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Myocardial integrated ultrasonic backscatter for early detection of cardiac involvement in patients with Wilson disease

LIVER

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Original Article

ABSTRACT

Background/Aims: Videodensitometry is a feasible noninvasive ultrasound tissue characterization method allowing early detection of myocardial changes. This study aimed to investigate ultrasonic backscatter properties of the myocardium in Wilson disease patients.

Materials and Methods: We compared cardiologically asymptomatic Wilson disease patients (W group) (n=18) with age-matched (26.7±9.6 years) healthy controls (C group) (n=15). Diagnosis of Wilson disease was made on the basis of clinical manifestations, family history, and laboratory findings and confirmed by liver biopsy. Transthoracic echocardiographic quantitative texture analysis was performed on data from the septum and left ventricular posterior wall, and mean gray level (MGL) histograms at end-diastole (d) and end-systole (s) were obtained after background correction (c). Cyclic variation index (CVI) was calculated using the formula [(cMGLd - cMGLs) / cMGLd] ×100.

Results: There were no significant differences in sex, age, body mass index, heart rate or blood pressure, and conventional echocardiographic parameters between the 2 groups. The cMGLs value of the posterior wall was higher in the W group than in the C group (30.9±2.6 vs. 22.2±2.7, p=0.033). The W group had a significantly lower CVI of the septum than did the C group (-22±4.4% vs. 43.4 ±12.9%, p<0.001), and there was no significant difference in the CVI of the posterior wall (-67.0±15.9% vs. 41.7±18.6%, p=0.32).

Conclusion: Abnormalities in two-dimensional echocardiographic grey-level distributions were present in Wilson disease patients. These videodensitometric myocardial alterations were significantly lower in Wilson disease patients than in the controls, and this probably represents an early stage of cardiac involvement.

Keywords: Wilson disease, heart, echocardiography, tissue Doppler, videodensitometry

INTRODUCTION

Wilson disease is a severe genetic metabolic disorder that is associated with intracellular copper storage and multiorgan involvement including arrhythmias, cardiomyopathy, ventricular fibrillation, cardiac death, and autonomic dysfunction (1,2). Electrocardiographic abnormalities occur in 34% of cases, including left ventricular hypertrophy, biventricular hypertrophy, early repolarization, ST depression and T inversion, premature atrial or ventricular contractions, atrial fibrillation, sinoatrial block, and Mobitz type I atrioventricular (AV) block. Major pathological findings of the myocardium in Wilson disease patients include the presence of interstitial and replacement myocardial fibrosis, intramyocardial small vessel disease, focal myocarditis, cardiac hypertrophy, AV nodal degeneration, and occlusive atherosclerosis at an early age (1,3) These alterations are nonspecific but similar to those observed in other cardiomyopathies (4). Their existence in a relatively young group of patients without other significant etiology for the development of heart disease suggests the possibility of a direct relationship between Wilson disease and cardiac degeneration (1).

Ultrasonic tissue characterization with integrated backscatter (IBS) provides quantitative information about the structural and functional states of the myocardium (5).

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Quantitative characterization of myocardial texture by IBS imaging has been experimentally (6-9) and clinically (10-13) shown to be useful for detecting the pathologic changes affecting the myocardium, such as an aging heart (14), myocardial ischemia (15), hypertrophic and dilated cardiomyopathy (16,17), hypertensive heart disease (18), and acute cardiac rejection (19), resulting in alterations in its fundamental physical properties.

The aim of this study was to detect changes in myocardial structure by using ultrasonic videodensitometric analysis in Wilson disease patients without clinical evidence of ventricular dysfunction or other cardiac complications.

MATERIALS AND METHODS

Subjects

This study included 18 cardiologically asymptomatic patients with Wilson disease and 15 healthy subjects. We excluded patients with previous acute myocardial infarction, thyroid dysfunction, uncontrolled diabetes mellitus, chronic renal disease, valvular heart disease, cardiomyopathy, chronic obstructive pulmonary disease, systemic or pulmonary hypertension, and alcohol abuse. All patients were in sinus rhythm, and none of them were using any cardiac medications. Diagnosis of Wilson disease was made on the basis of clinical manifestations, family history of neuropsychiatric manifestations, jaundice, premature death attributable to Wilson disease, evidence of Kayser-Fleischer rings on slit-lamp examination, low serum copper and ceruloplasmin levels, and increased 24-h urinary excretion of copper. Radiologic investigations included a cranial computed tomography scan with or without iodinated contrast and/or magnetic resonance imaging and radiography of long bones, pelvis, and chest to evaluate skeletal abnormalities (15). The diagnosis was confirmed by liver biopsy and quantitative liver copper assay.

