Determinants of Augmentation of ECG QRS Complexes and R Waves in Patients after Hemodialysis

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Background: Hemodialysis (HD) leads to an augmentation in the amplitude of QRS complexes (QRS-c), and R waves (R-w); some correlates of this phenomenon have been identified, but the exact mechanism for these ECG changes remains elusive. The objective of this study is to search for the underlying mechanism(s) of the post-HD augmentation of QRS-c and R-w.

Methods: The sum of the amplitudes of ECG QRS-c and R-w, along with a host of other parameters (body weight, fluid volumes, echocardiographically-derived left ventricular dimensions and volumes, serum potassium, hemoglobin, hematocrit, and others) was measured, before and after HD, in 17 patients with end-stage renal failure.

Results: While there were many correlations noted between the changes in the QRS-c and R-w and some of the above variables in numerous univariate analyses carried out, multivariate analyses did not identify any of the examined variables as exerting an independent influence on the observed ECG changes after HD.

Conclusion: Augmentation of QRS-c and R-w following HD is engendered by an interplay of a decrease in the LVEDD/LVEDV, and K⁺, loss of fluid volume, and a rise in Hb and Ht, without any of the above being an independent variable; also other factor(s) (e.g., increase in the body electrical impedance) exerting an influence in this ECG phenomenon cannot be excluded.

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The mechanism of augmentation of the amplitude of QRS complexes (QRS-c) and R waves (R-w) in patients with end stage renal failure after hemodialysis (HD) continues to be elusive, after intense investigative activity spanning almost 30 years.¹⁻¹⁰ Certainly some correlates have been identified, but it is not clear as to the independent or causative role of each of them producing these ECG changes; also these correlates have not been found consistently in different studies. Parameters after HD studied (but not necessarily well correlated with the ECG changes) have included the volume of fluid removed, loss of weight,^{3,4,6-8} decreased extracellular water,^{8,10} left ventricular end diastolic dimensions (LVEDD)⁴ and volumes (LVEDV),^{2,6} increase in hemoglobin (Hb)^{4,8} and hematocrit

(Ht),^{4,8} decrease in serum potassium (K⁺),^{5,8} and a change in a host of other serum constituents.⁸ Augmentation of the amplitude of QRS-c and R-w in patients after HD has been variably attributed to loss of extracellular water,⁷ or specifically to the increase in electrical impedance of the body volume conductor,^{8,9} or not specifically to any of the variables changed by HD.⁶ Some have attributed these ECG changes to myocardial ischemia,^{2,3} in the context of reports then connecting increase in the R-w with exercise stress testing-induced ischemia,^{11,12} To add to the complexity, the response to HD of some of the above variables in relation to the changes in the ECG has been at variance with what has been found in other clinical or experimental settings. Thus decrease in LVEDD and LVEDV

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is expected to be associated with a decrease in the amplitude of QRS-c and R-w as per "Brody effect,"¹³ while a consistent increase in these variables has been documented with HD; increase in Hb/Ht are associated with decrease in the QRS-c and R-w,^{14,15} while the opposite is seen with HD. In contrast, decrease in K⁺ is associated with an increase in QRS-c and R-w, in both HD and other settings, although in the latter marked hypokalemia is required.^{16,17} It is conceivable that all these simultaneously altered parameters in response to HD exert an influence on the ECG, to a varying degree in individual cases, but their interrelationship is such that by acting either synergistically or antagonistically prevent the emergence of one or more of them as independent determinants of the ECG alterations. Finally in all correlative attempts of the ECG variables and volume of fluid losses with HD heretofore, fluid volumes lost due to insensible causes, and gains consequent to fluid oral intake of patients during HD, have not been taken into consideration, resulting in inexact calculation of the true fluid volume losses. Thus, to reappraise all the above was the impetus to design and implement this prospective study.

