Title
Psychophysiological assessment in patients with chronic pain

Author
Perry, Franklin,

Publication Date
1987

Peer reviewed|Thesis/dissertation

PSYCHOPHYSIOLOGICAL ASSESSMENT IN PATIENTS WITH CHRONIC PAIN

by

Franklin Perry

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

Psychology

in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA

San Francisco

[redacted]

Date University Librarian

Degree Conferred: Jan. 9, 1987

DEDICATION

To all the persons who, despite suffering from chronic pain, have given generously of their time and energy so that research projects like this one can be done. With admiration and gratitude and hope that increased knowledge may lead to relief.

ACKNOWLEDGEMENTS

Although a great many people have contributed to the success of this project, the author would like to thank the following people in particular for their invaluable contributions (in alphabetical order): Jack Belgum, Tom Coates, Dawn Cortland, Paul Davidson, Bill Donovan, Ken Fye, Nancy Gordon-Leibel, Philip Heller, Don Jewett, Joe Kamiya, Jon Levine, Scooter Morris, Rick Nahass, Tony Piccione, Ann Warger, the staff of the UCSF Rheumatology Clinic, and of course, all the patients and "normal" volunteers who served as research subjects. Heartfelt thanks to all of you.

ABSTRACT

PSYCHOPHYSIOLOGICAL ASSESSMENT IN PATIENTS WITH CHRONIC PAIN

by

Franklin Perry

This dissertation, on psychophysiological assessment in patients with chronic pain, consists of three separate chapters, each with its own summary and bibliography. The first chapter reports on a pharmacological analysis of the human pupillary light reflex (PLR), undertaken to allow the PLR to be used as a tool to investigate parasympathetic and sympathetic pupillary function in patients with chronic pain. By analyzing multiple parameters of the PLR in the presence of autonomic blocking agents in normal subjects, a model of the PLR was developed. This model allowed interpretation of the parasympathetic and sympathetic components of the patients' responses without the need for pharmacological agents. The second chapter reports on the use of the PLR along with measurement of heart rate and skin conductance, measured at rest and during two dynamic maneuvers, the valsalva maneuver and performance of mental arithmetic. We compared autonomic function in two patient groups, one with demonstrable organic pathology (inflammatory arthritis) and one without demonstrable organic pathology (primary fibrositis). In patients with arthritis, compared to normals, we observed the following indications of altered autonomic function: (1) smaller

baseline pupil size and smaller amplitude and rate of constriction of the PLR; (2) elevated resting heart rate and diminished bradycardia during the valsalva maneuver; and (3) greater increase in skin conductance during mental arithmetic. In patients with fibrositis we observed an elevated resting heart rate and diminished amplitude and rate of constriction of the PLR. The third chapter reports on correlations between multiple pain measures, the McGill Pain Questionnaire and the Visual Analog Scale, administered to the two patient groups at the time of evaluation of their autonomic function, to investigate whether there were differences in subjective report of pain in patients with what is classically referred to as "organic" pain and "functional" pain. The patients with organic pain (arthritis) demonstrated significantly greater correlations between many of the pain measures despite reporting less pain. The patients with functional pain (fibrositis) demonstrated much weaker correlations, suggesting that pain scales validated in patients with pain of organic pathology may not be adequate for evaluating functional pain syndromes.

Joe Kamiya

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1.

Pharmacological Investigation of the Human Pupillary Light Reflex

SUMMARY

Chapter 1. Pharmacological analysis of the human pupillary light reflex.

The pupillary light reflex (PLR) is well suited for the study of the contribution of the autonomic nervous system (ANS) to clinical pain, since its eliciting stimulus may be precisely controlled, and there is evidence that its sympathetic and parasympathetic components may be distinguished. Previous studies of the ANS in patients with pain have relied exclusively upon measures of cardiovascular or sudomotor function. Since autonomic activity is heterogeneous (different measures of autonomic activity in an individual often do not correlate highly with each other), to evaluate autonomic function adequately requires multiple autonomic measures. Cardiovascular responses are controlled by concurrent activity in the two limbs of the ANS, so their separate contributions are difficult to identify. Sudomotor responses, known to be controlled by sympathetic activity, yield no information regarding parasympathetic activity. In addition, the results of most tests of ANS function that have been used are affected by the level of effort of the subject, a difficulty that is avoided with the PLR.

It has been shown, in animal experiments, that sympathetic and parasympathetic contributions to the PLR are

separated in time such that changes in pupil size at particular times reflect activity in the different branches of the ANS. In order to identify the sympathetic and parasympathetic contributions to the PLR in man, we measured the pupillary response to light flash before and after pharmacological blockade in the eye. Parasympathetic blockade with tropicamide resulted in an increase in baseline pupil area, decreases in the magnitude and maximum rate of pupillary constriction, and an increase in latency of constriction. Thus, constriction in the PLR is due to cholinergic activation of the sphincter pupillae muscle. Tropicamide also resulted in a significant increase in the percentage recovery of the pupil (i.e. amount of redilation), which we postulate is due to cholinergic inhibition of the dilator pupillae muscle. The PLR was not altered, however, by the alpha-sympathetic blocker, thymoxamine, demonstrating the independence of the PLR from what is thought to be the predominant sympathetic receptor type in the pupil. Therefore, in humans, in contrast to other species, the peripheral SNS does <u>not</u> contribute significantly to the PLR. Thus, using selective pharmacological blockade, we have been able to identify the peripheral autonomic activity controlling the PLR in man, establishing the PLR as a noninvasive tool that can be used to investigate the contribution of the ANS to clinical pain.