This study conformed to the guidelines of the Helsinki Declaration. Written informed consent was obtained from each subject, and institutional ethics committee approval was obtained for this study.

All patients underwent slit-lamp examination for Kayser-Fleischer rings and neurologic examinations at the time of diagnosis. The mean treatment duration was 11.43±7.99 years. Eleven patients received D-penicillamine, 6 received zinc sulfate, and 1 received trientine treatment. All patients were treated with copper chelation therapy.

Healthy volunteers underwent routine biochemical analysis; complete blood count (CBC); measurements of serum copper, ceruloplasmin, 24-h urine copper, hepatitis B antigen, and hepatitis C antibody levels; abdominal ultrasound; electrocardiography (ECG); and cardiologic examination.

Echocardiographic measurements

In all subjects, two-dimensional (2D), M-mode, pulsed Doppler, and color flow Doppler echocardiographic examinations (Vivid 7 Dimension, GE, Horten, Norway) were performed by the same examiner. Internal left ventricular end-diastolic and end-systolic diameters, interventricular septal and posterior wall thickness at end-diastole, and left atrial dimension were measured from the parasternal long-axis window in M-mode echocardiography (20). The left ventricular ejection fraction was measured using the modified Simpson method (21).

Echocardiography was performed within 24 h after examination of serum copper, 24-h urine copper, and serum ceruloplasmin levels; routine biochemical analysis; CBC analysis; hemostasis; telecardiography; and ECG assessment by the same echocardiographer blinded to patient status in order to eliminate variations in hemodynamic status.

Conventional Doppler echocardiography

Early diastolic wave peak velocity (E), late diastolic wave peak velocity (A), early-to-late velocity (E/A) ratio, and E-wave deceleration time of left ventricular inflow velocities were measured using pulse-wave Doppler by placing the sample volume between the tips of the mitral valve leaflets in the apical 4-chamber window. Isovolumetric relaxation time was obtained from the apical 5-chamber view by placing the sample volume between the tip of the mitral anterior leaflet and left ventricular outflow tract.

Quantitative texture analysis

IBS analysis

Ultrasonic tissue characterization with IBS was performed using transthoracic echocardiography. Echocardiographic quantitative texture analysis was performed on data from the septum and left ventricular posterior wall from the parasternal long-axis view, and mean gray level (MGL) histograms at end-diastole (d) and end-systole (s) were obtained after background correction (c).

One cardiac cycle (R-R wave) was automatically divided into 12 frames independently of heart rate, and the images corresponding to the end-diastolic and end-systolic phases, all in the left parasternal long-axis view, were selected by an optimal visualization of the interventricular septum (IVS) and left ventricular posterior wall. Using an interactive computer program, the region of interest, which was always the same size (32×42 pixels), was placed at the mid-septum and mid-posterior wall level, both in end-systole and end-diastole, including only the myocardium and excluding the endocardial and epicardial specular echoes to avoid areas of echo dropouts and obvious artifacts. For each region of interest, a histogram of the echocardiographic gray-level distribution was generated to plot the gray-level distribution on the abscissa and the frequency of the occurrence on the ordinate.

Table 1. Demographic and laboratory characteristics of the patients and controls

	Wilson disease patients (n=18)	Healthy controls (n=15)	p value
Sex (M/F)	11/7	7/8	NS
Age (range) (years)	49±26 (10-49)	44±11(17-44)	NS
Height (cm)	165.42±9.81	165.35±8.27	NS
Weight (kg)	63.28±14.32	62.57±12.40	NS
BMI	23.17±5.61	22.75±3.38	NS
AST (U/L)	46.93±33.60	21.88±4.98	0.003
ALT (U/L)	50.93±41.19	20.44±7.98	0.009
GGT (U/L)	68.93±83.52	14.11±5.32	0.000
ALP (U/L)	376.66±147.96	193.44±84.18	0.001
Albumin (g/dL)	4.21±0.71	4.63±0.28	NS
Globulin (g/dL)	3.10±0.56	2.82±0.28	NS
Total bilirubin (mg/dL)	1.68±1.08	0.70±0.25	0.013
Direct bilirubin (mg/dL)	0.53±0.42	0.18±0.04	0.017
Cholesterol (mg/dL)	131.35±37.87	160.80±29.08	NS
Triglyceride (mg/dL)	82.21±51.59	112.20±59.14	NS
Hb (g/dL)	13.84±1.76	14.64±1.85	NS
Plt ($\times 10^3$/μL)	142200±116.25	269.71±34.61	0.007
Serum copper (μg/dL)	71.21±42.36	136.00±25.23	0.044
24-h urine copper (μg/dL)	194.26±75.96	42.02±24.23	0.001
Serum ceruloplasmin (μg/dL)	22.59±28.65	39.00±9.64	0.051

