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Impaired Left Ventricular Filling in Patients with Essential Hyperhidrosis: An Echo-Doppler Study

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Saglam, M., Esen, A.M., Barutcu, I., Karaca, S., Kaya, D., Karakaya, O., Kulac, M., Esen, O., Melek, M., Onrat, E., Celik, A. and Kilit, C. *Impaired Left Ventricular Filling in Patients with Essential Hyperhidrosis: An Echo-Doppler Study.* Tohoku J. Exp. Med., 2006, **208** (4), 283-290 —— Essential hyperhidrosis is a well recognized dermatologic and neurologic disorder, characterized by excessive sweating of the eccrine sweat glands. It is also associated with cardiac autonomic dysfunction because sympathetic fibers to eccrine glands of palms of the hand arise from stellate and upper thoracic ganglia, which also innervate the heart. In this study, we investigated cardiac function in patients with essential hyperhidrosis by conventional and tissue Doppler imaging methods. Eighteen subjects with essential hyperhidrosis and eighteen control subjects were included in this study. Pulsed-wave Doppler parameters of the left and right ventricles, which represent diastolic filling abnormalities, were obtained by conventional Doppler and tissue Doppler imaging. Isovolumetric relaxation time, isovolumetric contraction time, ejection time and myocardial performance index were also calculated. Mitral inflow peak early (E_M) and late (A_M) velocities and E_M/A_M ratio, which represent diastolic filling of left ventricle, were significantly lower in hyperhidrotic subjects than in controls. Also, mitral lateral annulus early and late velocities and early/late velocity ratio, reflecting diastolic filling of left ventricle, were significantly lower in hyperhidrotic subjects than those of controls. However, there were no differences between hyperhidrotic subjects and control subjects with regard to the other echocardiographic indices of left and right ventricle diastolic functions. In conclusion, decreased mitral inflow suggests left ventricle diastolic dysfunction in patients with essential hyperhidrosis. This indicates that hyperactivity of sympathetic nervous system in patient with hyperhidrosis may alter cardiac function in long term. ———— essential hyperhidrosis; cardiac function; echocardiography

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Essential hyperhidrosis, characterized by excessive sweating of the eccrine sweat glands, is a frequently encountered dermatologic and neurologic disorder (Sato et al. 1989). The pathophysiology of this condition is unknown but it has been attributed to overactivity of the sympathetic fibers that pass through the upper thorasic sympathetic ganglia (Noppen et al. 1996). Sympathetic fibers to eccrine glands of palms of the hand arise from stellate and upper thoracic ganglia which also innervate lung, heart, and blood vessels of the upper limb (Firestone 1989; Kingma et al. 2002). Therefore, it has been speculated that essential hyperhidrosis is not only a local disturbance but also results from general dysfunction of the autonomic nervous system, involving cardiaovascular system. Previous studies have shown that cardiac autonomic autonomic function is altered in patients with hyperhidrosis compared to healthy subjects (Shih et al. 1983; Noppen et al. 1995). It has also been shown that left ventricular stimulation increases left ventricular ejection fraction in patients with essential hyperhidrosis (Wong and Wong 1999). However, echocardiographic findings of patients with essential hyperhidrosis have not been studied yet. Therefore, in this study we investigated cardiac functions in patients with essential hyperhidrosis by conventional and tissue Doppler imaging.

Methods

Subjects

Eighteen subjects with palmar, axillary hyperhidrosis or both were included in this study. As a control group, sex-age matched, eighteen healthy subjects were investigated. Diagnosis of essential hyperhidrosis was established by ninhydrin sweat test on the hyperhidrotic regions (Moberg 1959). Exclusion criteria were as follows: known coronary artery disease, peripheral vascular disease, diabetes mellitus, congestive heart failure, valvular heart disease, cardiomyopathy, left ventricular hypertrophy, vasculitis, pulmonary, renal, and hematological disorders, history of smoking and those on medications known to affect cardiac function.

