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Hypertension and pain sensitivity: effects of gender and cardiovascular reactivity

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Abstract

Repeatedly, hypertensives have been found to appraise physical stressors as less aversive than normotensives. The main aim of the present study was to examine the effects of gender and cardiovascular reactivity in the relationship between hypertension and appraisal of pain. Forty-two unmedicated hypertensives and 21 normotensive controls of both genders were exposed to an electric current stimulus, while various cardiovascular parameters and pre-stressor anxiety were measured. In general, hypertensive women, but not men, showed diminished pain sensitivity compared to their normotensive counterparts. When the analyses were repeated with controlling for cardiovascular reactivity, the between-group effects were no longer significant. The results indicate that (i) profound gender differences exist in hypertension-related pain sensitivity and (ii) these effects seem to be mediated, at least partly, by cardiovascular reactivity. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Baroreceptor; Gender; Cardiovascular reactivity; Hypertension; Pain sensitivity

1. Introduction

Repeatedly, elevated blood pressure has been found to be associated with diminished sensitivity to painful physical stimulation. This has been demonstrated for electrical (Zamir et al., 1980), thermal (Sheps et al., 1992), and finger pressure pain stimulation techniques (Bruehl et al., 1992). Moreover, also in normotensive

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samples, an inverse relationship between blood pressure and perceived painfulness of physical stressors has been obtained (Bruehl et al., 1992). This inverse relationship has been found in both between-subjects (Zamir and Shuber, 1980) and within-subjects designs (Dworkin et al., 1979), in animal (Randich and Maixner, 1984) as well as in human studies (Sheps et al., 1992).

However, until now, most studies on the relationship between cardiovascular activity and pain sensitivity have been conducted on male subjects (Zamir and Shuber, 1980; Elbert et al., 1988; Bruehl et al., 1992; Sheps et al., 1992). The few studies conducted on both genders have revealed conflicting results. For instance, Fillingim and Maixner (1996) found an inverse association between resting systolic blood pressure (SBP) and pain sensitivity only in men, not in women. In another study, partially a reverse effect was found: resting SBP and blood pressure reactivity to a speech task were associated with lower pain sensitivity to a thermal stimulus only in women (Bragdon et al., 1994). The latter outcome is in agreement with an investigation showing that parental history of hypertension was related to lower retrospective pain ratings after venipuncture in women, not in men (France et al., 1994). In light of these discrepancies, in the present study, the primary aim was to examine gender differences in various pain conditions more systematically.

In most studies showing diminished pain sensitivity in hypertensives, subjects had little control over the physically aversive stimuli (Zamir and Shuber, 1980; Bruehl et al., 1992; Sheps et al., 1992). Therefore, it may be hypothesized that having little control over a stressor moderates the relationship between hypertension and pain sensitivity. For instance, Rau et al. (1994) argued that their failure to find differences in pain threshold between hypertensives and normotensives may be attributed to the fact that the participants had some feeling of control over the stimulus: as soon as the pain threshold was reached, the stimulation was stopped by the participants. Therefore, in the present study, electric stimulation was used both in an externally controlled condition, in which stimulus intensity was controlled automatically by a computer and a self-controlled condition, in which the participants themselves had full control over stimulus intensity. Furthermore, it has been proposed that stimulus duration and frequency may be important variables influencing the pathways involved in antinociception (Terman et al., 1984). For example, it has been suggested that in exposure to short-duration aversive stimuli, an opioid system may be involved, whereas non-opioid mechanisms may predominate when the organism is exposed to stressors of long-duration (Terman et al., 1984). It is conceivable that involvement of qualitatively different systems might also influence the degree of antinociception (Randich and Maixner, 1984). In the present study, the externally controlled condition included two subconditions: one with only a few slow, relatively long stimuli and one in which more frequent, but short stimuli were presented.

Furthermore, it was examined whether appraisal of pain would be related to indices of cardiovascular *reactivity*, a putative risk factor or marker for hypertension (Manuck et al., 1990). Bruehl et al. (1992) demonstrated that SBP reactivity during a finger pressure stimulus trial was positively related to pain ratings, in contrast to negative correlations with baseline SBP. Similar results were obtained in

another study (Peckerman et al., 1991). However, France and Stewart (1995) recently found that heart rate and blood pressure reactivity to a cold pressor test were negatively related to pain ratings obtained during an ischemic pain stressor. All three studies were conducted on healthy young male normotensive subjects, indicating that sample characteristics probably did not account for the difference. Bruehl et al. (1992) attributed their effect to pain-induced arousal or anticipatory anxiety on blood pressure. France and Stewart (1995) argued that exaggerated general cardiovascular responsiveness to stressors may be associated with diminished pain appraisal, possibly via baroreceptor stimulation (Dworkin et al., 1979). Although occasionally negative findings were obtained with respect to the role of baroreceptor stimulation (France et al., 1991; Rau et al., 1994), the majority of the evidence strongly suggests mediation by the baroreceptors: links have been reported between afferent pathways of the baroreceptors to central nervous system areas involved in pain perception (Randich and Maixner, 1984) and also direct associations have been found between experimental baroreceptor stimulation and diminished pain sensitivity (Dworkin et al., 1979; Elbert et al., 1988).