ALT: alanine aminotransferase; ALP: alkaline phosphatase; AST: aspartate aminotransferase; BMI: body mass index; F: female; GGT: gamma glutamyl transferase; Hb: hemoglobin; M: male; Plt: platelet; NS: non significant

Gray-level difference measurements

The MGL of each cavity region (background signal) was subtracted from the absolute MGL of the myocardium to obtain both the end-systolic MGL (MGLs) and end-diastolic MGL (MGLd). Cyclic variation (CV) was determined as the difference between the diastolic and systolic IBS values. CV and IBS are expressed in decibels (dB). The CV index (CVI) of gray-level amplitude was also calculated using the following formula: [(MGLd - MGLs) / MGLd] × 100 (22). All measurements were obtained from the average of 5 consecutive cardiac cycles. The intraobserver variability was 0.3±0.1 dB for CV and 2.2±1.5 dB for the maximal intensity of backscatter signal.

Statistical analysis

SPSS 11.0 (Chicago IL, USA) for Windows was used for all statistical analyses. The number of samples was expressed as n, continuous variables were expressed as means±standard deviations, and categorical variables were expressed as percentages. Pearson correlations were used to compare the relationships between indexes. Categorical variables were compared using the Pearson chi-square test. Continuous variables between the 2 groups were compared using the unpaired Student *t*-test. The relationships between videodensitometric and 2D echocardiographic measurements were determined using linear regression analysis. For all tests, a value of $p<0.05$ was considered statistically significant.

Table 2. Conventional Doppler echocardiographic measurements of the Wilson disease patients and controls

	Patients (n=18)	Controls (n=15)	p value
Left atrium (cm)	3.1±0.4	3.2±0.6	NS
Left ventricular end-diastolic diameter (cm)	4.5±0.3	4.7±0.4	NS
Left ventricular end-systolic diameter (cm)	2.8±0.3	3.0±0.3	NS
Interventricular septum thickness (cm)	0.8±0.1	0.9±0.1	NS
Posterior wall thickness (cm)	0.9±0.1	0.8±0.1	NS
Ejection fraction (%)	66.6±6.6	64.6±6.1	NS
E (cm/s)	93.7±14.3	88.2±12.5	NS
A (cm/s)	68.8±14.6	75.2±25.1	NS
E/A	1.3±0.4	0.8±0.2	NS
EDT (ms)	177±53.2	167±34.2	NS
IVRT (ms)	68.4±12.0	72.2±22.4	NS

A: transmitral late diastolic peak velocity; E: transmitral early diastolic peak velocity; E_{DT}: e-wave deceleration time; IVRT: isovolumetric relaxation time; NS: non significant

RESULTS

This study included 18 Wilson disease patients (age: 49±26 years, range: 10-49 years) and 15 healthy controls (age: 44±11 years, range: 25-50 years). In Wilson disease patients, the patient age at diagnosis was 42±18 years (range: 2.5-42 years), and the mean disease duration was 9.6±7 years (range: 1-29 years). Serum copper, ceruloplasmin, and urinary copper excretion levels were 1670±800 μg/L, 300±120 mg/L, and 167±80 μg/dL, respectively. Aspartate aminotransferase, alanine aminotransferase, hemoglobin, total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglyceride levels were 53.2±42 IU/L, 45.6±35 IU/L, 138±18 mg/L, 131±37 mg/dL, 50±31 mg/dL, 66±23 mg/dL, and 95±16 mg/dL, respectively.

All subjects were cardiologically asymptomatic. The demographic and laboratory characteristics of the Wilson disease patients and controls are shown in Table 1. There were no significant differences in sex, age, body mass index, heart rate, or blood pressure between the 2 groups. All patients were treated with copper chelation therapy. Of the patients, 17 received D-penicillamine (0.75-1 g orally 3 times a day) and 1 was switched to trientine (750 mg orally 3 times a day) because of drug-related thrombocytopenia.

