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REVIEW ARTICLE

Heart rate variability dynamics in women with urinary incontinence: a systematic review

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Abstract

Introduction and hypothesis Sympathetic and parasympathetic pathways of the autonomic nervous system (ANS) regulate the lower urinary tract. The aim of the present study was to synthesize the evidence regarding ANS regulation in women with urinary incontinence (UI) evaluated through heart rate variability (HRV).

Methods This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. Five databases were researched in April 2021 (PubMed, CINHAL, Scopus, Web of Science and Cochrane Library) and included cross-sectional studies in full-length publications in the English language. Studies assessed the HRV during bladder filling (group A) and after voiding (group B). The Joanna Briggs Institute (JBI) checklist was applied for methodological quality assessment purposes.

Results A total of 920 articles were identified and 5 studies were included. Most studies analyzed the HRV by linear indexes. Studies from group A ($n=2$) presented fair methodological quality; one study from group B ($n=3$) showed fair methodological quality (Im et al. Korean J Urol. 51:183, 2010) whereas the others presented high methodological quality. One study from group A found an increase in both modulations between women with overactive bladder (OAB) versus women with stress UI, whereas a decrease was reported between incontinent and continent women. Studies from group B showed a decreased sympathetic and parasympathetic modulation in AOB with detrusor overactivity (DO), whereas one study found an increase in both modulations in women with OAB compared with stress UI.

Conclusion Parasympathetic and sympathetic modulation increased during bladder filling and rest in UI with OAB associated or not with DO. Both modulations decreased during bladder filling in incontinent women and during rest in OAB.

Keywords Cardiovascular system · Women's health · Urinary incontinence

Introduction

According to the International Continence Society (ICS), the urinary incontinence (UI) is defined as any involuntary loss of urine. The UI can be classified into three types: stress urinary incontinence (SUI), when the urine loss occurs during physical efforts, such as coughing or sneezing; urgency urinary incontinence (UUI), when the loss of urine is associated with urinary urgency (i.e., a sudden and strong urge to urinate); and mixed urinary incontinence (MUI), when there is a concomitant presence of SUI and UUI symptoms [1]. The UI often impacts the quality of life, as it affects physical, psychological, and social well-being [2], leading to an increase in the overall morbidity, mortality, and health care costs [3, 4].

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In relation to the pathophysiological mechanisms involved in UI development, there are still controversies in the literature. One of the hypotheses is that the imbalance of sympathetic and parasympathetic pathways of the autonomic nervous system (ANS) may be involved in UI pathophysiology, as this system is one of the main regulators of the lower urinary tract and the detrusor muscle [5, 6]. It is known that sympathetic fibers inhibit the detrusor contraction during bladder filling, and it is responsible for contracting the internal urethral sphincter, avoiding the urgency to urinate or urinary loss. Moreover, the parasympathetic pathway is responsible for producing the contraction of the detrusor muscle, controlling the internal urethral sphincter relaxation during voiding [7]. Therefore, it seems reasonable that changes in the ANS may reflect a dysregulation of normal bladder filling and storage, contributing to the development of UI [8].

Thus, the study of ANS pathways dynamics may provide additional information about the neural changes involved in UI development and progression. The ANS dynamics can be assessed non-invasively through the study of heart rate variability (HRV), that describes the oscillation of the intervals between consecutive heart beats [9]. In adults, a decrease in HRV is related to poor psychophysiological health outcomes, such as: atherosclerosis, diabetes mellitus, major depressive disorder, and early mortality. Moreover, lower HRV is also associated with harmful lifestyle behaviors (i.e., physical inactivity, poor diet, smoking, and stress) [9, 10]. Therefore, regular HRV monitoring has been widely applied in different areas of health. In addition, patients can now assess their daily ANS status through the variety of commercial HRV measurement devices available [10], which could result in a greater knowledge about their health and engagement in health interventions. The HRV have great reproducibility, feasibility and a low-cost measurement that allows the effects of interventions, disease progression, and optimization of training protocols to be verified in clinical settings [9, 11].

Despite the study of ANS through HRV measurements being widely applied in several fields of health, little is known about the behavior of HRV and its application in clinical practice in women with UI. Therefore, this study was aimed at conducting a systematic review to investigate ANS regulation, assessed non-invasively through HRV in women with UI. This knowledge may be useful for elucidating the pathophysiology of UI, as well as for the development of therapeutic strategies.

