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Original Research Article

Heart Rate Variability Parameters Do Not Correlate with Pain Intensity in Healthy Volunteers

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Abstract

Objective. When patients cannot indicate pain,
physiological parameters may be useful. We tested
whether heart rate variability (HRV) parameters, as
reflection of sympathetic and vagal tone, can be
used to quantify pain intensity.

Design. Prospective study.

Subjects and Setting. A standardized heat stimulus
was applied to the forearm in 75 healthy volunteers
during three study periods of 2 minutes.

Methods. Before and after each application, pain
intensity was measured by a visual analog scale
(VAS) and inter beat interval (IBI) was recorded.
Standard deviation of normal to normal beat inter-
vals (SDNN) of the IBI, the power of the low (LF,
0.07–0.14 Hz) and high frequency (HF, 0.15–0.50 Hz)
band, and LF/HF ratio were calculated. Log transfor-
mation resulted in normal distribution. Correlation
between HRV parameters and pain intensity was
assessed by Pearson's correlation coefficient.

Results. Data from 73 volunteers (44 women) could
be analyzed. The mean age was 30 ± 11 years. Com-
pared with baseline, during all heat periods, pain
intensity measured by VAS increased from
2 ± 3 mm, 3 ± 5 mm, and 2 ± 4 mm, to 40 ± 20 mm,
42 ± 21 mm, and 44 ± 22 mm, respectively. Log
transformed SDNN (lnSDNN) and LF (lnLF)
decreased; lnSDNN from 4.0 ± 0.4 to 3.9 ± 0.5,
$P = 0.002$; 4.0 ± 0.4 to 3.9 ± 0.5, $P = 0.016$; and
4.1 ± 0.4 to 3.9 ± 0.4, $P = 0.004$, respectively; lnLF
from 6.3 ± 1.0 to 6.1 ± 1.2, $P = 0.001$; 6.4 ± 1.0 to
6.2 ± 1.1, $P = 0.019$; and 6.5 ± 1.0 to 6.2 ± 1.1,
$P = 0.020$, respectively. No correlation of any HRV
parameter with VAS score was found.

Conclusion. HRV parameters may detect responses
to heat pain, but are not suitable to assess pain
intensity.

Key Words. Experimental Pain; Heat Pain; Pain
Measurement; Heart Rate; Autonomic Nervous
System

Introduction

Measuring pain is complex in its nature. Pain is a subjec-
tive experience, influenced by psychosocial, emotional,
and spiritual factors [1,2]. Acknowledging this complexity,
multidimensional pain measurement scales have been
developed [3,4]. However, in daily clinical practice, one-
dimensional measures, such as the visual analog scale
(VAS), are commonly used [5]. The VAS is a 100 mm-long
line on which the intensity of pain can be noted from no
pain (0 mm) to the worst pain imaginable (100 mm).
Although it is an easy tool to use in the (outpatient) clinic,
it needs patients' understanding and cooperation [6,7].

In clinical conditions where patients cannot indicate their
pain, such as sedated patients on intensive care units,

self-reported pain measurement tools like the VAS are not useful. In these settings, pain intensity is measured using behavioral indicators (facial expression, sweating, clutching) and physiological parameters (heart rate, blood pressure) [8–10]. This practice is based on the belief that pain elicits a stress response, resulting in physiologic changes that correlate with pain intensity. A central assumption is that the autonomic nervous system reacts to stress, with an increase of sympathetic and/or a decrease of parasympathetic tone. These changes in the sympatho–vagal balance, meant to reroute blood flow to the organs most in need, result in an increase in blood pressure and/or heart rate [11,12].

However, in a clinical setting, no correlation between pain intensity and heart rate variability (HRV) parameters has been established until now [13,14].

HRV is the fluctuation of the heart rate around the intrinsic heart rate [15]. Rapid fluctuations are mainly induced by the input of the autonomic nervous system [15]. HRV may be a measure of experienced pain intensity as the stress response is likely to be related to the subjective experience of pain, as established in experimental settings using pain stimuli shortly (up to 1 minute). Heart rate analysis in those studies might be influenced by the initial short increase in heart rate, after which a more stable heart rate during the stimulus was obtained [16–18].

The aim of our study was to investigate whether HRV parameters can measure pain intensity induced by a standardized heat stimulus in healthy volunteers. The primary end point of the study was the correlation between pain intensity measured by VAS and HRV parameters. Secondary end points were changes in HRV parameters induced by the pain stimulus and the reproducibility of HRV parameters.

Methods

Volunteers

Healthy volunteers, aged 18 years or older, without pain or altered pain sensation, not using medication, and with no history of medical conditions possibly interfering with autonomic function were eligible for this study. Volunteers were recruited by posters and personal communication within the University and University Medical Center Groningen, The Netherlands.