Conventional echocardiographic and tissue Doppler imaging (TDI) indexes in the Wilson disease patients and controls are listed in Tables 2 and 3.

Table 3. Echocardiographic quantitative texture analysis data from the septum and left ventricular posterior wall to obtain mean gray level (MGL) histograms at end-diastole (d) and end-systole (s) with background correction (c)

	Patients (n=18)	Controls (n=15)	p value
Interventricular septum			
MGLd	34.2±8	28.8±6	0.069
MGLs	26.3±5	24.4±6	0.448
cMGLd	13.9±9	14.3±5	0.886
cMGLs	21.8±6	18.7±4	0.153
CVI	-22.0±4.4	43.4±12.9	<0.001
Posterior wall			
MGLd	28.1±7	26.3±4	0.460
MGLs	17.2±9	21.0±8	0.299
cMGLd	20.1±8	16.8±5	0.230
cMGLs	30.9±2.6	22.2±2.7	0.033
CVI	-67.0±55	41.7±72	0.327

MGLd: diastolic mean gray level histogram; MGLs: systolic mean gray level histogram; cMGLd: corrected diastolic mean gray level histogram; cMGLs: corrected systolic mean gray level histogram; CVI: cyclic variation index

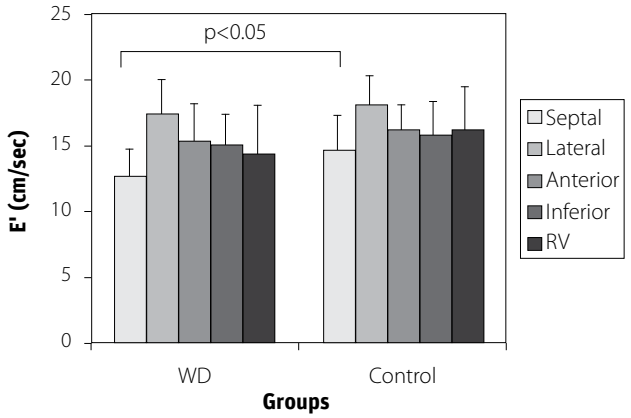

Figure 1. Regional myocardial early diastolic peak velocity in the Wilson disease patients and controls.

The left ventricular and left atrial diameters, left ventricular ejection fraction, and left ventricular mass index were similar between the groups. The pulmonary artery pressure was within normal limits in all Wilson disease patients. No moderate-to-severe cardiac valve regurgitation was observed in the Wilson disease patients, and no differences in the IVS or posterior wall diameter were observed between the 2 groups. However, Wilson disease patients had a lower peak early diastolic velocity of the septum (E' septal) (12.67±1.99 cm/s) than the controls (14.71±2.58 cm/s) (p=0.042) (Figure 1). No statistical difference was found in the other regional myocardial velocities between the 2 groups.

The corrected MGLs values of the posterior wall were lower in Wilson disease patients than in the controls (-30.9±2.6 vs. 22.6±2.7, respectively; p=0.03). The echo intensity variations showed a paradoxical behavior compared with those of normal subjects. Wilson disease patients had a significantly lower CVI of the septum than did the controls (Wilson disease patients vs. controls: -22±4.4% vs. 43.4±12.9%, p<0.001). There was no significant difference in the CVIs of the posterior wall (Wilson disease patients vs. controls: -67.0±15.9% vs. 41.7±18.6%, p=0.32) (Table 4).

Table 4. Regional myocardial systolic and diastolic functional parameters of the ventricles obtained by pulse-wave tissue Doppler imaging

