Heart Rate Variability as a Measure of Disease State in Irritable Bowel Syndrome

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Heart rate variability (HRV) is a noninvasive measure of sympathovagal balance in the autonomic nervous system (ANS). This review will: (a) consider HRV measurement in irritable bowel syndrome (IBS); (b) discuss the applicability of HRV measurement in IBS by addressing strengths and limitations; and (c) propose future directions in this field of gastrointestinal research and clinical practice. As a strength, analyzing HRV components is a useful method and appears most suitable for detection of changes in ANS sympathovagal balance in both stress and non-stress conditions with good validity and reliability. Also, it is an appropriate measure for ANS in studies with large populations, in both laboratory and clinical settings, and for longitudinal studies because of its noninvasive assets. With regard to limitations of measuring HRV, these are poor standardization, additional human editing, not considering medication or other confounding factors, inconsistent results in gastrointestinal vagal tone study, and different time periods. [Asian Nursing Research 2008;2(1):5–16]

**Key Words** autonomic nervous system, heart rate variability, irritable bowel syndrome

**INTRODUCTION**

Heart rate variability (HRV) may provide a new and more powerful approach for evaluating the autonomic nervous system (ANS) in patients with irritable bowel syndrome (IBS). IBS is a common chronic functional gastrointestinal (GI) disorder characterized by chronic intermittent symptoms including abdominal discomfort/pain, diarrhea, constipation, and bloating. More than 80% of IBS patients complain of stress-induced exacerbation of GI symptoms (Levy, Cain, Jarrett, & Heitkemper, 1997; Whitehead, Crowell, Robinson, Heller, & Schuster, 1992). Several studies have demonstrated an increased visceral sensitivity and gut dysmotility caused by various stimuli such as mental stress and meals (Clemens, Samsom, Van Berge Henegouwen, & Smout, 2003; Elsenbruch & Orr, 2001; Gupta, Sheffield, & Verne, 2002; Hausken et al., 1993; Mayer, 2000; Mertz, Naliboff, Munakata, Niazi, & Mayer, 1995; Naliboff et al., 1997; Verne, Robinson, & Price, 2001). The pathophysiology of IBS remains poorly understood. Hence many investigators try to seek the pathogenesis of IBS in patients using several tests. Dysfunction of
the ANS may be important for the development of abnormalities of GI motility and visceral perception. The first study dates back to 1928, when Bockus, Bank, and Wilkinson suggested IBS symptoms were associated with an imbalance of ANS function. More recently, there are a growing number of studies using HRV to assess the function of the ANS in patients with IBS.

Thus, the objectives of this review are to: (a) consider the relationship between IBS and HRV measurement; (b) discuss the applicability of HRV measurement in IBS by addressing strengths and limitations; and (c) propose future directions in this field of GI research and clinical practice. This paper provides a review of current knowledge of the usefulness of measurement of HRV in IBS.

**HRV**

HRV is a noninvasive, indirect method of measuring balance/imbalance of the parasympathetic nervous system (PSNS) and sympathetic nervous system (SNS). Originally it was assessed manually from calculations of the mean R-R interval and its standard deviation measured on short-term (2–5 minutes) electrocardiograms (ECG). Recently, the availability of increased computing power, innovative microprocessor technology, and the remarkable technological developments in recording have enabled the analysis of 24-hour long-term records (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996).

Analysis of HRV can be divided into time domain analysis and frequency domain analysis. Time domain analysis, known as nonspectral or statistical analysis, is a general measure of ANS balance. Time domain analysis of HRV is correlated with total variance of the heart signal and PSNS (Hayano et al., 1991; Kleiger, Stein, Bosner, & Rottman, 1992; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). The SD 24-hr is the simple standard deviation of the set of R-R intervals in a 24-hour period. SD-5-min is the mean of the standard deviations of normal R-R intervals for all 5-minute blocks in a full 24-hour ECG recording. The root mean square successive difference (RMSSD) is the squared difference between two adjacent normal R-R intervals computed over the entire 24-hour period. The RR50 is the total number of occurrences in a 24-hour period in which the difference between two successive R-R intervals exceeds 50 milliseconds. The %RR50 (pNN50) is the percentage of the absolute difference between adjacent normal R-R intervals that are greater than 50 milliseconds computed over the entire 24 hours (Kleiger et al.; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology).