Study Design

After providing informed consent, volunteers were randomized 2:1 to perform the study session once (on day 1) or twice (on day 1 and 8). The study session was performed twice in a subgroup to test reproducibility of the pain intensity measured by VAS and of the HRV parameters. The study was approved by the medical ethical committee of our hospital.
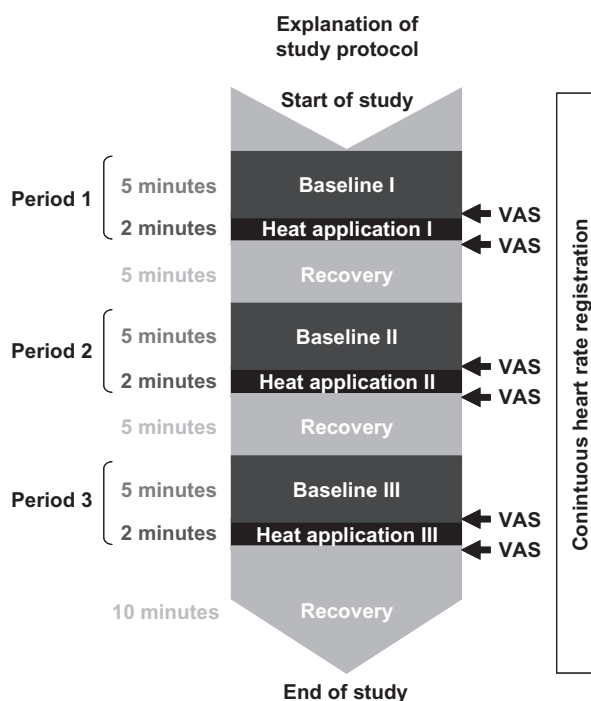
Study Session

Directly before a study session, the procedures were explained to the volunteers (Figure 1). Each study session consisted of three pain periods, in which a heat stimulus was applied during 2 minutes. Pain periods were preceded by a 10-minute rest period. The last 5 minutes of this rest period were defined as the baseline period for the following heat stimulus period.

Measures

Pain Stimulus

During 2 minutes, a heat stimulus was applied to the nondominant volar forearm, using a thermode of 3 by 3 cm attached to the Medoc Pathway Sensory Evaluation system®, Ramat Yishai, Israel. This thermode can be heated instantaneously to a desired temperature, whereas the heat can also be turned off instantly. A heat stimulus of 45°C will result in an adequate pain stimulus [19,20]. Our data indicate that when this heat stimulus is given during 1 minute, pain intensity on a VAS is rated between 40 and 50 mm initially, wearing off to less than 10 mm after 60 seconds. When the heat is increased every 10 seconds by 0.1°C, stable pain intensity is obtained. We found that this stimulus can be given during 2 minutes and be repeated without harmful effects. Therefore, the heat stimulus

Figure 1 Study flow diagram. The study flow diagram of one study session. In a random sample of the volunteers, the same study session was repeated on day 8. VAS = visual analog scale (pain intensity).

started at a temperature of 45°C and increased every 10 seconds by 0.1°C to correct for adaptation to the heat stimulus during the 2 minutes of application.

VAS

Before application of the heat stimulus, volunteers were instructed how to fill out the VAS regarding their pain intensity. The VAS consisted of a 100 mm-long horizontal line, ranging from 0 mm (no pain) to 100 mm (worst pain imaginable). They were informed that there is no "good" or "wrong" answer. The volunteers were asked to indicate their pain intensity at baseline (before heat application) and during each heat application. This last pain intensity had to be indicated directly at the end of the heat application.

HRV Assessment

Heart rate was assessed by noninvasive pulse wave measurement using a Portapres® device (Finapres Medical Systems BV, Amsterdam, The Netherlands). This device uses an inflatable finger cuff with built-in photoelectric plethysmograph (volume clamp method of Peñáz modified by Wesseling and coworkers) to derive the pulse wave [21,22]. The cuff of the Portapres was placed on the middle finger of the dominant arm. All measurements of each patient were performed with the same cuff on the same finger. The volunteers were in the supine position during the study period, holding the hand with the Portapres cuff at heart level. Volunteers were not allowed to talk or to move during the measurement, apart from putting a mark on the VAS at the required moments. During the study periods, the room in which the measurements were taken was quiet and of constant temperature (22°C). All data derived with the Portapres were stored on a computer.

Analysis

HRV

Analysis was performed by one trained person (JJM) blinded to the VAS outcomes. Before HRV analysis, the pulse wave data were preprocessed to exclude non-sinus rhythm, ectopic beats, and artifacts. The HRV parameters were derived per period (baseline or heat stimulus). As time domain parameter, the time between two normal heartbeats, the so called inter beat interval (IBI) and the standard deviation between normal to normal inter beat intervals (standard deviation of normal to normal beat interval [SDNN]) were measured [15]. The SDNN represents both sympathetic and parasympathetic tone influences [15]. The frequency domain measures were assessed using spectral analysis of all consecutive IBIs of each baseline or heat stimulus period. The low frequency domain (LF) was defined 0.07–0.14 Hz, the high frequency domain (HF) 0.15–0.50 Hz [23]. The HF band is thought to reflect respiratory modulation of the heart rate, and is abolished by atropine [24]. The LF band is influenced by both parasympathetic and sympathetic tone [15,24].