METHODS

Patients

Seventeen subjects with end-stage renal failure attending a routine midweek HD session were recruited in this study, after informed consent was obtained. All were receiving twice weekly bicarbonate based HD sessions lasting ~5 hours, using polysulfone capillaries and bicarbonate dialysate containing 138 Na⁺, 2.0 K⁺, 1.75 Ca⁺⁺, and 0.5 Mg⁺⁺ mmol/l. All HD sessions were uncomplicated. Patient #5 had hypotension in spite of a conservative HD (removal of 500 cc of fluid) and received an infusion of 500 cc of saline solution. Patient # 6 could not tolerate HD, and thus only 1500 ml of fluid were removed. However, both these patients had appropriate dialysis with urea rate reduction (URR) >75% (URR was 85% for patient # 5 and 76% for patient #6). HD was uncomplicated in all 17 patients. All patients were appropriately dialyzed (URR = 82.38 ± 9.73%). No patient passed any urine during HD. The patients ate and drank fluids during HD, and the nephrologists estimated the fluid intake to be ~500 cc; this is considered routinely when the HD intensity (volume of fluid to be removed) is being planned with the goal for patients to reach their "dry weight."

Study Variables

Information pertaining to history, comorbidity, etiology of chronic renal failure, and demographic data were considered as study variables. Before and after HD the subjects were weighed by the nephrologists carrying out the HD, had their blood pressure and heart rate obtained, underwent echocardiography testing, had a 12-lead ECG recorded, and a blood specimen was drawn for measurement of plasma electrolytes, Hb, and Ht. In addition to the fluid volume removed by HD (FVR), the estimated net fluid volume removed (NFVR) was calculated by subtracting 500 cc from the FVR, to account for the patients' oral intake. Because HD lasted for ~5 hours, all patients ate the same sandwich, provided by the same food supplier, and drunk water and soda and the estimated fluid intake amounted to ~500 cc. Also estimated total fluid volume lost (TFVL) were considered which consisted of the sum of the NFVR and the estimated insensible losses, adjusted to the patients' pre-HD weight and post-HD "dry weight," and duration of HD (~5 hours, for all patients) as per formula: $TFVL = NFVL + 10 \times \text{weight (Kg)} \times 5/24$ (hours) cc.

Electrocardiography and ECG Measurements

ECGs were recorded using a Heart Screen 112D (Innomed Medical, Budapest, Hungary) electrocardiograph at paper speed of 50 mm/s, and standardizations of 20 mm and 10 mm = 1.0 mV. The double standardization was deemed necessary for greater accuracy of measurement of the amplitude of QRS-s and R-w; however in some patients, the amplitudes

Table 1. Baseline Characteristics of Subjects

Characteristics	Frequency
Male/female	8/9
Age (yr)	31 ± 10 [17–48]
Hypertension	3 (17.6%)
Diabetes	0
Average duration of chronic HD (yr)	11 ± 5 [2–21]
Cause of end-stage renal failure	7 (41%)
Glomerulonephritis	1 (6%)
Nephrosclerosis	1 (6%)
Obstructive	1 (6%)
Hereditary	1 (6%)
Autosomal dominant polycystic	6 (35%)
Unknown	

Table 2. Study Variables Before and After Hemodialysis

Variable	Pre-HD	Post-HD	P-Value
Potassium (mM/l)	5.59 ± 0.99	3.77 ± 0.74	0.0001
Urea (g/l)	1.77 ± 0.51	0.31 ± 0.18	0.0001
Creatinine (mg/dl)	10.8 ± 32	3.3 ± 16	0.0001
Hemoglobin (g/dl)	9.02 ± 2.46	11.15 ± 3.10	0.0001
Hematocrit (%)	25.80 ± 7.23	31.46 ± 8.95	0.0001
Systolic BP (mmHg)	133 ± 25.9	130 ± 24.7	0.403
Diastolic BP (mmHg)	77 ± 13	75 ± 14	0.565
Heart rate (beats/min)	78 ± 18	87 ± 19	0.001
Body weight (kg)	49.8 ± 13.0	47.2 ± 12.3	0.0001
ΣQRS (mm)	177.8 ± 59.0	217.4 ± 64.9	0.004
ΣR (mm)	103.7 ± 39.6	129.7 ± 48.9	0.0001
Sokolow (mm)	37.9 ± 16.4	42.7 ± 19.3	0.019
Cornell (mm)	13.3 ± 6.6	16.8 ± 11.1	0.071