Frequency domain analysis of HRV, known as power spectral analysis, contains two major spectral components: the high frequency (HF) component (0.15–0.40 Hz) and the low frequency (LF) component (0.03–0.15 Hz or 0.04–0.15 Hz or 0.05–0.15 Hz depending on the research) (Akselrod et al., 1981). Normal frequency range has not yet been firmly established. Some studies used medium-frequency power (MF) (0.07–0.15 Hz) (Heitkemper et al., 1998; Karling et al., 1998; McCraty, Atkinson, Tiller, Rein, & Watkins, 1995). Total power is the energy in the heart period power spectrum up to 0.40 Hz. Frequency domain analysis of HRV has been used as a sensitive index of ANS activities because it can help distinguish SNS from PSNS regulation of the sinoatrial node. Dominance by the SNS leads to the *fight/flight* reaction and PSNS dominance tends to have a *rest/digest* effect. The HF component has been considered the respiratory sinus arrhythmia (RSA) and is mediated solely by the PSNS, whereas the LF component corresponds to blood pressure oscillations and is jointly modified by the PSNS and the SNS. Therefore, HF is considered a *pure* measure of PSNS activity and LF is less clear and considered a *mixed* ANS marker. HF is highly correlated with the time domain variables of RMSSD and %RR50; these three components provide an estimate of PSNS activity (Delaney & Brodie, 2000; Kleiger, Miller, Bigger, & Moss, 1987; Ori, Monir, Weiss, Sayhouni, & Singer, 1992). In addition, the LF/HF ratio is a useful parameter that reflects the balance of ANS activities. The LF/HF ratio was significantly greater in healthy subjects (Achten & Jeukendrup, 2003).
The polar software system consists of very low frequency (VLF) power from 0.0033 Hz to 0.04 Hz, LF power from 0.04 Hz to 0.15 Hz, and HF power from 0.15 Hz to 0.40 Hz. VLF indicates SNS activity. The ultra low frequency (ULF) at 0–0.0033 Hz may represent humoral and thermoregulatory factors. However, as very slow rhythms are assessed only over long periods, this component is not always analyzed (Pagani et al., 1986). The physiological mechanisms of the ULF and VLF band widths can be modulated by renin-angiotensin system and/or temperature regulation (Akselrod et al., 1981).

The logarithms (e.g. ln%RR50, lnRMSSD, lnHF, lnLF) or logit transformation (e.g., logit50) are sometimes chosen because the individual median values are not distributed normally, but fit a normal log or logit distribution. The logarithms or logit transformation are easy to calculate and are highly correlated with the spectral estimate of cardiac vagal tone. In addition, the logarithm or logit transformation are useful for a small sample and for subjects with a very low level of HRV (Burr, Motzer, Chen, Cowan, & Heitkemper, 2003; Moser et al., 1998). Hence, indicators of ANS imbalance are LF/HF, SD-5-min/RMSSD, and sqLF/HF. These three higher values represent greater SNS and lower PSNS activity. Indicators of general ANS activity are SD-5-min and lnLF. Indicators of PSNS activity are HF, RMSSD, and %RR50 (Jarrett et al., 2003; Kleiger et al., 1987).

**Effects of confounding variables on HRV**

There are several possible different confounding variables that affect HRV, such as gender, age, body position (supine/standing), breathing frequency, body mass index (BMI), systolic blood pressure, physical and mental stress, pain, hormonal fluctuation, family history, genetic, medication, and life-style factors such as eating, smoking, alcohol, coffee consumption, and habitual physical activity (Parati & Di Rienzo, 2003). Age and gender, in particular, have been found to influence PSNS tone. There is a significant tendency for decreased HRV with increasing age (Cowan, Pike, & Burr, 1994). This is reflective of a reduction in the absolute values of PSNS and SNS activity (Aubert, Seps, & Beckers, 2003). In general, healthy women have a lower HRV than do healthy men due to the reduced variance in sympathetic activity (reduced LF and HF) in females (Cowan et al.; Jensen-Urstad et al., 1997; Thayer, Smith, Rossy, Sollers, & Friedman, 1998). Also, the luteal phase of the menstrual cycle was associated with a greater increase in LF and a greater decrease in HF, resulting in a higher LF/HF ratio. This suggests SNS activities in young college women (mean age: 19.2 years) are predominant in the luteal phase as compared with the follicular phase during the menstrual cycle despite using a small number of subjects (N = 20) (Sato, Miyake, Akatsu, & Kumashiro, 1995).

