

Central effects of baroreceptor activation in humans: Attenuation of skeletal reflexes and pain perception

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ABSTRACT Activating the arterial baroreceptors blunts pain sensation and produces other forms of central nervous system inhibition in animals. These effects may be important to blood pressure regulation but have not been rigorously verified in humans. We describe (i) a noninvasive behaviorally unbiased method for baroreceptor stimulation and (ii) the application of this method to measurement of baroreceptor-mediated attenuation of pain perception and of the Achilles tendon reflex. The findings are relevant to basic mechanisms of blood pressure stabilization and cardiovascular reactivity and may also have implications for noncompliance with antihypertensive medications and for the pathophysiology of essential hypertension.

Mechanoreceptors in the carotid sinus and aortic arch are the afferent limb of reflexes that regulate blood pressure. The vagal cardioinhibitory and sympathoinhibitory vascular effects of these reflexes have been studied for >60 years. That reflex effects of baroreceptor activation help buffer rapid changes in arterial pressure is undisputed; however, in addition to these peripheral cardiovascular effects, stimulation of the baroreceptors produces less known, but clearly documented, general inhibition of central nervous processes: Independent of changes in general circulation, the activation of baroafferent pathways by electrical nerve stimulation, mechanical stretch, or elevation of blood pressure will decrease somatic muscle tone (1, 2), inhibit spinal somatic sensory pathways (3) and sham rage (4), induce synchronization of the electroencephalogram (5), increase cortical positivity (6), blunt pain sensations (7), reduce anxiety (8, 9), and induce sleep (10) or even clinically significant syncope (11). Arousing emotional and pain stimuli elevate blood pressure (12–18), and the central nervous system (CNS) inhibitory effects of barostimulation most simply can be seen to provide supplementary negative feedback, which, along with cardioinhibition and vasodilatation, helps to restore excessively elevated blood pressure to a safer level.

Dworkin *et al.* (19) reported that rats escape from and avoid a mildly aversive trigeminal nucleus stimulus to a lesser degree when their blood pressure is pharmacologically elevated and that the effect can be abolished by denervation of the baroreceptors. They also showed that the impaired avoidance behavior persists into extinction, suggesting that, in addition to pain perception, anxiety is affected. In an extensive series of experiments using more conventional pain stimuli, Randich and Maixner (20) replicated the findings of Dworkin *et al.* (19), and by blocking the cardiac vagal efferents with methyl atropine further showed that reflex

bradycardia (the perception of which might increase anxiety levels) was not a factor in the altered pain sensitivity. These recent studies in rats are the best controlled and most technically sophisticated, but in fact the experimental animal literature on baroreceptor-mediated CNS inhibition is quite extensive and began in 1932 with Koch's observations (2) that intact dogs could be induced to sleep by rhythmic inflation of a balloon in a carotid sinus cul de sac. In 1953, experimental analysis in decerebrate cats of the supramedullary neurophysiology of the effects of aortic nerve stimulation by Bonvallet *et al.* (5, 21) pointed to the possible involvement of the ascending reticular activating system, and a number of animal experiments have since confirmed that stimulation of the baroreceptors produces typical manifestations of barbiturate-like CNS inhibition [refs. 1–6 and 8–10; for a discussion of the relay and possible integrative function of the nucleus tractus solitarius and the possible involvement of additional descending (spinal) pain inhibition mechanisms, see reviews by Randich and Meller (22), Basbaum and Fields (23), and Gebhart and Randich (24)].

In humans baroreceptor CNS inhibition can be pronounced and even have substantial medical consequences: Weiss and Baker's detailed 1933 clinical study (11) showed that certain forms of frank and intractable syncope had a purely "neural carotid mechanism" that did not depend on perfusion compromising circulatory antecedents, and the anthropologists Schlager and Meier (10) described how native practitioners in the Balinese islands routinely used therapeutic carotid massage to induce sleep. Recently, there have been efforts to experimentally evaluate barostimulation effects on pain thresholds, electroencephalogram spectra, and cortical slow waves in human subjects (25–30). On the whole, the results of these studies are concordant with the animal results, but the human experiments have not included fully convincing control conditions. The main obstacle has been to devise effective and noninvasive manipulations that unequivocally separate baroreceptor activation from other effects on the CNS: For example, although vasoconstrictive or cardio-stimulating drugs, such as phenylephrine, norepinephrine, or dopamine, elevate blood pressure and unquestionably stimulate the baroreceptors, without an experimental design that includes comparison between intact and denervated control subjects, something possible only in animal studies, central and peripheral side effects of the drug, which are unrelated to barostimulation, could as well explain their impact on perception and general CNS function.