TDI indices	Patients (n=15)	Controls (n=14)	Total (n=29)	p value
Lateral E' (cm/s)	17.40±2.58	18.07±2.27	17.72±2.41	NS
Lateral A' (cm/s)	8.80±3.60	9.71±3.19	9.24±3.39	NS
Lateral E'/A'	2.27±0.88	2.04±0.67	2.16±0.78	NS
Lateral S (cm/s)	12.00±2.88	11.71±2.70	11.86±2.75	NS
Septal E' (cm/s)	12.67±1.99	14.71±2.58	13.66±2.48	0.042
Septal A' (cm/s)	8.80±2.73	10.07±2.89	9.41±2.83	NS
Septal E'/A'	1.57±0.55	1.59±0.54	1.58±0.54	NS
Septal S (cm/s)	9.43±2.28	9.71±1.44	9.57±1.87	NS
Inferior E' (cm/s)	15.00±2.39	15.78±2.64	13.66±2.48	NS
Inferior A' (cm/s)	9.80±2.04	10.71±2.67	10.24±2.37	NS
Inferior E'/A'	1.61±0.46	1.51±0.25	1.56±0.37	NS
Inferior S (cm/s)	9.60±1.64	10.15±1.63	9.86±1.63	NS
Anterior E' (cm/s)	15.27±2.94	16.29±1.77	15.76±2.46	NS
Anterior A' (cm/s)	8.27±1.62	8.57±2.47	8.41±2.04	NS
Anterior E'/A'	1.89±0.39	2.08±0.72	1.98±0.57	NS
Anterior S (cm/s)	10.73±1.87	11.29±2.33	11.00±2.09	NS
RV E' (cm/s)	14.40±3.66	16.30±3.17	15.29±3.52	NS
RV A' (cm/s)	12.87±3.78	13.00±3.83	12.93±3.73	NS
RV E'/A'	1.18±0.39	1.32±0.35	1.25±0.38	NS
RV S' (cm/s)	13.47±2.10	13.31±1.80	13.39±1.93	NS

A': myocardial late diastolic peak velocity; E': myocardial early diastolic peak velocity assessed by pulse-wave tissue Doppler imaging; NS: non significant; S': myocardial systolic peak velocity; RV: right ventricle; TDI: pulse-wave tissue Doppler imaging

No significant correlations were found between the CVI and septum or posterior wall thickness, ejection fraction, and diastolic Doppler transmitral flow parameters (peak E, peak A, E/A ratio).

DISCUSSION

Ultrasonic tissue characterization with IBS provides quantitative information about the structural and functional states of the myocardium (5,23). It is based on the analysis of the reflection of an ultrasound wave (scattering), which is derived from the interaction of myocardial tissue elements that are smaller than the ultrasound wavelength (5). Time-domain analysis of

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this radiofrequency signal provides its IBS intensity and the systolic-to-diastolic CV of the intensity. CV decreases substantially in the presence of contractile dysfunction, variation in the elastic properties, or alterations in the scatter geometry (13). Although IBS analysis has been performed more often on the left ventricle, a previous study shows that it enables differentiation between normal and abnormal myocardium (24).

The baseline assumption underlying the use of ultrasonic tissue characterization is that pathologic changes affecting the myocardium, such as an aging heart (14), myocardial ischemia (15), hypertrophic and dilated cardiomyopathy (16,17), hypertensive heart disease (18), and acute cardiac rejection (19), result in alterations of its fundamental physical properties that can be detected by IBS imaging. The extracellular matrix has been shown to represent an important source of myocardial IBS, and several experimental studies have demonstrated that IBS correlates with the collagen content within the myocardium (9,25). IBS measurements show CV, which may reflect the contractile performance of the myocardium (26), although the phenomenon is more complex than that (27). A direct correlation between reduced CV of IBS and deterioration of left ventricular diastolic function has been shown previously by Maceira et al. (13).

In this study, ultrasonic videodensitometric analysis showed myocardial tissue changes in Wilson disease patients. In particular, the CVI, which is an expression of the intrinsic myocardial structural function, was significantly lower at both the septum and posterior wall in Wilson disease patients than in the age-matched controls. These findings may be an expression of preclinical myocardial involvement; in fact, all Wilson disease patients had normal left ventricular systolic function as well as normal left ventricular wall thickness. Moreover, patients with coronary artery disease and other disorders responsible for myocardial damage, such as arterial hypertension, diabetes, and other cardiomyopathies, were excluded from this study. The diastolic changes observed in Wilson disease patients are mainly related to the relaxation phase, resulting in a decrease in peak velocity of the early diastolic filling wave (peak E) (28).

Left ventricular diastolic function depends on the complex interaction between ventricular isovolumetric relaxation, diastolic filling, and compliance (28). The rarity of diastolic changes and, much more so, the absence of systolic left ventricular dysfunction in our Wilson disease patients emphasize the clinical relevance of myocardial tissue changes detected by videodensitometry. Several clinical studies focusing on cardiac involvement in Wilson disease patients were performed using traditional echo-Doppler methods, which showed various abnormalities such as an increase in the thickness of the IVS and posterior myocardial wall, biventricular hypertrophy, valvular abnormalities, cardiomyopathy, and cardiac failure (29-31).

