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Parameters derived by ultrasonic myocardial characterization in dialysis patients are associated with mortality

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Background. Autopsy studies have shown that hypertrophic hearts of uremic patients have peculiar characteristics. Changes in tissue structure are detectable by ultrasound as changes in echo reflectivity.

Methods. We studied 96 dialysis patients, 18 hypertensive subjects with normal renal function and 52 healthy subjects. The echo pattern of interventricular septum was assessed by videodensitometry (VDT) (i.e., a computer-assisted quantitative analysis of gray levels). For each pixel a numerical value from 0 (black) to 255 (white) was assigned. From the resulting histogram of gray level frequency distribution, we obtained indexes of central tendency (reflectivity) and of homogeneity of distribution (uniformity).

Results. For the same septum thickness, dialysis patients showed a significantly greater reflectivity (87 ± 19 and 70 ± 17) ($P < 0.001$) and lower uniformity (137 ± 32 and 184 ± 71) ($P < 0.007$) compared with hypertensives. Hypertensive patients showed VDT parameters similar to control subjects in spite of significantly higher septum thickness ($P < 0.003$). Followed up after 5 years, dialysis patients with a reduced homogeneity of distribution of gray levels (lower uniformity) showed a significantly shorter survival (HR by Cox 2.5, 95% CI 1.21-5.27).

Conclusion. For a similar degree of cardiac hypertrophy, dialysis patients differed widely from hypertensives in their VDT parameters. By contrast, the hypertensive heart differed from the normal heart in the degree of hypertrophy but not in terms of VDT parameters. VDT parameters are independent predictors of all-cause mortality in dialysis patients.

Left ventricular hypertrophy (LVH), the most frequent cardiac alteration on patients in chronic hemodialysis [1–3], is an independent risk factor for survival [1, 4, 5].

Few studies suggest that not only the cardiac mass per se, but also the type of geometric patterns of remodeling, has an impact on survival [6, 7].

Key words: videodensitometry, tissue characterization, myocardial texture analysis, uremic cardiomiopathy, hemodialysis, cardiac mortality risk.

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In the uremic heart some characteristics are found microscopically that are overexpressed in comparison with other types of LVH. In fact, increased volume density of interstitial tissue with reduced capillary density has been described in experimental studies [8] and a nonreplacement type of interstitial fibrosis was found in uremic patients to be more marked than in subjects with primary hypertension [9]. Moreover, deposition of calcium salts [10] and sometimes amyloids [11] have also been described in uremic patients.

Changes in cardiac tissue structure resulting from morbid processes can be detected by ultrasound as a change in echo reflectance [12]. It has been suggested that echocardiographic tissue analysis may be clinically useful in various types of cardiac pathology [13–17], including uremic cardiopathy [18–26].

Extending our previous experience [24–26], in this study we hoped to determine whether echocardiographic tissue analysis is capable of (*1*) capturing in vivo differences in the echo signal of the hypertrophic myocardium of uremic subjects in comparison with the hypertrophic myocardium of subjects with arterial hypertension and normal renal function; and (*2*) whether the ultrasonic alterations of the hypertrophic uremic myocardium are independent risk factors for survival.

METHODS

We studied an overall total of 166 subjects subdivided as follows: 96 uremic patients in hemodialytic treatment for 61 ± 45 months, 18 hypertensive subjects with normal renal function, and 52 healthy subjects. The hypertensive subjects were recruited from our outpatient clinics, the controls were chosen among hospital medical and nursing staff.

The characteristics of the population analyzed are described in Table 1.

The 96 dialysis patients represent 62% of the patients in hemodialytic treatment in our unit, excluding patients with an inadequate acoustic window for the echo, or with paradox movements of the septum as an expression of infarctual areas in that location, or with a dialysis vintage

Table 1. Subject characteristics

	Number	Male/ female	Age years	Body surface m^2
Controls	52	37/15	48.3 ± 15.4	1.84 ±.19
Hypertensives	18	6/12	52.0 ± 14.3	1.82 ± .15
Dialysis patients	96	55/41	60.0 ± 14.2[a]	1.69 ± .18[b]
Total	166	98/68		

[a] $P < 0.001$ vs. controls; [b] $P < 0.001$ vs. controls and hypertensives.

