Impact of endo- and exogenous estrogens on heart rate variability in women: a review

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ABSTRACT
Measurement of heart rate variability (HRV) is an established method to assess the activity of the autonomic nervous system. The aim of this review was to examine the link between HRV, reproductive life stages and menopausal hormone therapy. A literature review was performed using the Medline database. Based on title and abstract, 45 studies were extracted out of 261 citations screened. Due to different study designs and evaluation methods, HRV indices were not directly comparable. Qualitative comparisons in between the vast majority of studies, however, demonstrated a decrease of the vagal dominance on the heart from the follicular to the luteal cycle phase, although some studies asserted no change. The intake of oral contraceptives appeared not to alter the vagal modulation of the heart. All investigations agreed on a decline of HRV towards higher sympathetic control after menopause. Different menopausal hormone therapy approaches showed a supporting impact of estrogen on HRV in most studies. A combined therapy of estrogen and progestogens revoked this benefit. Further research is needed to demonstrate how this process might be attenuated by different menopausal hormone therapies.

Introduction
Cardiovascular disease (CVD) is the leading cause of death in women and increases exponentially with aging. In particular, postmenopausal women with hot flushes seem to have an increased risk of CVD events compared to asymptomatic women. The main reason for initiating menopausal hormone therapy (MHT) is vasomotor symptom control. Considerable evidence suggests that estrogen contributes to delaying the onset of atherosclerotic coronary heart disease (CHD) events in postmenopausal women, especially if MHT was initiated close to menopause. This phenomenon is referred to as the timing hypothesis. Estrogen receptor-mediated vasodilatation and inhibition of inflammatory processes are thought to be the main mechanisms that slow down the progression of coronary artery atherosclerosis. The activity of the autonomic nervous system (ANS), however, may also contribute to CHD pathogenesis. A surrogate marker for ANS activity is heart rate variability (HRV), the recording of in-between heartbeat variations that are modulated by parasympathetic and sympathetic inputs. The aim of this review was to examine the link between HRV, reproductive life stages and MHT.

Heart rate variability
The cardiac sinuatrial (SA) node generates an intrinsic, autonomic and constant heartbeat, responsible for the sinus rhythm. However, it can be modulated and adjusted to internal and external stimuli, mainly by the ANS, resulting in beat-to-beat changes. The respiratory sinus arrhythmia assumes a crucial role in this mechanism. These fluctuations are called HRV. The sympathetic and parasympathetic parts of the ANS regulate the electrical and contractile activity of the myocardium. The resulting HRV stand as a surrogate marker for the ANS. Importantly, parasympathetic changes affect the heart rate faster than sympathetic effects, which appears to be the result of receptor processes and postsynaptic responses. HRV assessment requires a normal sinus rhythm and reasonable signal quality. There are two ways to measure HRV. First, HRV can be assessed under controlled laboratory conditions with short-term measurements using drugs, controlled ventilation, before and after tilt or other maneuvers selected to challenge the ANS. Second, HRV can also be assessed from 24-h electrocardiographic (ECG) recordings made while subjects perform their usual daily activities. HRV quantification can be categorized as a ‘time domain method’ or ‘spectral or frequency domain method’, as well as geometric and non-linear measures of intervals between QRS complexes. HRV quantification can be categorized as a ‘time domain method’ or ‘spectral or frequency domain method’, as well as geometric and non-linear measures of intervals between QRS complexes. The ‘time domain method’ detects all intervals between QRS complexes resulting from SA depolarization (NN intervals). A variety of statistical variables can be calculated from the intervals directly, and others are derived from the differences between the NN intervals (Table 1).
Table 1. Time domain measures of heart rate variability calculated over 24 h

| Time domain measures | Description |
|---------------------|-------------|
| SDNN (ms)           | Standard deviation of all normal-to-normal (NN) intervals; reflects all the cyclic components responsible for variability in the period of recording |
| SDANN (ms)          | Standard deviation of the average of NN intervals in all 5-min segments of the entire recording |
| SDNN index (ms)     | Mean of the standard deviations of all NN intervals for all 5-min segments of the entire recording |
| rMSSD               | Square root of the mean of the squares of successive NN interval differences |
| NN50                | The absolute number of NN intervals differing by >50 ms from the preceding interval |
| pNN50               | The percentage of NN intervals >50 ms different from the preceding interval |

for ANS function evaluation with a reduction in HRV having been reported in various cardiac and non-cardiac disorders.

In cardiology, for example, HRV is used as a predictor for arrhythmias and sudden cardiac death in patients after myocardial infarction, as an increased sympathetic tone would increase the risk by cardiac electrical instability. Furthermore, reduced HRV has been found to predict overall mortality in the general population.

Methods

Inclusion criteria

The studies chosen had to be published between the years 1997 and 2015. The year 1997 was chosen because in 1996 the guidebook Task Force Of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology was published that set the standards for measurement, physiological interpretation and clinical use of HRV. Furthermore, studies were only included if the full text was available in English. Only healthy participants were included, excluding participants with hypertension, heart rhythm disorders, liver or kidney disease, diabetes, carcinomas, cerebrovascular disease, and severe osteoporosis, respectively. Participants with premenstrual syndrome (PMS) or premenstrual dysphoric disorders (PMDD) and climacteric symptoms, however, were included. Studies investigating changes of HRV across the menstrual cycle had to measure at least one ECG during the follicular and one during the luteal phase.