of QRS-c and R-w were large, especially in leads 1 and V4, and the lower standardization had to be used. To ensure reproducibility of the ECGs before and after HD, the V1-V6 leads were obtained from fixed chest landmarks, made with a skin marker. The QRS-s and the R-w in all 12 ECG leads were measured from peak to nadir in mm to the nearest 0.5 mm, and the sum (ΣQRS and ΣR) were calculated; also sums for these 2 variables for the 6 limb leads and the 6 precordial leads were calculated, although the paired ECGs before and after HD were obtained from identical V₁-V₆ thoracic loci. The separate analysis based on the 6 limb and the 6 precordial leads was deemed useful since a HD-induced possible change in heart dimensions could have influenced the post-HD ECG precordial recordings (vide infra). The heart rate was calculated in beats per minute. All measurements were done by one observer (A.D.), who was blinded to the pre-, and post-HD status of the patients. Percent change (Δ%) in the ΣQRS and ΣR after HD were also used as variables. Sokolow-Lyon voltage (sum of the amplitudes of S wave in V₁ and R wave in V5 or V6 >3.5 mV), and sex-specific Cornell voltage (sum of the amplitudes of S-wave in V3 and R-wave in aVL >2.0 mV in women, and >2.8 mV in men) were used as ECG criteria for left ventricular hypertrophy (LVH).

Echocardiography

Two dimensional echocardiography/Doppler studies were performed $\frac{1}{2}$ hour before HD and after HD. Echocardiograms were obtained

using a Phillips Sonos 5500 ultrasonographic machine equipped with a 3.5 MHz transducer. The same experienced echocardiographer (A.D.) performed all measurements. M-mode measurements were made by use of the American Society of Echocardiography leading-edge-to-leading-edge convention.¹⁸ LVEDD and left ventricular end systolic dimensions (LVESD) were measured using standard M-mode echocardiographic methods guided by parasternal long-axis two dimensional images. Standard parasternal short axis and apical 4-chamber views were also recorded. LVEDV and left ventricular (LV) end systolic volume (LVESV) and ejection fraction were estimated with the use of Simpson's method. Endocardial border detection was enhanced using second-harmonic imaging. LV mass was calculated from Penn convention measurements according to Devereux and Reichek.¹⁹ LV mass indexed (LVMI) adjusted by height was used for the diagnosis of LVH according to the Framingham study.²⁰ LVMI ≥143 g/m for men and ≥102 g/m for women was considered diagnostic of echocardiographically derived LVH. Measurements of the left atrium (LA) were obtained at end systole;²¹ M-mode-derived anteroposterior linear dimension from the parasternal long-axis view using 2D guidance to position the cursor was obtained, as described by the American Society of Echocardiography; digitized planimetry of the LA cavity from the apical 4-chamber view was also obtained. From the digital measurements the volume of LA was derived from the M-mode dimension using the cube method ($\frac{4}{3}\pi r^3$) ($r = d/2$, and $d =$ M-mode anteroposterior dimension), which assumes a spherical shape.²²

Table 3. Echocardiographic Parameters Before and After Hemodialysis

Parameter	Pre-HD	Post-HD	P-Value
LV end-diastolic diameter (mm)	51.6 ± 7.4	45.3 ± 6.3	0.0001
LV end-systolic diameter (mm)	30.5 ± 6.9	28.2 ± 7.6	0.003
LV end-diastolic volume (ml)	85.2 ± 27.9	61.5 ± 24.8	0.0001
LV end-systolic volume (ml)	37.4 ± 15.2	30.2 ± 13.6	0.001
LV ejection fraction	70.1 ± 9.9	68.1 ± 9.4	0.130
LA area (cm ²)	18.8 ± 3.4	13.4 ± 2.1	0.083
LA volume (cm ³)	29.46 ± 8.19	15.56 ± 5.43	0.0001

LA = Left atrium; LV = left ventricle.

