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Establishing a Link Between Heart Rate and Pain in Healthy Subjects: A Gender Effect

Yannick Tousignant-Laflamme,* Pierre Rainville,† and Serge Marchand*

Abstract: **Heart rate (HR) is currently used by rehabilitation clinicians as a complementary objective measure of pain. The premise is that, as pain increases, HR should also increase. However, this relationship is not clearly established. The goal of this study was to verify the relationship between HR and pain perception. Thirty-nine healthy volunteers participated in this experimental study. Painful stimuli were induced by a 2-minute immersion of the hand in hot water (47°C). HR was recorded before and during the stimulation and was matched to a pain rating. We observed a rise of 11% in HR after 2 minutes of immersion. There was a significant intrasubject correlation between HR and pain intensity ($r = 0.50$, $P < .001$) and pain unpleasantness ($r = 0.55$, $P < .001$). Furthermore, there was a strong gender effect in the intersubject correlations. Men presented a strong correlation between mean HR and mean pain perception (intensity: $r = 0.77$, unpleasantness: $r = 0.86$), whereas this relationship was absent in women (intensity: $r = -0.2$, unpleasantness: $r = 0.001$). In conclusion, results show that, for healthy volunteers, experimental pain can elicit a rise in HR up to 11%. Moreover, the relationship between HR response and pain is gender related. Considering that a positive relationship between HR and pain perception was only found in men, these results do not support a clinical significance of the use of HR for pain evaluation in women. Clinical implications need to be further evaluated with patients before clinicians can use HR as a complementary tool in pain assessment.**

Perspective: ***A positive correlation between HR and pain was observed for men but not for women. These differences underline the importance of taking into account gender differences in the development of complementary pain assessment. Further research should be conducted to verify the role of sex hormones on heart rate and pain.***

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Key words: *Pain perception, heart rate, gender differences, electrophysiology, autonomic nervous system.*

Pain is the first reason for the consultation of a rehabilitation health specialist in musculoskeletal pathologic conditions. A significant role of the physical therapist is to assess pain while evaluating a patient's physical condition or functional capacities. However, because pain is a subjective experience, its evaluation requires the collaboration of the patient, and few reliable alternative tools are currently available to clinicians. Nevertheless, clinicians frequently use heart rate (HR) measurements interindividually to "validate self-report of pain."[17] The current use of HR is based on the principle that, as a patient's pain level rises, HR should rise accordingly. It is well established that a painful stimulus does produce many physiologic changes; however the slope of the relationship between pain and physiologic responses has been shown to vary noticeably between individuals.[5]

Consequently, the validity of this principle and its current application have been rightfully criticized mostly by the absence of good literature exposing the relationship between HR and pain and allowing the generalization of these findings to clinical pain.[17] Moreover, HR is subjected to many sources of variations that may affect its association with pain. For example, it is well known that emotional factors related to pain or to the context of a clinical evaluation may affect autonomic activity and reactivity (eg, anxiety, vigilance).[12,13]

In spite of methodologic limitations and potential con-

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founding factors, relationships between pain and autonomic nervous system (ANS) activation have been demonstrated in a variety of contexts.[4,7,11] Physiologic reactivity to painful stimuli is associated with intrinsic adjustments of the sympathetic and parasympathetic divisions of the ANS. This mainly reflects an adaptation response to painful stimuli through the sympathetic and parasympathetic efferent pathways.[4] There is usually a balance between the two divisions of the ANS where the HR reflects a net effect of both sympathetic and parasympathetic influences. Studies have shown that the rise in HR as a result of pain is mostly related to an increase in sympathetic activity.[6] However, the activation of the sympathetic system may be followed by a rise in parasympathetic activity to play an antagonistic role and reestablish the homeostatic balance.[11] Furthermore, modern models of cardiac regulatory processes now include the possibility of coactivation and codeactivation in addition to the classic reciprocal interactions of the sympathetic and parasympathetic systems.[3] These observations and theoretic models emphasize the need to obtain measures of both divisions to fully account for the autonomic cardiac regulation. The physiologic fluctuations in ANS activity can be measured by beat-to-beat heart rate variations and by use of spectral analysis of the tachogram.[31] Measurement of heart rate variability (HRV) provides a noninvasive method to obtain reliable and reproducible information on the relative involvement of the sympathetic and parasympathetic systems in the autonomic modulation of the cardiac response.