Materials and methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12] and Cochrane Collaboration recommendations for systematic reviews [13]. A standardized electronic tool, called State of the Art through Systematic Review (StArt), was used to assist and systematize the search and data extraction (Available from: http://lapes.dc.ufscar.br/tools/start_tool) [14].

Search strategy

The search was performed in April 2021 and no restriction regarding the year of publication was applied during the searches. The following electronic databases were screened: PubMed, CINHAL, Scopus, Web of Science, and Cochrane Library. The following Medical Subjects Headings (MeSH) terms were selected and combined: ("Heart Rate" OR "Autonomic Nervous System") AND ("Urinary Incontinence" OR "Stress Urinary Incontinence" OR "Urge Urinary Incontinence"). No additional search filters were applied. Finally, the reference lists of the articles included were checked to identify other possible eligible studies.

Inclusion and exclusion criteria

Observational cross-sectional studies that were aimed at assessing the ANS through HRV in women with SUI and/or with UUI associated or not with overactive bladder (OAB) or detrusor overactivity (DO), were included in this systematic review. OAB was defined by the urge to urinate usually accompanied by increased of daytime frequency and nocturia, that may or may not be associated with UUI, in the absence of lower urinary tract infections or other pathological conditions. DO was characterized by the presence of an involuntary contraction of the detrusor muscle during the cystometry, that may or may not be associated with urgency and/or UUI [1]. Only cross-sectional studies were included in the present review because the design of the studies was supposed to explore the relationship between the ANS and the different types of UI.

In addition, only full-length publications in English language were included. The exclusion criteria considered studies that were conducted in children, men or continent women; studies that included participants with other associated diseases (e.g., cardiovascular, neurological, psychological diseases, and patients with OAB without UI symptoms) and articles that analyzed only other pelvic floor dysfunctions (e.g., fecal and/or anal incontinence, pelvic organ prolapse, sexual dysfunctions). Abstracts, letters to editor, thesis, conference papers, guidelines, reviews, theses, and dissertations were also excluded.

Selection process

Two independent researchers (J.B.S. and R.M.A.) screened the studies following the eligibility criteria. The selection process was performed in two sequential evaluation phases: (I) selection by title and abstract and (II) analysis of the full text in order to determine their inclusion. The reference lists of the studies included were also screened independently by these two reviewers, to identify possible studies not retrieved by the electronic search. In the case of any disagreements in some of the selection steps between these two reviewers, a third independent reviewer (J.F.P.) was consulted to reach a consensus decision.

Data extraction

From each study included, the data were extracted by two independent reviewers (J.B.S and R.M.A.) using standardized forms, that included information related to the characteristics of studies, participants, and groups (first author, year of publication, groups and sample size, age, body mass index, inclusion criteria, type of UI, urodynamics assessment, HRV recording device, HRV measures, and HRV analysis condition), and outcomes of interest (linear and nonlinear HRV indexes). Moreover, secondary results relevant to UI pathophysiology and cardiovascular health were also extracted (overactive bladder occurrence, maximum bladder capacity, maximum urethral closure pressure, detrusor overactivity, cardio-ankle vascular index, and ankle-brachial pressure index). Studies were allocated into two groups only for organizational purposes. Group A included articles that evaluated HRV during all the phases of bladder filling that were monitored and controlled by the researchers. Studies from group B analyzed HRV after voiding and did not control the bladder filling phases. Therefore, we considered that studies from group B analyzed HRV during after voiding.

Heart rate variability analysis

Heart rate variability analysis measures were extracted and divided according to methods of analysis, such as the linear (time and frequency domains) and nonlinear (cardio-sympathetic and cardio-vagal indexes) methods.

Linear indexes

The time domain method takes into account the numerical analysis between successive RR interval (RRi) beats, such as: standard deviation of the RRi (SDNN), which represents the conjoint sympathetic and parasympathetic modulation; and square root of the mean squared differences of successive RRi (RMSSD), which indicate the cardiac parasympathetic modulation [9].

