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Does the lower nitric oxide level cause cardiovascular changes in major depressed women?

AYSE ARSLAN[a], METEHAN UZUN[b]

[a]Goverment Hospital of Kars, [b]Department of Physiology, University of Kafkas, Kars, (Turkey)

Abstract. – In the recent years, studies have revealed higher incidence of cardiovascular diseases in patients with major depression (MD). A role of plasma nitric oxide (NO) levels in these diseases has been suggested. Hence, aim of the current study was to determine plasma NO, QT, corrected QT (QTc) and systolic and diastolic blood pressures (SBP-DBP) in healthy women (HW) and in women with MD and to interrelate these values with plasma NO levels.

Thirty MD women (average 32 years old) and 28 HW (average 28-years old) were included in this study. Nitric oxide values were determined from plasma by spectrophotometric method. Blood pressure was measured in the left arm using an auscultation method. QT and QTc values were obtained from electrocardiographic records. For the calculation of QTc values Bazett's formula was applied. MD group had significantly lower plasma NO levels compared to HW (12.7 ± 1.4 vs 21.82 ± 3.5 µM, respectively, $p < 0.05$). Mean SBP and DBP were higher in MD group (120/72 vs 109/65 mmHg; $p \leq 0.001$). In MD patients, QT and QTc intervals were significantly longer compared to the HW ($p < 0.01$ and $p < 0.001$, respectively). There was a significant negative correlation between plasma NO levels and SBP in MD group ($r = -0.50$; $p < 0.01$). There was no relationship between plasma NO levels and QT or QTc intervals.

In conclusion, lower plasma NO levels, longer QT and QTc intervals and higher SBP and DBP values in MD patients suggest (1) that cardiovascular disease risk is higher in these patients and (2) this needs a special attention by the clinicians.

Key Words:

Major depression, QTc, Nitric oxide, Blood pressure, Women.

Introduction

Major depression (MD) is a common psychiatric disorder[1], associated with hypothalamic-pituitary-adrenal (HPA) axis abnormalities[2], and is accepted as a risk factor for cardiovascular disease (CVD)[3].

The biological mechanism of relationship between depression and CVD has been investigated and some conclusions were obtained. Chrapko et al.[4] have found a decrease of both platelet eNOS activity and plasma nitric oxide (NO) levels in MD patients. Decreased NO production by the endothelium and platelets may explain the relationship between MD and CVD.

Nitric oxide is synthesized from L-arginine by a family of isoformic enzymes (eNOS, nNOS and iNOS) known as NO synthase (NOS). Plasma concentration of NO are often used as a marker of vascular NO production[3]. The endothelial isoform of NO (eNOS), one of the most important regulators of autonomic balance, can be regarded as a vasodilatatory force that helps to maintain an equilibrium with vasoconstrictor forces[5].

The QT interval is the electrocardiographical signature of ventricular repolarization time. Variability in the QT interval reflects beat-to-beat fluctuations in myocardial recovery time. The increased variability is a significant predictor of arrhythmic events and sudden cardiac death[6].

It is well known that depression, prevalent in women respect to men[7], is a risk factor for cardiac morbidity and mortality with coronary heart disease, especially after acute myocardial infarction[8].

[#]This study was partly summarized from the M.Sc. thesis of first author.

Corresponding Author: Metehan Uzun, MD; e-mail: metehanuzun@hotmail.com

However, the association between depression and cardiac events in patients who had no cardiac and other systems history was not well documented.

Therefore, the purpose of this study was to determine whether MD is associated with blood pressure, and corrected QT (QTc) values and plasma NO levels in major depressed middle age women without cardiac and other diseases.

Materials and Methods

Study Design and Recruitment of Participants

This study was carried out with total of 58 women. The study population included healthy control (HW) and MD patient groups. Healthy women group consisted of 28 subjects (16 non-smoker and 12 smoker women), aged mean 28 ± 1.1 years. MD group consisted of 30 women (15 non-smoker and 15 smoker), aged mean 32 ± 1.4 years. The HW population, comprised of hospital staff and volunteers, was chosen following these criteria: a) no regular use of prescribed or over-the-counter drugs; b) no history of cardiovascular system diseases, hypertension, diabetes, depression, schizophrenia, bipolar disorder and post-traumatic stress disorders. Women on hormonal therapy for contraception, and in pregnancy and lactation period, were excluded. The women were roughly in the same phase of their menstrual cycle. The smokers were defined as those who had smoked ≥ 10 cigarettes per day for one year. All of the depressed patients had experienced their first depressed episodes by a Physician in Psychiatry, Department of Kars State Hospital. All cases were scored in the Hamilton Depression Rating Scale. The measurements in this group were performed as soon as the patients were diagnosed as MD without any use of antidepressant drugs. All participants gave written informed consent before participation in the enrolment.