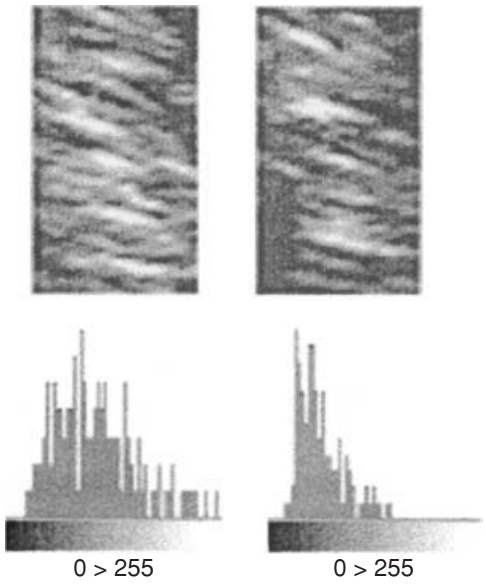

Fig. 1. A representative histogram of frequency distribution of gray levels (lower panel) derived by echocardiographic images of interventricular septum (upper panel) in a dialysis patient (left) and in a normal subject (right). In comparison to normal, uremic heart appears more brilliant and this is heralded by a higher reflectivity. Histogram is more scattered (lower uniformity).

lower than or equal to 3 months. Prevalence of their cardiovascular comorbidity was as follows: seven with diabetes, 18 with myocardial infarctions, 24 with chronic heart failure, seven with arrhythmias, and 12 strokes. Their predialysis blood pressure values were 145 ± 79 mm Hg, on average; almost half of them, 45 out of 96, were on antihypertensive treatment; interdialytic body weight increase was 2.5 ± 0.8 kg. Predialysis hemoglobin was 10.5 ± 1.8 g/dL, intact parathyroid hormone (iPTH) 239 ± 253 pg/mL, and urea reduction rate 72% ± 6%.

Bidimensional echocardiography was performed with an echocardiograph with a 2.5 MHz electronic transducer (SIM 7000; CFM, Esaote, Genoa, Italy). Dialysis patients were examined 30 minutes after the end of the dialytic session. Left ventricular mass indexed for body surface area was calculated using the Penn cube formula. Tissue analysis was performed by means of videodensitometry (VDT), that is, an analysis of gray levels in the ultrasound images. Details of the technique were described in our earlier papers [25, 26] and are summarized here. After conventional echocardiographic examination was completed, an echocardiographic examination with preset and standardized parameters was performed. The echocardiographic image obtained in the four-chamber mode and corresponding to the telediastolic phase of the cardiac cycle was selected and digitized by an image processing computer (Mipron; Kontron, Muenchen, Germany) and transformed into a pixel matrix (256 × 256) with a gray level numerical value for every individual pixel ranging from 0 (black) to 255 (white).

For a first-order statistical analysis (i.e., without considering spatial interdependencies), a region was selected, measuring about 9 × 9 pixels, within the central part of the interventricular septum (IVS), with particular care being taken to exclude hyperreflective areas like the endocardium. From the matrix of values thus obtained, a histogram of the distribution frequency of grays was constructed. First-order statistics provide a large variety of parameters for the quantitative description of the shape of the histogram of the gray level amplitude (tonal) distribution of the selected region of interest. The mathematical formulas relative to those parameters are given in the Appendix. The parameters we used to describe the histogram are the following: (*1*) reflectivity, or mean, quantifies the average amplitude of the echographic response and represents the gray level around which the image is developed; and (*2*) uniformity, or tonal homogeneity, evaluates whether the pixels are clustered around a defined gray level. Mathematically, it is the summation of the single probabilities.

In a preceding study [25] we tested the reproducibility of such parameters by analyzing paired data obtained from two different samplings, from 1 to 3 months distant from each other; we found an error less than 3% and 9% for reflectivity and uniformity, respectively.