The time domain measures (IBI, SDNN) and frequency domain measures (LF and HF) were obtained by using the transfer function technique using the CARSPAN program (Rijks Universiteit Groningen, Groningen, The Netherlands) [25]. The natural logarithm of the SDNN, LF, and HF was obtained to achieve a normal distribution of the values. These transformed parameters are referred to as log transformed (ln)SDNN, lnLF, and lnHF, respectively. As a measure of the sympathetic–vagal balance, the LF/HF ratio was calculated.

Sample Size Calculation

In previous studies in horses and neonates, correlations between pain intensity scores and HRV parameters in the order of r = 0.3–0.4 have been observed [26,27]. To detect a correlation of r = 0.35 (Pearson) between VAS and HRV with 95% power and alpha = 0.05, 75 volunteers were needed. For the reproducibility study, data from 26 volunteers from two sessions of the study protocol were needed to detect a correlation of 0.8 between the measurements of the same individuals on 2 different days, based on an expected mean difference of 0.35 standard deviation between measurements, with a power of 80% and an alpha = 0.05.

Statistical Analysis

One-way analysis of variance was used to assess whether adaptation to the heat stimulus occurred. To test for changes over time between the two study sessions, the intraclass correlation coefficients were calculated between baseline period 1, 2, and 3. This was also performed for the heat application periods.

Within a study session, the pain intensity measured with VAS as well as the HRV parameters during the three heat application periods were tested. Differences in HRV parameters between baseline and the subsequent heat stimulus period were tested using paired t-test. The Pearson correlation was calculated between the VAS scores and the HRV parameters of the first study session. Whether a change in a HRV parameter correlated to the change in pain intensity measured by VAS was studied. The change in a HRV parameter (the delta HRV parameter) was calculated by subtracting the HRV parameter measured during the heat application period from the HRV parameter measured during the preceding baseline period. Moreover, the delta pain intensity measured by VAS was calculated in the same way. The Pearson correlation between the delta HRV parameter and the delta VAS was calculated.

A VAS of 40 mm or more is defined as moderate pain, indicating a need for treatment adjustment in a clinical situation [28]. Whether delta HRV parameters differed between the subgroup of volunteers who indicated a VAS ≥ 40 during heat application compared with the other volunteers was studied using the Student's t-test.

Table 1 Pain intensity measured by visual analog scale (VAS)

Study Session	Period	VAS at Baseline (mm)	VAS During Heat Application (mm)
I (N = 73)	1	2 ± 3	40 ± 20
	2	3 ± 5	42 ± 21
	3	2 ± 4	44 ± 22
II (N = 22)	1	2 ± 3	45 ± 14
	2	2 ± 4	48 ± 15
	3	2 ± 5	52 ± 17

Pain intensity measured by VAS per study session (on day 1 [I] and, in a subgroup, on day 8 [II]) for each period within the study session at baseline and during heat application. No significant differences were found between the three baseline periods or the heat application periods within one study session.

Results

Volunteers

Of the 75 volunteers, 46 (61%) were women. The mean age was 30 ± 11 years. HRV data from 73 volunteers could be analyzed (44 women, mean age 30 ± 11 years). Two volunteers had frequent ventricular extra systoles interfering with heart rate analysis. Of the 23 volunteers randomized to perform the study protocol twice, the mean age was 30 ± 10 years and 13 (56%) were women. HRV data from 22 volunteers could be analyzed, due to frequent ventricular extra systoles in one volunteer.

Pain Intensity Measured by VAS

At baseline, volunteers did not experience pain (Table 1). The heat stimulus elicited a mean pain intensity of 40 ± 20 mm during the first application. During the experiment, the mean elicited pain intensity did not change (Table 1). Also during the second study session, the mean elicited pain intensity remained stable. Thirty-six (49%) volunteers reported a pain intensity ≥ 40 mm during the first heat application period of the first study session.

HRV

HRV parameters did not change significantly over the three baseline periods nor over the three heat application periods (Table 2). Compared with baseline, during all heat application periods, the lnSDNN and the lnLF decreased significantly (Table 2).

Correlation between Pain Intensity Measured by VAS and HRV Parameters

No significant correlation between pain intensity measured by VAS and any of the HRV parameters measured during the first study session was found (Table 3, Figure 2).

Table 2 Heart rate variability (HRV) parameters per study period (data from the first study session)

HRV Parameter		Mean ± Standard Deviation per Period Within First Study Session			P Value for Trend*
		1	2	3	
IBI (milliseconds)	Baseline	910 ± 181	943 ± 177	978 ± 179	NS
	Heat application	911 ± 181	943 ± 179	976 ± 183	NS
	P value**	NS	NS	NS	
lnSDNN	Baseline	4.0 ± 0.4	4.0 ± 0.4	4.1 ± 0.4	NS
	Heat application	3.9 ± 0.5	3.9 ± 0.5	4.0 ± 0.4	NS
	P value**	0.002	0.016	0.004	
lnLF	Baseline	6.3 ± 1.0	6.4 ± 1.0	6.5 ± 1.0	NS
	Heat application	6.1 ± 1.2	6.2 ± 1.1	6.2 ± 1.1	NS
	P value**	0.001	0.019	0.020	
lnHF	Baseline	6.7 ± 1.2	6.8 ± 1.2	6.9 ± 1.1	NS
	Heat application	6.6 ± 1.3	6.7 ± 1.2	6.8 ± 1.2	NS
	P value**	0.013	NS	NS	
LF/HF	Baseline	1.1 ± 1.4	1.1 ± 1.3	1.1 ± 1.3	NS
	Heat application	1.0 ± 1.4	0.9 ± 1.1	0.9 ± 1.4	NS
	P value**	NS	NS	NS	