Abbreviations: CNS, central nervous system; CSPP, carotid sinus pulse pressure; PRES, phase-related external suction; EMG, electromyographic or electromyogram; G-G, Greenhouse-Geisser.

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Barostimulation Methods in Humans. Balloon distention of a surgically isolated carotid sinus cul de sac of a dog is the "gold standard" of experimental barostimulation methods, and a related, but noninvasive, pressure stimulation method can be used in humans: The baroreceptors are actually stretch receptors in the arterial wall, and pressure inside the artery normally *pushes* the wall outward, but the wall also can be artificially *pulled* outward by extravascular suction applied through a pneumatic collar that encircles the neck. In the usual arrangement, a constant or static *negative* pressure in the "neck chamber," summed with the pulsatile intracarotid *positive* pressure, increases the average stretch of the sinus and simulates an elevated mean arterial pressure. The "static pressure" neck chamber has been used extensively to study the peripheral physiology of the human baroreflex, but the static neck chamber has a serious drawback for behavioral studies: Although not at all painful, neck suction is distracting, and distraction itself could affect perceptual/behavioral results through mechanisms that are unrelated to barostimulation.

Instead of static or constant neck-chamber suction, in the experiments that follow we used sequences of brief cardiac-cycle-coordinated pressure changes to stimulate or inhibit baroreceptor activity. Eckberg (31) first observed that brief suction pulses applied randomly during various parts of the cardiac cycle differentially affected subsequent P-P intervals. Dworkin (32) elaborated on Eckberg's method using a cardiac-cycle-synchronized train of repeatedly alternating pressure and suction pulses to stimulate or inhibit the carotid receptors continuously for as long as several minutes. Alternating suction during systole with positive pressure during diastole increases the carotid sinus pulse pressure (CSPP), whereas the opposite phase relationship decreases the CSPP. With this method, heart rate was 5–10% lower during stimulation compared to the control condition, and blood pressure was only slightly affected (Fig. 1). Rau and colleagues (30) further refined the cardiac-phase locked-neck-chamber method by including a variable-length atmospheric pressure pulse along with the appropriately phased symmetrical suction and positive pressure pulses. He called this three-phase method PRES for phase-related external suction. PRES produces barostimulation (cardiac phase synchronized) and control conditions (cardiac phase inverted) with exactly the same mean pressure. In signal detection experiments, Furedy *et al.* (33) have shown that the control and stimulation (PRES)

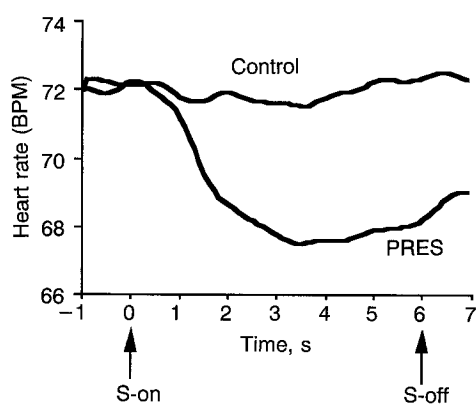


FIG. 1. Time-locked averaged effect of the PRES condition and the control condition on the heart rate of 11 subjects. The start of the manipulation is indicated by S-on and the end of the manipulation is indicated by S-off. Note that the control condition is without substantial effect on heart rate. If the control condition efficiently suppressed the intraarterial pulse, the heart rate would have increased; that it doesn't reflects a technical limitation imposed by the rectangular shape of the neck-chamber pressure waveform. BPM, beats per min.

conditions are indistinguishable even to subjects who had been instructed to try to discriminate them; thus, PRES is almost certainly free of nonspecific behavioral or perceptual effects.