In the literature on hypertension and self-reported stress, diagnosis or awareness of hypertension has often been regarded as an important confounding variable. Whereas diagnosed hypertensives frequently report more medical symptoms (Monk, 1980; Zonderman et al., 1986) and more life stress (Myers and Miles, 1981) than individuals with normal blood pressures, undiagnosed or unaware hypertensives sometimes report even less medical symptoms (Davies, 1970; Kidson, 1973) and life stress (Linden and Feuerstein, 1983; Theorell et al., 1986) than normotensive persons. Although the baroreceptor mechanism—which has been suggested to be responsible for hypertension-related effects on pain appraisal (Dworkin et al., 1979; Randich and Maixner, 1984)—is expected to be equally effective in aware and unaware hypertensives (Dworkin et al., 1979), in order to control for any potential confounding effect of hypertension awareness/diagnosis, in the present study both aware and unaware hypertensives were included.

The main hypotheses were: (a) hypertensives have higher pain threshold and tolerance levels, especially in conditions with limited-control, (b) hypertensives show greater cardiovascular reactivity during the task, and (c) the relationships mentioned in (a) are (partly) mediated by the cardiovascular response differences between the groups. In addition, given the earlier inconsistencies in the research outcomes, no specific gender differences were anticipated.

2. Method

2.1. Participants

The present study is the second part of a project on hypertension and appraisal of stressors, the first part being a population screening study on hypertension, self-reported problems, and defensiveness in a sample of 1120 women and 903 men between 20 and 55 years of age (Nyklíček, 1997). In order to investigate the effect

of being aware of one's blood pressure level in both studies, 50% of the subjects participating in the population study were not told their blood pressure level. These participants would obtain their blood pressure levels after the whole project (including the present study) was ended, except when very high pressures were discovered (> 170/110 mmHg). In the latter case, they were informed about the high pressure and discarded for the present laboratory study (this applied only to one person out of the eligible unaware participants). In this way, subjects could be included, who had elevated blood pressures at the screening, but still were unaware of this condition (not being aware was again checked at the moment of making the appointment for the laboratory session). Of the population study sample, 1203 (59.5%) individuals agreed to participate in the present study, if selected. Exclusion criteria were use of anti-hypertensive medication, presence of diabetes mellitus, any form of kidney disease, a history of myocardial infarction or other heart disease, and use of any medication that may influence perception and mood.

A sample of 63 subjects was drawn to obtain three groups matched mainly on age and gender (with both genders represented approximately equally), but also as much as possible on body mass index (BMI), alcohol use, smoking, physical exercise, and level of education: 21 aware but untreated hypertensives, 21 unaware hypertensives, and 21 normotensives. Definition of hypertension was based on the mean of at least three valid resting blood pressures measured during the population screening study using an automatic digital device, described below, at the participants' homes. A mean SBP of at least 140 mmHg or a mean DBP (diastolic blood pressure) of equal to or higher than 90 mmHg was considered hypertensive. In the laboratory, blood pressure status appeared to be changed in five participants: in four unaware hypertensives (three men and one woman), the values were in the normal range in the laboratory, for one normotensive woman the reverse was true. These five persons were excluded from all analyses. No significant differences between the groups were found on any of the matching variables, although a trend appeared for a slightly higher BMI for the aware hypertensive group (see Table 1).

According to recent recommendations (Shapiro et al., 1996), participants were asked to refrain from using alcohol on the day of the experiment, from caffeine consumption for at least 3 h and from smoking for at least 2 h prior to the laboratory session. The subjects received NLG 40 (approximately $20) for their participation.

2.2. Tasks

The participants performed the tasks in the same order as described below. Standardized instructions to the tasks were presented on the screen of a Commodore 486 SX-25 personal computer, which ran the complete session.

2.2.1. Music perception
A relaxing music fragment (new age) of 290 s duration was presented with the instruction just to "listen attentively to the music". The music source was a Philips tape recorder N2 503/00 and the speakers were Philips 22 RH 497. In addition, the

participants were instructed as follows: "after the music, some questions will be asked about the feelings you think are expressed by the music". These questions were included in a 12-item questionnaire regarding affective content of the music, largely based on a checklist used in a previous study (Nyklíček et al., 1997). This task was intended to be a fake-task, providing an opportunity for the subjects to get familiar with performing a task in the present setting, resulting in a more relaxed state before starting the pain conditions.