* Significance level of the change of visual analog scale (VAS) or HRV parameter over the periods within the first study, tested with analysis of variance.
** Significance level of the change of VAS or HRV parameter between baseline and heat application, within a study period, tested using paired *t*-test.
Significance level $P < 0.05$; NS = not significant.
HF = high frequency; IBI = inter beat interval; LF = low frequency; lnHF = log transformed high frequency; lnLF = log transformed low frequency; lnSDNNs = log transformed standard deviation normal to normal inter beat intervals.

Table 3 Correlation between pain intensity and heart rate variability (HRV) parameters

HRV parameter	Pearson Correlation per Study Period		
	1	2	3
IBI	−0.095	−0.182	−0.156
lnSDNN	−0.097	−0.083	−0.081
lnLF	−0.058	−0.083	−0.096
lnHF	−0.136	−0.026	−0.091
LF/HF	0.026	−0.023	0.008

Pearson correlation between perceived pain intensity measured with visual analog scale and HRV parameters during heat application of the first study session (N = 73). None of the correlations was significant at the $P < 0.05$ level.
HF = high frequency; IBI = inter beat interval; LF = low frequency; lnHF = log transformed high frequency; lnLF = log transformed low frequency; lnSDNNs = log transformed standard deviation normal to normal inter beat intervals.

Reproducibility

The intraclass correlation coefficients of the two study sessions were assessed for pain intensity measured by VAS and HRV measures (Table 4). During baseline, the intraclass correlation coefficient was low for pain intensity measured by VAS. All HRV measures did have reasonable to good intraclass correlation coefficients, apart from the LF/HF.

Correlations

Despite the significant change in lnSDNN and lnLF between the heat application period and the preceding baseline period, no significant correlation was found between delta pain intensity measured by VAS and delta lnSDNN nor between delta VAS measurement and delta lnLF. The delta HRV parameters did not differ significantly between volunteers who indicated a VAS of less than 40 mm or at least 40 mm during heat application (Table 5).

Discussion

Despite significant changes in HRV parameters during heat application compared with baseline, no correlation between pain intensity measured by VAS and HRV parameters was found in this study.

During all three heat application periods, the lnSDNN and lnLF were significantly lower compared with the preceding baseline periods. This finding corresponds with results of previous studies [16,18]. In one study, pain unpleasantness (but not pain intensity), elicited by a 4°C cold plate, was negatively correlated to the LF in 59 male students [16]. Although the LF band is influenced by both parasym-

pathetic and sympathetic tone, it is regarded to reflect mainly the parasympathetic tone, as atropine almost abolished the LF peak in an experimental setting [24]. This suggests that the decrease in lnLF during heat application found in our study is due to a decrease in parasympathetic tone.

The other study measured heart rate, HRV, skin conductance level, number of skin conduction fluctuations, and photoplethysmographic pulse wave amplitude during heat application in 55 volunteers. Three levels of pain intensity (low, medium, and high) were calibrated individually [18]. All of the parameters successfully discriminated between no pain and pain. However, none of the parameters differentiated between all three pain categories. In contrast to each single autonomic parameter, a linear combination of parameters significantly discriminated not only between pain and no pain, but also between all pain categories. The authors did not report on the correlation between experienced pain and autonomic responses. However, by individual calibration of the experienced pain levels, this study anticipated the lack of a correlation between experienced pain and autonomic responses during a standard stimulus by heat application. This approach made it possible to study, within individuals (and not between individuals), the relation between experienced pain level and autonomic responses. In their model, pain was induced during 60 seconds. Within that time frame, observations of heart rate and HRV might be largely influenced by the initial heart rate increase at the moment the painful stimulus is delivered, as has been shown previously [17]. To be of use in the clinical practice, HRV parameters should not only be discriminative at the early onset of pain, but especially for the measurement of chronic pain. A recent study in 84 postoperative patients addressed the application on HRV parameters in a clinical setting [13]. In that study, pain was induced by minor surgical procedures, i.e., elective orthopedic surgery distal of elbow or knee joint or plastic surgery. During admission in the postoperative anesthetic care unit (PACU), pain intensity was rated every 5 minutes by numeric rating scale (ranging from 0, no pain, to 10, unbearable pain). Heart rate was measured continuously by electrocardiography. The median pain intensity on admission to the PACU was 4, and decreased to 3 on discharge. If the score was above 3, patients received fentanyl intravenously.