HRV decreases significantly with increasing BMI due to depressed sympathetic modulation of the heart associated with excessive body weight (Karason, Molgaard,Wikstrand, & Sjostrom, 1999). Exercise training studies have shown to have a significantly positive effect on HRV (Aubert et al., 2003). Also, biofeedback and relaxation tasks have been found to be beneficial (Cowan, Kogan, Burr, Hendershot, & Buchanan, 1990).

With regard to medication, treatment with tricyclic antidepressants (TCAs) reduces HRV (Agelink, Boz, Ullrich, & Andrich, 2002; Khaykin et al., 1998). Treatment with selective serotonin reuptake inhibitors (SSRIs) normalizes HRV (Tucker et al., 1997; Yeragani & Rao, 2003). The effects of beta-blockers increase HRV, as reflected by augmented vagal activity under stress (Sandrone et al., 1994).

**FINDINGS**

Articles were searched from Medline and CINAHL from 1990 through November 2007 to identify studies with the key words IBS and HRV. Studies where the measurement of HRV was assessed in a single group of subjects before and after a procedure were excluded. Table 1 shows the summary of the measurement of HRV in IBS studies including sample size, characteristics of subjects, methods, parameters of HRV, and results.

Most studies were published recently—all but two (Aggarwal et al., 1994; Jorgensen et al., 1993) since
### Table 1