2.2.2. Pain stimulation

Constant electric current was delivered to the ventral side of the left forearm of the participants using a Tursky concentric electrode (Tursky, 1974). The skin below the electrode was lightly abraded in order to keep resistance below 10 kΩ. The current was a 60 Hz bipolar 50%-duty square pulse which could reach a maximum of 6 mA. The task consisted of three conditions presented in a fixed order: (i) self-controlled intensity regulation, (ii) slow automatic intensity regulation, and (iii) fast automatic intensity regulation. In the first condition, participants were asked to raise the current slowly by themselves by using an intensity control switch starting from 0 mA. During the task, they were asked to indicate, by pushing a reaction button, when the stimulus was "perceived for the first time" (sensory threshold),

Table 1
Characteristics of the samples: means, standard deviations, and percentages[a]

Variable	NT ($n = 20$)	UHT ($n = 16–17$)	AHT ($n = 20–21$)	$F(p)$
SBP[b]	119.8 (9.3)	145.9 (21.6)	157.5 (20.9)	23.33***
DBP[b]	78.7 (5.3)	97.2 (12.2)	103.9 (9.7)	39.58***
Age	44.8 (5.6)	44.1 (5.3)	43.5 (6.7)	0.26
% Men	55.0%	52.9%	52.4%	0.01
BMI	24.4 (2.3)	24.9 (3.5)	26.7 (4.1)	2.66 #
Partner[c]	95.0%	88.2%	95.2%	0.43
Education[d]	11.2 (3.5)	11.2 (2.9)	10.5 (3.3)	0.35
Employment[e]	80.0%	76.5%	76.2%	0.05
Smoking[f]	55.0%	58.8%	33.3%	1.50
Coffee[g]	5.55 (2.63)	6.19 (2.56)	4.67 (3.07)	1.40
Alcohol[h]	8.1 (9.0)	11.0 (8.7)	10.7 (12.4)	0.48
Sport[i]	1.10 (1.51)	1.06 (1.60)	1.20 (1.36)	0.04

[a] NT, normotensives; UHT, unaware hypertensives; AHT, aware hypertensives. Percentages instead of means are reported for dichotomous variables. ***$p < 0.001$ (with Tukey's HSD post hoc tests revealing no significant differences between the two hypertensive groups); # $p = 0.79$.
[b] Values of systolic blood pressure (SBP) and diastolic blood pressure (DBP) are means of pre-session and post-session values.
[c] Percent married or living together.
[d] Years of education.
[e] Percent employed.
[f] Percent smoker.
[g] Cups per day.
[h] Glasses per week.
[i] Hours per week.

when it began to be "painful" (pain threshold), and when it reached the point to be "unpleasant to a degree that the subject wanted to terminate the current" (pain tolerance), at which point the stimulation stopped. Three identical trials were performed in this condition, which on average lasted approximately 180 s. The second condition was very similar to the first condition (also with regard to the duration: on average 160 s), with the exception that the current was raised automatically with a fixed rate instead of being raised by the participant at his or her own pace, resulting in lower control over this condition. The current increased in a linear way starting from 0 mA at a rate that would reach the maximum of 6 mA in 40 s if the participant would not terminate the stimulus earlier at the pain tolerance level. In this condition, five trials were performed. Also, in the last condition (during 160 s on average), the current increased automatically from 0 mA at a fixed rate, only this time much faster: the current would reach the 6 mA in 4 s if the participant would not terminate the stimulus earlier. Given the very limited time in this condition, the participants only had to push the button once: when the stimulus became painful. Twenty trials were performed in this last condition.

Given the fact that the present study was part of a larger project, after the pain conditions, a number of other tasks were completed: a mental arithmetic, free speech, and two film fragments. The results on these tasks fall outside the aims and scope of this paper and will therefore not be discussed here.

2.3. Self-report instruments

First, to get an impression of the psychological state of the participants, at the very start of the session, several questions were asked about the current participants' mood and how they experienced the day. The questions were largely based on the adjectives of the Profile of Mood States (POMS; McNair et al., 1971). The list contained five questions about the past day and eight questions about the current mood of the participants. The questions were answered using 5-point Likert scales ranging from 1 = not at all to 5 = very much.

An index of pre-task anxiety was assessed in order to control for possible effects of pre-task state anxiety on pain sensitivity. This was measured before the music task and before the three pain stimulation conditions by asking the question: "Are you feeling tense?", which was answered on a 5-point Likert scale with the same range as above.