Search strategy

A literature search was done using the Medline database. We combined the MeSH term “heart rate variability” with “menopause”, “hormone replacement therapy”, “estrogen” and “menstrual cycle”, always using the logical connection AND. The term “hormone replacement therapy” was chosen since the new term “menopause hormone therapy (MHT)” has been introduced only recently. A total of 48 studies were included out of 281 hits (Table 3). There was a certain overlap of studies after each search with a new MeSH term combination. Those were not listed again.

Results

Impact of endogenous estrogens on HRV

HRV across the menstrual cycle

During the reproductive life stage, serum steroid hormones fluctuate across the menstrual cycle affecting cardiac electrical stability, as the prevalence of arrhythmias has been shown to be higher during the luteal cycle phase.
In total, 15 studies were found investigating the impact of the different menstrual cycle phases on HRV indices\(^{20–34}\) (see Supplemental Table S1: http://dx.doi.org/10.3109/13697137.2016.1145206). None of the female participants took oral contraceptives. One study compared women in different cycle phases in a cross-sectional study design\(^{20}\). The other studies used a prospective study design, where the participants were examined several times during their menstrual cycle\(^{21–34}\). Sato and Miyake\(^{21}\) included men in comparison with age-matched women. The mean age of the women ranged from 20.2 years\(^{21}\) to 38.5 years\(^{22}\) and the sample size ranged from six\(^{23}\) to 62\(^{24}\) participants.

The time point of the ECG was during the follicular and luteal phases. Most measurements in the follicular phase were performed during cycle days 4–12\(^{20,22,24–29}\), in the luteal phase during cycle days 16–28\(^{20,23,28–30}\), or 3–8 days prior to the next menstruation\(^{21,24–27}\), respectively. Some authors also assessed HRV during menstruation\(^{20,23,30,35}\) or at ovulation\(^{30,32,35}\); these results will not be further discussed.

Similarly, methods for HRV assessment varied. While two investigators used 24-h ECG recordings\(^{20,25}\) or an ECG during the sleep stages\(^{26,33}\), the majority preferred ECG recordings of several minutes\(^{21–24,27–32,34}\).

Due to the different study designs and statistical analysis, absolute values of time and frequency domain HRV indices were not comparable. However, qualitative comparisons in between studies provided a good impression of HRV changes across the menstrual cycle.

Most investigators came to the conclusion that there was a decrease of the vagal dominance on the heart from the follicular to the luteal phase with higher LF power and LF/HF power ratio toward the luteal phase and HF power decreasing from the follicular to the luteal phase\(^{20–22,25,28–29,32,34}\). One study came to the opposite conclusion\(^{23}\). They found an increase of TP and HF power indices from the follicular to the luteal phase, whereas the LF power component decreased in the luteal phase and therefore increased cardiac vagal control. Finally, two investigators asserted no change across the menstrual cycle\(^{30,31}\).

Furthermore, five studies focused on the changes of the HRV between groups of women with PMS\(^{24,26,27,33}\) or PMDD\(^{22,24}\) in comparison to controls who showed no such symptoms. Three studies\(^{24,26,27}\) described a decrease of cardiac vagal activity in the symptomatic luteal phase of severe PMS, whereas no change in the control group was seen across the whole menstrual cycle. De Zambotti and colleagues\(^{33}\) observed no difference between the HRV indices of women with or without PMS, since both groups showed a decrease of the cardiac vagal activity in the luteal phase. Two studies compared women with PMDD and symptom-free controls and observed either no significant difference\(^{22}\) or decreased HRV indices across the whole cycle\(^{24}\) in these women.

**HRV after menopause**

In comparison to premenopause, HRV indices have not been found to change significantly during perimenopause\(^{46}\). Alterations in HRV, however, emerged 1 year after menopause in MHT non-users and changed little in the following years\(^{36}\). A total of 14 studies focused on the changes of the cardiac vagal activity measured by HRV across the menopausal transition\(^{36–49}\) (see Supplemental Table S1: http://dx.doi.org/10.3109/13697137.2016.1145206). Nine studies were identified that focused on the differences in HRV between pre- and postmenopausal women\(^{36–44}\). There are four additional studies investigating perimenopausal women\(^{45–47}\) or postmenopausal women, respectively, that focused on how HRV was affected by the presence of climacteric symptoms. All but one study\(^{48}\) had a cross-sectional set-up. The mean age of the postmenopausal women ranged from 48.5\(^{39}\) to 64.2\(^{38}\) years and the sample size ranged from 11\(^{35}\) to 930\(^{38}\) participants.

The investigators used different HRV assessments. All but four studies\(^{37,42,45,49}\) chose an ECG of a few minutes. The others used a 24-h ECG\(^{42,49}\) or 8-h ECG during the day\(^{37}\), while one used an ECG during sleep\(^{45}\).