Figure 1 shows a representative picture of VDT analysis. In comparison with the septum of a normal subject, the septum of a dialysis patient appears more brilliant and this is associated with an increasingly less clustered frequency histogram more distributed toward the white.

For the dialysis patients, we extracted from our computerized clinical records data on previous cardiac events and peripheral vascular events. Cardiac events were defined as a clinically evident and instrumentally documented myocardial infarct and/or ischemic cardiopathy; peripheral vascular events as amputation or the presence of clinically evident claudicatio intermittens always associated with instrumentally (arteriography and/or Doppler) documented peripheral arteriopathy. Dialysis patient survival was tracked following VDT analysis.

Values are expressed as mean ± SD. For statistics we used the SPSS statistical package. Analysis of variance (ANOVA) with Bonferroni post hoc test for multiple comparisons, multivariate analysis, simple correlations,

Table 2. Parameters from conventional echocardiography and videodensitometry

	Interventricular septum *mm*	Reflectivity	Uniformity (×1000)
Controls	9.3 ± 0.9	72.1 ± 15.3	184.5 ± 86.1
P value	0.003	NS	NS
Hypertensives	11.0 ± 1.6	69.9 ± 16.9	183.8 ± 71.1
P value	NS	0.001	0.007
Dialysis patients	11.8 ± 2.2	86.9 ± 19.1	137.3 ± 32.5

and linear regression were employed when appropriate. Using regular Cox proportional hazards regression analysis we compared the mortality risk of hemodialysis patients according to whether their VDT parameters were above or below the median with adjustment for potential confounders. Covariates for adjustment include age at study entry, previous cardiac and/or vascular events, and left ventricular mass index. Number of covariates was selected according to the events observed (e.g., 1 covariate every 10 events). Patient survival times were recorded at event occurrence (all-cause mortality), loss to follow-up, or at the follow-up end, whichever came first.

RESULTS

Table 2 summarizes the echocardiographic results of interest for this study. Thickness of the IVS (i.e., the location of VDT parameter sampling) was not significantly different in dialysis patients and hypertensives, even if the values are numerically lower in the latter. Values in both groups of patients are significantly increased as compared to the controls. Dialysis patients show a significantly greater myocardial reflectivity and a reduced homogeneity of distribution of gray levels (lower uniformity) in comparison both with hypertensive patients and normal controls. Multivariate analysis rules out that such differences can be explained by gender, age, and body surface area, all of them parameters not well balanced in the three populations (Table 1).

To summarize, dialysis patients differed from hypertensive patients for their VDT parameters but not for IVS thickness, while hypertensive patients did not differ from healthy controls in VDT parameters in spite of significantly higher IVS thickness (Table 2).

Left ventricular mass index in controls, hypertensive, and dialysis patients was 97 ± 18 g/m^2, 119 ± 23 g/m^2, and 151 ± 41 g/m^2, respectively, whichever comparison being significant.

In the three categories of analyzed subjects none of the VDT parameters shows any correlation with left ventricular mass index, IVS thickness, or ejection fraction. On the contrary, in dialysis patients we found a fairly good correlation between early/atrial (E/A) diastole fillup and reflectivity ($r = 0.38$, $P = 0.003$).

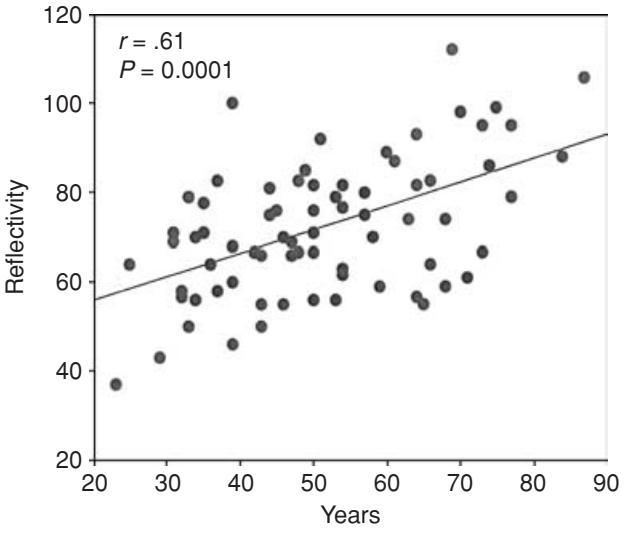

Fig. 2. Correlation between age and reflectivity in normal subjects.