Effects of Barostimulation on Reflexes and Pain Perception. Because the PRES method affects the CSPP and not the mean carotid sinus pressure, and although some net depressor effect usually results from asymmetrical rate sensitivity of the baroreceptors, the PRES condition increases the range of baroreceptor firing over a cardiac cycle much more than the mean rate. PRES stimuli occurring during systole thus coincide with differentially enhanced baroreceptor activity, while those falling in diastole coincide with lower than normal firing. When the PRES method is combined with appropriately brief (<50 ms) cardiac-cycle-coordinated test stimuli, such stimuli can be presented during any of four systematically graded baroactivity levels. In order of baroactivity level, these are (i) PRES condition with a systolic stimulus, (ii) control condition with a systolic stimulus, (iii) control condition with a diastolic stimulus, and (iv) PRES condition with a diastolic stimulus (Fig. 2A).

The variations in the response to brief sensory stimuli placed at different points in the natural cardiac cycle have been studied by other investigators, but their results have been inconsistent. Some (34, 35) have reported substantial attenuation of stimuli presented during systole, whereas others (36) failed to find any cardiac cycle effect. Given the physiology, these inconsistencies are understandable: For any subject, there is substantial moment-to-moment variability in both pulse amplitude and mean arterial pressure, and these factors interact with the individual's baroreceptor adaptation level to determine the modulation of the baroreceptor output over a particular cardiac cycle. The random variability thus introduced limits the power of any natural cycle experiment. In contrast, in each cardiac cycle, the PRES condition adds a constant pressure to the systolic level and subtracts a constant pressure from the diastolic level of the carotid pulse; it thus standardizes the minimum variation in baroreceptor activity within a cycle and a subject and, to a degree, between subjects. Moreover, a true randomized differential experiment can be created by addition of a counterbalanced phase-reversed control condition that, with the identical sequence of neck-chamber pressures, reduces rather than enhances the pulse amplitude. In the experiments reported here, we have used the PRES condition with cardiac-synchronized test stimuli to measure the effect of different levels of baroreceptor activity on the reported painfulness of discrete electrical stimuli and on the magnitude of the Achilles tendon reflex to a standard hammer blow. We have also compared the cardiac cycle effects between the PRES and control conditions.

METHODS

There were three experiments at three institutions with three groups of subjects. At Tilburg in the Netherlands (in a specially equipped laboratory), we studied the effects of baroreceptor activity on the amplitude of an electrically elicited Achilles tendon reflex. The two other studies were done in Germany, and both used similar methods to assess the effects of baroreceptor activity on pain perception. One involved a small group of cardiac ischemia patients at the Benedikt Kreuz Rehabilitation Center for Cardiovascular Diseases in Bad Krozingen near Freiburg. (This group was originally of interest because of the potential involvement of baroreceptors in the mechanism of conversion from silent to nonsilent ischemia when blood pressure is lowered with antihypertensive drugs.) The other was a large heterogeneous group of normal subjects from the Tübingen region.