**Summary of Studies on the Relationship Between HRV and IBS**

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects (mean age = yr)</th>
<th>Methods/Variables</th>
<th>Parameter of HRV</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adeyemi et al., 1999</td>
<td>IBS (n = 35, mean age = 39.1 ± 9.5, M:26, F:9, 27 [77%]; C-IBS) vs. healthy C (n = 18, mean age = 38.2 ± 6.5, M:12, F:6)</td>
<td>Supine, standing position, and deep breathing</td>
<td>FD (HF, LF, VLF, HRav)</td>
<td>*IBS: ↑SNS in the rest, ↓PSNS in orthostatic stress</td>
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<tr>
<td>Aggarwal et al., 1994</td>
<td>C-IBS (n = 10, F:7, M:3) vs. D-IBS (n = 11, F:5, M:6) vs. C (n = 49, F:28, M:21 - ANS test) Using manning criteria Mean age = 42.3 yr *More women have C-IBS symptom</td>
<td>VC (vasoconstrictor), PAR (postural adjustment ratio), STMP, deep respiration, RRI V(R-R interval), colon transit (radio-opaque markers)</td>
<td>RRIV</td>
<td>*C-IBS: ↓PSNS during deep breathing</td>
</tr>
<tr>
<td>Burr et al., 2000</td>
<td>IBS (n = 106, 18–45) women vs. C (n = 41, 18–45) women, total mean age: 33 yr</td>
<td>HRV (Holter-monitoring)</td>
<td>TD (SD-5-min, RMSSD, %RR50, SD-5-min/ RMSSD, HRate 24-hr)</td>
<td>*Women with severe pain (39%) and without postprandial pain (49%): ↓PSNS</td>
</tr>
<tr>
<td>Elsenbruch &amp; Orr, 2001</td>
<td>Postprandial response in C-IBS (n = 12) women vs. D-IBS (n = 12) women vs. C (n = 20, mean age = 32.5 ± 1.1) women, IBS (mean age = 32.8 ± 1.4)</td>
<td>Saliva cortisol concentration, HR, HRV (two 30-min postmeal recording), GI symptoms (baseline and after meal)</td>
<td>FD (HF, LF, LF/HF, %HF, %LF)</td>
<td>*D-IBS: ↑SNS/PSNS balance (LF/HF ratio), ↓PSNS (HF) after meal and a significant postprandial in ↑cortisol</td>
</tr>
<tr>
<td>Heitkemper et al., 1998</td>
<td>IBS women (n = 25, mean age = 32.6 ± 8.0) vs. C women (n = 15, mean age = 32.5 ± 8.6)</td>
<td>HRV (Holter-monitoring: mid-luteal phase). One menstrual cycle with a symptom diary</td>
<td>FD (HF, MF, LF, MI, LF/HF) logarithmic transforms (LF, MF, HF), square-root transform (LF/HF)</td>
<td>*IBS ↓PSNS (HF) vs. C at night *35% presence of significantly low level of vagal tone observed in patients with IBS during the sleeping interval *Systemic sympathovagal imbalance in women with IBS</td>
</tr>
<tr>
<td>Heitkemper et al., 2001</td>
<td>IBS women (n = 103, mean age = 32.6 ± 8.1) vs. C women (n = 49, mean age = 32.2 ± 7.7)</td>
<td>HRV (Holter-monitoring: mid-luteal phase), E/I ratio, Valsalva, posture changes, cold pressor</td>
<td>TD (SD-5-min, SDANN, SD-24-hr, RMSSD, %RR50, SD-5-min/ RMSSD), FD (HF, LF, LF/HF, square root of LF/HF), MI</td>
<td>*Women with severe to very severe symptom have differences in 24-hr HRV *Severe D-IBS: ↑PSNS &amp; ↓SNS/PSNS balance *Severe C-IBS: ↓PSNS &amp; ↑SNS/PSNS balance</td>
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<tr>
<td>Jarrett et al., 2003</td>
<td>IBS women (n = 163, anxiety: 73, depression: 86) with history of</td>
<td>HRV (24-hr Holter monitoring)</td>
<td>TD (SD-5-min, RMSSD, %RR50, SD-5-min/)</td>
<td>*No differences in SNS/PSNS balance between groups</td>
</tr>
<tr>
<td>Study Authors</td>
<td>Participants</td>
<td>Methods</td>
<td>Results</td>
<td>Notes</td>
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<td>Jorgensen et al., 1993</td>
<td>Functional abdominal pain ((n=22, \text{mean age }=37 [16–60], F:14, M:8)) vs. organic abdominal pain ((n=26, \text{mean age }=42 [18–62], F:11, M:15)) vs. healthy controls ((n=14, \text{mean age }=36 [23–50], F:9, M:5))</td>
<td>ACTH and serum cortisol HR and systolic blood test, HRV (every 5 min during rest and stress)</td>
<td>RMSSD), FD (HF, LF, LF/HF, square root of LF/HF)</td>
<td>*IBS-Anxiety &amp; IBS-Depression: ↓PSNS relative to IBS-Control *Patients with functional abdominal pain: ↑PSNS (RMSSD [basal PSNS neural effect]) &amp; ↓SNS (reduced SNS neural response) in patients with both functional organic pain *No significance in HR, SBP, ACTH, adrenaline, cortisol</td>
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<td>Karling et al., 1998</td>
<td>IBS ((n=18, \text{mean age }=31.6 [20.6–52.3], F:14, M:4)) vs. C ((n=36, \text{mean age }=31.4 [20.8–52.3]))</td>
<td>During supine and tilting (up to 70°)</td>
<td>FD (LF, MF, HF)</td>
<td>*Significant increased sympathetic activity (MF): ↑SNS in IBS group than C during supine and tilting *No differences in PSNS activity in IBS group</td>
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<tr>
<td>Lee et al., 1998</td>
<td>C-IBS ((n=20, \text{mean age }=48.9±16.3, F:6, M:14)) vs. D-IBS ((n=20, \text{mean age }=49.2±15.6, F:6, M:14)) vs. healthy C ((n=20, \text{mean age }=50.7±17.4, F:6, M:14))</td>
<td>SSR, RRIV (R-R interval variation) during rest and deep breathing</td>
<td>RRIV</td>
<td>*C-IBS: ↓PSNS (RRIV) than D-IBS or C during deep breathing *No group differences in psychological distress</td>
</tr>
<tr>
<td>Orr et al., 2000</td>
<td>IBS ((n=15, \text{mean age }=34.9±2.1, F:13, M:2)) vs. C ((n=15, \text{mean age }=36.2±2.3, F:13, M:2))</td>
<td>HRV: 1 hr of pre-sleep waking and 7 hr sleep</td>
<td>FD (LF, HF, LF/HF)</td>
<td>*LF is significantly greater in IBS group during waking. LF/HF ratio is significantly greater in IBS group during REM sleep *IBS group has greater sympathetic activity during waking and during REM sleep. Greater sympathetic dominance in IBS group</td>
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<tr>
<td>Thompson et al., 2002</td>
<td>IBS women ((n=33, \text{mean age }=37)), IBS + D ((n=17)) vs. healthy C women ((n=38, \text{mean age }=38)) Using Rome I criteria</td>
<td>HRV: 30 min of pre-sleep waking and BDI, GI symptom questionnaire</td>
<td>FD (LF, %HF, LF/HF)</td>
<td>*During REM sleep, IBS only group: ↓PSNS relative to IBS + D and C group *During REM sleep, the ratio LF/HF is significantly higher in IBS only patients</td>
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</tbody>
</table>