Statistical Analysis

Data are reported as mean ± SD. Analysis used the student's *t*-test for paired data to determine the significance of differences before and after HD. Pearson's correlation coefficient for linear regression analysis of percent change ($\Delta\%$) of the study variables resulting from HD was used, considering the Σ QRS and the Σ R as the dependent variables. In addition multivariate regression analyses were used with the Σ QRS and the Σ R as the dependent variables and $\Delta\%$ of LVEDD, LVEDV, K+, Hb or Ht, weight, or different volumes of fluid removed, adjusted by pre-HD or post-HD weight, in various combinations, as the dependent variables. $P < 0.05$ was considered as statistically significant. The SPSS (version 11.5) statistical package was used.

RESULTS

Characteristics of the patients are shown on Table 1. Changes in measured variables are shown on Tables 2 and 3. FVR was 2705.88 ± 1046.70 cc; NFVR was 2176.47 ± 1117.21 cc; TFVL was 2288.38 ± 1134.37 cc. Following HD, significant changes in electrolytes, Hb and Ht, urea, creatinine, and heart rate were observed in association with a fall of the patients' weight by 2.70 ± 1.04 (0.5–5) Kg.

Weight lost correlated well with NFVR adjusted by pre-HD weight ($r = -0.698$, $P = 0.002$), TFVL adjusted by pre-HD weight ($r = -0.698$, $P = 0.002$), and FVR adjusted by pre-HD weight ($r = -0.562$, $P = 0.0019$).

Also weight lost correlated with NFVR adjusted by post-HD weight ($r = -0.692$, $P = 0.002$), TFVL adjusted by post-HD weight ($r = -0.692$, $P = 0.002$), and FVR adjusted by post-HD weight ($r = -0.559$, $P = 0.020$).

Significant ECG and echocardiography changes (Tables Table 2 and 3, Figs. 1–5) precipitated by HD included an increase in Σ QRS and Σ R, decrease in LVEDD, LVESD, LVEDV, and LVESV.

LVH was diagnosed in 8 patients before, and 9 patients after HD based on Sokolow criterion, and 1 patient before, and 2 patients after HD based on the Cornell criterion. However, only 1 patient with LVH by echocardiography was positive for LVH by Sokolow criterion, and 4 patients with LVH by echocardiography were negative for LVH by both ECG criteria. LVMI measured before HD was 155 g/m (53 to 439 g/m) for men and 115 g/m (72 to 184 g/m) for women. LVMI measurements after HD were significantly different (125 g/m, 56 to 364 g/m for men, $P = 0.01$; 92 g/m, 49 to 152 g/m for women, $P = 0.0001$). Thus, 1 of 8 men met criteria for LVH as measured both before and after HD while 4 of 9 women met criteria for LVH before HD and only two still met these criteria after HD.

Percentage change in Σ QRS correlated poorly with $\Delta\%$ in LVEDD ($r = -0.267$, $P = 0.299$), LVESD ($r = -0.379$, $P = 0.134$), LVEDV ($r = -0.325$, $P = 0.204$), LVESV ($r = -0.283$, $P = 0.271$), weight ($r = -0.315$, $P = 0.218$), K+ ($r = -0.427$, $P = 0.087$), Hb ($r = 0.313$, $P = 0.221$), Ht ($r = 0.313$, $P = 0.222$), NFVR adjusted by pre-HD weight ($r = 0.423$, $P = 0.091$), TFVL adjusted by pre-HD weight ($r = 0.423$, $P = 0.091$), FVR adjusted by pre-HD weight ($r = 0.466$, $P = 0.060$), and NFVR adjusted by post-HD weight ($r = 0.421$, $P = 0.092$), TFVL adjusted by post-HD weight ($r = 0.420$, $P = 0.093$), FVR adjusted by post-HD weight ($r = 0.461$, $P = 0.063$).