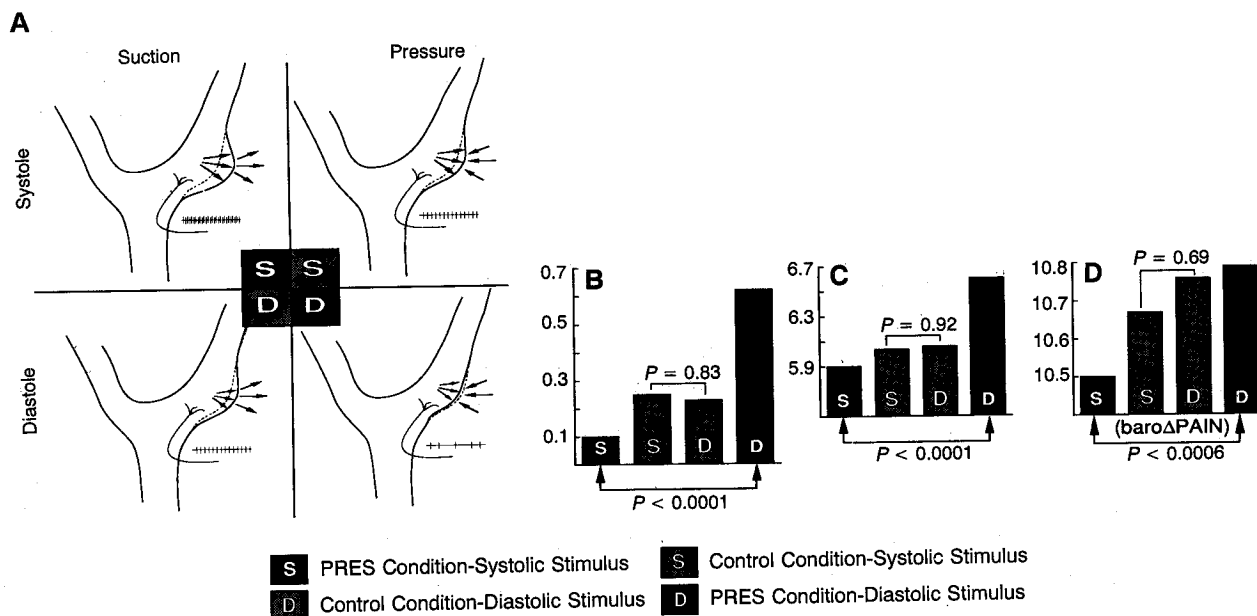


FIG. 2. (A) PRES technique for stimulating the human carotid baroreceptors. The extravascular arrows represent the cardiac-cycle-synchronized pressure (or suction) levels in the external neck chamber. In upper left, the extravascular suction adds to the systolic pressure, maximizing the carotid sinus stretch and stimulation of the neural pathway, and in lower right, the extravascular pressure subtracts from the diastolic level, further reducing the vascular distention; thus, the largest difference in baroreceptor activity is between these conditions in which the internal and external pressure levels are synergistic. In the control condition (upper right and lower left), the natural carotid sinus pulse pressure is suppressed by opposing it with external pressure in systole and suction in diastole. (Because the approximately rectangular waveform of the neck suction attenuates but does not completely obliterate the intraarterial waveform, this is a conservative estimate of the actual zero-pulse baseline.) (B) Mean tendon reflex amplitude (arbitrary EMG units) of 12 normal subjects at Tilburg: A total of 64 stimuli in an individually pseudo-randomized sequence was presented to each subject (16 in each of the four conditions). The scores were averaged across trials and the resulting averages were entered into a repeated measures ANOVA as follows: $F(11/3) = 13.073$; $P < 0.0001$; $P(\text{Greenhouse-Geisser}) [P(G-G)] < 0.0001$; $\epsilon = 0.701$. For the contrast between the PRES systolic and diastolic conditions, $F = 35.579$; $P < 0.0001$; $P(G-G) < 0.0001$. (C) Mean pain perception of 19 cardiac ischemia patients at Bad Krozingen: 16 stimuli of each condition were applied in pseudo-randomized sequence to each subject. Stimuli consisted of biphasic 10-ms electrical impulses applied intracutaneously to the finger. After each trial, subjects rated the perceived intensity of the pain stimulus on a computer screen. Ratings were averaged across trials, separated by conditions and subjects; means were entered into a repeated measures ANOVA as follows: $F(18/3) = 8.859$; $P < 0.0001$; $P(G-G) = 0.0002$; $\epsilon = 0.868$. For the contrast between the PRES conditions, $F = 22.017$; $P < 0.0001$; $P(G-G) < 0.0001$. (D) Mean pain perception of 116 normal subjects at Tübingen (same procedures as C) as follows: $F(115/3) = 4.844$; $P = 0.0026$; $P(G-G) = 0.0031$; $\epsilon = 0.945$. For the contrast, $F = 11.951$; $P = 0.0006$; $P(G-G) = 0.0008$. [The PRES systolic–diastolic difference is the $\text{baro}\Delta\text{PAIN}$ score used in a longitudinal blood pressure study to be published elsewhere (41).]

