the fluid loss in patients with HF. The latter is what is novel about this work, and it is important

that it was shown by implementing three different ECG systems (ΣQRS_{12} , ΣQRS_2 , and ΣQRS_6), and for modest fluid loss (3.2 ± 1.43 L), occurring over a short time interval (40 ± 23 hours). Also, the strength of the relationship ($r = -0.70$) was similar to the one noted in patients with AN of varying etiology ($r = -0.61$), for much larger weight gains (mean of 22.2 kg), and for longer observation time interval (17.1 ± 11.4 days) employing in both studies the ΣQRS_{12} .⁴ This indicates that the response of the ECG to shifts of body fluid is not specific disease-dependent, and reveals sensitivity to even small fluid losses, realized over short time periods. This corroborated the degree of sensitivity of ECG previously shown by registering increases in ΣQRS_{12} with small fluid losses (3.2 ± 1.1 L), in the short time course of hemodialysis (195.0 ± 62.8 min).²² Although the correlation of ΣQRS_2 and ΣQRS_6 with the net fluid lost was statistically significant even at the ECG2 time point when the patients had only lost $\sim 1.9 \pm 1.4$ L of fluid, change in these two ECG systems was not significant between ECG1 and ECG2 or ECG1 and ECG3 (Table 1); the corollary of this is that the physician can rely only on the ΣQRS_{12} to monitor patients undergoing diuresis for HF. It is possible that the small number of patients studied, and the modest level of

12-lead ECG vs. net fluid loss

Figure 2. Abbreviations: Ad. Wt = admission weight; other abbreviations as in the text. Numerals “1,” indicate a single correlation point, and numeral “2,” two correlation points in the plot.

fluid loss were at play here to render the changes of $\sum QRS_2$ and $\sum QRS_6$ statistically insignificant (type II error).^{20,21} Accordingly, a larger study cohort and/or a study employing larger fluid losses could have shown these two ECG systems to be equally useful follow-up instruments as the $\sum QRS_{12}$. How-

ever, this remains to be shown. The practical connotation of this is that had the $\sum QRS_2$ and $\sum QRS_6$ values been shown to change significantly during diuresis, clinicians could employ them for monitoring patients with HF who had serial ECGs obtained without attention to proper placement of precordial

6-lead ECG vs. net fluid loss

Figure 3. Abbreviations: Ad. Wt = admission weight; other abbreviations as in the text. Numerals “1,” indicate a single correlation point, and numeral “2,” two correlation points in the plot.

2-lead ECG vs. net fluid loss

Figure 4. Abbreviations: Ad. Wt = admission weight; other abbreviations as in the text. Numerals "1," indicate a single correlation point, and numeral "2," two correlation points in the plot.

ECG leads (an unfortunate but common practice in clinical medicine). As it stands now what can only be recommended is that the $\sum QRS_{12}$ can be used as an index of fluid loss in patients with HF undergoing diuresis, provided that the ECGs before and during/after therapy are obtained from the appropriate precordial landmarks (marking of the chest wall for reproducible placement of chest leads in repeat recordings, or retaining the precordial electrodes for the entire length of therapy, or placing the leads for each recording identifying precisely the loci for V1–V6 lead positioning).³ The need for manually calculating the $\sum QRS_{12}$ from serial ECGs at the bedside should not be considered an impediment in using this index; currently available automated measurement and ECG interpretation programs incorporated in ECG-machines provide measurements of R and S waves for all 12 ECG leads instantly upon recording the ECG,²³ and this easily could be extended to the calculation of the $\sum QRS_{12}$.

It had been noted in the early 1950s that patients with HF showed ATT-QRS during decompensation, in comparison with time periods when they had experienced clinical improvement,²⁴ and this was also reflected in the German literature of that time, quoted by Ishikawa, Berson, and Pipberger.²⁵ Also, it had been noted that hypertensive patients with high ECG potentials developed reduced QRS voltage after several episodes of HF. Since that time,

and except for the work done in 1971,²⁵ and two recent reports,^{1,2} nothing relevant has appeared in the literature. In the above cited work,²⁵ the authors studied 15 patients with HF, 12 of whom following clinical improvement over the course of a mean of 10 days showed increase in the magnitude of spatial maximal QRS vector and decrease in the heart size (cardiothoracic ratio from chest x rays); the correlation of these two variables was poor ($r = 0.27$, $P = 0.1$). It was also revealing that the 3 patients who deteriorated clinically showed a decrease in the recorded QRS vectors.²⁵ Commenting on their findings, these workers, whose basic hypothesis was that the changes in the QRS amplitude of patients with compensated HF were due to alterations in the cardiac size, admitted that their results were opposite to what the previous experimental work and theoretical formulation²⁶ had predicted, and that "other factors are involved in the ECG changes that occur in HF."²⁵ The work that the authors of that study²⁵ referred to relates to intense scientific activity to correlate change in cardiac volumes with the amplitude of the ECG potentials recorded at the body surface. This is relevant for the topic at hand since therapy of HF is expected to be associated with reduction of heart size, and this was noted in the study of Ishikawa, Berson, and Pipberger.²⁵ However, such reduction of heart size is expected to produce reduction of

QRS complexes (the so-called "Brody effect"),²⁶ the opposite of what was found in the study of patients with HF²⁵ and in our patients. Thus, this effort²⁵ led to no mechanistic explanation for the phenomenon of AUG-QRS in patients treated for HF.