In addition to the sympathetic indices of heart rate activity, electrodermal measurements also reflect the sympathetic response as a function of the sweat gland activity. The measurement of fluctuations in skin conductance provides a simple method and reproducible electrophysiologic data to investigate more specifically the sympathetic nervous system function and the response to arousing or emotional stimuli. In this study, we included measures of skin conductance because it may provide confirmatory evidence of peripheral sympathetic activation correlated to pain perception.

The link between autonomic responses and experimental pain has been studied in healthy volunteers. The main advantage of using experimental pain relies in the ability to control stimulation parameters and on its reproducibility. Numerous researchers have shown a rise in HR from 6% to 8% among healthy subjects after the application of experimental pain.[10,14,16,22,23,30] However, those studies present methodologic limitations that reduce their inferential potential to a clinical perspective. These limitations concern mainly small sample sizes, the poor ecologic validity of the nociceptive stimuli used, and the single- dimension evaluation of pain.

Pain can be categorized into sensory-discriminative (eg, sensory intensity) and motivational-affective (eg, unpleasantness) dimensions, which vary in relative importance depending on the type of pain.[26,28] These dimensions can be measured reliably in both experimental and clinical settings by use of visual or numeric analog scales of pain intensity and pain unpleasantness.[9,20,21,26,28] Sustained (tonic) experimental pain tests are relatively more unpleasant (after subjective pain intensity is controlled) and may be more comparable to clinical pain than to brief (phasic) pain tests.[28] Tonic pain tests lasting a few minutes may also simulate better the transient exacerbation of clinical pain in physical challenges typically performed in rehabilitation assessment. Consequently, we relied on the administration of a tonic pain test using multidimensional measures of pain and refined measures of sympathetic and parasympathetic activity, to determine whether autonomic responses reflect more specifically one or another dimension of the pain experience.

Overall, HR may be a promising objective tool, liable to reveal important information related to pain. The clinical applications could be numerous and may have an impact on both the rehabilitation setting and the medical practice in general.

The goal of this experimental study was (1) to verify the relationship between HR and multidimensional aspects of pain perception (pain intensity and unpleasantness) among healthy volunteers with use of a tonic experimental pain test, (2) to examine the relative contribution of sympathetic and parasympathetic activity to pain-related autonomic responses, and (3) to contribute to the development of better guidelines to interpret HR as a complementary pain evaluation tool in rehabilitation.

Material and Methods

Participants

After approval from the hospital review board, we collected data from 39 healthy volunteers, 19 men and 20 women. The mean age was 26.5 years (SD 7.2 years) for women and 23.1 years (SD 4.4 years) for men. None of the participants had any known diseases and none were taking medications. No subject with self-reported hypotension or hypertension, or any other clinical condition, was included in this study. The entire experimental procedure lasted about 15 minutes. The experiment took place at the Clinical Research Centre of the Sherbrooke University Hospital, Sherbrooke, Quebec, Canada. Subjects were recruited through advertisement and were all French-speaking, community-dwelling individuals. All participants gave written informed consent for their participation in the study.

Experimental Procedures and Pain Measurements

Before the hand-immersion test was performed, subjects were comfortably seated and were asked to relax. Baseline physiologic measures were recorded for 2 minutes before the procedure. After this baseline recording, we proceeded to a hand-immersion pretest of 1 minute to familiarize the subject with the experimental protocol and to reduce the stress or anxiety that could be related to the procedure. The subjects were then given 5 minutes to rest before the experimental test.

The pain test consisted of the immersion of the right hand (up to the wrist) in circulating hot water main-

tained at 47°C for 2 minutes. Because of the relatively higher levels of affective responses it produces, a tonic (sustained) experimental pain test was preferred because it has been argued to better reflect the experience of clinical pain than phasic (brief) pain tests.[28] This procedure has been shown to produce moderate levels of pain in healthy subjects.[19] Subjects rated their perceived pain every 15 seconds for the 2-minute immersion. Ratings of pain intensity and unpleasantness were obtained using a separate visual analog scale (VAS) with numeric and verbal descriptors ranging from 0 (no pain/not unpleasant) to 100 (most intense/unpleasant pain imaginable).[19-21] Subjects were informed that they could remove their hands at any moment if the stimulation was too painful or uncomfortable.