Barostimulation and General Procedures. Each subject reclined in a comfortable chair and was fitted with a foam-lined half-moon-shaped malleable-metal pneumatically sealed chamber that encircled the lateral and anterior aspects of the neck (37). Precordial electrocardiogram electrodes were connected to a Schmitt trigger, which produced an output pulse at the R wave. This pulse triggered the neck-chamber pressure cycle. Rigid hoses connected the chamber to the output side of a high-flow-rate pneumatic valve. The input side of the valve was connected to high-volume sources (built from commercial vacuum cleaner components) of negative or positive (approximately ± 40 torr; 1 torr = 133.3 Pa) pressure and to an atmospheric pressure vent. A computer controlled the pneumatic switch and alternated the pressures in the chamber in relation to the R wave. In both the PRES and control conditions, the initial neck cuff pressure pulse commenced 100 ms after the ventricular R wave (in the PRES condition this was suction; in the control condition it was positive pressure); this “systolic” pulse was immediately followed by an opposite pulse. The duration of each pulse was one-half of the mean cardiac interbeat interval less 100 ms. Immediately after the second pulse, the chamber was returned to atmospheric pressure. The same PRES or control sequence was repeated for each heart beat in a 6-s trial; then, according to a balanced pseudorandom sequence, the condition was switched. There were a total of 64 trials in each experiment: 32 PRES and 32 control trials. The actual

pressure in the neck chamber was monitored with a strain gauge type transducer: for a typical subject the positive pressure was approximately +10 torr and the negative pressure was approximately –30 torr (the asymmetry and attenuation of the pressures are due to practical limitations in the pneumatic seal to the neck) (for additional details, see ref. 38). A technical limitation of the present method results from the approximately rectangular shape of the neck-chamber suction and pressure waveforms. When these waveforms are hydrostatically summed with the natural intraarterial pulse wave, the resultant waveform is distorted. For the PRES condition, the distortion increases the magnitude of both the rising and falling slopes, and this further enhances the differences in baroreceptor firing over the cardiac cycle; but for the control conditions, because of the lack of shape conformity, there is only partial cancellation of the intraarterial wave, and the control condition only roughly approximates the actual zero-pulse baseline.

Tendon Reflex Experiment. Subjects. Twelve university students, mean age 29.1 ± 11.6 years, were recruited by advertisement. Informed consent was obtained and the procedures conformed to the requirements of the human subjects committee of Tilburg University.

Measurement of the Achilles tendon reflex. An electrically operated “hammer” struck the subject’s ankle, while electromyographic (EMG) electrodes recorded the reflex response of the soleus muscle. The reflexes were evoked in the

right leg by a 5-cm-long 2-cm-diameter plastic rod that struck the Achilles tendon at a 90° angle. The rod was mounted on a piston, creating a T-shaped hammer. Activation was by a vibration transducer (Brüel & Kjaer Instruments, Marlborough, MA) that was triggered by a 9-ms half wave, produced by a Brüel & Kjaer 2706 power amplifier. Fixation of both the leg and the stimulator assured that the hammer blow was repeatable. The response magnitude was measured from a pair of Ag-AgCl EMG surface electrodes placed 4 cm apart over the distal portion of the right soleus muscle. The signal was amplified by a Hellige EE preamplifier (-3 dB; band width, 0.3–150 Hz) and sampled at a rate of 1 kHz. The EMG was scored by averaging peak-to-peak amplitudes in the interval 30–80 ms after the stimulus. In addition, a rectified EMG was obtained from two adjacent electrodes, amplified through a Beckman type 9852A coupler, and also digitized continuously with 1000 samples per s. This second channel served to control for variations in tonic EMG.

Pain Perception Experiments. Cardiac ischemia subjects (Bad Krozingen group). Nineteen patients at the Benedikt Kreutz Rehabilitationszentrum für Herz und Getaberkrankungen at Bad Krozingen, Germany, with diagnoses of cardiac ischemia were recruited with the assistance of their physicians. The patients had a mean age of 55.5 ± 6.3 years. They were medically screened for potential intolerance to the procedure and informed consent was obtained. The procedures conformed to the human subject regulations of the hospital.