What is then the underlying mechanism for the reduction of QRS potentials seen in patients with HF responding to therapy? Body surface ECG recordings are influenced by the potentials at the heart's surface and the electrical properties of the conducting medium enveloping the heart.^{27,28} In addition, changes in the cardiac volumes in patients with other edematous states, e.g., end-stage renal failure²⁹⁻³² and hemoglobin levels²⁷ could impart changes on the surface ECG. In reference to cardiac volume reduction, as discussed above, a decrease in the amplitude of QRS is expected with alleviation of HF, the opposite noted. Also, anemia increases and polycythemia decreases the surface ECG potentials,²⁷ and thus possible hemoconcentration, as occasionally is noted with diuresis in patients with HF, or hemodialysis,²² is expected to decrease the QRS potentials, the opposite of what actually occurs with management of HF. Moreover, hemoglobin levels were stable in both the previous study,²⁵ and the present communication (Table 1) after diuresis of patients with HF. Alteration of the potentials generated by the heart (intrinsic) with therapy of HF is also a plausible mechanism of change of the body surface ECG potentials. Thus, stretching of the heart fibers or edema during the stage of decompensation with subsequent alleviation could theoretically produce changes of the potentials generated by the heart. However, experimental work has suggested that even marked stretching does not alter resting or action cardiac potentials,²⁵ and thus it is unlikely that the stretching imparted by cardiac dilatation during HF, or the alleviation of HF with resultant reduction of cardiac fiber stretching could produce the ECG findings encountered. As for cardiac edema, we are not aware of previous work correlating cardiac water content with the potentials generated by the heart. In addition, our previous work with patients with AN of varying etiology suggested that changes in the surface potentials were extrinsic to the heart since augmented surface QRS potentials with weight loss were associated with unaltered intracardiac electrograms.⁴ In all probability, the mechanism of increased ECG QRS potentials with diuresis in patients with HF appears to be exter-

nal to the heart, and hinges upon the decrease in the body volume conductor water content, with resultant increase in this compartment's resistivity and increase in the surface ECG potentials.^{4,16,22} Indeed, increased body electrical resistance was documented in a patient treated for HF,² and after hemodialysis.²² Changes in the lung electrical properties due to congestion could produce ATT-QRS, and with alleviation of congestion AUG-QRS in turn; these changes in the thoracic impedance have been implemented in the patient monitoring in critical care units.³³ However, with pulmonary congestion leading to ATT-QRS, and cardiac dilatation resulting in AUG-QRS, the net effect often is an unaltered ECG during management of pulmonary edema (in the absence of peripheral edema).³⁴

No other ECG variables changed in our study, save for the slowing of the heart rate, in keeping with what is expected in patients with HF in the course of therapy, by an average of 7 and 10 beats/min between ECG1 and ECG2 and ECG3 correspondingly (Table 1). This would not have been expected to influence the amplitude of QRS complexes. The phenomenon of AUG-QRS with increase in heart rate during episodes of supraventricular tachycardia or with atrial pacing has been recently described;¹⁷⁻¹⁹ however, heart rates ~150 beats/min were associated with AUG-QRS, and in our study, modest slowing of the heart rate was noted, which if anything would impart ATT-QRS, the opposite of what was observed. QRSd was stable, as in the previous study,²⁵ although reduction with therapy of HF has been found by others.³⁵ Perhaps, the modest fluid loss was the reason that shortening of the QRSd was not observed herein.⁵ No changes in the axis of the P, QRS, and T waves, or PR-interval and QTc were noted with therapy as documented previously.²⁵ Also, the P-wave duration was unchanged with therapy of HF,²⁵ while it decreased in the study, whose data base was used herein.¹⁵ We have not used brain natriuretic peptide in this investigation; this signaling molecule has been found useful in the diagnosis and management of HF.³⁶ However, there was no diagnostic ambivalence in our cohort, which comprised of patients with known chronic HF, admitted expeditiously with clinical decompensation.

Management of patients with HF has become a large part of the work of physicians. This study advocates the use of the increase in the QRS voltage from standard ECGs obtained before and

after therapy (and used as the ΣQRS_{12}), as an easily/ubiquitous, automation-supported, and inexpensive bedside method for monitoring diuresis in patients with HF.

In summary, changes in sums of the amplitude of QRS complexes of the standard ECG correlate well with net fluid loss in response to short-term diuresis in patients with HF. Change in the ΣQRS_{12} , ΣQRS_6 , and ΣQRS_2 from ECGs before and after diuresis can be used as an easily obtainable and universally available bedside index of the net fluid loss, experienced by bedridden patients with HF undergoing diuretic therapy.

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