Frequency domain method consist of decomposition of RRi through the spectral analysis, to calculate the power spectral density (PSD), which provides the basic information of how power distributes as a function of frequency [9]. The main spectral components calculated are: low frequency (LF: 0.04–0.15 Hz), which is modulated by both sympathetic and parasympathetic outflows, with a predominance of sympathetic outflow [15]; high frequency (HF: 0.15–0.4 Hz), corresponds to parasympathetic modulation [9, 15–17]; LF/HF ratio represents the "sympatho-vagal balance," where possibly an increase is related to sympathetic predominance and a decrease indicates greater parasympathetic modulation [18]; ultra-low frequency (ULF: ≤0–0.03 Hz) requires a recording period of at least 24 h and it seems to be related to very slow-acting biological processes, such as metabolism, the renin–angiotensin–aldosterone system, and thermoregulation; very low-frequency (VLF: ≤0.04 Hz) ideally requires a long-term recording period and seems to be related to the heart's intrinsic nervous system and its oscillations are influenced by the sympathetic nervous system [19]; and the total power (TP) of RRi, which represents the total variance and corresponds to the sum of the powers in the ULF, VLF, LF, and HF bands for 24 h and the VLF, LF, and HF bands for short-term recordings [9, 19]. The main components are expressed in absolute values (abs) and in normalized unit data (nu). The LF absolute values (LFabs) are modulated by both branches of the ANS, with a predominance of sympathetic modulation [15], whereas the LF expressed in normalized units (LFnu) is an indicator of sympathetic predominance, and HF (HFabs and HFnu) corresponds to cardiac parasympathetic modulation [9, 15].

Nonlinear indexes

The nonlinear methods identified in this review included the cardio-vagal and cardio-sympathetic indexes, which were calculated according to Toichi [20]. The method consists of the calculation of two indices from a Lorenz plot in which each RRi is plotted against the subsequent RRi (RRn + 1). The length of the transverse axis (T) in the resultant graph reflects beat-to-beat variability with deviations along this axis predominantly reflecting parasympathetic modulation. The length of the longitudinal axis (L) reflects the overall range of RRi owing to both sympathetic and parasympathetic influences. Finally, the measures derived from this plot are called the cardio-vagal index (CVI = Log10 [L·T]) and cardio-sympathetic index (CSI = L/T) [20].

Methodological quality assessment

The risk of bias of cross-sectional studies was evaluated by the checklist proposed by the Joanna Briggs Institute (JBI) [21]. The JBI checklist is composed of eight items that should be answered using four responses options: yes, no, unclear, or not applicable. The score for each item is zero when the quality criterion is absent (no, unclear, or not applicable) and is pointed as one if the quality criterion is present. The studies included were grouped into two levels according to their final score: fair methodological quality (≥5) or high methodological quality (>7) [22]. Two independent reviewers (J.B.S. and R.M.A.) were responsible for conducting risk of bias assessment. In the case of any disagreement between them, a third researcher (J.F.P.) was consulted in order to reach a consensus.

Results

Study selection

The initial electronic search resulted in a total of 920 records. No additional articles were identified in other sources. After removing duplicate papers, 849 titles and abstracts were screened. Of these, 833 studies did not match the eligibility criteria and were excluded. After revising 16 full text papers, five articles fulfilled the inclusion criteria and were included in this systematic review. The main reasons for full text exclusion were:

1. Conference abstract, letters, pilot study, and/or protocol study
2. Studies that included men
3. Women with an absence of UI
4. Non-English language

The flow diagram for study selection is shown in Fig. 1.

Characteristics of participants and groups

The characteristics of the participants and groups at baseline are described in Table 1. Two articles compared the HRV in women with SUI and OAB [5, 8], one study included women with OAB and UI symptoms [23], two studies analyzed women with DO associated with UI symptoms [8, 24], and one study verified the HRV in incontinent women [25]. Three studies included a control group without urinary symptoms [23, 24, 25]. The total sample size of all the studies included was 365 women (ranging from 10 to 150) and the groups numbers ranged from 3 to 85 women per group. The average age of participants was 54 years (ranging from 39 to 67).

Only one study assessed UI by urodynamics [1], whereas two articles analyzed the urodynamics results associated with voiding diary [8, 23]. One paper does not report the tool applied to assess UI [5] and one article evaluated UI symptoms using the International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF) [25]. All studies analyzed the HRV using an ECG and assessed linear indexes.