Normal subjects (Tübingen group). One hundred and twenty normal adults were recruited by newspaper announcements in the Tübingen area and paid for participation in this experiment and a subsequent longitudinal analysis of blood pressure change, which will be published elsewhere. Exclusion criteria were any kind of chronic or acute disease, including hypertension. This resulted in an initial sample of 73 male and 47 female healthy subjects with a wide range of occupational backgrounds and the following measurements: weight, 69.7 ± 8.8 kg; height, 173.0 ± 8.8 cm; age, 31.4 ± 6.0 years; blood pressure, 103.5 ± 9.5 mm Hg. Informed consent was obtained and all procedures conformed to the human subject regulations of Tübingen University.

Pain Estimation. The pain stimuli and pain measurement procedures described below were used for subjects in Bad Krozingen and Tübingen.

Pain Stimuli. The stimuli were single 10-ms bipolar pulses delivered by an optically isolated constant-current generator, applied through a 0.5-mm-diameter 1.0-mm-long gold electrode on the tip of the left middle finger. To minimize cutaneous resistance, the epidermis was mildly abraded with a hand-held dental burr (diameter, 1 mm). A large stainless steel reference electrode was strapped to the wrist of the same hand (for additional details see ref. 39).

Pain Measurements. Initial threshold determination. At the beginning of the experiment each subject's pain threshold (the maximum stimulus was always <1 mA) was determined by a low-to-high successive approximation procedure. After each stimulation the subject made a rating on a computerized vertical visual analog scale. The scale ranged from 0, representing no perception, to 24, representing substantial pain. The first time that the midscale "pain" threshold was reached, the current was returned to the detection threshold level, and the series was repeated until the "pain" level was reported a second time. If the difference between the two "pain" thresholds was <20%, the mean of the two readings plus 20% was used as the test stimulus. If the values differed by >20%, the entire procedure was repeated. A second estimate was required in <15% of the subjects.

Test procedure. Several initial practice trials assured that the subjects understood the procedure. To allow time for stabilization of the baroreceptor stimulus, the electrical pain

stimuli were delivered 100 ms after the change in cuff pressure. The experiment itself consisted of 64 trials, each including a 1-s baseline period, a 6-s baroreceptor manipulation period, and a 1-s post-stimulus period (see Fig. 1). Intertrial intervals varied pseudo-randomly between 5 and 13 s. The pain stimuli were delivered after the second and fourth heart beat of the baroreceptor manipulation period. At the end of each trial, the subjects were prompted to perform a computerized subjective magnitude estimation of each of the two stimuli. The entire procedure required ≈ 1 h.

RESULTS

Tendon Reflexes: Tilburg Group. We found that the Achilles tendon reflexes were substantially attenuated when test stimuli were applied during periods of higher baroreceptor activation. Fig. 2B summarizes the results for the 12 subjects in the tendon experiment (each bar corresponds to one of the conditions diagrammed in Fig. 2A). The scores were averaged across trials and the resulting averages were entered into a repeated measures ANOVA with the following results [in such a design the error terms are correlated, violating the sphericity assumption of ANOVA; the G-G statistic is the appropriately corrected estimate of P]: $F(11/3) = 13.073$; $P < 0.0001$; $P(G-G) < 0.0001$; $\epsilon = 0.701$. For the contrast between the PRES systolic and diastolic conditions, $F = 35.579$; $P < 0.0001$; $P(G-G) < 0.0001$. For the control condition, $F = 0.04$; $P > 0.8$. Thus, for the PRES conditions (systolic suction/diastolic pressure), the difference between diastole (the minimal carotid stretch) and systole (the maximal carotid stretch) is in the predicted direction; i.e., the reflex was reliably weaker with enhanced baroreceptor input, whereas for the control conditions (diastolic suction/systolic pressure) in which the carotid pulse is partially suppressed, the response magnitudes as predicted were similar to one another, and their absolute strength was between those of the PRES values. In addition to clear group differences shown, the differences within the PRES condition were reliably in the predicted direction for each one of the 12 subjects; thus, the Achilles reflex inhibition by barostimulation is both robust and consistent.