None of the VDT parameters was found to be significantly different in dialysis patients with and without preceding cardiac infarcts. On the contrary, dialysis patients with history of peripheral vascular disease showed, in comparison with dialysis patients without, a significantly higher reflectivity (110 ± 21 vs. 82 ± 15, respectively) ($P < 0.001$) and IVS thickness (13.7 ± 3.5 vs. 11.5 ± 2.2 mm) ($P < 0.001$).

In the normal subjects we found a good correlation between age and reflectivity (Fig. 2). This correlation disappears in the dialysis patients in whom we found, on the other hand, a slight correlation between reflectivity and dialytic vintage ($r = 0.23$, $P = 0.03$).

In dialysis patients follow-up was 4.6 ± 2.9 years. Dialysis patients with uniformity values above the median showed a significantly longer survival than those with uniformity values below the median (Fig. 3). On the contrary, the reflectivity was not predictive of all-cause mortality.

The adjusted hazard ratios with confidence intervals (95% CI) for each covariate are given in Table 3.

DISCUSSION

The study by Bhandari and Nanda [18] was the first to describe the characteristics of uremic myocardial tissue. Using a qualitative approach, these authors found a peculiar echo pattern characterized by the presence of very bright or highly refractile echoes. Bhandari's pioneering study was subsequently confirmed by other researchers [19–21].

Using a quantitative approach, other researchers were able to confirm in dialysis patients a peculiar echo pattern as compared to normal controls or hypertensive subjects with normal renal function [22, 23].

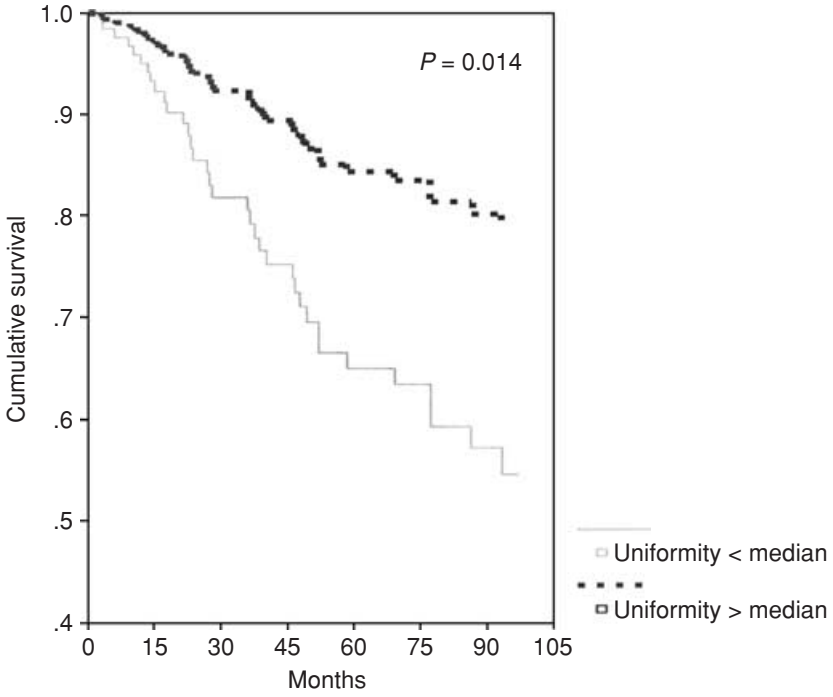

Fig. 3. Predictive effect of Uniformity on all-cause mortality adjusted for age, cardiovascular comorbidity, and left ventricular hypertrophy.

Present study was designed for the specific purpose of ascertaining whether echocardiographic tissue analysis can capture in vivo differences in the hypertrophic myocardium between hypertensives with normal kidney function and uremics in hemodialytic treatment, and whether the ultrasonic alterations in the hypertrophic uremic myocardium are independent risk factors for survival.