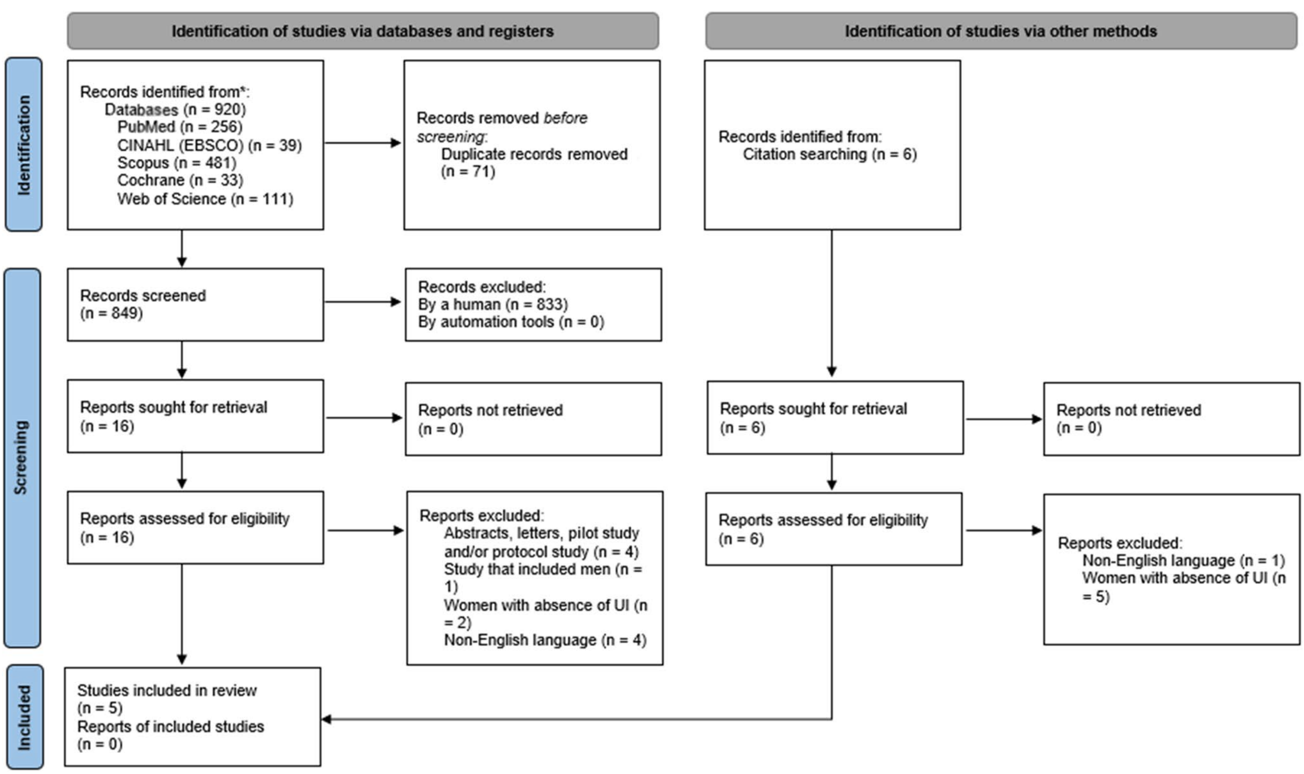

Fig. 1 PRISMA 2021 flow chart for search strategy and retrieval of articles

Table 1 Methodological and participants' characteristics of articles that assessed heart rate variability (HRV) of women with urinary incontinence (UI) during bladder filling and rest (group A and group B)

Groups	Reference	Population	Groups and sample size	Age (years)	BMI (kg/m^2)	Inclusion criteria	UI evaluation	HRV evaluation tool	HRV analysis conditions	HRV measures	
										Linear indexes	Nonlinear indexes
A	Hubeaux et al., 2007 [5]	Women with isolated OAB or SUI	OAB ($n=3$)	OAB (39 ± 22.6)	OAB (21.4 ± 2.3)	18–59 years with isolated OAB or SUI	NR	ECG	Artificial bladder filling	Time domain (SDNN, RMSSD)	NR
			SUI ($n=7$)	SUI (46 ± 14.8)	SUI (23.4 ± 3.9)					Frequency domain (VLF, LF, HF, LF/HF)	
B	Im et al., 2010 [24]	Incontinent women with and without DO	DO ($n=12$)	DO (57.3 ± 11.0)	NR	NR	Urodynamic	ECG	Rest	Time domain (SDNN, RMSSD)	NR
			CG ($n=53$)	CG (56.8 ± 9.8)						frequency domain (total power, VLF, LF, HF, LF/HF)	
B	Kim et al., 2010 [8]	Women with SUI or OAB	SUI ($n=47$)	SUI (46.4 ± 13.1)	NR	≥ 18 years, UI at least once a day	Voiding diary, urodynamic	ECG	Rest	Time domain (SDNN, RMSSD)	NR
			OAB ($n=29$)	OAB (58.3 ± 13.4)							
			Without DO ($n=53$) with DO ($n=2$)	Without DO (47.4 ± 13.5 with DO (57.3 ± 11.0)						Frequency domain (total power, VLF, LF, HF, LF/HF)	
B	Hsiao et al., 2014 [23]	Women with OAB	OAB ($n=85$)	OAB (53.2 ± 11.6)	OAB (24.1 ± 3.5)	≥ 18 years, 3-month history of OAB (urgency, urinary frequency, nocturia or urge UI)	3-day bladder diary	Holter ECG	Rest	Time domain (SDNN, RMSSD)	NR
			CG ($n=65$)	CG (52.3 ± 12.9)	CG (23.3 ± 2.8)	≥8 micturition per 24-h period	Urodynamic			Frequency domain (total power, VLF, LF, HF, LF/HF)	