Echocardiographic parameters

All participants were asked to refrain from alcohol and caffeine-containing beverages for 24 hours prior to study. Then, all participants underwent a complete transthoracic echocardiographic examination (two-dimensional, pulse wave Doppler recording of the transmitral, transtricuspid, and recordings of the mitral and tricuspid annular velocity by tissue Doppler imaging, respectively) by using 3.5 MHz sector transducer (A Hawlet-Packard Sonos 5500, Andover, MA, USA). Two-dimensional and pulsed wave Doppler echocardiograhic studies were performed in the left lateral decubitus position with the conventional views (parasternal long and short axis, apical four chamber). An electrocardiogram was recorded simultaneously with the M-mode and Doppler tracings in the same monitor. Diastolic left ventricular septal thickness, diastolic posterior wall thickness, and left ventricular end-diastolic and end–systolic dimensions were measured in the parasternal long-axis view. Righ atrium dimension was determined in the four-chamber view by the maximal medial to lateral dimension at end-ventricular systole.

Mitral inflow velocity was recorded from the apical four-chamber view by pulsed-wave Doppler sample during diastole. Peak early (E_M) and late (A_M) mitral inflow velocity, E_M/A_M ratio, and deceleration time of E_M were obtained. Similarly, tricuspid inflow velocity was recorded from the apical four-chamber view by pulsed-wave Doppler sample during diastole. Peak early (E_T) and late (A_T) tricuspid inflow velocity, E_T/A_T ratio and deceleration time of E_T were obtained. Left ventricle ejection time (LVET) was measured from the onset to the end of left ventricle outflow. Right ventricle ejection time (RVET) was also measured from the onset to the end of right ventricle outflow.

Isovolumetric relaxation time of left ventricle ($IVRT_L$) was obtained as the time interval from the cessation of left ventricle outflow to the onset of mitral valve inflow. Isovolumetric contraction time of left ventricle (ICT_L) was determined from the cessation of mitral inflow to the onset of left ventricle outflow. Myocardial performance index of left ventricle (MPI_L) was calculated by the formula (ICT_L + isovolumetric relaxation time of left ventricle [IRT_L])/LVET (Polusen et al. 2000). Also, isovolumetric relaxation time of right ventricle ($IVRT_R$) was obtained as the time interval from the cessation of right ventricle outflow to the onset of tricuspid valve inflow. Isovolumetric contaction time (ICT_R) was determined from the cessation of tricuspid inflow to the onset of right ventricle outflow. Myocardial performance index (MPI_R) was calculated by the formula (ICT_R + iso-

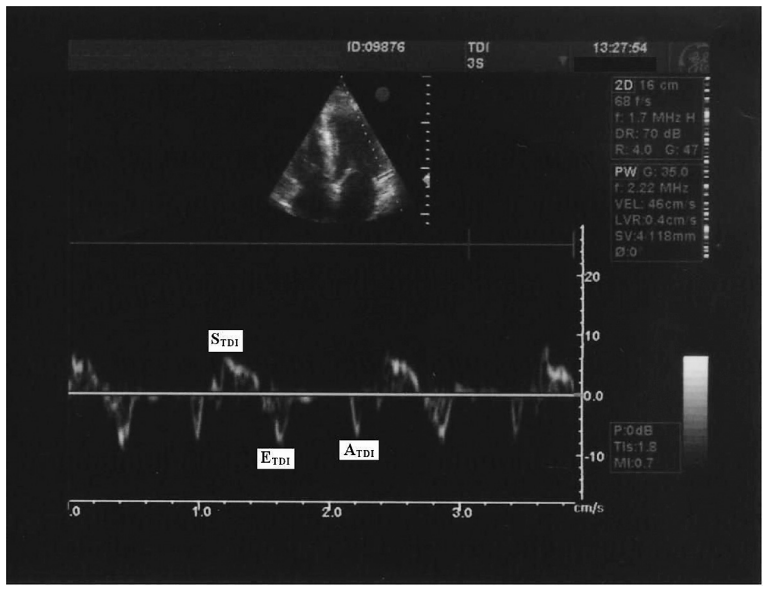

Fig. 1. Measurement of tissue Doppler paramaters recorded in a patient with essential hypehidrosis. S_{TDI}, systolic velocity; E_{TDI}, early diastolic velocity; A_{TDI}, Late diastolic velocity.