Blood Sample Collection and Biochemical Analyses

Blood samples were collected from brachial vein from women in hospital. The concentration of nitrate and nitrite were determined from deproteinised plasma samples using a spectrophotometric method according to Miranda et al[9]. The NOx values were calculated from the plasma total nitrite and nitrate levels.

Blood Pressure and ECG Measurements

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured indirectly from left arm using an auscultation method.

ECG recording was taken from both MD patients and HW control group at paper speed of 25 mm/s. QT interval duration was recorded for 3 consecutive beats through lead II, aVR, V2 and V3. Each QT interval was measured from the beginning of QRS complex to the visual return of the T wave to the isoelectric line. Corrected QT values were calculated using the Bazett's formula of $QTc = QT/(RR)^{1/2}$[1,2,10].

Statistical Analysis

All data was expressed as the mean ± SEM. The MINITAB program was used for statistical analysis (Version 11.2, MINITAB Inc., State College, PA, USA). Student t Test was performed for comparison of QT, QTc, SBP, DBP, RR, plasma nitrate, nitrite and NO levels between the groups. The "Pearson correlation" test was used to find out the correlation between plasma NO and SBP, DBP, QT and QTc values.

Results

The mean ± SEM values RR, QT, QTc, SBP, DBP, plasma nitrate, nitrite and NO in HW and MD groups are given in Table I. There was a statistically significant decrease in plasma NOx values in MD group when compared to the HW ($p < 0.05$). Also, a remarkable statistically significant prolongation of QT and QTc interval were observed in MD group compared to HW ($p < 0.01$ and $p < 0.001$, respectively). The SBP and DBP were higher and statistically significant different among MD group compared to HW group ($p \leq 0.001$).

Figure 1 shows the individual plasma NO levels in HW and MD groups. There was a negative correlation between the plasma NO levels and SBP values in MD group (Figure 2; $p < 0.01$, $r = -0.50$).

Discussion

Our data show that in MD women, plasma NO levels decreased while SBP and DBP increased. Plasma NO values influenced blood pressure. QT and QTc interval significantly prolonged in MD women.

Table I. The mean RR, QT, QTc, DBP, SBP, nitrate, nitrite and nitric oxide levels in healthy and major depressed women.

Parameters	Groups		*p* values
	Healthy (n = 28)	*MD (n = 30)*	
RR (msec)	769 ± 5.2	757 ± 5.9	Ns
QT (msec)	354 ± 1.8	364 ± 2.9	0.006
QTc (msec)	402 ± 1.9	423 ± 5.3	0.000
SBP (mmHg)	109 ± 1.8	120 ± 2.2	0.001
DBP (mmHg)	65 ± 1.3	72 ± 1.4	0.001
Nitrate (μM)	21.7 ± 3.5	12.7 ± 1.4	0.02
Nitrite (μM)	0.07 ± 0.0	0.07 ± 0.0	Ns
Nitric oxide (μM)	21.8 ± 3.5	12.7 ± 1.4	0.02

(Values are mean ± SEM; QTc: QT interval corrected using Bazett's formula, ns: non-significant).

Previously a study involving MD patients of both gender[4] revealed a decrease both in plasma NOx levels and platelet NOS activity: NO level was 14.02 in MD vs 32.37 μmol/L in control subjects. This result was also observed in our research where plasma NO level was 12.7 ± 1.4 in MD vs 21.8 ± 3.5 μmol/L in HW. This finding was also supported by other studies where plasma NO level was lower in MD patients respect to controls[11].