2.4. Physiological data collection

Blood pressure data were collected in two ways. Blood pressure was measured immediately before and after the session, using the same device as in the population screening home measurements: a Philips HP 5330 automatic digital device, based on the oscillometric method. This was done in order to check whether the blood pressure status in the laboratory did not differ from the one based on the home blood pressure measurements, on which the initial classification of the participants was based. This device proved to be a valid instrument in a pilot study (described

in Nyklíček, 1997). In the present study, two consecutive blood pressure measurements were taken just after the electrodes were attached and two at the end of the experiment, while the subjects were sitting. During the entire experiment blood pressure was measured using an Ohmeda 2300 Finapres for within-subject blood pressure reactivity, which the Finapres assesses reliably (Gerin et al., 1993). The signal was recorded continuously by a cuff placed around the middle finger of the left hand of the participants (all subjects were right-handed).

An electrocardiogram (ECG) was obtained from disposable Hellige Ag-AgCl electrodes that were placed on the sternum and the lateral margin of the chest. The ECG was recorded using a Beckman R611 with a time constant of 0.3 s and a 30-Hz high frequency cut-off filter.

2.5. Procedure

The participants were welcomed and seated in a comfortable chair. After an informed consent was obtained from the participants, the electrodes and transducers were attached. Blood pressure was measured twice using the Philips device described above with a 2-min interval between the measurements. On average, 45 min after the participants entered the experiment room, the computer started the experimental program. Having completed the mood checklist (which on average took 91 s), the participants started with the music perception task. The pain tasks followed after a 5-min rest period. All pain stimulation conditions were preceded by the pre-task anxiety question and followed by a 90-s rest period. After the pain conditions, a rest period of 5-min followed. Then the other tasks were presented, with usually 5-min rests in between. The whole experiment was ended by a recovery period of 10 min and lasted on average for 120 min. After the experiment, again blood pressure was measured twice using the Philips digital sphygmomanometer.

2.6. Data reduction

For each task and rest period, means and standard deviations were taken of the following cardiovascular variables: (a) inter-beat-interval (IBI), defined as the time in ms between successive R-waves, (b) systolic blood pressure (SBP), and (c) diastolic blood pressure (DBP). Moreover, an index of the baroreceptor activity was derived using the sequence method based on the technique described by Parati et al. (1988). In the present study, a non-invasive version of the technique was applied, which earlier has been demonstrated to be adequate (Steptoe and Sawada, 1989; Watkins et al., 1995). This method is based on taking sequences of three or more heart cycles with successive IBI lengthening accompanied by SBP elevations or vice versa. The resulting mean regression slope is used as an index of baroreceptor sensitivity. In light of the fact that only the up-sequences are relevant for the potential baroreceptor-related link between hypertension and pain sensitivity (Dworkin et al., 1979; Elbert et al., 1988)—only baroreceptor stimulation caused by blood pressure *elevations* counts in that mechanism—, only the slope of the up-sequences was used here. Moreover, the results with respect to the down-se-

quences were not substantially different. The thresholds for minimal change were set at 5 ms and 1 mmHg, which is about the mean of the thresholds applied in previous studies (Parati et al., 1988; Steptoe and Sawada, 1989; Watkins et al., 1995). Because the duration of the tasks and the amount of artefact data were not equal across participants, the number of sequences was defined as the number per 100 valid IBI and SBP data in a condition. To obtain greater reliability for the slope measures, the mean slopes had to be based on at least three sequences. If not, the value was recoded as missing. Across conditions, the mean number of participants with missing slopes was 6.5.

The four last minutes of the resting period immediately before the pain conditions were used as baseline. After computing the mean values, responses were defined as the true difference scores (T) between the mean task value and the mean baseline value corrected for its reliability, according to Fahrenberg et al. (1995):

$$T_{ij} = y_{ij} - [x_j + r_{xxj}(x_{ij} - x_j)]$$

in which y_{ij} and x_{ij} are the respective task and baseline score for subject i and condition j and x_j is the mean and r_{xxj} is the reliability coefficient of baseline measures across subjects[1] (see Huitema, 1980, p. 312).

Within each of the three electric current conditions, the pain sensitivity parameters of interest (threshold and tolerance) were simply the means across all trials.

Due to a little noise on the ECG signal, baroreflex sensitivity—which is very sensitive to beat-to-beat IBI variability noise—was discarded for two participants for the entire experiment. As a result of noise on the Finapres signal, blood pressure and more baroreflex data were excluded from the analyses for another participant.