Comparable with our results, no correlation between pain intensity and physiologic parameters of the sympathetic-mediated stress response was found. Whether medication influenced HRV assessment is questioned. It has been argued that these findings are not surprising as behavioral context influences the pain experience [29]. In our study, the behavioral context was standardized as much as possible. Volunteers were aware of the induction of pain and could habituate to the pain stimulus. However, throughout our study, pain intensity caused by the heat application within an individual remained unchanged. Also the baseline HRV parameters did not shift during the study periods. Therefore, it is unlikely that the pain stimulus was anticipated by the volunteers and influenced the
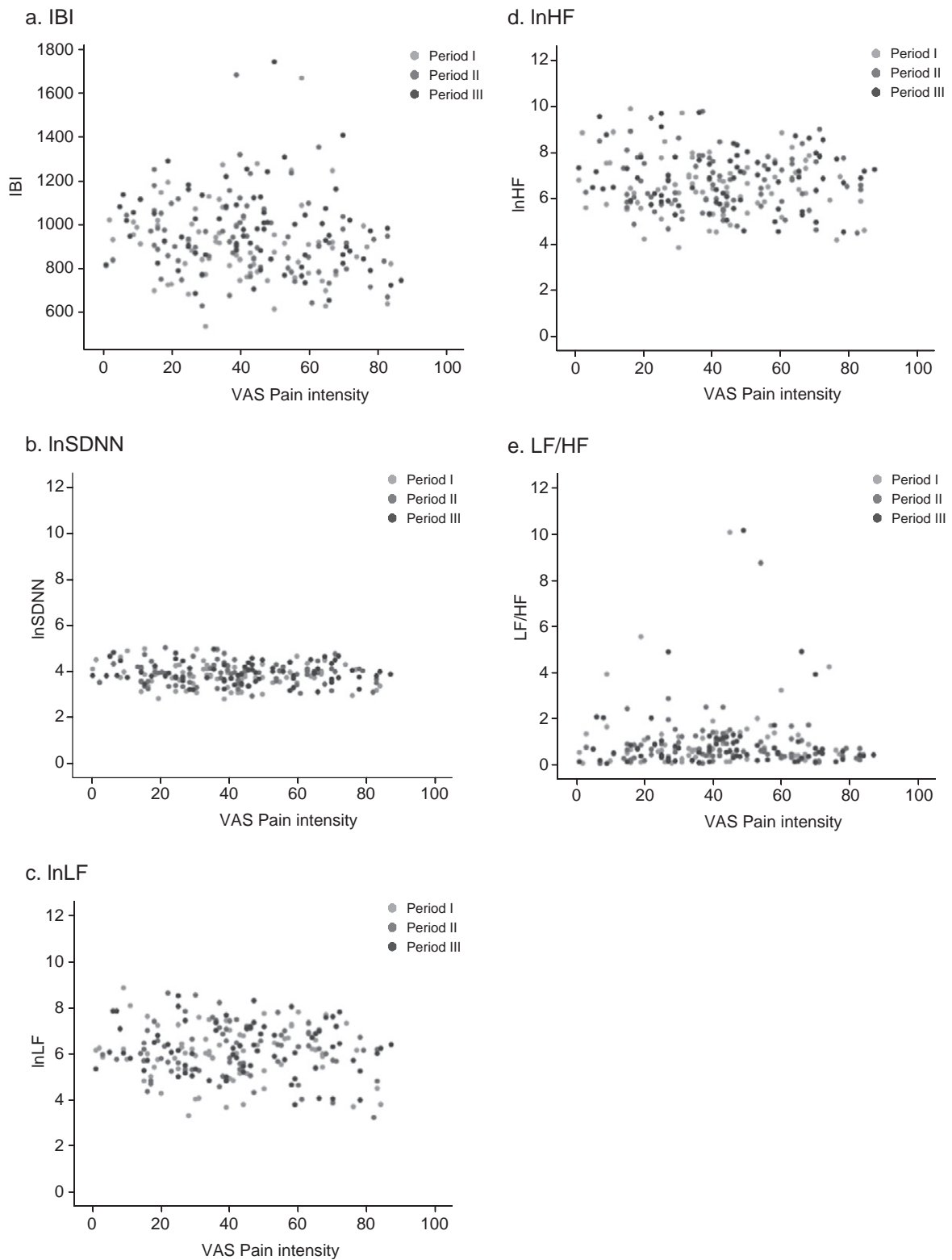
Figure 2 Scatter plot visual analog scale (VAS) pain intensity and. HF = high frequency; IBI = inter beat interval; LF = low frequency; lnHF = log transformed high frequency; lnLF = log transformed low frequency; lnSDNNs = log transformed standard deviation normal to normal inter beat intervals.