volumetric relaxation time of right ventricle [IRT_R])/ RVET (Polusen et al. 2000). Tissue Doppler imaging was applied in the pulsed-Dopler mode of the mitral and tricuspid annulus velocity at their lateral corners with the same echocardiographic unit, and systolic (S_{TDI}), early diastolic (E_{TDI}), and late diastolic (A_{TDI}) velocity and E_{TDI}/A_{TDI} ratio was measured (Fig. 1). The same investigator performed all echocardiograms. The echocardiographic measurements were repeated to assess interobserver variablity in ten subjects by the same investigator. All measurements were averaged over three cardiac cycles.

Statistical analysis

Statistical analysis was performed with SPSS for Windows version 10.0 (SPSS Inc., Chicago, IL, USA). Data are presented as mean ± S.D. For continuous variables Mann-Whitney's U-test and for categorical changes chi-square test was used. A p value < 0.05 was considered to indicate statistical significance.

Results

Demographic properties of study subjects

Clinical characteristics of hyperhidrotic subjects and control subjects are given in Table 1. There was no significant difference between the two groups in demographics of age, sex, heart rate, blood pressure, left-right ventricular diamters, left-right atrial diamters, ejection fraction, fractional shortening and aortic root diamter.

Electrocardiographic findings

All subjects had sinus rhythm. However, some ECG abnormalities were detected, including ST segment depression (2 patients with hyperhidrosis and 1 control subject), T wave inversion (4 patients with hyperhidrosis and 2 control subjects), abnormal Q wave in inferor derivations (1 patient with hyperhidrosis). In additon, corrected QT (QTc) interval duration had significantly increased in patients with essential hyperhidrosis than in controls (403 ± 25 vs 378 ± 14 ms, p = 0.003). These ECG abnormalities are summarized in Table 1.

Echocardiographic findings

On echocardiographic examination no valvular disorders, left ventricular hypertrophy, wall motion abnormalities and clinically significant valvular regurgitation were detected in study subjects. E_M velocity and the E_M/A_M ratio were significantly lower in hyperhidrotic subjects than in controls. However, the other pulsed-Doppler indices of left ventricle diastolic function including A_M velocity, deceleration time, isovolumetric

TABLE 1. *General characteristics of study subjects*

Variable	Hyperhidrotic patients	Control subjects	*p* values
Age, years	26 ± 6	28 ± 7	NS
Gender, male/female	7 / 11	9 / 9	NS
BMI, kg/m^2	24 ± 5	25 ± 4	NS
mSBP, mmHg	120 ± 8	119 ± 9	NS
mDBP, mmHg	69 ± 8	71 ± 8	NS
mHR, beat/min	77 ± 7	75 ± 6	NS
ST depression	2	1	NS
T wave inversion	4	2	NS
Abnormal Q wave	1	-	
QTc interval, ms	403 ± 25	378 ± 14	$p = 0.003$
LVDd, mm	44.8 ± 4.0	4.6 ± 3.7	NS
LVDs, mm	28.1 ± 2.8	26.9 ± 3.0	NS
LVPWDd, mm	7.8 ± 1.6	8.5 ± 1.2	NS
IVSd, mm	8.0 ± 1.6	8.8 ± 1.4	NS
EF %	68 ± 4	69 ± 3	NS
FS %	37 ± 3	37 ± 3	NS
LA, mm	29.0 ± 3.9	3.0 ± 2.6	NS
AO, mm	26.5 ± 1.4	27.5 ± 1.4	NS
RA, mm	31.1 ± 1.8	29.8 ± 1.9	NS