Table 1 (continued)

Groups	Reference	Population	Groups and sample size	Age (years)	BMI (kg/m^2)	Inclusion criteria	UI evaluation	HRV evaluation tool	HRV analysis conditions	HRV measures	
										Linear indexes	Nonlinear indexes
A	Padilha et al., 2017 [25]	Women with UI	UI ($n=33$) CG ($n=31$)	UI (67.1 ± 6.67) CG (62.4 ± 6.09)	UI (28.8 ± 5.10) CG (27.5 ± 3.85)	50–80 years, menopausal or postmenopausal and self-reported UI	ICIQ-SF	ECG	Bladder filling	Time domain (SDNN, RMSSD) Frequency domain (total power, VLF, LF, HF, LF/HF	Cardio-sympathetic Index, Cardio-vagal Index

CG control group, *DO* detrusor overactivity, *ECG* electrocardiogram *HF* high frequency, *HR* heart rate, *ICIQ-SF International Consultatoin on Incontinence Questionnaire - Short Form* *LF* low frequency, *NR* not reported, *OAB* overactive bladder, *RMSSD* square root of the mean squared differences of successive N-N intervals, *SDNN* standard deviation of the N-N, *SUI* stress urinary incontinence, *TP* total power, *UI* urinary incontinence, *VLF* very low frequency, *FSF* first sensation of bladder filling, *FUU* first urge to urinate, *SUU* strong urge to urinate, *MBC* maximum bladder capacity

Only one study also included the assessment of nonlinear indexes on HRV analysis [25].

Cardiac autonomic control in group A

Table 2 showed the outcomes from the HRV assessment according to frequency and time domains. In relation to the studies allocated to group A [5, 25], one study [5] reported significant changes in HRV in women with OAB, characterized by the increase in LFnu and HFnu indexes, between empty bladder and the end of bladder filling, as well as between before and after a strong desire to void. Moreover, the authors found an increase in LF/HF ratio before the first desire to avoid and after a strong desire to avoid, and before and after a strong desire to void. One study [25] identified a significant decrease in LogLF and LogHF indexes during the phases of the bladder filling (empty bladder, first sensation of bladder filling; first urge to urinate, strong urge to urinate, and after bladder voiding), except for the maximum bladder capacity. Changes were also found during the first sensation of bladder filling (decrease in LogVLF, LogLF), first urge to urinate (decrease of LogLF) and after bladder voiding (decrease of LogVLF and LogLF). Regarding the time domain indexes, one study did not found significant differences [5] and only one study [25] reported a decrease in LogSDNN only after voiding. Table 3 presented the HRV analysis according to cardio-vagal and cardio-sympathetic indexes. The uathores found a significant decrease of the cardio-sympathetic index while teh bladder was empty and during the first sensation of bladder filling (FSF).

Cardiac autonomic control in group B

Three studies were included in group B [8, 23, 24]. Taking into account the frequency domain analysis, one study found a decrease of LFabs and HFabs in women with DO [24]. Considering the LF/HF ratio, controversial results were identified among the papers included; although some authors suggest that this index might be increased in women with DO and OAB [8, 24], others suggest a decrease of LF/HF ratio in women with OAB symptoms [23]. Moreover, decreases in the LF/HF ratio were also observed in women with SUI [8]. In relation to the time domain analysis, one study found a decrease in the RMSSDabs values in women with DO [24].