Percentage change in Σ R correlated with $\Delta\%$ in LVEDD ($r = -0.483$, $P = 0.049$), LVEDV ($r = -0.489$, $P = 0.047$), K+ ($r = -0.508$, $P = 0.037$), Hb ($r = 0.634$, $P = 0.006$), and Ht ($r = 0.603$, $P = 0.010$). There was a poor correlation between $\Delta\%$ in Σ R and $\Delta\%$ in LVESD ($r = -0.429$, $P = 0.089$),

Figure 1. Patient # 3, before HD (Weight = 32.0 Kg, $\sum$ QRS = 104.25 mm); after HD (weight = 30.0 Kg, $\sum$ QRS = 186.50 mm). Abbreviations as in the text.

Figure 2. Patient #14, before HD (Weight = 45.5 Kg, $\sum$ QRS = 280.0 mm); after HD (weight = 43.0 Kg, $\sum$ QRS = 384.0 mm). Abbreviations as in the text.

Figure 3. Patient #17, before HD (Weight = 55.7 Kg, Σ QRS = 97.0 mm); after HD (weight = 53.5 Kg, Σ QRS = 130.0 mm). Abbreviations as in the text.

and LVESV ($r = -0.322$, $P = 0.207$), weight ($r = -0.40$, $P = 0.111$), NFVR adjusted by pre-HD ($r = 0.336$, $P = 0.187$), TFVL adjusted by pre-HD ($r = 0.336$, $P = 0.187$), FVR adjusted by pre-HD ($r = -0.116$, $P = 0.659$), and NFVR adjusted by post-HD weight ($r = 0.338$, $P = 0.184$), TFVL adjusted by post-HD weight ($r = 0.339$, $P = 0.183$), FVR adjusted by post-HD weight ($r = 0.401$, $P = 0.111$).

There was correlation between $\Delta\%$ Σ QRS from limb leads and weight ($r = 0.546$, $P = 0.023$), LVEDD ($r = -0.499$, $P = 0.041$), LVEDV ($r = -0.570$, $P = 0.017$), Hb ($r = 0.564$, $P = 0.018$), Ht ($r = 0.560$, $P = 0.019$), and K+ ($r = -0.558$, $P = 0.020$). There was a poor correlation between $\Delta\%$ in Σ QRS and $\Delta\%$ in LVESD ($r = -0.408$, $P = 0.104$), and LVESV ($r = -0.339$, $P = 0.184$), NFVR adjusted by pre-HD ($r = 0.430$, $P = 0.085$), TFVL adjusted by pre-HD ($r = 0.430$, $P = 0.085$), FVR adjusted by pre-HD ($r = 0.455$, $P = 0.073$), and NFVR adjusted by post-HD weight ($r = 0.430$, $P = 0.085$), TFVL adjusted by post-HD weight ($r = 0.430$, $P = 0.085$), FVR adjusted by post-HD weight ($r = 0.447$, $P = 0.072$).