NS, statistically not significant; BMI, body mass index; mSBP, mean systolic blood pressure; mDBP, mean diastolic blood pressure; mHR, mean heart rate; QTc interval, corrected QT interval duration; LVDd, left ventricle diastolic diameter; LVDs, left ventricle systolic diameter; LVPWDd, left ventricle posterior wall distolic diameter; IVSd, Interventricular septum diastolic diameter; EF, ejection fraction; FS, fractional shortening; LA, left atrial diameter; AO, aortic root diameter; RA, right atrium diameter.

TABLE 2. *Pulsed-Doppler indices of left ventricle in patients with hyperhidrosis and controls*

Variable	Hyperhidrotic patients	Control subjects	*p* values
E_M (cm/s)	65 ± 16	84 ± 19	0.02
A_M (cm/s)	53 ± 9	54 ± 14	NS
E_M/A_M ratio	1.2 ± 0.3	1.6 ± 0.3	0.031
Deceleration time of E_M(ms)	180 ± 18	158 ± 46	NS
Isovolumetric relaxation time (ms)	76 ± 12	75 ± 10	NS
Isovolumetric contraction time (ms)	44 ± 7	42 ± 5	NS
Ejection time (ms)	325 ± 37	312 ± 67	NS
Myocardial performance index	0.34 ± 0.04	0.39 ± 0.08	NS

E_M, early velocity; A_M, late velocity.

TABLE 3. *Pulsed-Doppler indices of right ventricle in patients with hyperhidrosis and controls*

Variable	Hyperhidrotic patients	Control subjects	*p* values
E_T (cm/s)	63 ± 10	62 ± 9	NS
A_T (cm/s)	49 ± 12	47 ± 11	NS
E_T/A_T ratio	1.3 ± 0.2	1.4 ± 0.2	NS
Deceleration time of E_T (ms)	160 ± 27	164 ± 44	NS
Isovolumetric relaxation time (ms)	74 ± 9	68 ± 8	NS
Isovolumetric contraction time (ms)	42 ± 5	40 ± 4	NS
Ejection time (ms)	325 ± 50	322 ± 81	NS
Myocardial performance index	0.36 ± 0.07	0.35 ± 0.1	NS

E_T, early tricuspid inflow velocity; A_T, late tricuspid inflow velocity.

TABLE 4. *Tissue Dopper paramaters in patients with hyperhidrosis and controls*

Variable	Hyperhidrotic patients	Control subjects	*p* values
Mitral			
Systolic velocity (cm/s)	14.3 ± 3.2	12.3 ± 2.8	NS
Early diastolic velocity (cm/s)	15.2 ± 3.1	18.3 ± 4.1	NS
Late diastolic velocity (cm/s)	12.3 ± 1.9	11.1 ± 3.0	NS
E_{TDI}/A_{TDI} ratio	1.3 ± 0.3	1.7 ± 0.5	0.008
Tricuspid			
Systolic velocity (cm/s)	13.7 ± 2.6	15.6 ± 4.3	NS
Early diastolic velocity (cm/s)	15.1 ± 3.9	17.5 ± 3.5	NS
Late diastolic velocity (cm/s)	11.1 ± 3.0	11.7 ± 3.4	NS
E_{TDI}/A_{TDI} ratio	1.5 ± 0.7	1.6 ± 0.5	NS

relaxation time, isovolumetric contraction time, ejection time and myocardial performance index were similar in hyperhidrotic subjects and controls (Table 2).

Among the pulsed-Doppler indices of right ventricle, we observed no significant difference in the peak E_T and A_T velocity, E_T/A_T ratio, and decelaration time of E_T (Table 3). Also, there were no differences in the echocardiographic indices of right ventricle performance between hyperhidrotic subjects and controls (Table 3). Measurement of tissue Doppler parameters in a hyperhidrotic subject is shown in Fig. 1.