C-IBS = constipation-predominant IBS; D-IBS = diarrhea-predominant IBS; TD = time domain analysis of HRV; FD = frequency domain analysis of HRV; BDI = Beck Depression Inventory; D = dyspepsia; MI = mean interval; MSSD = mean square successive differences; HF = high frequency; LF = low frequency; VLF = very low frequency; HRav = mean of all average heart rate; SSR = sympathetic skin response.
1998. A total of 12 studies were identified using criteria of key words IBS and HRV, and publication in English. All studies had healthy controls as comparing groups. One study included an organic abdominal pain group as a comparing group as well (Jorgensen et al.).

**Study population**

Studies ranged from 30 to 209 total subjects, with an average sample size of 85, and a median sample size of 60. The number of IBS subjects ranged from 12 to 163, with an average sample size of 42, and a median sample size of 22. IBS subjects sometimes were divided by stool type or severity even though a large sample size was used. Therefore, most studies utilized a small number of subjects for analysis.

The subgroups of constipation-predominant and diarrhea-predominant patients with IBS were too small to enable comparison (Karling et al., 1998). Many studies failed to clearly describe the number and characteristics of non-participants. Some studies described only age range or total mean age so it was difficult to estimate a mean age and a median age in all studies. If selecting studies shown mean age, the mean age of study subjects was 37 years old with the median age 36 years old. The duration of symptoms was reported in all studies and was typically chronic. While all subjects in six studies were women, men participated in six studies in both IBS and control groups, though in smaller numbers than women. However, Adeyemi, Desai, Towsey, and Ghista (1999) used a predominantly male sample of IBS patients (26 men and 9 women) and healthy controls (12 men and 6 women). Average subjects had attained at least a high school education. Few studies mentioned race or ethnicity. Most studies used Caucasians. The country was the US in eight studies, United Arab Emirates in one (Adeyemi et al.), Denmark in one (Jorgensen et al., 1993), Sweden in one (Karling et al.), and Taiwan in one (Lee et al., 1998).

All but two studies (Aggarwal et al., 1994; Jorgensen et al., 1993) used Rome criteria. IBS patients were referred to gastroenterology clinics or institutes of health research in five studies (Adeyemi et al., 1999; Aggarwal et al.; Elsenbruch & Orr, 2001; Karling et al., 1998; Orr, Elsenbruch, & Harnish, 2000), outpatient clinics in two studies (Jorgensen et al.; Lee et al., 1998), and community care in the other five studies. Therefore, several studies mainly recruited in a restricted geographical area. The selection subgroups were constipation-predominant IBS versus diarrhea-predominant IBS, postprandial pain, pain severity, functional versus organic disorders, IBS with a history of depression or anxiety versus IBS without a history of depression or anxiety, and IBS versus IBS with dyspepsia. Four studies classified subgroups into predominant bowel habit (Aggarwal et al.; Elsenbruch & Orr; Heitkemper et al., 2001; Lee et al.) and one study divided subgroups into postprandial pain intensity (Burr, Heitkemper, Jarrett, & Cain, 2000). One study classified subgroups into women with a history of anxiety and depression who have IBS (Jarrett et al., 2003) and other studies divided into IBS versus Control.