There was correlation between $\Delta\%$ of Σ R waves from the 6 limb leads and weight ($r = -0.554$, $P = 0.021$), LVEDD ($r = -0.568$, $P = 0.017$), LVEDV ($r = -0.522$, $P = 0.031$), and LVESV ($r = -0.521$, $P = 0.032$). There was a poor correlation between $\Delta\%$ in Σ R and $\Delta\%$ in LVESD ($r = -0.404$,

$P = 0.108$), NFVR adjusted by pre-HD ($r = 0.420$, $P = 0.093$), TFVL adjusted by pre-HD ($r = 0.420$, $P = 0.093$), FVR adjusted by pre-HD ($r = 0.455$, $P = 0.066$), and NFVR adjusted by post-HD weight ($r = 0.426$, $P = 0.088$), TFVL adjusted by post-HD weight ($r = 0.426$, $P = 0.088$), FVR adjusted by post-HD weight ($r = 0.462$, $P = 0.062$), Hb ($r = 0.278$, $P = 0.280$), Ht ($r = 0.318$, $P = 0.214$), and K+ ($r = -0.473$, $P = 0.055$).

There was poor correlation between $\Delta\%$ Σ QRS from the 6 precordial leads and weight ($r = -0.200$, $P = 0.441$), LVEDD ($r = -0.191$, $P = 0.462$), LVEDV ($r = -0.211$, $P = 0.416$), Hb ($r = 0.190$, $P = 0.465$), Ht ($r = 0.189$, $P = 0.467$), and K+ ($r = -0.366$, $P = 0.148$), LVESD ($r = -0.344$, $P = 0.176$), and LVESV ($r = -0.244$, $P = 0.346$), NFVR adjusted by pre-HD ($r = 0.326$, $P = 0.201$), TFVL adjusted by pre-HD ($r = 0.326$, $P = 0.201$), FVR adjusted by pre-HD ($r = 0.375$, $P = 0.138$), and NFVR adjusted by post-HD weight ($r = 0.325$, $P = 0.204$), TFVL adjusted by post-HD weight ($r = 0.325$, $P = 0.204$), FVR adjusted by post-HD weight ($r = 0.370$, $P = 0.144$).

There was correlation between $\Delta\%$ Σ R from 6 precordial leads and Hb ($r = 0.667$, $P = 0.003$), Ht ($r = 0.602$, $P = 0.011$), and poor correlation with % changes of weight ($r = -0.152$, $P = 0.560$), K+ ($r = -0.347$, $P = 0.173$). LVEDD ($r = -0.266$, $P = 0.303$), LVEDV ($r = -0.269$, $P = 0.297$), LVESD

Figure 4. Upper panel: Patient #9, left atrial area decreased from 18 cm² to 12.5 cm² after HD. Lower panel: Patient #9, LVEDV decreased from 72.5 cc to 51.1 cc after HD. Abbreviations as in the text.

($r = -0.247$, $P = 0.339$), and LVESV ($r = -0.025$, $P = 0.925$), NFVR adjusted by pre-HD ($r = 0.152$, $P = 0.561$), TFVL adjusted by pre-HD ($r = 0.152$, $P = 0.561$), FVR adjusted by pre-HD ($r = 0.202$, $P = 0.437$), and NFVR adjusted by post-HD weight ($r = 0.150$, $P = 0.565$), TFVL adjusted by post-HD weight ($r = 0.150$, $P = 0.565$), FVR adjusted by post-HD weight ($r = 0.200$, $P = 0.442$).

Multivariate analysis of $\Delta\% \Sigma R$ from all the 12 leads with all variables and in different combinations did not show any significance for the individual variables, but overall multivariate analysis was significant in these combinations: a) Overall ($P = 0.013$): K+ ($P = 0.069$) - Hb ($P = 0.102$) - LVEDV ($P = 0.449$). b) Overall ($P = 0.022$): K+ ($P = 0.118$) - Ht ($P = 0.235$) - LVEDV ($P = 0.207$). c) Overall ($P = 0.023$): K+ ($P = 0.170$) - Ht ($P = 0.121$) - LVEDD ($P = 0.259$). d) Overall ($P = 0.013$): K+ ($P = 0.088$) - Hb ($P = 0.057$) - LVEDD ($P = 0.457$).