HR and HRV Measurement

The electrocardiogram (ECG) was recorded continuously at 1000 Hz with a Powerlab monitor (ADInstruments, Colorado Springs, Colo) and filters were used according to Powerlab's guidelines (low pass: 1000 Hz, high pass 0.3 Hz). The monitor sampled the ECG signal and measured the time interval between successive QRS wave complexes to obtain the instantaneous, normal to normal (NN) interval tachogram. Time series analyses of the interbeat intervals were done offline with HRV software from ADInstruments according to the manufacturer's guidelines. The mean HR was calculated for the 2-minute pretest baseline and at each 15-second interval during the hand-immersion test. In addition, we calculated various indices of HRV for the whole hand-immersion time and the pretest baseline. Frequency-domain analysis of HRV was performed to obtain high-frequency power (HF: 0.15-0.40 Hz) and low-frequency power (LF: 0.04-0.15 Hz) components. The LF band reflects both sympathetic and parasympathetic modulation, and the HF band reflects primarily vagal (parasympathetic) regulation of HR.[31] The number of NN interval differences greater than 50 milliseconds, NN50, was also used to estimate HF variations in heart rate, thus reflecting vagal activity. The ratio of LF/HF was used as a measurement of sympathovagal balance.[31]

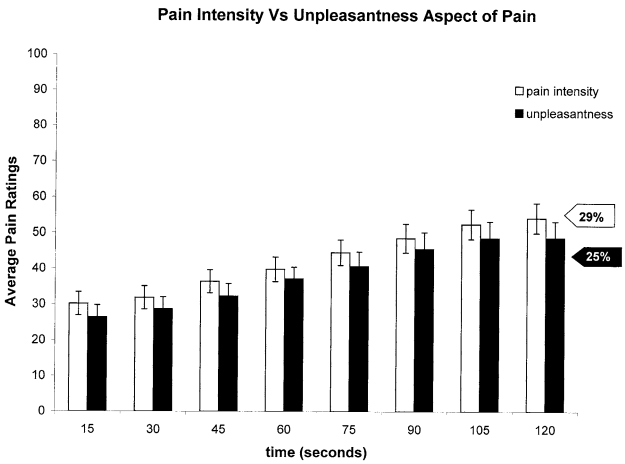

Figure 1. Pain intensity versus unpleasantness aspect of pain. A linear relationship between immersion time and pain perception was recorded. After 120 seconds of immersion, we observed an average rise of 29% in pain intensity and 25% in unpleasantness. There was a 0.90 correlation between both aspects of pain perception.

Electrodermal Activity

Skin conductance levels (SCL) were obtained with use of a Powerlab monitor (ADInstruments) according to the manufacturer's guidelines (no filters were used for SCL measurements). After the skin was cleaned, electrodes were firmly connected to the patient's middle phalanx of the first and second fingers of the left hand. The subjects were asked to keep their hands still to avoid movement artifacts and were asked to relax before baseline conductivity measurements before immersion.

Data Analysis and Statistics

Comparative analyses were conducted to examine pain perception and autonomic activity before and during the hand-immersion test. Repeated measures analysis of variance (ANOVA) was used to evaluate the effect of the subject's sex and immersion time (time 0-120 seconds) on self-reports of pain intensity and pain unpleasantness and on HR. The effect of sex and pain (hand-immersion vs pretest baseline) was also evaluated on HF activity, NN50, LF/HF, and SCL.

Correlation analyses were calculated to examine the relationship between pain intensity, pain unpleasantness, and HR changes, both within and between subjects. The within-subject approach examines whether the gradual changes in HR (mean HR at each 15-second interval) measured during the immersion are correlated with the gradual increases in pain reported by the participants. Correlations were first calculated for each subject. Then we calculated an overall within-subject correlation by combining all data points from each subject and partialling out the variance associated with individual differences (subject factor included as a dummy variable). These analyses test the consistency of subjects to report more pain when the HR increases. Both intrasubject correlations (within subject) and intersubject correlations (between subjects) were performed. Intraindividual correlations were calculated using the 9 time points of data collection starting at time 0 with no pain (preimmersion) and baseline HR (see Figures 1 and 2). Analyses were done with Statview software (SAS Institute, Cary, NC) or SPSS (version 11.0; SPSS, Chicago, Ill).