**Parameters of HRV**

Four studies used 24-hour Holter monitoring (Burr et al., 2000; Heitkemper et al., 1998; Heitkemper et al., 2001; Jarrett et al., 2003) and other studies have been obtained during a short period of 2–5 minutes. The Heitkemper studies used all women subjects so there is no study using both gender and 24-hour Holter monitoring. Selecting between the short and the long periods of EKG recording depends on the objective of the study. For example, a 24-hour ECG recording provides an average value of each component for the entire recording period. However, there are inconsistent recordings underlying HRV because of sleep, exercise, deep breathing, and others (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Also, it is important to differentiate responses noted under stressful conditions and data obtained from individuals under resting conditions in short-term recording. If subjects have arrhythmia, ectopic beats, and missing data, long-term recording is better than short-term recording. On the other hand, short-term recording is better than long-term recording if subjects do not have ectopic beats, arrhythmia, or noise effects (Bigger et al., 1992).
Five studies tested HRV during postural change or deep breathing or tilting (Adeyemi et al., 1999; Aggarwal et al., 1994; Heitkemper et al., 2001; Karling et al., 1998; Lee et al., 1998) and two studies tested during sleep (Orr et al., 2000; Thompson, Elsenbruch, Harnish, & Orr, 2002). The majority of studies used female populations, so it is difficult to find a gender-difference in HRV of IBS. Also, gender-related differences in HRV have not been studied or analyzed very well in this area. Comparisons of the vagal tone in males and females based on symptom subgroups remain to be studied. Most studies used frequency domain analysis; only one study used time domain analysis (Jorgensen et al., 1993) and the other two studies used only RR-interval (Aggarwal et al.; Lee et al.). Frequency domain analysis is a more sophisticated method for distinguishing between the different components (e.g., PSNS, SNS, SNS/PSNS) in HRV than the time domain method; it would be good to compare the diarrhea-predominant with the constipation-predominant subgroup of patients with IBS in terms of differences in ANS function.

RESULTS

There were inconsistent results in the studies. It was difficult to generalize the conclusions because each study had a small sample size (IBS subgroup subjects: 10–86) and used different subgroup categories as mentioned before. Twenty-five women with IBS had lower vagal tone compared to 15 healthy controls (Heitkemper et al., 1998). Subjects with constipation-predominant IBS had lower PSNS tone (HF, RRIV) and elevated ANS balance (LF/HF) while those with diarrhea-predominant IBS had greater PSNS tone and depressed ANS balance (Aggarwal et al., 1994; Heitkemper et al., 2001; Lee et al., 1998). In the Heitkemper study, there was no difference in 24-hour HRV measure between women with IBS (n = 103) compared to controls (n = 49). However, there was a difference in those women who reported severe IBS symptoms. Therefore, certain subgroups were more or less suitable for HRV measurement. A similar result was demonstrated in patients in the constipation group (n = 27 out of 35 IBS patients) in deep breathing (Adeyemi et al., 1999). The same result was shown in women in the diarrhea-predominant group (n = 12) after a meal in Elsenbruch and Orr’s study (2001). In this study, there were no significant differences between women with predominant constipation and the control group related to meals.

Karling et al. (1998) showed significantly increased SNS activity (MF) in the IBS group (n = 18) when compared to the control group (n = 36) during the supine position and tilting (head up to 70°). No differences in PSNS activity (HF) was found in the IBS group (Karling et al.). With regard to symptom severity, HRV measurement was effective in subgroups who reported severe and very severe symptoms (Heitkemper et al., 2001). In addition, women with severe pain and without postprandial pain had lower vagal tone (Burr et al., 2000). Both functional and organic abdominal pain related to reduced SNS responses were shown (Jorgensen et al., 1993). Significantly greater SNS activity (LF) was shown in IBS patients (n = 13) during waking and a significantly greater LF/HF ratio was shown in IBS patients during REM sleep (Orr et al., 2000). Similarly, higher SNS activity (elevated LF/HF ratio) during REM sleep was shown in the IBS only group (n = 16) (Thompson et al., 2002). Regarding anxiety and depression, reduced vagal tone in women with IBS had been associated with depression and anxiety (Jarrett et al., 2003); this study provided evidence for the relationship between mood state and physiological indicator, which changes visceral motility.