Secondary outcomes

None of the studies from group A reported secondary outcomes. Table 2 presented the secondary outcomes found from two studies included in group B [8, 23]. One article reported a higher LF/HF ratio in women with DO when compared with continent women [24]. Moreover, one study

Table 2 Heart rate variability analysis according frequency and time domains from the studies included in the systematic review

Group	Reference	Condition	Frequency domains					Time domains		Secondary outcomes
			TP	VLF	LF	HF	LF/HF	SDNN	RMSSD	
A	Hubeaux et al., 2007 [5]	OAB	NA	NA	↑**,***	↓**,***	↑****,*****	n.s	n.s	NA
		SUI			n.s	n.s	n.s	n.s	n.s	
B	Im et al., 2010 [24]	DO	↓	↑	↓*	↓*	↑*	↑	↓*	NA
B	Kim et al., 2010 [8]	SUI	↑	n.s	n.s	n.s	↓*	↑	↑	Women with DO present higher LF/HF compared with CG
		OAB	↓	n.s	n.s	n.s	↑*	↓	↓	
		With DO	n.s	n.s	n.s	n.s	↑*	↓	↓	
B	Hsiao et al., 2014 [23]	OAB	NA	NA	↓	↓	↓*	↓	↓	OAB (RMSSD was associated with nocturia, LF was associated with urgency episodes, and maximum urethral closure pressure was negatively associated with CAVI)
		CG			↑	↑	↑	↑	↑	
A	Padilha et al., 2017 [25]	Empty	NA	↓	↓	↑	↓	↓	↑	NA
		FSF	NA	↓*	↓*	↓*	↓*	↓	↓	
		FUU	NA	↓	↓*	↑	↓*	↓	↑	
		SUU	NA	↑	↓	↓	↓*	↑	↑	
		MBC	NA	↓	↓	↑	↓	↓	↑	
		After voiding	NA	↓*	↓*	↓	↓*	↓*	↓	

↑,↓ indicate increase or decrease

n.s. indicates no change ($p \geq 0.05$)

CAVI cardio-ankle vascular index, *CG* control group, *DO* detrusor overactivity, *HF* high frequency, *HR* heart rate, *LF* low frequency, *NA* not applicable, *NR* not reported, *OAB* overactive bladder, *RMSSD* square root of the mean squared differences of successive N-N intervals, *SDNN* standard deviation of the N-N, *SUI* stress urinary incontinence, *TP* total power, *UI* urinary incontinence, *VLF* very low frequency. *FSF* first sensation of bladder filling, *FUU* first urge to urinate, *SUU* strong urge to urinate, *MBC* maximum bladder capacity

*Significant increase or decrease ($p \leq 0.05$)

**Significant differences ($p > 0.05$) between bladder empty and end of bladder filling

***Significant differences ($p > 0.05$) between before and after strong desire to void

****Significant differences ($p > 0.05$) between before first desire to void and after strong desire to void

*****Significant differences ($p > 0.05$) between before and after strong desire to void

Table 3 Heart rate variability analysis according to cardio-vagal and cardio-sympathetic indexes from the studies included in the systematic review

Group	Reference	Condition	Cardio-vagal index	Cardio-sympathetic index
A	Padilha et al., 2017 [25]	Empty	↓	↓*
		FSF	↓	↓*
		FUU	↓	↓
		SUU	↑	↓
		MBC	↑	↓
		After voiding	↓	↓

FSF first sensation of bladder filling, *FUU* first urge to urinate, *SUU* strong urge to urinate, *MBC* maximum bladder capacity; *Significant increase or decrease ($p \leq 0.05$)

reported a significant and positive association between RMSSDabs and nocturia, LFabs and urgency episodes, and a negative association between the maximum urethral closure pressure and the cardio-ankle vascular index in women with OAB compared with continent women [23].

Methodological quality assessment

The methodological quality assessment results are shown in Table 4. The average JBI checklist score was 5.8, being considered of fair methodological quality. Both studies included in group A were considered to be of fair methodological quality [5, 25]. Regarding group B, one study was considered to be of fair methodological quality [24] whereas the other two showed a total score of 7 points and were classified as being of high methodological quality [8, 23]. All the studies included in the present systematic review lacked reporting of the strategies used to deal with confounding. In addition, the studies included in group A [5, 25] did not describe the setting where the study was conducted. Moreover, the study conducted by Hubeaux et al. [5] did not report how they measured the presence of UI. Finally, one study from group B did not clearly report the sample characterization and the study setting[24].