Only one subject withdrew his hand before the 120 seconds because it was intolerable, which resulted in no HR readings for the time interval between 105 seconds and 120 seconds. The missing data points were assigned using the equation of the regression line computed on this subject's data obtained before 105 seconds.

Results

Pain Perception

Both pain intensity and unpleasantness ratings increased as a function of time during the hand immersion

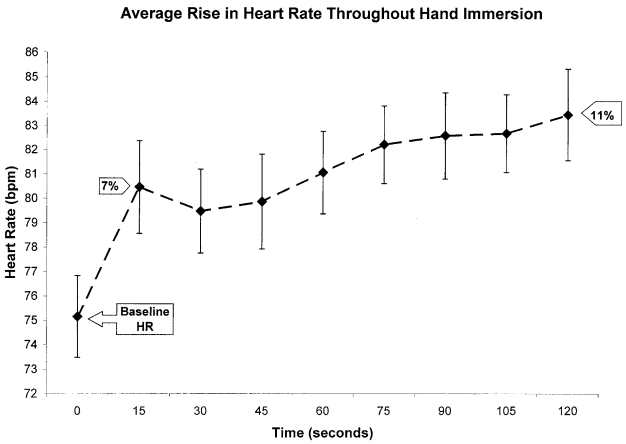

Figure 2. Average rise in heart rate throughout hand immersion. An average rise of 7% in HR was seen in all subjects for the first 15 seconds of hand immersion. After a slight drop in HR for the second interval, a constant rise in HR was observed resulting in an 11% total rise in HR for all subjects.

test (main effect of time on pain intensity: $F_{8,296} = 83.84$, $P < .0001$; unpleasantness: $F_{8,296} = 56.74$, $P < .0001$). There was no significant effect of sex on pain intensity ($F_{1,37} = 0.057$, $P = .81$) or pain unpleasantness ($F_{1,37} = 0.164$, $P = .69$) and no significant interaction between sex and time ($Ps > .05$). Significant increases between the baseline and each successive time interval were observed for both pain ratings ($Ps < .0001$). All subjects rated pain intensity slightly higher than pain unpleasantness, and we observed an overall rise of 29% for intensity and 25% for unpleasantness from 15 seconds to 120 seconds (see Figure 1). The two dimensions of pain perception were highly correlated ($r = 0.90$, $P < .001$).

Cardiovascular Response

The mean resting HR was established at 77.04 beats/min (SD 10.46 beats/min) for the 39 subjects. Women had a slightly higher mean HR than men at all time points, but this difference was not significant ($P = .47$). Only a main effect of time was obtained ($F_{8,296} = 15.19$, $P < .001$). Significant HR differences were observed between the baseline HR and all successive time intervals ($Ps < .001$). The first 15 seconds produced a 7% rise in HR, which was followed by a slight decrease in HR at 30 seconds. We then observed a second rise in HR reaching 11% after 120 seconds of immersion, which translated into a mean 8.87 beats/min increase (see Figure 2).

HRV and Electrodermal Activity

Autonomic responses were further examined by using indices of sympathetic (SCL and LF/HF ratio) and parasympathetic activity (NN50 and HF). Skin sympathetic activity increased during hand immersion as revealed by the significant difference between SCL before and during the stimuli ($P < .001$). The same tendency was observed in the LF/HF ratio ($P = .052$). Parasympathetic activity decreased during the noxious stimuli as shown by the decrease in NN50 ($P < .001$) and a similar tendency was observed in HF ($P = .16$). We observed no gender differences in the autonomic responses ($Ps > .05$). Table 1 illustrates mean and SD for each variable.

Correlations Between HR and Pain Perception (Table 2)

Individual Pearson r values ranged from -0.55 to 0.92 for intensity (mean $\pm$ SD: 0.50 ± 0.36) and from -0.19 to 0.95 for unpleasantness (mean $\pm$ SD: 0.55 ± 0.30). Mean r values were not statistically different between men and women (t tests, $Ps > .10$). The combined intrasubject correlations between HR and pain perception (after partialling out individual differences, analysis of covariance [ANCOVA]) were highly significant both for pain intensity ($r = 0.49$, $P < .001$) and pain unpleasantness ($r = 0.54$, $P < .001$). The correlation was still present for unpleasantness after changes in pain intensity were controlled (partial correlation: $r = 0.26$, $P < .001$). In contrast, the correlation with pain intensity was no longer significant (partial correlation: $r = -0.06$, $P = .27$) after the variance associated with unpleasantness was removed.