Overall, these studies suggested changes in ANS function were shown in patients with IBS and may differ among subgroups. For example, the majority of patients were those with alternating symptoms of diarrhea and constipation, the ANS function abnormality was obscure. It may be there are different results in the alternating IBS symptom subgroup or in those who experience constipation alone. It is still unclear if ANS function may increase GI symptoms including visceral sensitivity and motility alteration or is the result of abdominal pain sensitivity and discomfort. Pain and bloating may reflect visceral hypersensitivity (Ragnarsson & Bodemar, 1999). They found
there was no relationship between pain/bloating and prone bowel pattern so there might be different mechanisms in symptoms. There has been no study regarding the relationship between bloating symptoms and ANS function so far. The inclusion of a group of women with bloating symptoms in a future study is both critical and significant for HRV database development and understanding of the underlying mechanisms of IBS in IBS research.

DISCUSSION

Strength
Firstly, HRV and its components were a useful and simple method and appeared the most suitable for detection of changes in integrated ANS sympathovagal balance in both static and dynamic conditions in IBS patients. Many studies have shown HRV was a useful tool to assess the ANS characteristics and responses in IBS patients because it could help distinguish sympathetic from parasympathetic regulation of the sinoatrial node. Therefore, it could provide valuable information to health care providers and researchers. The use of this methodology has proven to be pathophysiologically and clinically reliable, valid and more sensitive in both psychological and physiological variables than conventional cardiovascular tests. It may offer a unique insight, including the possibility of predicting disease outcome and assessing a combination of enhanced mental load and other stressors. It may allow monitoring of the effect of therapeutic interventions on gut autonomic regulation as compared to other ANS measures. For instance, skin temperature was an insensitive measurement of sympathetic cholinergic response. Studies using laboratory measures of ANS function have only found differences when stool-type subgroups are compared (diarrhea-predominant vs. constipation-predominant) or in IBS patients with severe symptoms (Burr et al., 2000; Heitkemper et al., 2001). Also, heart rate and blood pressure were found to be less sensitive than HRV between IBS patients and healthy controls in laboratory testing (Heitkemper et al.; Huikuri et al., 1999; Jorgensen et al., 1993; Karling et al., 1998; Sato et al., 1995); there is a difference using HRV as an outcome variable even though there are no differences using heart rate and blood pressure in the same study. Thus, study of the effects of exposure to stressors may be misleading if only differences in heart rate are examined.

Secondly, HRV is an appropriate measurement in studying large populations, in both laboratory and clinical settings, and in longitudinal studies because it is easily and noninvasively performed. Hence subjects have less stress and need only minimal subject collaboration. In addition, it suggests cost-effective measurements compared to other cardiovascular tests.

Thirdly, the analysis of continuous 24-hour ECG data recordings allows one to observe variations occurring throughout the day and night for circadian pattern detection. It is a comprehensive assessment not only of fast, but also of slower and sometimes less regular, heart rate fluctuations. A more sophisticated approach to the study of HRV based on spectral methodology proves to adequately assess the sympathovagal balance. In addition, it provides various naturalistic activities under a natural environment rather than a laboratory environment.

Limitations
First of all, even though there have been progressive technological improvements in Holter processing systems, most studies require additional human editing. HRV is calculated after removal of aberrant beats. Some software packages contain an automatic default filtering procedure and a removal of any aberrant beats manual procedure. Also, ambulatory ECG recording has difficulty in controlling for activity, posture, and respiration. In addition, most software and analysis methods are different. Standardization of HRV measurement has remained poor even though it has been Task force presented (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). There is a need for standardization in methodology to facilitate the interpretation and comparison of results. More exact methodology is essential to extract the information embedded in HRV.
Secondly, there is the limitation that cardiac vagal tone may not reflect gastrointestinal vagal tone. Even though it is a sensitive method for balance (LF/HF) or PSNS activity (HF), it is less sensitive for SNS activity (LF: mixed marker of SNS and PSNS) in the GI system (Jarrett et al., 2003; Jorgensen et al., 1993). Heitkemper and coworkers (2001) have shown it is more sensitive to test ANS symptoms in women who report severe and very severe symptoms. Therefore, further studies of the relationship between GI and cardiac vagal tone is needed; is there any different role between GI vagal fiber and cardiac vagal fiber? Also, it would be better practice to combine HRV measures with biochemical measures such as epinephrine and norepinephrine.

