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Review

Cardiovascular autonomic dysfunction in women with polycystic ovary syndrome: a systematic review and meta-analysis

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KEY MESSAGE

We performed a meta-analysis on cardiovascular autonomic dysfunction in women with polycystic ovary syndrome (PCOS), based on eight studies, with 243 women with PCOS and 211 healthy women. We found that women with PCOS showed cardiovascular autonomic dysfunction, with reduced total and parasympathetic cardiac modulation, and increased sympathetic activity.

A B S T R A C T

Recent studies reveal that polycystic ovary syndrome (PCOS) might be associated with cardiovascular autonomic dysfunction, but with inconsistent results. The aim of this meta-analysis was to study whether women with PCOS have cardiovascular autonomic dysfunction. PubMed, Web of Science, Cochrane Library and SCOPUS were searched for studies comparing cardiovascular function between women with PCOS and controls. A random-effects model was used to evaluate cardiac autonomic modulation and muscle sympathetic nerve activity (MSNA) between women with PCOS and controls. Eight studies were included, including 243 PCOS and 211 controls. Overall, women with PCOS had significantly lower standard deviation of normal-to-normal RR intervals (SDNN) and percentage of the number of interval differences of successive normal-to-normal RR intervals greater than 50 ms among the total number of RR intervals (pNN50), higher MSNA frequency and higher MSNA incidence than controls. Therefore, this meta-analysis provides evidence that women with PCOS might show cardiovascular autonomic dysfunction, with reduced total and parasympathetic cardiac modulation, and increased sympathetic activity.

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age (Conway et al., 2014), with a prevalence ranging from 5 to 10% worldwide, depending on different study populations and diagnostic criteria (Diamanti-Kandarakis et al., 1999; Ehrmann, 2005; Li et al., 2013; Norman et al., 2007). Although the classic form of PCOS is characterized by hyperandrogenism and chronic anovulation, the clinical manifestations of PCOS are

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heterogeneous (Ehrmann, 2005), according to the presence and severity of hyperandrogenism, menstrual irregularities and infertility (Norman et al., 2007). It is also an important metabolic disorder, often accompanied by many cardiovascular risk factors, such as obesity, dyslipidaemia, insulin resistance, impaired glucose tolerance and hypertension (Moran et al., 2010). Recent studies reveal that these cardiovascular risk factors are also associated with cardiovascular autonomic dysfunction with a compromised modulation of heart rate and blood pressure (Lambert et al., 2010; Thayer et al., 2010). Normally, the cardiovascular autonomic nervous system modulates heart rate and peripheral vascular tones continuously, to maintain a homeostasis of the cardiovascular system (Guyenet, 2006; Palma and Benarroch, 2014). The resting heart rate is modulated by both parasympathetic and sympathetic cardiac branches (Lahiri et al., 2008), while the regulation of blood pressure is largely dependent on the sympathetic nervous system (Guyenet, 2006).

Emerging studies have shown that women with PCOS have cardiovascular autonomic dysfunction, manifesting as increased sympathetic nerve activity (Lambert et al., 2015; Sverrisdottir et al., 2008), and decreased parasympathetic and overall cardiac modulation (Hashim et al., 2015; Saranya et al., 2014; Tekin et al., 2008; Yildirir et al., 2006). Yet there are discrepancies in the reported data. Lambert et al. (2015) found no difference in heart rate variability between women with PCOS and controls. Özkececi et al. (2016) also found no alteration in cardiac autonomic functions in women with PCOS compared with controls.

A meta-analysis pools data from different studies into a greater single-estimate measure of effect. To our knowledge, there has been no meta-analysis to date on cardiovascular autonomic function in patients with PCOS. In this study, we therefore conducted a meta-analysis to assess the cardiovascular autonomic function in patients with PCOS. The primary objective was to compare the cardiovascular autonomic parameters between women with PCOS and women in the control group.

Methods

Search strategy

The meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009) and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000). We searched the peer-reviewed articles in PubMed/Medline, Web of Science, Cochrane Library and SCOPUS (last search updated in September 2016) using the following syntax: ('polycystic ovary syndrome' OR 'PCOS') and ('heart rate variability' OR 'HRV' OR 'autonomic' OR 'sympathovagal' OR 'sympathetic' OR 'vagal' OR 'parasympathetic').

Study selection

After removing duplicates, studies were included if they met the following criteria: (i) diagnosis of PCOS according to the Rotterdam consensus statement (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004); (ii) the study reported mean and standard deviation (SD) of at least one cardiovascular autonomic parameter or provided other surrogate data to calculate these values (e.g. standard error of mean, median value and interquartile range, etc.); (iii) the study reported data in both PCOS patients and control participants; and (iv) the study was written in English.

Data extraction

We extracted first author, publication year, sample size, age and cardiovascular autonomic parameters from the included studies. The cardiovascular autonomic parameters included: (i) biosignals: heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP); (ii) time-domain parameters of heart rate variability (HRV): standard deviation of normal-to-normal RR intervals (SDNN, RR interval indicates interval between two consecutive R waves of the electrocardiogram), square root of mean squared differences of successive normal-to-normal RR intervals (RMSSD), and percentage of the number of interval differences of successive normal-to-normal RR intervals greater than 50 ms among the total number of RR intervals (pNN50); (iii) frequency-domain parameters of HRV: low frequency (LF) powers, normalized units of LF (LFnu) powers, high frequency (HF) powers, normalized units of HF (HFnu) powers, total powers, LF/HF ratio; (iv) muscle sympathetic nerve activity (MSNA): MSNA frequency (number of integrated bursts per minute), MSNA incidence (bursts per 100 heartbeats).

SDNN and total powers reflect overall cardiac autonomic modulation; RMSSD and pNN50 are considered to be indices of cardiovagal modulation (Lahiri et al., 2008; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). LF powers mainly reflect the sympathetic cardiac modulation but also reflect cardiovagal modulation to an unknown extent, and the HF powers reflect cardiovagal modulation only (Lahiri et al., 2008; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). LFnu powers and HFnu powers reflect sympathetic cardiac modulation and cardiovagal modulation, respectively (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996), and LF/HF ratio is considered to be an index of sympathovagal balance (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). MSNA directly measures the sympathetic outflow to peripheral arteries (White et al., 2015).

We also extracted the anthropometric parameters, including body mass index (BMI) and waist/hip ratio (WHR), and metabolic parameters, including fasting plasma glucose (FPG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c) and triglyceride (TG), as well as total testosterone (TTE).

Statistical analysis

The meta-analysis was based on a single effect size of standardized mean differences (SMDs). Values were transformed from available statistics (e.g. means and SDs) to SMD, i.e. Hedges' *g*. A random-effects model was used in this meta-analysis, as it is a more conservative model that more reliably assumes true effect size in heterogeneous studies and provides more generalizable results in comparison with the fixed-effects model (Hedges and Olkin, 1985). The heterogeneity was evaluated by the I^2 statistic. I^2 values of 25%, 50% and 75% were considered to imply small, moderate and high levels of heterogeneity, respectively (Higgins et al., 2003). Publication

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