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Menopause and Cardiovascular Function : Importance of New Noninvasive Techniques

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OBJECTIVES – To review the literature relating menopause causing increased cardiovascular mortality and cardiac autonomic dysfunction and to study the possible beneficial and unwanted effects of hormone replacement therapy. **METHODS** – A critical review was made of the utility of newer noninvasive techniques such as beat-to-beat blood pressure variability and QT interval variability in addition to heart rate variability in understanding cardiovascular autonomic function. **RESULTS** – Majority of the studies suggest a decrease in cardiac vagal function and an increase in sympathetic function after menopause, which could result in serious cardiac disease. Hormone replacement therapy, once widely used is not popular any more due to serious side effects including uterine cancer and thromboembolic phenomena leading to cardiovascular mortality. **CONCLUSION** – Use of some new drugs having beneficial effects from cardiovascular point of view is suggested for the treatment of menopausal symptoms.

Key words : menopause, cardiovascular mortality, autonomic dysfunction, QT interval, heart rate, blood pressure

Introduction

Menopause, a natural event that occurs in the life cycle of women marks the transition from the reproductive phase to the nonreproductive phase. Menopause indicates the occurrence of the last menstrual period. The average age of menopause is 51 years. There is going to be a substantial increase in the number of post-menopausal women in future as life expectancy has been increasing. After menopause, there is a significant decrease of estrogens, which results in degenerative changes in the female reproductive tract. Gonadotropin levels increase because of the lack of positive feedback resulting from the diminished ovarian production of estradiol. Hot flushes occur in 60 to 90% of women after menopause. Other symptoms include sleep disturbances, depression, irritability and anxiety. In this article, we review the cardiovascular function in post-menopausal women and the importance of some of the newer noninvasive measures to evaluate the risk of increased cardiovascular mortality in this population and suggest directions for future research.

ardiovascular mortality

Post-menopausal women have higher rates of coronary heart disease than premenopausal women[1]. The protective effects of estrogens probably are due to their effect on lipid metabolism. Another contributor to the development of coronary heart disease is the large cardiovascular response to mental stress. Owens et al[2] found that menopause is associated with enhanced stress-induced cardiovascular responses and elevated ambulatory blood pressure (BP) during the work day, which may contribute to the risk of cardiovascular morbidity after menopause.

Hot flushes

Though the mechanism of hot flushes is not well understood, Freedman et al[3] reported that administration of yohimbine was associated with induction of hot flushes and clonidine had the opposite effect. These findings suggest a central alpha-2 adrenergic mechanism and sympathetic hyperactivity in the initiation of hot flushes.

Heart rate variability

Heart rate (HR) or the inter-beat interval (R-R interval) changes every beat and the time series appear intrinsically chaotic. Spectral analysis of HR variability using Fourier Transorm, usually reveals a peak between 0.040-0.14 Hz (low frequency: LF), and 0.15 – 0.5 Hz (high frequency : HF). In normal controls, orthostatic stress is accompanied by a marked increase of the relative spectral energy in the LF band, and a significant decrease in the HF component[4,5]. Available evidence suggests that the HF power in both postures is modulated by the cholinergic system and the LF power is influenced both by cholinergic and adrenergic systems. Decreased HR variability is a strong

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independent predictor of cardiovascular mortality[6]. Several studies have used the ratios of LF/HF powers to study cardiac sympathovagal interaction, as there is a significant increase of relative LF power and a decrease of HF power during standing posture[4]. An increase in this ratio suggests a relative sympathetic predominance, which may be deleterious in certain cardiac conditions

Beat-to-beat QT interval variability

QT interval on the surface electrocardiogram (ECG) reflects time for repolarization. The usual duration of QT interval corrected for HR is above 400 milliseconds and is dependent upon HR to some extent. Thus, it is customary to correct QT interval for HR (QTc) in clinical situations. Prolongation of QTc may be more dangerous in the setting of a higher HR. QT interval can be prolonged in several different conditions including congenital long QT syndrome. This condition can be associated with serious cardiac arrhythmias including torsades de pointes. Several studies have shown a relationship between prolonged QTc and life-threatening arrhythmias[7]. Recent literature also implicated abnormal repolarization in serious cardiac arrhythmias[8,9].

An increase in QT variability is reportedly associated with symptomatic patients with cardiomyopathy and also sudden cardiac death[10,11]. We recently found that patients with panic disorder and depression have significantly increased QT variability, compared to normal controls[12]. This is especially important due to the fact that an increase in cardiac sympathetic activity is associated with an increased Qtvi (a common log ratio of QT interval variability corrected for mean QT squared divided by HR variability corrected for mean HR squared)[13].

Blood pressure variability

Heart rate and blood pressure (BP) variabilities also appear to be closely coupled together and the beat to beat variation in systolic BP appears to be concentrated in the LF and HF regions as described above. Blood pressure waves around 0.1 Hz are referred to as Mayer waves, which occur at a frequency slower than that of respiration and these produce large amplitude fluctuations in arterial BP around O.1 Hz[4,5]. Previous reports suggest that these waves can be suppressed by the intake of clonidine and may be elicited by yohimbine[5], thus reflecting sympathetic activity. An increase in BP variability is usually associated with increased sympathetic activity and results in end organ damage[14].

New nonlinear techniques

The beat-to-beat HR, QT and BP series are intrinsically chaotic and nonlinear, and thus the newer measures including the computation of fractal dimensions, approximate entropy, measures of Chaos and quantification of nonlinearity appear to be very promising and sensitive tools to study cardiac autonomic function[15-17]. These measures give additional information to the traditional time and frequency domain ones.

Risk for cardiovascular morbidity and autonomic function

A decrease in cardiac parasympathetic tone and an increase in sympathetic tone of cardiovascular neural regulatory mechanisms have been reported after acute myocardial infarction, heart failure, cardiac arrhythmias and in patients who are prone to sudden death[18]. Reduced cardiac vagal function in patients with coronary artery disease and following acute myocardial infarction is a significant predictor of cardiac morbidity. Thus, while an increase in HR variability is generally cardio-protective, an increase in QT interval or BP variability is associated with serious arrhythmias or end organ damage.

Hormone replacement therapy (HRT)

HRT has been in use for several years and several reports suggested the beneficial effects on hot flushes, mood swings and protection against cardio-cerebrovascular events. However, recent studies have shown that there is a considerable risk associated with HRT[19]. Though HRT is associated with an increase in cardiac vagal activity and a decrease in peripheral vascular resistance[20], it can cause prolongation of QT interval and/or QT dispersion and ventricular repolarization[21,22]. However, the evidence is controversial[23]. To our knowledge, there are no reports on the effects of HRT on beat-to-beat QT interval variability in post-menopausal women on HRT.

New treatments for menopausal symptoms

Some of the antidepressants such as paroxetine, a serotonergic reuptake inhibitor (SRI) appears to be a promising new agent to treat hot flushes[24]. This is interesting and important finding as we have recently shown that sertraline, another SRI antidepressant which is commonly used to treat anxiety and depression produces a significant decrease of Qtvi[24].

Conclusion

There is a need for systematic studies in menopausal women to investigate cardiac function using noninvasive techniques such as beat-to-beat QT interval and BP variability, especially before and after treatment with some of the newer drugs such as SRIs for hot

flushes and menopausal depression. This should include linear as well as nonlinear technique as some of the newer measures appear to be valuable additions. Beta-blockers may be of additional value in a select group of patients because of the cardio-protective nature of these agents.

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