Pain Perception: Bad Krozingen Group. Fig. 2C summarizes the results from the pain perception experiment in a group of 19 silent and nonsilent cardiac ischemia patients at Bad Krozingen. Pain ratings were averaged across trials, separated by conditions and subjects; mean values were entered into a repeated measures ANOVA as follows: $F(18/3) = 8.859$; $P < 0.0001$; $P(G-G) = 0.0002$; $\epsilon = 0.868$. For the contrast between the systolic and diastolic stimuli in the PRES condition, $F = 22.017$; $P < 0.0001$; $P(G-G) < 0.0001$. For the control condition, $F = 0.009$; $P > 0.9$. Thus, similar to the tendon reflex result, the difference between the PRES conditions is reliably in the direction that is consistent with baroreceptor activation reducing the painfulness of noxious stimuli, and the control condition mean values fall between the PRES values.

Pain Perception: Tübingen Group. Fig. 2D gives the results of a larger pain perception experiment conducted in Tübingen with an initial group of 120 normal volunteers (4 subjects did not yield usable data). The procedures were the same as in Bad Krozingen. Pain ratings were averaged across trials, separated by conditions and subjects; mean values were entered into a repeated measures ANOVA as follows: $F(115/3) = 4.844$; $P = 0.0026$; $P(G-G) = 0.0031$; $\epsilon = 0.945$. For the contrast between the systolic and diastolic stimuli in the PRES condition, $F = 11.951$; $P = 0.0006$; $P(G-G) = 0.0008$. For the control condition, $F = 0.25$; $P > 0.6$. Thus, in this experiment also, the pain rating was reliably lower in the PRES systolic (compared to diastolic) stimulation condition, and again, the mean pain ratings in the control

conditions fell between those of maximal and minimal baroreceptor activation achieved in the PRES conditions.

In summary, for all three experiments, the difference between systolic and diastolic stimulus presentation in the control condition was far from significant (the F values for the contrasts were all <1), whereas the difference in the PRES condition was highly reliable; also in all three experiments, the means for both stimulus phases of the control condition fell between the corresponding means for systolic and diastolic stimulus presentation in the PRES condition.

The above analyses are based on a one-way repeated measures ANOVA, in which the specific contrasts addressed the difference between the effectiveness of stimuli presented in the systolic and diastolic phases of the carotid-pulse-pressure-enhanced PRES condition. An alternative approach is a 2×2 ANOVA, containing the factors "cardiac cycle" (presentation during systole vs. presentation during diastole) and "neck-chamber phase condition" (PRES condition vs. control condition). For the two-way analysis, the baroreceptor effect is found in the interaction between the cardiac cycle and the experimental condition. The two-way analysis more completely controls for any non-baroreceptor-mediated effects of the neck chamber, but at the same time, because the control condition only partially suppresses the carotid pulse (see barostimulation methods above), the interaction substantially underestimates the actual effect. Notwithstanding, the interaction terms for all three of the 2×2 analyses were reliable and are as follows: For the Achilles tendon reflex experiment, $F = 37$; $P < 0.0001$. For the Bad Krozingen pain study, $F = 18.5$; $P < 0.0005$. For the Tübingen pain study, $F = 4.99$; $P < 0.03$.

CONCLUSIONS

Thus these three experiments, combining the PRES neck-chamber method with brief stimuli differentially positioned in the cardiac cycle, show that stimulation of the high-pressure baroreceptors has general CNS inhibitory effects. These effects have been reported since 1932^{††}; more recently, we (19) and others (20, 22, 24) have refined the experimental methods for animals to eliminate confounding artifacts and confirm that the inhibition is an authentic product of baroreceptor stimulation. The present results extend a similar level of experimental verification to humans. It can now be said that baroreceptor CNS inhibition is a robust physiological mechanism that rests on a broad empirical foundation and that it probably has a unique regulatory function: When acute sensory or emotional excitation raises blood pressure excessively, CNS dampening can augment vagal and sympathoinhibitory negative feedback mechanisms to help restore safer levels.

^{††}In fact, the root verb of the Greek word *καροτιδες* (karotides) is *καρο*, to fall into a deep, heavy sleep (40).

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