Employing the VDT analysis we found that the echo signals from the uremic heart appear different from those of the hypertensive heart. In fact, compared with hypertensives, dialysis patients show a significantly greater myocardial reflectivity and a reduced homogeneity of distribution of gray levels (lower uniformity) for comparable septum thickness. On the contrary, hypertensive patients show VDT parameters similar to normal control subjects in spite of significantly higher septum thickness (Table 2). Thus, by means of a quantitative observer-independent ultrasonic assessment, we have demonstrated that the uremic myocardium shows high refractile and inhomogeneous echoes. These abnormalities seem peculiar to uremic myocardial hypertrophy since they are not found in hypertensive subjects with normal renal function and a comparable degree of IVS hypertrophy.

In the uremic heart, some characteristics were found microscopically [8, 9, 11] that are overexpressed in comparison with other types of LVH (e.g., cardiac hypertrophy resulting from hypertension not associated with renal disease). It is tempting to speculate that these abnormalities, namely intermyocytic fibrosis and/or calcium deposition, provide the anatomic basis for the changed echo pattern in the uremic heart. Not having performed cardiac biopsies, we lack direct evidence that might validate this hypothesis. However, other studies have shown that VDT parameters are influenced by the degree of fibrosis present in the tissue examined [27] and our earlier studies have provided indirect evidence of a possible association between alteration of VDT parameters and calcium phosphorus metabolism in uremic patients [24, 25]. However, the present study was not designed to investigate the mechanisms underlying altered cardioreflectance, and that question thus remains open for later studies.

Table 3. Adjusted hazard ratios for all-cause mortality

Covariates	HR	95% CI	*P* value
Age (per year)	1.062	1.016–1.110	0.007
Cardiovascular comorbidity	2.837	1.318–6.106	0.008
Uniformity	2.521	1.207–5.268	0.014
Left ventricular mass index (per g/m^2)	1.010	1.002–1.018	0.016

It is legitimate to ask if the results we obtained are simply a mirror of preceding myocardial infarcts and the ensuing fibrotic scars. To eliminate such a possibility, we excluded from the study patients with paradoxal movement of the septum, a possible expression of previous infarct in the site of VDT sampling. Moreover, we subdivided the dialytic population according to the presence or absence of a preceding history of myocardial infarcts. The fact that none of the VDT parameters differed in

these two populations suggests that the previous cardiac events do not account for the altered VDT values in the dialysis patients.

The relation between reflectivity and a parameter of diastolic dysfunction such as E/A ratio might indicate that both parameters point to the same phenomenon, that is, an altered myocardial structure that involves a minor compliance of the left ventricle.

The association between alteration of VDT parameters and peripheral vasculopathy history agrees well with a series of works on the role of arterial stiffness in inducing cardiopathy [1, 3]. We evaluated vascular damage only anamnestically both with clinical and instrumental parameters; we did not perform peripheral echo color Doppler coincidentally with VDT analysis. We were therefore unable to compare alterations in VDT with objective stiffness parameters such as pulse wave velocity. This is one limitation of the work that may be covered by later studies.

The positive correlation between calendar age and myocardial hyperreflectivity in the controls disappears in the dialysis patients, where on the contrary we found a slight correlation between reflectivity and dialytic age, as if uremia per se had obscured the natural association between aging and VDT alterations. On these grounds, it is interesting to note how VDT parameters in the 18 patients in dialysis for less than 12 months are significantly more compromised (reflectivity 85 ± 10, uniformity 135 ± 25) than those found in normal subjects. These data seem to indicate that myocardial structural alterations appear in the early stages of chronic kidney disease; we are conducting studies to gain more insight into this issue.