2.7. Statistical analysis

The following statistical analyses were performed using the SPSS statistical software package. First, differences between groups on background variables were tested by means of one-way analyses of variance. In general, for the main between-group differences, three-way (Group × Gender × Condition) multivariate repeated measures analysis of variance (MANOVA) were performed using unique sums of squares, which controls for every other effect when testing the significance of an effect. The multivariate approach to repeated measures analyses has been recommended by Vasey and Thayer (1987), in order to prevent violation of the sphericity assumption. Where appropriate, lower-order analyses (simple effects), were performed in order to examine the differences more closely. When covariates were used, first it was tested whether the parallelism assumption was met. Because of the possibility of finding significant results in the direction opposite to that stated in the hypotheses, all tests were performed applying a two-tailed level of significance.

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[1] The correlation coefficient between the pre-task baseline and the mean of the post-task baselines is used, which is conservative in the sense of being somewhat lower than the Cronbach α. Both possibilities are discussed by Huitema (1980). These reliability estimates were of equivalent magnitudes across the groups [χ^2 (1) < 1.50, p > 0.10 on the Fisher z-transformed rs].

Table 2
Pain sensitivity: means (mA) and standard deviations[a]

Pain Variable	Normotensives		Hypertensives		
	Women ($n = 6$–7)	Men ($n = 10$)	Women ($n = 16$)	Men ($n = 16$)	$F(p)$
	Pain threshold				
Condition 1	1.64 (0.74)	2.74 (0.78)	2.25 (0.89)	2.32 (0.56)	*4.34**
Condition 2	1.65 (0.76)	3.05 (1.09)	2.47 (0.94)	2.79 (0.86)	2.84 #
Condition 3	2.66 (1.12)	4.44 (0.93)	3.82 (1.04)	4.56 (0.91)	
	Pain tolerance				
Condition 1	2.28 (1.18)	3.74 (0.86)	3.00 (1.11)	3.59 (0.89)	*3.77 #*
Condition 2	2.17 (1.04)	4.02 (1.09)	3.28 (1.17)	3.79 (1.06)	

[a] Condition 1, self-controlled intensity; Condition 2, automatic intensity control (slow rise); Condition 3, automatic intensity control (fast rise). Only (marginally) significant effects involving Group are shown: Group × Gender interaction (italic fonts) and Group × Condition interaction (normal fonts). *$p < 0.05$; # $p < 0.08$.

3. Results

Because the two hypertensive groups exhibited very similar scores for most variables regarding pain sensitivity, pre-stressor anxiety, and cardiovascular parameters, data of these two groups were pooled in all analyses. The only clear difference between the hypertensive groups was revealed during analyses of the pre-experiment mood items. Only one significant effect emerged, concerning reported Irritation During the Day [$F(2, 55) = 3.58$, $p < 0.05$], indicating that aware hypertensives experienced the most feelings of irritation during the day (M = 2.67, SD = 1.24), normotensives intermediate levels (M = 2.00, SD = 1.12), and unaware hypertensives being the least irritated (M = 1.76, SD = 0.83).

3.1. Pain sensitivity

In each group, three persons were suspected to potentially have had cream leakage between the two parts of the electrode, as indexed by both extremely low resistance (below 0.5 kΩ) and reaching repeatedly the maximum possible current intensity during the trials. These participants were excluded from the analyses[2]. For the means and standard deviations of the groups, see Table 2.

3.2. Pain threshold

In the analysis on pain threshold, two main effects emerged. First, a Condition main effect [$F(2, 42) = 101.74$, $p < 0.001$] indicated that the pain thresholds became

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[2] If these subjects were included in the analyses, the results would be the same.

higher with later conditions. A Gender main effect [$F(1, 42) = 10.41$, $p < 0.01$] revealed that men had higher thresholds than women. No Group main effect was obtained [$F(1,42) = 1.95$, $p < 0.10$]. However, the Group × Gender interaction appeared significant [$F(1, 42) = 4.34$, $p < 0.05$]. Post hoc analyses showed that while no effects were present for men ($p > 0.10$), among women, hypertensives exhibited higher pain thresholds than normotensive individuals [$F(1, 18) = 4.73$, $p < 0.05$]. Finally, a trend for a Group × Condition interaction [$F(2, 42) = 2.84$, $p = 0.07$] reflected the tendency for hypertensives to have higher pain thresholds than normotensives in the last condition only. No Gender × Condition interaction, nor the three-way interaction (Group × Gender × Condition) emerged.

3.3. Pain tolerance

Slightly different results were obtained for pain tolerance. The Condition main effect was only a trend now [$F(1, 44) = 3.43$, $p = 0.07$], pointing at the tendency for higher tolerances in the second condition than in the first. Men tolerated higher intensities than women [$F(1, 43) = 10.75$, $p < 0.01$]. Again, no Group main effect was obtained [$F(1, 43) = 1.93$, $p > 0.10$]. The Group × Gender interaction approached significance [$F(1, 43) = 3.77$, $p = 0.06$]. Post hoc analyses showed that, although no differences existed between the male groups ($p > 0.10$), female hypertensives tended to tolerate higher intensities than female normotensives [$F(1, 19) = 4.26$, $p = 0.053$]. No other interaction effects were obtained.