Table 4 Intraclass correlation coefficients of the first and second study session

Parameter	Period		Mean $\pm$ Standard Deviation per Study Session		Intraclass Correlation Coefficient
			I (N = 22)	II (N = 22)	
VAS (millimeters)	Baseline	1	2 $\pm$ 3	2 $\pm$ 3	0.102
		2	2 $\pm$ 3	2 $\pm$ 4	0.302
		3	2 $\pm$ 3	2 $\pm$ 5	0.206
	Heat application	1	44 $\pm$ 18	45 $\pm$ 14	0.583
		2	50 $\pm$ 17	48 $\pm$ 15	0.767
		3	53 $\pm$ 17	52 $\pm$ 17	0.892
IBI (milliseconds)	Baseline	1	928 $\pm$ 213	931 $\pm$ 206	0.858
		2	961 $\pm$ 199	987 $\pm$ 205	0.927
		3	994 $\pm$ 217	1,006 $\pm$ 196	0.890
	Heat application	1	922 $\pm$ 198	940 $\pm$ 194	0.828
		2	955 $\pm$ 200	982 $\pm$ 197	0.896
		3	991 $\pm$ 203	1,002 $\pm$ 205	0.910
lnSDNN	Baseline	1	4.0 $\pm$ 0.3	3.9 $\pm$ 0.5	0.670
		2	4.0 $\pm$ 0.4	4.0 $\pm$ 0.5	0.812
		3	4.1 $\pm$ 0.4	4.1 $\pm$ 0.5	0.710
	Heat application	1	3.9 $\pm$ 0.4	3.8 $\pm$ 0.5	0.702
		2	3.9 $\pm$ 0.4	3.9 $\pm$ 0.6	0.700
		3	4.1 $\pm$ 0.4	3.9 $\pm$ 0.5	0.595
lnLF	Baseline	1	6.6 $\pm$ 0.7	6.3 $\pm$ 1.0	0.707
		2	6.5 $\pm$ 1.0	6.6 $\pm$ 1.2	0.722
		3	6.5 $\pm$ 0.7	6.7 $\pm$ 1.0	0.636
	Heat application	1	6.3 $\pm$ 0.9	6.1 $\pm$ 1.0	0.539
		2	6.3 $\pm$ 0.9	6.2 $\pm$ 1.4	0.581
		3	6.5 $\pm$ 0.9	6.2 $\pm$ 1.1	0.576
lnHF	Baseline	1	6.8 $\pm$ 1.0	6.6 $\pm$ 1.0	0.784
		2	6.9 $\pm$ 1.0	6.9 $\pm$ 1.4	0.838
		3	6.9 $\pm$ 1.0	7.0 $\pm$ 1.0	0.721
	Heat application	1	6.7 $\pm$ 1.1	6.6 $\pm$ 1.2	0.851
		2	6.9 $\pm$ 1.1	6.7 $\pm$ 1.3	0.772
		3	7.1 $\pm$ 1.0	6.6 $\pm$ 1.0	0.647
LF/HF	Baseline	1	1.4 $\pm$ 1.0	1.1 $\pm$ 0.9	0.334
		2	1.0 $\pm$ 0.9	1.0 $\pm$ 0.7	0.605
		3	1.0 $\pm$ 1.2	1.0 $\pm$ 0.5	0.417
	Heat application	1	1.1 $\pm$ 1.3	1.0 $\pm$ 1.3	0.907
		2	0.7 $\pm$ 0.5	1.1 $\pm$ 1.4	0.171
		3	0.8 $\pm$ 0.8	0.9 $\pm$ 0.9	0.160

HF = high frequency; IBI = inter beat interval; LF = low frequency; lnHF = log transformed high frequency; lnLF = log transformed low frequency; lnSDNNs = log transformed standard deviation normal to normal inter beat intervals; VAS = visual analog scale.

autonomic response. Moreover, the intraclass correlation coefficients of HRV parameters indicate reasonable reproducibility of the measurements after 1 week, except for the LF/HF. Therefore, our results obtained in healthy volunteers within a standardized setting affirm the conclusion of the clinical study that no meaningful relation exists between HRV measures and pain intensity.

The absence of any correlation between HRV parameters and pain intensity measured by VAS questions the general conception that pain elicits a stress response resulting in physiologic changes that correlate with pain intensity. This conception is based on observations that pain resulted in changes in sympathetic and parasympathetic parameters [11,12,16,18]. The absence of a correlation between these changes and pain intensity may not be that surprising, as suggested by Jänig [29]. Apart from the nociceptive stimulus, the affective-motivational perception, the cognitive-evaluative meaning, and the social context of someone will influence the individual reaction to pain [30]. Furthermore, neurophysiologic imaging studies suggest that the autonomic response to pain is part of interrelated somatic, autonomous, and neuroendocrine reactions, with internal feedback mechanisms to affective-motivational and cognitive-evaluative centers [31–35]. Therefore, the reaction to pain seems not