Several mechanisms have been put forward to explain lower plasma NOx level in MD patients. The most likely explanation is the role played by cortisol and Corticotropin Releasing Factor (CRF). This latter plays a central role in the adaptation of the organism after exposure to an acute stress. Furthermore, it acts as a neurotransmitter in several brain regions[12]. Catalan et al. have found an increased level of CRF and cortisol in depressed patients[13]. Elevated plasma cortisol promotes the development of atherosclerosis and accelerates injury of vascular endothelial cells[14] resulting in a decreased endothelial NO production[15]. On the other hand, the administration of glucocorticoids resulted in a decreased eNOS activity and plasma NO levels in cows and rats[16,17]. Therefore, an augmented HPA activity or an increased asymmetrical dimethylarginine (ADMA) activity may explain the observed decreased plasma NO levels. Vallance et al.[18], in fact, observed *in-vitro* and *in-vivo* on inhibition of NO synthesis by an endogenous compound ADMA. In MD patients while the ADMA activity increased plasma NO levels decreased[19]. Serotonin is an important regulatory agent in stress and depression[20]: an increased ADMA activity could inhibit serotonin release through an inhibition of plasma NO diffusion from the endothelial into the neuronic cells[11]. This hypothesis may explain the relationship between plasma NO and the depression.

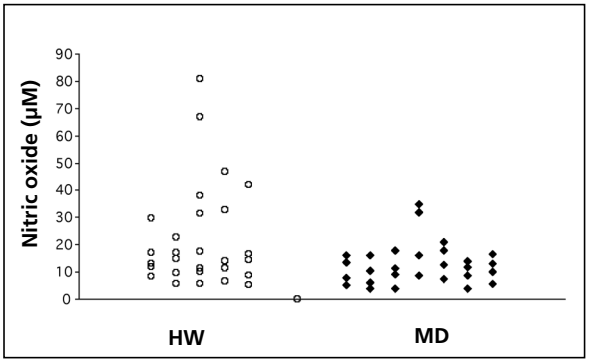

Figure 1. Individual levels of plasma NOx in healty and MD women.

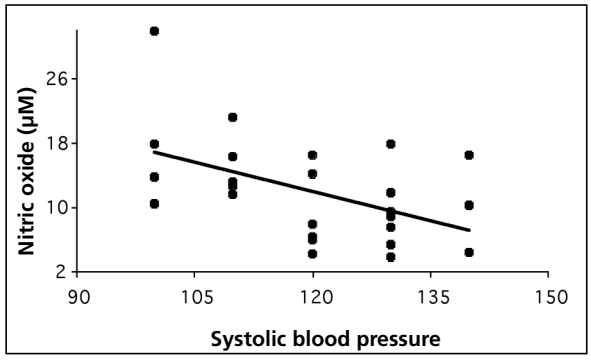

Figure 2. Relationship between plasma NO and systolic blood pressure in MD women (r = -0.50; $p < 0.01$).

In our study MD patients with low plasma NO levels had high SBP and DBP respect to controls. We observed a negative correlation between the plasma NO level and SBP (p <0.01, r = –0.50). Nitric oxide is known as endothelial vasodilatative agent and eNOS activity has remarkable effects on the vascular tone[5]. Costa et al.[21] showed that L-arginine had an hypotensive effect in rats given L-arginine and nitro-L-arginine-methyl ester (L-NAME) while L-NAME increased mean arterial blood pressure[21]. Therefore, the higher levels of blood pressure observed in HW patients respect to CG could be due to decreased NO level.

In our research QT and QTc values statistically significant were prolonged in MD patients. Prolonged QT interval may induce cardiac and arrhythmic death in different patient population[22]. Nahshoni et al.[23] reported a significant prolongation of QT dispersion interval in elderly MD patients when compared to controls. This enlargement was related to an increased sympatic and a decreased parasympatic activation[24]. The autonomic imbalance is a risk factor for cardiac deaths[25]. Decreased parasympatic and increased sympatic activities cause coronary artery disease, myocardial ischemia, ventricular tachycardia and fibrillation which may result in cardiac death[26,27]. The QT prolongation observed in our MD patients may not be the only reason of *torsade de pointes* inducing lethal arrhythmia. It should be underlined that the antidepressant therapy *per sé* prolongs the QT interval[28].

In conclusion, plasma NO levels were significantly low in MD patients. QT and QTc intervals were significantly prolonged compared to healthy subjects. Although QT and QTc interval values of our two groups were within the reference range, MD women have an higher risk of cardiac death due to ventricular arrhythmia. A negative correlation between plasma NO and SBP has been observed. The increased blood pressure must be regarded as another risk factor.

Finally, all factors which influence blood pressure in MD patients should be needed further investigation.

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