3.4. Cardiovascular measures

3.4.1. Baseline
First, baseline differences between the groups were examined by means of 2 (Group) × 2 (Gender) analyses of variance. These ANOVAs were based on overall means across all rest periods.

None of the variables showed a Group × Gender interaction or a Gender main effect (all $ps > 0.10$). There was, however, a significant main effect of Group on IBI [$F(1, 52) = 4.71$, $p < 0.05$], showing higher resting heart rates in hypertensives, compared with normotensives: 784.9 ms (SD = 105.6) versus 852.5 ms (SD = 115.7), respectively. As one may expect, large differences were found between the groups on SBP [150.4 mmHg (19.2) versus 118.1 mmHg (9.8), $F(1, 52) = 44.43$, $p < 0.001$] and DBP [99.6 mmHg (16.8) versus 76.6 mmHg (7.5), $F(1, 52) = 30.74$, $p < 0.001$]. Hypertensives also exhibited smaller baroreflex slopes [5.73 ms/mmHg (2.62) versus 7.96 ms/mmHg (3.06), $F(1, 49) = 7.63$, $p < 0.01$]. There were no significant differences between the groups on the number of sequences [3.92 (2.33) for hypertensives and 4.95 (2.00) for normotensives, $F(1, 49) = 2.57$, $p > 0.10$].

3.4.2. Reactivity

No three-way interaction (Group × Gender × Condition) emerged for any of the cardiovascular reactivity variables (see Table 3). For IBI, the only significant effect was a main effect of Condition [$F(2, 43) = 5.28$, $p < 0.01$], indicating heart rates becoming slower in the later conditions. With respect to blood pressure, men showed larger responses than women [$F(1, 44) = 13.03$, $p = 0.001$ for SBP and $F(1, 44) = 14.46$, $p < 0.001$ for DBP], and hypertensives reacted more strongly than their normotensive counterparts [$F(1, 44) = 6.13$, $p < 0.05$ for SBP and $F(1, 44) = 5.31$, $p < 0.05$ for DBP]. Besides these main effects, no other effects were significant for blood pressure. Only a trend for SBP towards a smaller difference between the hypertensives and normotensives in the second condition emerged [$F(2, 43) = 2.79$, $p = 0.07$]. For the baroreflex reactivity, only two effects were significant. First, a Gender × Condition interaction for the slope [$F(2, 31) = 6.31$, $p < 0.01$] showed that in the first and third condition, men enhanced their baroreflex sensitivity more than women, whereas in the second condition the reverse was true. Finally, a Condition main effect [$F(2, 31) = 13.30$, $p < 0.001$], reflected the slopes being the lowest in the second condition and highest in the third condition.

Table 3
Cardiovascular reactivity: means and standard deviations[a]

| Variable | Normotensives | | Hypertensives | | F (p) |
	Women (n = 5–8)	Men (n = 10–11)	Women (n = 10–18)	Men (n = 11–19)	
IBI					
Cond 1	7.0 (40.3)	−4.5 (42.0)	−4.9 (35.3)	6.1 (26.2)	5.28[c]**
Cond 2	11.4 (22.2)	5.5 (41.4)	2.8 (35.9)	15.5 (26.7)	
Cond 3	16.6 (28.1)	8.1 (35.1)	9.9 (38.5)	19.0 (26.7)	
SBP					
Cond 1	10.8 (8.2)	21.4 (6.9)	20.2 (9.6)	25.5 (6.6)	6.13[g]*
Cond 2	13.3 (8.2)	23.5 (6.9)	19.8 (8.5)	25.5 (7.8)	2.79[g×c] #
Cond 3	13.0 (9.7)	22.9 (8.5)	20.1 (8.1)	27.9 (8.4)	13.0[s]***
DBP					
Cond 1	5.0 (3.8)	9.4 (3 4)	8.1 (4.7)	13.0 (4.0)	5.31[g]*
Cond 2	5.3 (3.4)	10.3 (3.7)	7.5 (8.7)	12.5 (5.1)	14.5[s]***
Cond 3	6.0 (3.8)	9.9 (3 4)	8.3 (4 9)	13.8 (5.7)	
Slope					
Cond 1	0.34 (1.92)	0.69 (1.81)	−0.10 (1.30)	0.89 (1.54)	13.3[c]***
Cond 2	0.40 (1.32)	−0.58 (2.07)	−0.17 (0.88)	−0.38 (1.83)	6.31[s×c]**
Cond 3	1.13 (2.35)	0.50 (2.99)	0.05 (0.99)	1.86 (3.04)	

[a] Cond, Condition (see note Table 2). Slope, regression slope of the up-sequences (in ms/mmHg). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, # $0.05 < p < 0.09$. c, Condition main effect; g, Group main effect; s, Gender main effect; g × c, Group × Condition interaction; s × c, Gender × Condition interaction.