Table 5 Analysis of heart rate variability (HRV) response in volunteers reporting visual analog scale (VAS) < 40 mm or ≥40 mm during heat application

| HRV Parameter | Period | Pain Intensity (VAS) During Heat Stimulus | | | | | P Value |
| | | <40 mm | | ≥40 mm | | | |
		N	Mean ± SD	N	Mean (SD)		
Delta IBI (milliseconds)	1	37	5.6 ± 44.6	36	−5.1 ± 36.6		NS
	2	34	3.3 ± 39.2	39	−1.6 ± 39.8		NS
	3	30	4.7 ± 42.5	43	−2.1 ± 37.2		NS
Delta lnSDNN	1	37	−0.08 ± 0.24	36	−0.12 ± 0.28		NS
	2	34	−0.07 ± 0.28	39	−0.09 ± 0.28		NS
	3	30	−0.06 ± 0.28	43	−0.10 ± 0.28		NS
Delta lnLF	1	37	−0.19 ± 0.53	36	−0.32 ± 0.71		NS
	2	34	−0.18 ± 0.78	39	−0.23 ± 0.74		NS
	3	30	−0.18 ± 0.60	43	−0.23 ± 0.85		NS
Delta lnHF	1	37	−0.06 ± 0.44	36	−0.22 ± 0.48		NS
	2	34	−0.11 ± 0.42	39	−0.04 ± 0.46		NS
	3	30	−0.09 ± 0.42	43	−0.06 ± 0.45		NS
Delta LF/HF	1	37	−0.13 ± 0.55	36	−0.10 ± 0.68		NS
	2	34	−0.10 ± 0.70	39	−0.22 ± 1.55		NS
	3	30	−0.06 ± 0.60	43	−0.24 ± 1.52		NS

Comparison of delta HRV parameters between volunteers reporting VAS < 40 mm and volunteers reporting VAS ≥ 40 mm during the heat application in the first study session. Results are presented per period. The delta HRV parameter is defined by the difference in HRV parameter during heat application and the preceding baseline period. Significance level $P < 0.05$; tested with Student's *t*-test; NS = not significant.
HF = high frequency; IBI = inter beat interval; LF = low frequency; lnHF = log transformed high frequency; lnLF = log transformed low frequency; lnSDNNs = log transformed standard deviation normal to normal inter beat intervals; SD = standard deviation.

a straightforward stress response suitable for objective measurement.

No difference was found in the HRV response between volunteers indicating their pain as at least 40 mm during heat application with regard to volunteers who did report a lower score. This further supports the conclusion that HRV parameters cannot be used to measure pain intensity.

A weakness of our present study may be that the study population consisted of relatively young volunteers, without medication or comorbidity, tested in preset controlled conditions. This setting is completely different from clinical reality of pain measurement. In contrast with the clinic, during the study, the pain stimulus was controlled, of a determined length, known to the volunteer. This might have influenced the autonomic response. Furthermore, in clinical practice, many more interfering factors are present, like disease, comorbidity, and medication, which are likely to obscure a possible correlation between pain intensity and HRV parameters.

Possibly the heat stimulus itself caused the HRV response. This is suggested by a study in 60 healthy volunteers, who immersed their left hand in hot (47°C) and cold (7°C) water [36]. The power of LF and HF was found to decrease during immersion in hot water, while the LF and HF power increased during immersion in cold water. This might be induced by systemic vasomotor changes rather than autonomic responses to perceived pain as both heat and cold might be painful [36]. As in our study, only one noxious stimulus with constant intensity was used; this suggestion could not be tested.

Respiration has not been registered during this study. However, changes in respiration rate are likely to be reflected in the HF band, which was not detectable in our results. Moreover, gender effects can have contributed to the found study results [37,38]. Our study sample was too small to test this hypothesis.

We conclude that heat application lowers SDNN and LF, but no association exists between the experienced pain intensity and HRV parameters. Therefore, we confirm that HRV parameters detect responses to heat pain, but do not seem suitable to assess pain intensity in a clinical setting.

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References

1 Greenstreet W. The concept of total pain: A focused patient care study. Br J Nurs 2001;10:1248–55.

2 Saunders C, Sykes N. The Management of Terminal Malignant Disease. London: Hospital Medicine Publications; 1993.

3 Cleeland CS. Measurement of pain by subjective report. In: Chapman CR, Loeser JD, eds. Advances in Pain Research and Management, Vol. 12. New York: Raven Press; 1989:391–403.

4 Melzack R. The McGill pain questionnaire (major properties and scoring methods). Pain 1975;1:277–99.

5 Flaherty SA. Pain measurement tools for clinical practice and research. AANA J 1996;64:133–40.

6 Gagliese L, Weizblit N, Ellis W, Chan VWS. The measurement of postoperative pain: A comparison of intensity scales in younger and older surgical patients. Pain 2005;117:412–20.

7 Jensen MP. The validity and reliability of pain measures in adults with cancer. J Pain 2003;4:2–21.

8 Arbour C, Gelinas C. Are vital signs valid indicators for the assessment of pain in postoperative cardiac surgery ICU adults? Intensive Crit Care Nurs 2010; 26:83–90.

9 Li D, Puntillo K, Miaskowski C. A review of objective pain measures for use with critical care adult patients unable to self-report. J Pain 2008;9:2–10.

10 Walter-Nicolet E, Annequin D, Biran V, Mitanchez D, Tourniaire B. Pain management in newborns: From prevention to treatment. Paediatr Drugs 2010;12:353–65.

11 Bruehl S, Chung OY. Interactions between the cardiovascular and pain regulatory systems: An updated review of mechanisms and possible alterations in chronic pain. Neurosci Biobehav Rev 2004;28:395–414.