Considering limitations of research design in previous studies, there are issues related to subjects or covariance variables. Several studies have small sample sizes with limited statistical power. Also, several studies have a small number of patients across a wide range of ages, mainly recruited in a restricted geographical area (Aggarwal et al., 1994; Elsenbruch & Orr, 2001; Lee et al., 1998; Orr et al., 2000). There are limitations in age and gender differences as well as ovarian hormone status differences in women. As mentioned earlier, the age dependency of vagal tone is quite pronounced (Cowan et al., 1994; Jensen-Urstad et al., 1997; Thayer et al., 1998). Confounding variables might be responsible for IBS patients. Smoking is associated with decreased HRV so researchers should try to control for smoking status (Hayano et al., 1990). In addition, several studies did not include different ethnic groups. Most studies use Caucasians. Moreover, control groups have not always been matched for age and sex even though both factors are known to influence ANS function (Cowan et al.; Jensen-Urstad et al.; Thayer et al.). Some studies did not control for the menstrual cycle (Orr et al.). Even though the above review demonstrates medication or other conditions contribute to HRV, medicated and unmedicated patients were not carefully separated in some of studies; medicated patients are not physiologically comparable to unmedicated patients. Some studies reported washout periods for their drug free patients or included patients who were still taking medication at the time of the study. Also, some studies do not have a well-defined group of patients characterized by the presence or absence of other disease. Every researcher used different criteria for recruiting subjects: community or referral clinics. Some studies (Aggarwal et al.) have Manning criteria rather than Rome criteria to ensure maximum sensitivity even though Rome II was developed more recently than Manning criteria.

Thirdly, there are issues related to the time period. Some studies have only tested once so they need to determine stability over time. The short term HRV measurement has limitations. It may not adequately reflect the day-to-night fluctuation in ANS responses. More complicated analysis of HRV using a long period is necessary.

Fourthly, it was demonstrated hypnosis can produce a decrease in the LF/HF ratio in cardiovascular disease (Cowan et al., 1994). However, there is no study using HRV in measuring the effect of intervention on IBS area. In addition, most studies focus on negative emotions in the IBS field. There are no studies showing that positive emotions can significantly influence HRV in IBS patients. Also, many investigators have commonly divided subgroups only into categories of pain, predominant stool type or symptom severity and frequency, and postprandial pain. To date, there has been very little research on the bloating symptom. In addition, there is no study on classifying bloating subgroups using HRV measurement even though bloating symptoms are known to be the most troublesome disease symptoms in some studies (Lembo et al., 1999; Talley, Howell, & Poulton, 2001). Furthermore, there is no study using HRV in classifying constant pain groups or intermittent pain groups. Future research is necessary to take these into consideration.

Finally, recent studies raise issues related to genetic effects on HRV in the Framingham Heart Study (Singh, Larson, O’Donnell, & Levy, 2001; Singh et al., 2002; Singh et al., 1999). In these studies, using a 10 cM genome-wide scan in 725 subjects in 230 extended families, including 390 sibling pairs, they found evidence of linkage of LF to chromosome 1 at 153 cM and VLF to chromosome 15 at 62 cM even...
though there are limitations such as predominantly Caucasian, laboratory evaluation, and intermediate duration recordings (2 hours). Several studies have been limited in genetic homogeneity of populations.

**Future applications**
A novel approach for studying the abnormality of ANS function in IBS is essential. Further developed application of HRV measurements needs to be discovered. Also, further study needs to find if the IBS intervention research (both pharmacological and non-pharmacological) is associated with a dose-related decrease in HRV using prospective, randomized controlled long-term studies. A broader picture of ANS states in IBS would require HRV with additional checking of the sensitivity and specificity and using more complicated analysis, other measures of ANS in response to a standardized laboratory stressor test, as well as ambulatory monitor recordings that measure physiological responses to everyday stressors in different subgroups of IBS. Larger studies with a variety of individuals assessing the effects of behavioral intervention and examining assessments of HRV and outcomes are essential to determine the clinical utility of intervention. Moreover, gender-related differences in HRV regarding IBS with a larger sample size are necessary. To give IBS patients the best quality of nursing care, nursing should have multi-factorial views for this health care problem, including physiological indicators such as HRV and psychological distress. Nursing may bridge the gap between theory, practice, and research in future IBS study.

**References**