The frequency domain was measured by most\(^{36,38,39,41,45–47}\), frequency and time domain by some\(^{37,40,42,48,49}\), and two measured time domain only\(^{36,43}\).

All investigators comparing the HRV of pre- and postmenopausal women agreed that there was a significant reduction in cardiac vagal activity toward a higher sympathetic control after menopause. This was reflected by a reduced TP, higher LF power, and lower HF power components, respectively, and thus an increased LF/HF power ratio\(^{39,41}\). Similarly, in time domain analysis, lower SDNN and RMSSD indicated a decrease in overall and parasympathetic activity in postmenopausal women\(^{36,43}\). Once the menopause-related HRV decline has been established, HRV seems to remain stable: time since last menstruation has not been shown to have any impact on HRV\(^{36,47}\). Changes in HRV may be caused by both aging and hormonal changes, as aging itself has been found to be associated with a gradual reduction of the overall fluctuation in autonomic input to the heart, and a reduced HRV vagal index, respectively, leading to a sympathetic predominance\(^{39}\).

As menopausal hot flushes have been shown to be associated with an increased CVD risk\(^{2,3}\), one might expect different HRV profiles in symptomatic and asymptomatic postmenopausal women. A total of four studies differentiated between women with and without menopausal symptoms such as hot flushes\(^{45–48}\) and sweating\(^{46}\). The results were conflicting. While two studies did not find any differences between symptomatic and asymptomatic postmenopausal women\(^{47,48}\), one study\(^{46}\) reported a decreased parasympathetic dominance in women with hot flushes. An interesting observation was made, when assessing HRV and polysomnography in undisturbed sleep. A decreased cardiac autonomic vagal activity was seen specifically during hot flushes, supporting the hypothesis that the parasympathetic branch of the autonomic nervous system is involved in the cardiac response to a hot flush\(^{45}\).
HRV in MHT users

After menopause, exogenous hormones are primarily used to alleviate climacteric complaints such as hot flushes. MHT contains estrogen only in hysterectomized women, and estrogen combined with a progestogen in women with an intact uterus. There are various dosages of systemic estrogens available that are mostly applied orally or transdermal. In a total of 24 studies, the impact of MHT on HRV in postmenopausal women has been investigated. Some investigators used up to 24-h ECG recording, respectively, and analyzed by either frequency domain or time and frequency domain. Oral contraceptives contained ethinylestradiol combined with drospirenone or a variety of different progestins, respectively. Both investigators did not find any significant differences in ANS control when comparing HRV between healthy premenopausal women taking oral contraceptives and their controls.

Discussion

The results arbitrated an approximate summary of how HRV changes across a woman’s fertile period and continuing to menopause and postmenopause. The results were separated between women taking estrogens such as in oral contraceptives or MHT, and non-users. The investigators partly had conflicting conclusions on the same issues. These discrepancies will be discussed as well as the strengths and limitations of this review.
In addition, the time points at which HRV was assessed during the menstrual cycle varied enormously. Oral contraceptive use, however, did not seem to have any impact on HRV, although the search criteria produced only two studies.

HRV in women after the menopause
All studies identified agreed on a significant decline of the vagal HRV parameters towards a sympathetic dominance after menopause. This finding was highlighted by the observation that, in surgically menopausal women, there was a significantly decreased cardiac vagal modulation compared to women with hysterectomy but ovarian preservation as soon as 5 weeks after surgery. However, after 3 months of estrogen replacement therapy, their HRV parameters reached pre-surgical levels. Yet, study results on MHT have not always been that clear. Most studies revealed a positive impact of exogenous estrogens on the vagal cardiac activity, while others did not find any HRV changes in response to estrogen therapy. As only one in 21 studies revealed a deleterious effect of estrogen-containing MHT, those results must be considered with skepticism. On the other hand, the benefit observed with estrogens only is not detectable when combining estrogens with progestins. However, the reason why combining a progestin might abolish the beneficial effect of estrogens on the cardiac vagal activity has not been explored.

Discussion of the method
A literature review is a recognized option to give an overview of the large amount of published studies in recent years. The strength of this summary is the detailed research with specific MeSH terms and the subsequently precise analysis of the content of the studies and classification of their results. One drawback is that relevant studies were not found and therefore not included if they were not recorded in the Medline database, not published in English, or outside the specific time period. The study designs differed considerably, which impeded a quantitative comparison of the results, but enabled a content analysis. In addition, only studies investigating healthy women were included. It is therefore not possible to transfer those results to women with diseases such as CVD, hypertension, or neuromuscular diseases, as they alter the autonomic regulation.

Conclusion
We illustrated the link between HRV, reproductive life stages, and exogenous hormone therapy. Menstrual cycle phase is crucial when assessing HRV in fertile women. Cardiac vagal activity decreases from the follicular to the luteal phase. Premenstrual syndrome might have a negative impact on cardiac vagal activity. Oral contraceptives do not seem to alter the vagal modulation of the heart.

As reduced HRV is associated with a higher cardiovascular risk profile, women with hot flushes probably have a higher risk and may specifically benefit from estrogens. Further research is needed to elucidate the differences between estrogens and various estrogen–progestogen combinations on HRV.

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