3.5. Role of cardiovascular reactivity and anxiety in pain sensitivity

To assess the role of the cardiovascular reactivity parameters in pain sensitivity, first, Pearson's product-moment correlation coefficients were computed. All coefficients regarding correlations between blood pressure and both pain threshold and pain tolerance were positive, but only in the following cases significance was (nearly) reached: pain threshold in the third condition with SBP and DBP reactivity during that task ($r = 0.30$, $p < 0.05$ and $r = 0.34$, $p < 0.05$, respectively) and pain tolerance with DBP reactivity in the first condition ($r = 0.25$, $p = 0.088$). No other correlations, including those with baroreceptor activity, emerged.

The analyses on group differences regarding pain sensitivity described above were performed again with those cardiovascular reactivity variables as covariates, which showed some ($r > 0.20$; $p < 0.10$) association with the pain or appraisal measures. This involved only SBP and DBP. However, when meeting the parallelism assumption was tested, it was found that the βs of the regression line of the pain variables on SBP were different between women ($\beta = 0.34$) and men ($\beta = -0.25$). Therefore, an analysis of covariance was applied using separate slopes for men and women (Maxwell and Delaney, 1990, pp. 406–420). Residuals (studentized deleted) were computed from the linear regression of the pain measures on SBP- and DBP-reactivity for men and women separately (only SBP entered the analyses). These residuals were used in the new analyses, instead of the original pain variables. Applying this procedure, the Group × Gender interactions were no longer significant [$F(1, 42) = 2.72$, $p > 0.10$ for pain threshold and $F(1, 43) = 1.55$, $p > 0.10$ for pain tolerance, respectively]. Also the Group × Condition interaction for pain threshold disappeared [$F(2, 42) = 1.72$, $p > 0.10$].

Pre-stressor anxiety tended to be negatively correlated with both pain threshold and pain tolerance, especially during the second pain stimulation condition, but only one correlation proved to be significant: pre-stressor anxiety with pain tolerance in the second condition ($r = -0.29$, $p < 0.05$). When the between-group analyses on pain sensitivity were run again with pre-stressor anxiety as a covariate, the Group × Gender interaction effects became slightly smaller: $F(1, 41) = 3.80$, $p = 0.058$ for pain threshold and $F(1, 42) = 2.78$, $p = 0.10$ for pain tolerance.

4. Discussion

In the present study, the role of gender and cardiovascular reactivity in hypertension-related diminished sensitivity was examined. Diminished sensitivity to an electric pain stimulus was demonstrated, but only in women: female hypertensives showed higher pain thresholds and tended to have higher pain tolerances than their normotensive counterparts. No three-way interaction involving Condition was found indicating that this gender-specific effect of hypertension was equal in all three conditions. Also Group × Condition interaction effects on pain sensitivity were not present, apart from a trend for a difference between hypertensives and normotensives in the last condition only. Therefore, with respect to the effects of

control over stimulus delivery and duration/velocity of stimuli, it can be concluded that the manipulations of these factors hardly had any effects on hypertension-related pain sensitivity as measured in the present within-subject design. However, one must take into account that the applied fixed order of presentation of the conditions may have allowed carry-over effects to interact with the type of shock delivery in an unknown manner, a point which is discussed below in greater detail.

The profound gender differences that were found were not expected beforehand, although in the few previous studies conducted on both men and women substantial differences were also found (Bragdon et al., 1994; France et al., 1994; Fillingim and Maixner, 1996). However, the outcomes of those previous studies were not consistent. In one investigation, diminished pain sensitivity was related to higher resting blood pressure only in men (Fillingim and Maixner, 1996), whereas in the two other studies only in women lower pain ratings were associated with higher blood pressure (Bragdon et al., 1994) or parental history of hypertension (France et al., 1994). These discrepancies in findings are difficult to explain. No clear sample differences could be found that may account for the inconsistencies. Also, differences in pain stimulation modalities (i.e., electric, thermal, pressure) cannot explain these discrepancies, because two of the studies yielding mutually incongruous results used the same modality (thermal pain; Bragdon et al., 1994; Fillingim and Maixner, 1996). In addition, the present failure to show lower pain sensitivity in men also could not be explained by the different pain modality issue: in a previous study, male hypertensives have been found to exhibit higher pain thresholds for electric current (Zamir and Shuber, 1980). Perhaps the present design, in which all subjects had first full control over the electric stimulus, thereby diminishing anxiety, may have abolished group differences only among men for some unknown reason. For instance, Ditto et al. (1997) found that only among subjects high on anxiety, individuals with a parental history of hypertension reported lower pain ratings than participants with no parental history of hypertension. In the present study, pre-stressor anxiety ratings were generally quite low (for most groups lower than 1.5 on a scale from 1 to 5), the only significant difference between the genders being a relatively high score of only normotensive women (> 2). In the study of Ditto et al. (1997), also a large direct effect of anxiety on pain sensitivity was found. Although a tendency in the same direction was obtained in the present investigation (high anxiety associated with high pain sensitivity), controlling for anxiety did not affect the present gender-specific results substantially.