Multivariate analysis of $\Delta\% \Sigma QRS$ from the 6 limbs leads correlated only with K in 3 combinations: a) Overall ($P = 0.016$): weight ($P = 0.496$)-

LVEDV ($P = 0.319$)-K+ ($P = 0.028$)-Hb ($P = 0.528$). b) Overall ($P = 0.018$): weight ($P = 0.506$)-LVEDV ($P = 0.239$)-K+ ($P = 0.039$)-Ht ($P = 0.700$). c) Overall ($P = 0.024$): weight ($P = 0.310$)-LVEDD ($P = 0.850$)-K+ ($P = 0.041$)-Hb ($P = 0.350$).

Multivariate analysis of $\Delta\% \Sigma R$ from the 6 limbs leads correlated only with LVESV in one combination: overall ($P = 0.021$): weight ($P = 0.197$)-LVEDV ($P = 0.582$)-LVESV ($P = 0.048$).

No multivariate analyses were carried out with $\Delta\% \Sigma R$ from the 6 precordial leads as the dependent variable, since it only correlated in univariate analysis with Hb and Ht.

DISCUSSION

The salient findings of this study were as follows: a) a corroboration of the change in the variables found previously (Tables 2 and 3)¹⁻¹⁰ in connection with HD; b) the weight lost in our patients correlated well with volumes measured/calculated and adjusted in multiple ways, revealing the

Figure 5. Upper panel: Patient #9, LVEDV decreased from 31 cc to 27.9 cc after HD. Lower panel: Patient # 6, LVEDD decreased from 58.3 mm to 45 mm after HD. Abbreviations as in the text.

reliability and physiological relevance of the attempted calculations, which are presented as a model to be used in clinical conditions in general which are characterized by changing edematous states; c) As noted previously the diagnosis of LVH by ECG and echocardiography was not congruous, and further changes were imparted by HD; d) Σ QRS correlated poorly with all other variables, while Σ R correlated with LVEDD, LVEDV, and changes in K⁺, Hb, and Ht, in the analyses using all 12 ECG leads; e) Σ QRS correlated with weight, LVEDD, LVEDV, K⁺, Hb and Ht, while Σ R correlated with weight, LVEDD, and LVEDV, in the analyses using the 6 limb ECG leads; f) Σ QRS correlated poorly with all other variables, while Σ R correlated only with Hb and Ht in the analyses using the 6 precordial ECG leads; g) Σ QRS correlated poorly with all other variables, while Σ R correlated only with Hb and Ht in the analyses using all 12 ECG leads; h) in multivariate analyses Σ QRS did not show any overall or individual correlations, while Σ R showed an overall but not individual correlations

with various combinations of the other variables in the analyses using all 12 ECG leads; i) in multivariate analyses Σ QRS showed an overall correlations in various combinations with an independent correlation with K⁺, while Σ R showed an overall correlation with one combination of variables with individual correlation with LVEDV, in the analyses using the 6 limb leads; and finally j) no multivariate analyses were carried out for Σ QRS and Σ R since these variables did not correlate in univariate analyses using the 6 precordial ECG leads.

In this exhaustive analysis outlined above an effort was made to evaluate all the variables known to be changing with HD,¹⁻¹⁰ and to explore whether some of them are independently correlated with changes in QRS-c and R-c; what has been found is that although weight and fluid losses, LVEDD, LVEDV, hemoconcentration, and reduction in K⁺ correlate collectively with the ECG changes, no independent role of any of them has been detected. This issue was in addition dissected by adjusting the various fluid volumes implemented, by

pre-HD weight or post-HD ("dry weight"), as frequently used in the HD literature; however again these differently adjusted variables led to the same conclusions.

Separate analyses with QRS-c and R-c showed that correlations were better with the latter. The HD literature includes studies where either of these 2 modes have been used, without a reason discussed for the authors' preference.^{2-4,6,8} We have only used QRS-c in all our previous work,^{9,23-25} focussing on correlations of ECG changes and perturbations of various edematous states, and we do not have an explanation as to why R-c would correlate better.