Early diastolic and late diastolic velocity at the lateral corner of mitral annulus measured by tissue Doppler imaging were found to be similar in both groups (Table 4). However, E_{TDI}/A_{TDI} ratio of mitral lateral annulus was significantly lower in hyperhidrotic group than in control groups. In addition, systolic, early diastolic, late diastolic velocity and E_{TDI}/A_{TDI} ratio at the lateral corner of tricuspid annulus measured by tissue Doppler imaging were similar in hyperhidrotic group and control group (Table 4).

DISCUSSION

Excessive sweating or essential hyperhidrosis is a well-recognized dermatologic and neurological disorder. The etiology of this disturbance is unknown but it has been associated with an increased activity of the sympathetic nervous system (Shih et al. 1983; Noppen et al. 1995). Beta-blockers have also been proposed to reduce sweating in these patients (Mack et al. 1986). Blood pressure response to cold test and handgrip in essential hyperhidrosis were lowered by

sympathicolysis (Noppen et al. 1995, 1997). Transection of the sympathetic trunk between the first and second thoracic sympathetic ganglia, with diathermy coagulation of the lower end of the divided trunk, produces long-lasting ipsilateral sympathetic denervation of the upper limb, resulting in inhibition of eccrine sweat gland activity and an increase in forearm blood flow in 95% of the patients with essential hyperhidrosis (Fox et al. 1999). It has also been shown that left ventricular stimulation increases left ventricular ejection fraction and prolongs QT interval significantly, and that left stellate stimulation accelaretes heart rate and elevates heart rate and systolic blood pressure in patients with essential hyperhidrosis (Wong et al. 1999). The T_2 and T_4 ganglia are also in the direct pathway of sympathetic innervation of the heart (Firestone 1989; Kingma et al. 2002). Therefore, we have speculated that overactivity of sympathetic nervous system in patients with essential hypehidrosis enhance the catecholamine spill-over into the heart and thereby may affect cardiac functions. To our knowledge our study is the first attempt to investigate echocardiographic findings in patients with essential hypehidrosis.

Conventional echocardiographic Doppler parameters and newly developed tissue Doppler imaging have become well accented practical and safe non-invasive methods for diagnosis of left-right ventricular systolic and diastolic functions in the clinical setting (Nagueh et al. 1997; Galiuto 1998; Alam et al. 1999; Watanabe et al. 2005). Using pulsed wave tissue Doppler imaging, we recorded the systolic mitral annular velocity, which reflects left ventricle function. Recoding of the mitral annular velocity by tissue Doppler imaging is a simple and reproducible procedure (Alam et al. 1999). With this method in the present study, systolic LV function was found to be similar in patients with essential hypehidrosis patients and control subjects. In addition, assessment of left ventricle function by tissue Doppler imaging has been suggested to be a more sensitive method compared with conventional Doppler methods and is independent of filling pressure (Nagueh et al. 1997; Sohn et al. 1997).

In the present study we found a decrease in transmitral early velocity, and a decrease in the ratio between early and late velocity. In a previous study, the ratio between trasmitral early diastolic mitral annulus velocity determined by conventional Doppler echocardiography and early diastolic mitral annular velocity assessed by tissue Doppler imaging has been shown to be a reliable index for left ventricle filling pressure especially in the presence of diastolic dysfunction (Nagueh et al. 1997). We also observed that the early systolic velocity and E/A velocity measured at the lateral corners of mitral annulus by tissue Doppler imaging were different in patients with essential hyperhidrosis compared with controls while systolic and late diastolic velocities were similar. There is no clear explanation for this but these results may be interpreted as a disturbed relaxation of the left ventricle myocardium. Accordingly, it has been suggested that sympathetic overactivity and norepinephrine spillover to the heart may deteriorate cardiac systolic and dastolic functions (Esler and Kaye 2000; Chiu et al. 2005).