Although a note of caution should be expressed since the study is borderline underpowered for survival analysis, the most interesting result of our study is the finding that VDT parameters are independent predictors of mortality in dialysis patients. This result, to our best knowledge, has never before been described. Indeed, the mortality risk is about 2.5 times greater in patients with reduced homogeneity of distribution of gray levels. Lower uniformity values had independent prognostic power over left ventricular mass index. We chose that index because its association with mortality is well documented in the literature [1, 4, 5]. In reality, we derived VDT indexes from the septum (i.e., from a muscular component), while the left ventricular mass index is a composite index based on both cavitary and muscular components. However, when we entered IVS instead of the left ventricular mass index in the Cox model, we obtained a similar predictive value (RR 1.21, 95% CI 1.08-1.35, per mm of IVS increase) ($P = 0.001$). We should like to emphasize how in our study the predictivity of the VDT parameters is similar to that found for cardiovascular comorbidity (e.g., a very hard predictor), while E/A does not enter into our model.

We acknowledge some limitations peculiar to VDT technique. Quantitative measurements of myocardial structure by echocardiography can be affected by many variables, such as general instrument gains and time gain compensation curves. Thickness of the chest wall and distance of the heart from the transducer may differ between subjects and, therefore, affect VDT measurements. Moreover, quantitative echocardiographic parameters are dependent on the orientation of the echo reflectors because the same target (region of interest) could produce different patterns depending on the view selected. Last, but not least, different inclination of the transducer between subjects, or between different exams in the same subject, could also affect VDT measurements. To overcome at least some of these drawbacks, we kept fixed pre- and postprocessing echocardiographic settings. The ensuing lower quality of images does not interfere with the computerized gray level analysis.

CONCLUSION

In our study, the hypertensive heart differed from the normal heart by the degree of hypertrophy but not in terms of VDT parameters. By contrast, for similar degree of LVH, dialysis patients differed widely in their VDT parameters from hypertensives.

VDT parameters in dialysis patients did not correlate with calendar age and did not depend on previous cardiac events; instead they correlated with dialytic vintage, history of the peripheral vascular system disease, and E/A ratio. Most important, VDT parameters were independent predictors of all-cause mortality in dialysis patients.

Our experience indicates that myocardial quantitative ultrasonic analysis appears to be a promising technique for an observer-independent assessment of myocardial tissue characteristics in dialysis patients. We feel that most of the drawbacks potentially besetting VDT analysis can be overcome if this technique is implemented serially on the same patient.

APPENDIX. FIRST-ORDER STATISTICS: QUANTITATIVE DEFINITIONS

By defining *gij* as the gray level of the pixel of coordinates (i, j) inside the matrix of the region of interest R, and N the total number of gray values, typical parameters extracted from the gray level distribution are (*1*) the mean (*m*) reflectivity

$$\frac{1}{N}\sum_{i,j\varepsilon R} g_{ij}$$

which describes the average gray value of the distribution; (*2*) the standard deviation

$$\sqrt{\frac{1}{N-1}\sum_{i,j\varepsilon R}(g_{ij}-m)^2}$$

that is an expression of the spreading of the distribution from the mean value, that is of the overall contrast; (*3*) the skewness

$$\frac{\frac{1}{N}\sum_{i,j\varepsilon R}(g_{ij}-m)^3}{\left(\sum_{i,j\varepsilon R}g_{ij}^2-m^2\right)^{\frac{3}{2}}}$$

characterizing the deviation of the distribution from a symmetric reference one; positive values are for a left-skew distribution, while a skewness to the right is classified by negative values; and (*4*) the curtosis

$$\frac{\frac{1}{N}\sum_{i,j\varepsilon R}(g_{ij}-m)^4}{\left(\sum_{i,j\varepsilon R}g_{ij}^2-m^2\right)^{2}}-3$$

which is related to the steepness of the distribution with respect to a normal (Gaussian) distribution.

Furthermore, by defining *pk(g)* as the probability of the k-th gray level, that is, the ratio between its frequency of occurrence and the total number of pixels, two more first-order parameters can be introduced: (*1*) the uniformity

$$\sum_{k=2}^{256}p_k^2(g)$$

that is the level of tonal homogeneity; and (*2*) the entropy

$$-\sum_{k=2}^{256}p_k(g)\ln(p_k(g))$$

a measurement of the level of disorder inside the gray level distribution or the degree of tonal dishomogeneity. It is the reciprocal of uniformity. Mathematically, it is the inverse of the natural logarithm of the probabilities that the pixels cluster around a defined gray level.

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