Discussion

The main findings of this systematic review can address the fact that women with UUI associated with OAB and OAB associated with DO presented an increase in parasympathetic and sympathetic modulation during bladder filling [5] and after voiding [8] respectively, when compared with women with SUI only. However, when comparing continent with incontinent women (with SUI, OAB, or MUI), it seems that parasympathetic and sympathetic modulation decrease

Table 4 Methodological quality assessment according to the Joanna Briggs Institute (JBI) criteria

Groups	Reference	Question 1	Question 2	Question 3	Question 4	Question 5	Question 6	Question 7	Question 8	Final score
A	Hubeaux et al., 2007 [5]	Yes	No	No	No	Yes	No	Yes	Yes	4
B	Im et al., 2010 [24]	NC	No	Yes	Yes	Yes	NC	Yes	Yes	5
B	Kim et al., 2010 [8]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7
B	Hsiao et al., 2014 [23]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7
A	Padilha et al., 2017 [25]	Yes	NC	Yes	Yes	Yes	No	Yes	Yes	6

Scoring was based on the answers (Yes = 1 point; No, NC or NA = 0 point) to the following questions: 1) Were the criteria for inclusion in the sample clearly defined?; 2) Were the study subjects and the setting described in detail?; 3) Was the exposure measured in a valid and reliable way?; 4) Were objective, standard criteria used for measurement of the condition?; 5) Were confounding factors identified?; 6) Were strategies to deal with confounding factors stated?; 7) Were the outcomes measured in a valid and reliable way?; 8) Was appropriate statistical analysis used?

JBI checklist: fair methodological quality (≥5); high methodological quality (>7)

NC not clear, *NA* not applicable

during bladder filling [25], and after voiding for women with UUI associated with OAB [23, 24]. To the authors' knowledge, this is the first systematic review to analyze the response of cardiac ANS in women with UI during rest and bladder filling.

Two studies included in group A showed controversial results. In continent individuals, it is expected that sympathetic modulation increases slowly during all phases of bladder filling. However, at the end of bladder filling, when the patient usually reports a strong desire to void, a pronounced increase in the sympathetic response is expected. Therefore, a decrease in the sympathetic modulation during a strong desire to void or during an urgency to void would possibly indicate a deficiency in ANS response [26]. One study included in group A found a decrease in both sympathetic and parasympathetic modulation on frequency domain indexes in women with UI (SUI, UUI, or MUI) during all phases of bladder filling and after voiding, when comparing them with continent women [25]. Controversially, another study [5] concluded that women with UUI with OAB presented an increase in cardiac sympathetic and parasympathetic modulation and in the cardiac sympatho-vagal balance during bladder filling. However, authors compared women who had UUI plus OAB with women who had SUI, without the inclusion of a continent control group in the analysis. In addition, the small sample size of the study may have limited the statistical analysis and the results reported by the authors.

Another difference between studies is related to the bladder filling evaluation method; although one article performed it in an artificial way by cystometry [5], another analyzed it during a natural process and according to the participants' reports [25]. Previous studies suggest that the detrusor contraction pressure might be higher during the artificial process when compared with bladder filling under normal conditions, which may have an impact on ANS responses [27]. In addition, it is known that the natural bladder filling process (e.g., urine production) may interfere in the cystometry process, especially when urodynamics is taking a long time to finish [28]. Therefore, the results from both studies should be interpreted with caution when applied to scientific and clinical practice, as the ANS responses are still controversial during bladder filling.

Results from studies included in group B are also controversial. Under healthy conditions, an increase in the sympathetic modulation at rest, which is associated with the bladder and internal urethral sphincter control, is expected and consequently may avoid an urgency to void and UUI episodes [7]. Two studies included in the present systematic review reported a decrease in sympatho-vagal balance in incontinent women with OAB [23] and in those with UUI plus OAB concomitantly with DO [24]. This response may reflect a clinical marker of UI patients, as the lower the LF/HF values, the lower the sympathetic modulation [29]. However, an article by Kim et al. [8] found a higher sympatho-vagal balance in women with UUI compared with SUI. These findings may suggest that urinary symptoms, especially those related to UUI, might present a higher influence of ANS control than those symptoms associated with SUI. The pathophysiology of the different types of UI may justify these previous results as it is known that SUI is commonly associated with a weakness of the pelvic floor muscles [30], whereas UUI is often related to other lower urinary tract disorders (e.g., OAB) that are possibly associated with alterations of detrusor muscle activity (e.g., DO) [1].