Intersubject correlations between the percent increase of HR and pain perception was not statistically significant for pain intensity ($r = 0.22$, $P = .17$) but was significant for unpleasantness ($r = 0.39$, $P = .013$) (see Figure 3, *A*). However, we found important gender differences. Women showed very poor and nonsignificant correlations between the percent increase in HR and mean pain perception (pain intensity: $r = -0.204$, $P = .39$; unpleasantness: $r = 0.001$, $P = 1.00$) (Figure 3, *B*). In contrast, men did show higher and significant correlations between the percent increase in HR and mean pain perception (pain intensity: $r = 0.77$, $P < .001$; unpleasantness: $r =$

Table 1. Observed Mean and SD for HRV and Electrodermal Activity

Variable	Before (mean [SD])	During (mean [SD])	Paired t Test
NN50	28.57 (4.57)	19.15 (3.02)	$t = 4.82$, $P < .001$
HF activity (nu)	29.18 (4.73)	25.45 (4.02)	$t = 1.40$, $P = .16$
LF/HF ratio	2.67 (0.44)	4.23 (0.69)	$t = -1.99$, $P = .052$
GSR (microsiemens)	2.92 (0.45)	11.52 (1.74)	$t = -8.43$, $P < .001$

Abbreviations: HRV, heart rate variability; NN50, number of normal to normal interval differences greater than 50 milliseconds; HF, high-frequency power; LF, low-frequency power; GSR, galvanic skin response.

Table 2. Correlation Coefficients Between Mean Percentage Increase in HR and Pain Perception Ratings for All Subjects, Women Only, and Men Only

	Pearson r Values	*P Value (α = 5%)*
All subjects		
Pain intensity	0.22	.17
Pain unpleasantness	0.39	.013
Women		
Pain intensity	−0.204	.39
Pain unpleasantness	0.001	1.00
Men		
Pain intensity	0.77	$P < .001$
Pain unpleasantness	0.86	$P < .001$
Intrasubject correlations		
Pain intensity	0.49	$P < .001$
Pain unpleasantness	0.54	$P < .001$

Abbreviation: HR, heart rate.

NOTE: Combined intrasubject correlations were calculated with a partial-correlation approach where individual differences are accounted for using a covariance method (ANCOVA).

0.86, $P < .001$) (Figure 3, C). The partial correlations for men remained significant ($P < .05$) for unpleasantness after pain intensity was accounted for but not with intensity after unpleasantness was accounted for. Partial correlations for the women's group were very poor and not significant ($P > .05$) for both intensity ($r = -0.2$) and unpleasantness ($r = 0.001$).

Discussion

The main goal of this study was to examine the relationship between HR and pain during tonic experimental pain. Overall, we found a steady rise in pain perception with time for both pain intensity and unpleasantness, which showed a clear linear relationship and therefore an excellent correlation between pain perception and immersion time. The significant difference between each time interval mainly originates from the constant and prompt rise in pain perception as the immersion time increased.

On average, the experimental pain procedure evoked a 7% rise in HR after only 15 seconds and an additional 4% rise in HR to elicit a total of 11% rise in HR after 120 seconds. Both pain perception and HR rose with immersion time, creating a positive linear relationship and resulting in a significant correlation between HR and the immersion time. This observation has significant clinical implications. First, it goes with the findings of Moltner et al[23] that there is a brief "window" that reflects the most explicit rise in HR after a painful stimulus. Therefore, clinicians gathering HR information as an objective measure should be aware that there is a brief window of opportunity that is more sensitive to the patient's acute reaction to a painful stimulus. This is critical to the use of HR when determining the proper time to continue or to stop a therapeutic procedure. On the other hand, it is also within that initial time frame that other factors influencing HR such as stress, anxiety, anticipation, and personal characteristics manifest themselves. Interestingly, by looking closely at the determination coefficient, 85% of the HR variation seems to be explained by the immersion time. Therefore, even in a controlled experimental setting, the HR variations observed were not solely due to the painful stimuli. Recognizing these elements in the interpretation and use of HR is crucial to the clinician because it can bias the clinical interpretation.