Although the ECGs recorded in this study included comparable precordial components, based on thoracic skin markings for repositioning of 6 ecordial electrodes, 3 separate ECG analyses (for all the 12 leads, for the 6 limb leads, and for the 6 precordial leads) were carried out; the best univariate and multivariate correlations of ECG data with the other variables were found with the 6 limb leads and the worse with the 6 precordial leads systems, with the entire array of the 12 leads falling in between, as far as its performance. This indicates that the precordial ECG changes in an unpredictable way, even when it is based on reliable paired ECG recordings before and after HD. Perhaps this may reflect changes in LVEDD/LVEDV and/or alterations in the distance of the heart to the chestwall, imparted by HD. Of course changes in LVEDD/LVEDV due to HD may also influence the limb leads, although perhaps to a different degree than the precordial leads, while the heart-chestwall distance most probably should not have an effect on the limb leads (remote or distant leads).²⁶

It is physiologically and realistically sound to consider calculations of fluid volumes lost by HD, as were introduced in the present study; in the previous literature weights and FVR only have been considered and the additional fluid losses via insensible causes or the fluid via oral intake by the patients have not been considered. The approach implemented herein is presented as a model for use in clinical practice, and research in HD, and in other changing edematous states (e.g., peripheral edema from varying pathogenetic causes, or congestive heart failure).

The electrical properties of the passive body volume conductor were not evaluated in this investigation, although it was studied by us previously, in a patient undergoing HD who showed consistent

increases in body electrical resistance, measured with a bioimpedance device (Quantum, Model No. BIA-101Q, RJL Systems, Inc, Clinton Twp, MI, by attaching 4 electrodes to the right hand and foot, as per manufacture's instructions), during 26 sessions of HD.⁹ The method is well described and repeatedly used in the Nephrology literature, either as a gross way to estimate "dry weight" or in a more refined mode to calculate extracellular fluid, intracellular fluid, and total body fluid volumes before and after HD.²⁷⁻²⁹ A corollary of the above is the notion that increases in the QRS-c and R-w in patients after HD is to a large extent due to the increase in the passive volume conductor impedance resulting from decrease in the extracellular body fluid as a result of HD.^{8,9} The electrical resistivity of this fluid has been known to be low,³⁰ and its loss contributes to an increase in the overall electrical resistance of the body volume conductor. Although the body bioimpedance is invariably increased after HD in all previous work^{9,27-29} and probably this would have occurred herein if measured, it is unfortunate that this parameter was not included in the large array of variables implemented in our study. It is conceivable that increasing body bioimpedance would have been found not only to have a major influence on the QRS-c and R-w increase after HD, but that this role might have been that of an independent variable in the multivariate analysis, linking the ECG changes and all the other variables. Of course this remains a speculation, and the noninclusion of this variable in our study constitutes a limitation.

Many of the ideas invoked above about the influence of the decreased LVEDD, LVEDV, possible change of the distance of the heart from the chest wall, increase in Hb and Ht, decrease in the K⁺, and increase in the body electrical bioimpedance, on the QRS-c and R-w as a result of HD, stem from theoretical, laboratory, and clinical work completed in the past almost 30 years.³¹⁻³⁴

In conclusion it appears based on the present study that the changes in QRS-c and R-w imparted by HD are multifactorial in nature, and not due to the independent effect of alterations of 1 or 2 of the many variables changing during the procedure. A compelling evidence of the composite nature of the forces causing the augmentation of the QRS-c and R-w is the fact that some of the variables changed in such a direction that if they were acting alone they would attenuate the QRS-c and the R-w (e.g., decrease in LVEDD, LVEDV, and K⁺). Had

these variables not be changing during HD, the augmentation of the QRS-c and R-w would have been even larger; thus it is the modulating effect of the change of all these variables acting synergistically and antagonistically during HD, that produce the augmentation of the ECG voltage by ~25% during the procedure.⁹

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