Recent demonstration that the level of sympathetic nervous drive to the failing heart in patients with severe heart failure is a major determinant of prognosis, and that mortality in heart failure is reduced by beta-adrenergic blockade, indicate the clinical relevance of heart failure neuroscience research (Esler and Kaye 2000; Chiu et al. 2005). The cardiac sympathetic nerves are preferentially stimulated in severe heart failure, and in untreated patients cardiac norepinephrine spillover is increased as much as 50 folds, similar to the levels of release seen in the healthy heart during near maximal exercise (Esler et al. 2000). This preferential activation of the cardiac sympthetic outflow contributes to arrhythmia development and to progressive deterioration of the myocardium, and has been linked to mortality in both mild and severe cardiac failure. Although mechanisms for myocardial dysfunction are yet to be fully determined, abnormalities in myocardial intracellular Ca^{2+} handling have been observed in many experimental animal models of pressure-overload hypertrophy and in patients with heart failure (Morgan et al. 1990; Schwartz et al. 1993).

Therfore, abnormal intracellular calcium handling, a major cause of systolic and diastolic dysfunction in ventricular myocardium may also be associated with diastolic filling abnormalities in patients with essential hyperhidrosis.

On the other hand, because of complex geometry of the right ventricle and its position beneath the sternum, the echocardiographic assessment of right ventricular function is difficult. The myocardial performance index has been suggested for evaluation of ventricular function. It has been shown to be independent of changes in preload and afterload in the assessment of right ventricular performance. In a previous study, it has been reported that the index is not affected by heart rate, tricuspid regurgitation, right ventricular pressure or right ventricular dilatation (Tei et al. 1996). In the present study, we found that right and left ventricular MPI were also similar in patients with essential hyperhidrosis and controls. We have also found that the velocity measured at the lateral corners of tricuspid annulus by the tissue Doppler imaging were not different in patients with essential hyperhidrosis compared with controls.

The heart is a pump that ejects blood into the vessels by contraction and relaxation of the cardiac muscle. For effective performance, the heart is controlled by the autonomic nervous system and humoral agents. The autonomic nervous system regulates heart rate and cardiac contractile via a dual supply of sympathetic and parasympathetic nerves and, dysregulation of autonomic nervous system causes various cardiac disorders (Ishizuka et al. 1987; Matsuyama et al. 1992). Accordingly, several previous studies have investigated cardiovascular function in patients with essential hyperhidrosis in order to demonstrate putative role of sympathetic hyperactivity (Shih et al. 1983; Noppen et al. 1995; Iwase et al. 1997; Birner et al. 2000; Kingma 2002; Senard et al. 2003). However, controversial results have been reported concerning whether cardiac autonomic functions are altered in this disorder. While some authors (Shih et al. 1983; Noppen et al. 1995; Iwase et al. 1997; Kingma et al. 2002) reported an overfunctioning of sympathetic fibers running through T2-3 as the cause of palmar hyperhidrosis, the others found no evidence of cardiac sympathetic dysfunction, in contrast, observed parasympathetic dysfunction at autonomic stimulation in hyperhidrotic subjects compared to normal subjects (Birner et al. 2000; Senard et al. 2003). Also, Senard et al. (2003) showed that there was no difference with respect to plasma noradrenalin levels between hyperhidrotic and healthy control subjects either in resting or during Head-up tilt test. Noradrenalin plasma levels were also shown to be in the normal range in hyperhidrotic patients and decreased after sympathicolysis (Noppen et al. 1997). In the current study the fact that global ventricular functions are preserved in patients with essential hyperhidrosis.

Conclusion

In the present study we noted that left ventricle inflow and the velocity measured at the lateral corners of mitral annulus by tissue Doppler imaging were different in patients with essential hyperhidrosis compared with controls. Our overall findings suggest that impaired mitral inflow velocities may be early finding of left ventricle diastolic filling abnormality in patients with essential hyperhidrosis. This indicates that hyperactivity of sympathetic nervous system in patient with hyperhidrosis may alter cardiac function in long term.

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