However, when blood pressure reactivity was controlled for, the Group $\times$ Gender interactions were no longer significant, suggesting a mediating role of cardiovascular reactivity. This finding, together with the fact that systolic blood pressure reactivity tended to be positively correlated with pain threshold and pain tolerance in the subgroup in which hypertension-related differences were found (women) in contrast to an inverse tendency in the no-effects group (men), is in agreement with the baroreceptor stimulation hypothesis (Dworkin et al., 1979). According to this hypothesis, baroreceptor stimulation, as a result of blood pressure elevations, diminishes pain sensitivity (and appraisal of aversive stimuli in general) via effects in central nervous system areas, such as the nucleus tractus solitarius and several

nuclei of the hypothalamus (Randich and Maixner, 1984). However, these dampening effects would occur only in individuals sensitive to this mechanism (Elbert et al., 1988). In general, previous research tends to support this view (Dworkin et al., 1979; Elbert et al., 1988, 1994). However, there are two reasons for being prudent about interpreting correlations between cardiovascular reactivity and pain sensitivity. First, this correlation will always be an unpredictable result of (a) the above-mentioned negative association as a result of the central effects of baroreceptor stimulation on pain appraisal and (b) a positive association as a consequence of blood pressure elevations due to pain or anxiety (Bruehl et al., 1992). A second reason is that the specific effects of baroreceptor stimulation on appraisal of aversive stimuli only hold for a subgroup of individuals with a predisposition for sensitivity to this mechanism (Elbert et al., 1988). In addition, because the central nervous system effects of baroreceptor stimulation may be largely independent of the purely hemodynamic baroreflex per se (Schobel et al., 1996), the absence of effects of baroreflex sensitivity reactivity in the present study is not considered necessarily discordant with the baroreceptor stimulation hypothesis. The present findings only support the view that the purely hemodynamic part of the baroreflex does not account for the hypertension-related altered pain sensitivity (Schobel et al., 1996). With respect to studying the (central) appraisal effects of baroreceptor stimulation, it is recommended to individually assess effects on pain sensitivity as a result of direct experimental manipulation of the baroreceptor stimulation, for instance applying the PRES neck suction technique, as recently developed by Rau et al. (1992).

No clear differences were obtained between unaware and aware hypertensives. As stated in the introduction, this also would be expected, given the fact that, according to the Dworkin et al. (1979) hypothesis, the baroreceptor stimulation mechanism, which frequently has been held responsible for the hypertension-related effects on pain sensitivity, should be equally effective in both groups. The only clear difference between the hypertensive groups was the score on self-reported experienced irritation during the day, the direction of which was in concordance with previous findings on self-reported problems: high in aware hypertensives and low in unaware hypertensives (Nyklíček et al., 1996).

A limitation of the present study involves the relatively small numbers of subjects, especially in the normotensive group. In the pain stimulation task, this was partly due to possible cream leakage in three persons in each group, as a result of which their data were discarded from the analyses. In addition, some tasks may have been somewhat too short (< 2 min) for reliable indices of baroreflex activity, which resulted in missing values for 6.5 persons on average. This may have diminished the power to obtain effects on this particular measure. Another limitation involves the fixed sequence of presentation of the pain conditions. As stated above, because the full-control condition was always first, this may have reduced anxiety and enhanced feelings of controllability to an extent that the effect of the subsequent low-control conditions may have been lower than in a counterbalanced order. However, both the substantial blood pressure elevations in the three conditions and the non-significant differences between the conditions regarding pre-task

anxiety, suggests that the effects of the fixed presentation order on these variables was limited.

In summary, the present study demonstrated lower pain sensitivity in female hypertensives compared with their normotensive counterparts. For men, no between-group differences were obtained. Furthermore, evidence was found for a, at least partial, mediation of these between-group effects by blood pressure reactivity.

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