12 Lindh V, Wiklund U, Hakansson S. Heel lancing in term new-born infants: An evaluation of pain by frequency domain analysis of heart rate variability. Pain 1999; 80:143–8.

13 Ledowski T, Reimer M, Chavez V, Kapoor V, Wenk M. Effects of acute postoperative pain on catecholamine plasma levels, hemodynamic parameters, and cardiac autonomic control. Pain 2012;153:759–64.

14 Jänig W. Systemic and specific autonomic reactions in pain: Efferent, afferent and endocrine components. Eur J Anaesthesiol 1985;2:319–436.

15 Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: Standards of measurement, physiological interpretation and clinical use. Circulation 1996;93:1043–65.

16 Appelhans BM, Luecken LJ. Heart rate variability and pain: Associations of two interrelated homeostatic processes. Biol Psychol 2008;77:174–82.

17 Loggia ML, Juneau M, Bushnell MC. Autonomic responses to heat pain: Heart rate, skin conductance, and their relation to verbal ratings and stimulus intensity. Pain 2011;152:592–8.

18 Treister R, Kliger M, Zuckerman G, Aryeh IG, Eisenberg E. Differentiating between heat pain intensities: The combined effect of multiple autonomic parameters. Pain 2012;153:1807–14.

19 Granovsky Y, Granot M, Nir RR, Yarnitsky D. Objective correlate of subjective pain perception by contact heat-evoked potentials. J Pain 2008;9:53–63.

20 Neisser U. Temperature thresholds for cutaneous pain. J Appl Physiol 1959;14:368–72.

21 Peñáz J. Photo-electric measurement of blood pressure, volume and flow in the finger. In: Albert R, Vogt W, Helbig W, eds. Digest of the 10th International Conference on Medical and Biological Engineering. Dresden, Germany: International Federation for Medical and Biological Engineering; 1973:104.

22 Wesseling KH. Finapres, continuous noninvasive finger arterial pressure based on the method of Peñáz. In: Ruddel H, Curio I, eds. Noninvasive Continuous Blood Pressure Measurement. Frankfurt am Main: Verlag Peter Lang GmbH; 1991:9–17.

23 Mulder LJ. Measurement and analysis methods of heart rate and respiration for use in applied environments. Biol Psychol 1992;34:205–36.

24 Kleiger RE, Stein PK, Bigger JT, Jr. Heart rate variability: Measurement and clinical utility. Ann Noninvasive Electrocardiol 2005;10:88–101.

25 Mulder LJM, van Dellen HJ, van der Meulen P, Opheikens B. CARSPAN: A spectral analysis program for cardiovascular time series. In: Maarse FJ, Mulder LJM, Sjouw W, Akkerman A, eds. Computers in Psychology: Methods, Instrumentation and Psychodiagnostics. Lisse: Swets & Zeitlinger; 1988:39–47.

26 Rietmann TR, Stauffacher M, Bernasconi P, Auer JA, Weishaupt MA. The association between heart rate, heart rate variability, endocrine and behavioural pain measures in horses suffering from laminitis. J Vet Med A Physiol Pathol Clin Med 2004;51:218–25.

27 van Dijk M, de Boer JB, Koot HM, et al. The association between physiological and behavioral pain measures in 0- to 3-year-old infants after major surgery. J Pain Symptom Manage 2001;22:600–9.

28 World Health Organization (WHO). Cancer Pain Relief, Edition 2. Geneva: WHO; 1996.

29 Jänig W. Autonomic reactions in pain. Pain 2012;153:733–5.

30 Loeser JD. Perspectives on pain. In: Turther P, ed. Clinical Pharmacy and Therapeutics. London: Macmillan; 1980:313–6.

31 Peyron R, Laurent B, Garcia-Larrea L. Functional imaging of brain responses to pain. A review and meta-analysis (2000). Neurophysiol Clin 2000;30:263–88.

32 Schnitzler A, Ploner M. Neurophysiology and functional neuroanatomy of pain perception. J Clin Neurophysiol 2000;17:592–603.

33 Neugebauer V, Galhardo V, Maione S, Mackey SC. Forebrain pain mechanisms. Brain Res Rev 2009; 60:226–42.

34 Hayes DJ, Northoff G. Common brain activations for painful and non-painful aversive stimuli. BMC Neurosci 2012;13:60.

35 Farmer MA, Baliki MN, Apkarian AV. A dynamic network perspective of chronic pain. Neurosci Lett 2012;520:197–203.

36 Huang CM, Chang HC, Kao ST, et al. Radial pressure pulse and heart rate variability in heat- and cold-stressed humans. Evid Based Complement Alternat Med 2011;17:945–52.

37 Aslaksen PM, Myrbakk IN, Høifødt RS, Flaten MA. The effect of experimenter gender on autonomic and subjective responses to pain stimuli. Pain 2007;129: 260–8.

38 Tousignant-Laflamme Y, Rainville P, Marchand S. Establishing a link between heart rate and pain in healthy subjects: A gender effect. J Pain 2005; 6:341–7.