The ANS response seems to adequately reflect the subject's reaction to the stimulus. However, those observations are rarely available in a clinical setting. Still, for further analysis of the patient's response to the painful stimulus, we analyzed data from the SCL and HR with the NN50 and LF/HF ratio (visceral indicators of autonomic modulation of RR intervals). The observations we made definitely facilitate our interpretation of the cardiac response in relation to the painful stimulus. The rise in sympathetic activity and the drop in parasympathetic activity are congruent with the typical acute reaction of the ANS associated with a noxious stimulus.[11,23,27] These effects are consistent with the classic interpretation of HR responses to pain.

The correlation between HR and pain perception may have potential clinical relevance if properly and carefully used. If we look closely at the results from the intersubject correlation, we find a stronger correlation between HR and pain unpleasantness than with pain intensity. This finding is consistent with the current literature on the subject, as reported by Price et al[26] and Rainville et al,[27] suggesting that pain-related autonomic responses are functionally related to the affective dimension of the experience.

The extrapolation of the observed correlation coefficients between HR and pain perception in a clinical setting can lead to a dramatically different use of HR in men and women. Both men and women individually showed some HR increases during the nociceptive stimulation. However, men with the largest HR increases consistently reported higher levels of pain intensity and unpleasantness, but women with the largest HR increases did not report more pain (in fact, on average, they reported slightly less pain). Gender differences in cardiovascular responses to experimental pain were previously described indicating that only men had a positive correlation between pain tolerance and cardiovascular reactivity, which is in agreement with our results.[7] Furthermore, our results are also supported by previous findings suggesting sex differences in physiologic predictors of pain, in which only men showed a correlation between pain perception and cortisol level, a central component of the stress response influencing pain processing.[1]

This sex difference in the correlations might be explained by two factors. First, it is established that there are sex differences in the reactivity of the cardiovascular and autonomic nervous systems.[18,24,25] The fact that we did not observe sex differences in HF or LF/HF ratio could be due to the short duration of the recording (2 minutes), which is at the very lower end of the

