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Iron Overload or Oxidative Stress? Insight into a Mechanism of Early Cardiac Manifestations of Asymptomatic Hereditary Hemochromatosis Subjects with C282Y Homozygosity

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Abstract

Hereditary hemochromatosis (HH) is a genetic disorder which affects the heart due to systemic iron overload and concomitant elevated oxidative stress. Increasing numbers of patients are diagnosed at an asymptomatic stage due to genetic testing. Subclinical abnormal left ventricular diastolic function (LVDF) and increased arrhythmias are noted in this population; however, the mechanism leading to these observations has not been well understood. In this study, we assessed the relationship between arrhythmia activity and biomarkers of oxidative stress and iron overload in order to elucidate the role of oxidative stress in this population since we observed a significant association with LVDF previously. A significant correlation between plasma malondialdehyde, a biomarker of oxidative stress, and supraventricular arrhythmia activity without a significant association with iron overload was identified (n=22). Our findings further highlight a possible role of oxidative stress in early cardiac manifestations of HH. Further investigation is warranted to assess this role.

Keywords

hemochromatosis; arrhythmia; oxidative stress; iron overload; biomarkers; electrocardiogram

Hereditary hemochromatosis (HH) caused by HFE gene mutations may affect the heart (1), and more patients are now being diagnosed at an asymptomatic stage due to the availability of genetic testing (1). Subclinical, early cardiac manifestations include altered left ventricular diastolic function (2) and increased arrhythmias (3). Organ damage can be

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Disclosures

The authors declare that they have no conflict of interest.

Human subjects/informed consent statement

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the 1964 Helsinki declaration as revised in 2000. Informed consent was obtained from all individual participants for being included in this study.

resulted from either iron overload directly or secondary elevation of oxidative stress due to iron overload in HH (1); however, little is known about the precise etiology of the early cardiac manifestations in HH.

Based on our previous observation of a significant association of left ventricular (LV) diastolic function with oxidative stress, but not iron overload in HH (4), we hypothesized that oxidative stress also plays a significant role in arrhythmogenesis in this population. In order to further investigate this postulate, we additionally analyzed the relationship between biomarkers of both oxidative stress and iron overload and arrhythmia activity in this study, utilizing our clinical database of the National Heart, Lung, and Blood Institute(NHLBI)-sponsored “Heart Study of Hemochromatosis (Clinical Trials.gov; NCT00068159).”

The data from 22 newly diagnosed HH subjects with C282Y homozygosity in the database were analyzed. Oxidative stress was measured using plasma malondialdehyde (MDA), erythrocyte glutathione (GSH), and erythrocyte superoxide dismutase (SOD) levels (5). The arrhythmia activity was assessed with an hourly rate of supraventricular (SVE) and ventricular ectopic beats (VE) recorded on 48-hour Holter ambulatory monitoring (3). The correlations between biomarkers and arrhythmia activity were analyzed with a non-parametric Spearman correlation test. $P < 0.05$ was considered to be a statistically significant.

The demographic data, levels of iron overload and oxidative stress, and incidence of arrhythmias have been reported elsewhere (2–5). SVE activity significantly correlated with MDA (correlation coefficient; 0.499, probability; 0.021, Table) and showed near significant correlation with GSH (correlation coefficient; 0.385, probability; 0.077, Table) without correlating with iron overload. VE activity failed to correlate with either oxidative stress or iron overload.

As described, we previously showed a significant association between oxidative stress and LV diastolic function in asymptomatic subjects with HH (4). The present description of a relationship between arrhythmia activity and oxidative stress and its lack of association with iron overload in these subjects further supports this hypothesis. VE activity failed to correlate with oxidative stress and iron overload in this study, and further investigation is needed to determine whether another currently unidentified induction mechanism exists between VE and SVE in HH. Interestingly, we have reported that myocardial tissue iron accumulation did not occur at this stage of disease (4), and a lack of this accumulation may in part explain the absence of an association between iron overload and arrhythmia activity in asymptomatic subjects.

Although the subject number was small ($n=22$) and the association observed was limited, our findings suggest the possible importance of oxidative stress in cardiac involvement at an asymptomatic stage of HH. Further investigation on a larger scale is warranted to assess this relationship.

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Abbreviations

HH	hereditary hemochromatosis
LVDF	left ventricular diastolic function
LV	left ventricle
NHLBI	National Heart, Lung, and Blood Institute
GSH	glutathione
SOD	superoxide dismutase
MDA	malondialdehyde
SVE	supraventricular ectopic beat
VE	ventricular ectopic beat

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Table

Correlations between arrhythmia activity and biochemical markers of oxidative stress and iron overload in subjects with newly diagnosed hereditary hemochromatosis with C282Y homozygosity

Arrhythmia burden saturation n=22		GSH (RBC)	SOD (RBC)	MDA (plasma)	Ferritin (serum)	Fe (serum)	Transferrin (serum)
Supraventricular	R	0.385	0.355	0.499	-0.227	-0.118	-0.046
ectopy rate	P	0.077	0.105	0.021 *	0.310	0.609	0.844
Ventricular	R	0.134	0.005	0.267	0.145	0.289	0.241
ectopy rate	P	0.553	0.982	0.230	0.519	0.204	0.293

The source of specimen is indicated in the parenthesis. Non-parametric Spearman correlation tests were used for this analysis. n = 22 except Fe and transferrin saturation which have one missing data point.

* denotes a statistical significance with $P < 0.05$. RBC = erythrocytes, R = rho coefficient, P = probability, GSH = erythrocyte glutathione, SOD = erythrocyte superoxide dismutase, MDA = plasma malondialdehyde, Fe = serum iron.