Wilson disease is a severe genetic metabolic disorder, which is associated with intracellular copper overload and multiorgan involvement (32-35). Cardiac manifestations in Wilson disease patients include many ECG abnormalities and arrhythmias such as atrial fibrillation, early repolarization, ST depression, T inversion, sinoatrial block, Mobitz type I AV block, tremor artifact (1,3,4), supraventricular tachycardia and frequent supraventricular ectopic beats (36), post-transplant electrical storm (37), P-wave dispersion abnormalities (38), cardiomyopathy (3,29,30,39,40), orthostatic hypotension and autonomic dysfunction (1,41), and cardiac deaths due to ventricular fibrillation and cardiac failure (29). Morphologic abnormalities and myocardial alterations consistent with cardiomyopathy have been previously reported in autopsy specimens of the hearts of Wilson disease patients (30). Myocardial damage and the presence of myocardial copper deposition 10-100 times the normal concentration have also been reported in the autopsy tissues of Wilson disease patients (4,39). However, conflicting results on the clinical impact of myocardial copper levels have been reported in previous studies (1,39,40). A limitation of our study is that we have no data on the copper levels in regional myocardial tissues and magnetic resonance imaging was not performed.

The major pathological findings of the myocardium in Wilson disease patients include the presence of interstitial myocardial fibrosis, intramyocardial small vessel disease, focal myocarditis, cardiac hypertrophy, AV nodal degeneration, and occlusive atherosclerosis at an early age (30). These alterations are nonspecific but similar to those observed in other cardiomyopathies (30,42). Their existence in a relatively young group of patients without other significant etiology for the development of heart disease suggests the possibility of a direct relationship between Wilson disease and cardiac degeneration (43). A study by Kaduk et al. (39) on cardiomyopathy in Wilson disease patients suggested that mitochondrial alterations are the consequence of myocardial copper accumulation. These alterations are also nonspecific and present in some cases of limited severity; however, a previous study concluded that cardiac degeneration might contribute to death in Wilson disease patients (39).

In normal subjects, cardiac cycle-dependent variations in ultrasound signals within the myocardium have been detected: maximum values occurred at end-diastole and minimal values at end-systole (9,44,45). These cyclic changes could be related to intrinsic contractile function (26,46,47), distinct from myocardial wall thickening. To our knowledge, this is the first study in which videodensitometric analysis was performed in Wilson disease patients. The significantly lower values of CVI are essentially due to the abnormal increase in the MGL at end-systole in Wilson disease patients compared to the controls.

In our study, the decrease in CVI could be a manifestation of interstitial fibrosis, intramyocardial small vessel sclerosis, and focal inflammatory cell inflammation previously detected to

a variable degree, and the decrease in regional early diastolic wave velocity demonstrated by TDI of the IVS supports that there was a regional cardiac subclinical myocardial alteration in Wilson disease patients. Our findings support that cardiac involvement initially clearly exists in the septal region in Wilson disease patients, and this early myocardial dysfunction can be determined using videodensitometric myocardial analysis and TDI, which are simple, noninvasive, easily applicable echocardiographic techniques (47).

In conclusion, our study showed the abnormalities in 2D echocardiographic gray-level distribution in Wilson disease patients. These videodensitometric myocardial alterations were significantly lower in Wilson disease patients than in the controls, probably representing an early stage of cardiac involvement, and this was also supported by the TDI findings. Ultrasonic videodensitometric analysis is a feasible, noninvasive method for detecting early myocardial changes in Wilson disease patients, which could be related to both fibrosis and microcirculatory abnormalities or copper accumulation.

The potential evolution towards ventricular dysfunction and its relationship with severe conduction system and cardiac rhythm disturbances or cardiac death in Wilson disease patients should be further investigated, and the etiology of decreased CVI should be clarified.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-Review: Externally peer-reviewed.

Author Contributions: Concept - N.A.; Design - N.A., S.K.; Supervision - Z.G.; Resources - N.A., S.K., M.A., S.K.; Materials - S.K., M.A., S.K.; Data Collection and/or Processing - N.A., Z.G.; Analysis &/or Interpretation - N.A., S.K., Z.G.; Literature Search - S.K.; Writing - N.A., S.K.; Critical Reviews - Z.G.

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