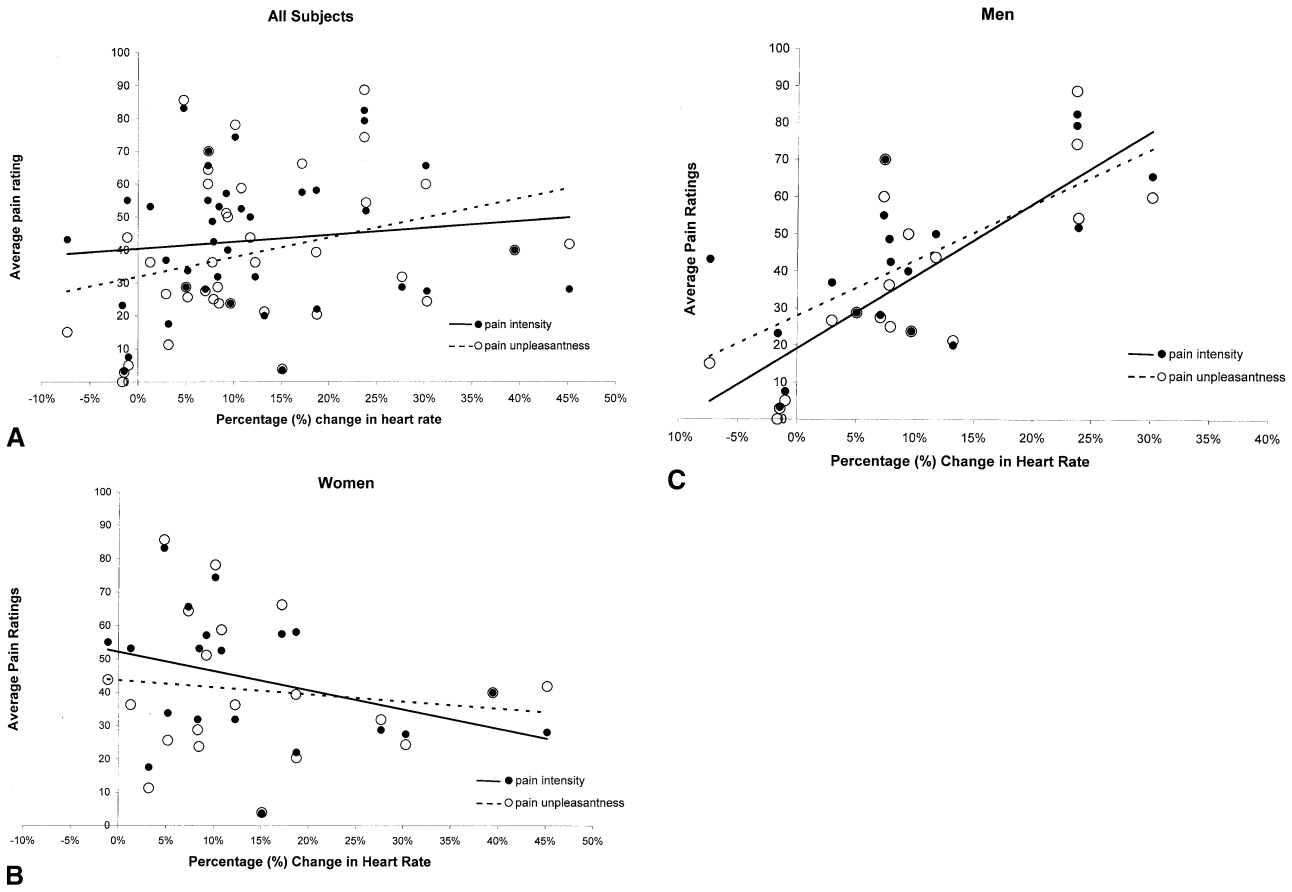

Figure 3. A, Correlation between HR increments (%) and mean pain intensity and mean pain unpleasantness ratings for all subjects. Intersubject correlations between rise percentage in HR and the mean pain intensity perception revealed a very poor correlation ($r = 0.22$) for pain intensity and poor correlation for unpleasantness ($r = 0.39$). **B,** Intersubject correlations between mean HR increments and mean pain intensity and mean pain unpleasantness ratings for women. Intersubject correlations between rise percentage in HR and the mean pain perception revealed a very poor correlation ($r = -0.204$) for pain intensity and for unpleasantness ($r = 0.001$). **C,** Intersubject correlations between mean HR increments and mean pain and mean unpleasantness ratings for men. Intersubject correlations between rise percentage in HR and the mean pain perception revealed a significant correlation for pain intensity ($r = 0.77$, $P < .05$) and for unpleasantness ($r = 0.86$, $P < .05$).

recommended recording time for proper HRV analysis[31]; therefore, caution should be applied when interpreting the spectral analysis derived data. Also, it is established that sex hormones, more precisely estrogen, seem to be responsible for an increase in vagal modulation and a decreased sympathetic modulation of the heart.[18] Moreover, sex hormones also play a major role in pain perception.[29] We then suspect that sex hormones could partly explain the sex differences observed in the intersubject correlations. However, because the sex differences were found after the data were collected and because neither the phase of the menstrual cycle nor the use of contraceptives was controlled, the role of sex hormones in the sex differences reported in this study still needs to be explored. It has also been reported that there are sex differences with regard to pain perception, where women are reporting higher pain ratings than men.[8] We did not find a significant sex difference in that regard. This could be explained by the fact that sex differences are dependent on the type of nociceptive stimuli.[2] Furthermore, some authors reported no sex differences with thermal pain[15] such as in this study.

The clinical interpretation of the current results must be done with caution. We found a good intersubject correlation between the rise in HR and pain perception for men, where 44% to 58% of the variation in HR was explained by the pain perception. Our observations might contribute to increase the understanding of the conditions in which HR responses are valid predictors of pain, especially where the higher range of HR increase (>20%) was always associated with moderate or high levels of pain (≥50/100). However, relatively high levels of pain were also reported in some men (up to 70/100) with only a 3% to 15% rise in HR (one also showed a decrease of more than 5% in HR [see Figure 3, *C*]). This means that, although HR increases may be generally considered a good indicator of pain levels in men, it cannot be used to discard a patient's evaluation of pain in a clinical setting. Indeed, our results show that even in the objective presence of a noxious stimulus producing moderate to high levels of pain,

some patients may show only modest HR increases and occasionally some patients may even show a decrease in HR. The current results support a relationship between HR and pain in men but not in women, suggesting that the actual use of HR as a complementary approach to pain measurement does not hold for women. Future research is needed to elucidate the role of sex hormones.

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