According to LF/HF values, the pathological conditions that lead to hyperactivity of both the detrusor muscle and the bladder, are demonstrated to increase the LF/HF index, which may be related to the sympathetic dominance, which occurs when we engage in fight-or-flight behaviors or parasympathetic withdrawal [31]. In contrast, a gradual LF/HF reduction was observed between empty bladder until after voiding condition, which may reflect a gradual parasympathetic dominance during bladder filling and after voiding [25, 31]. Nevertheless, some authors argue that the LF/HF index cannot accurately quantify cardiac "sympatho-vagal balance," neither in health nor under pathological conditions. First, LF power is not a pure sympathetic index. Second, the sympathetic and parasympathetic interactions are nonreciprocal and nonlinear [31–33].

Findings related to the parasympathetic modulation were also reported by one study included in group B. In the absence of dysfunctions, parasympathetic response is associated with a stimulus to contract the detrusor muscle that is positioned around the bladder [7]. However, the study conducted by Im et al. [24] found a decrease in parasympathetic modulation in incontinent women with DO compared with continent women. This result may indicate a possible ANS dysfunction in incontinent women with DO. However, this result may be interpreted with caution, as authors did not specify the type of UI reported by women included in their study (UUI or SUI). In addition, authors lack describing the study inclusion criteria and included a small sample of women with DO in their statistical analysis, which may be considered a study bias.

Although the aim of the present review was to assess the HRV in women with different types of UI (SUI, UUI, MUI), the relationship between SUI and the HRV response during bladder filling remains unclear. Hubeaux et al. [5] included women with SUI symptoms in their study, but the authors considered them as a control group, justified by the fact that SUI is not associated with the storage phase of bladder control but predominantly with pelvic floor muscle weakness [30]. In addition, the sample of women with SUI was too small and this may be a big bias of the study. Therefore, no studies included in the present review aimed to analyze

HRV response in women with MUI (both SUI and UUI symptoms concomitantly). Additional studies are needed to confirm the presence of autonomic dysfunction in women with SUI and MUI.

The present systematic review has some limitations. The first one is related to the few studies found in the literature. Moreover, the population included in the studies that we found were heterogeneous and presented different conditions. However, we were able to identify some patterns regarding autonomic regulation and dynamics, both during rest and bladder filling, in these different groups. Another limitation may be related to the lack of standardization related to the assessment of urinary symptoms, as not all studies included in this systematic review reported the technique to assess the condition. We also observed that all studies lack control of the cofounding factors of the sample and none evaluated the risk factors for UI, such as age, previous pregnancy, parity, and other associated pelvic floor muscle dysfunctions (e.g., anal incontinence, pelvic organ prolapse). We could not find analysis related to the nonlinear approaches to HRV assessment, which consider the nonlinear dynamic of the biological systems and could provide additional information about ANS behavior in women with UI symptoms. Moreover, there is an absence of HRV analysis during autonomic tests (e.g., Valsalva maneuver, handgrip challenges, and pacing breath); these tasks typically induce global changes in blood oxygenation and blood flow in addition to local changes related to increased or decreased neural activation; therefore, the global changes are excluded from analyses as confounding factors [34].

Although, the results from the present systematic review may be useful for understanding the ANS behavior and what is expected to be found in the groups studied (i.e., control, UUI with and without DO and SUI) and conditions (i.e., rest and bladder filling). This knowledge may be useful for health professionals in understanding what to expect from HRV indexes and implement this method as a complementary assessment of the patient's health status from the point of view of urogynecologist regulation and beyond.

Therefore, the synthetized evidence related to the cardiac ANS response assessed by HRV in women with UI may contribute to the design of future studies, as the present review highlighted a need for articles with high methodological quality that are aimed at elucidating the physiological response of HRV in the pathophysiology of different types of UI. We also encouraged researchers to analyze the causality between UI and ANS, as the fear or stress evoked by UI alone would induce heart rate variations. This result would be important for the understanding of the course of autonomic changes throughout the development and progression of the different UI types. In addition, this information would be useful for future clinical trials for better sample control in terms of confounding factors that may affect autonomic regulation (i.e., psychological factors, associated diseases, age, etc.).

Conclusion

Women with urinary symptoms with OAB or OAB associated with DO showed an increase in parasympathetic and sympathetic cardiac modulation during bladder filling and during rest. Controversially, it seems that parasympathetic and sympathetic modulation decreased during bladder filling in incontinent women with SUI, UUI, and/or MUI, and during rest in women with OAB. These HRV responses may be a clinical marker of women with UI; however, we emphasize the need for further studies on the topic for the effective application of this feasible measure into clinical practice.

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Declarations

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