INTRODUCTION

While it has been long known that constriction of the pupil to a light flash depends on parasympathetic outflow from the Edinger-Westphal (E-W) nucleus [3,16], the mechanisms underlying all the phases of the human pupillary light reflex (PLR) are not established. Employing pharmacological agents and surgical ablation, Lowenstein and Loewenfeld [13] suggested mechanisms for two constrictive phases and two redilatory phases of the PLR in cats and monkeys. They hypothesized that the initial constrictive phase was due to parasympathetic activation and that the secondary constrictive phase included a superimposed central sympathetic inhibition of the E-W nucleus. The primary redilation was thought to be due to parasympathetic relaxation, and the secondary redilation was thought to be due to an increase in peripheral sympathetic activity. Observations in a small number of patients with neurological lesions [9,10,11,12] suggest that this model may apply in humans. Information relevant to possible mechanisms underlying the PLR in man is also available from pharmacological analysis of human intraocular muscle. In vivo study has long demonstrated the presence of alpha-adrenergic stimulation of the dilator muscle, and cholinergic stimulation of the constrictor muscle as required by the Lowenstein and Loewenfeld model [8,13,14].

In vitro study has also demonstrated beta-adrenergic inhibition of both muscles, alpha-adrenergic inhibition of the sphincter and cholinergic inhibition of the dilator [6,23,28]. The contribution of these latter in vitro pharmacological effects to the PLR in humans is unknown.

In the present study we utilized agents producing parasympathetic and sympathetic blockade to investigate the mechanism of the PLR in humans. Our data confirm the expected cholinergic contribution to constriction but failed to substantiate a significant peripheral sympathetic contribution to the redilatory phase. Instead we found that the recently described cholinergic inhibition of the dilator muscle controls, at least in part, the rate of redilation.

METHODS

The PLR was studied in normal subjects (16 males and 11 females) between the ages of 20 and 40 years. The experimental protocol for this study was approved by our Committee on Human Research. Pupil area was measured every 50 ms. by infrared video pupillometry (Micromeasurements Inc., Berkeley, Ca.). The light stimulus was a 200 msec. square-wave pulse of collimated white light, generated by a glow-modulator tube (Sylvania R-1131C). The light beam was focused to a width of 2 mm. at the plane of the pupil (Maxwellian view) to provide an open-loop stimulus, i.e. a stimulus that remains constant regardless of pupillary response, since the pupil size is always greater than stimulus size, containing the entire stimulus [22,26]. The duration of the stimulus was chosen to be shorter than the latency of the PLR [4] to further ensure elimination of variation in effective stimulus intensity. Microcomputer controlled tracking was used to compensate for minor head and eye movements. Pupil area data were stored in a PDP-8 computer.

The PLR was measured after five minutes of adaptation to a constant dim level of illumination (0.34 ft-candles, measured on the wall at one meter in front of the subject). Starting shortly before a trial, the subject fixated on a red light-emitting diode which was coaxial with the stimulus

and placed at optical infinity to eliminate accommodation effects. The subject pressed a button to begin each period of recording of the pupil area, which continued until five seconds after the stimulus was delivered. Length of the prestimulus interval was randomly set at either three or four seconds in order to reduce possible effects of flash anticipation on the pupillary response. Up to twelve responses were obtained at one minute intervals.

Nine subjects were also tested after conjunctival administration in the consensual eye, of one to two drops of either 0.5% thymoxamine (Warner-Lambert, Morris Plains NJ) or 0.5% tropicamide (Alcon Laboratories, Fort Worth TX). These agents produce a sympathetic (alpha-adrenergic) or parasympathetic block, respectively [21,25]. Before administration of tropicamide, subjects were examined by tangential light beam to exclude the presence of a narrow anterior chamber. The only adverse reaction noted following either drug was the routinely observed transient burning sensation with thymoxamine [20,25]. PLR measurements were obtained ten to fifteen minutes after drug administration.

For each pupillary response a smoothed curve [24] of pupil area vs. time and its time differential curve were plotted. These curves were analyzed using parameters similar to those employed by Lowenstein and Lowenfeld: baseline pupil area (BPA), latency of constriction (tc), size of

constriction [C(%)], maximum rate of constriction and its time (mrc, tmrc), maximum rate of primary redilation and its time (mrdl, tmrdl) and percentage recovery [rec(%)] [13]. Under our experimental conditions, unlike those of Lowenstein & Loewenfeld, the secondary redilation was often partially overlapped by the primary redilation; therefore we used the percent redilation occurring during the time interval 2.2-2.6 seconds [d2(%)] after the stimulus to define secondary redilation. This time interval was selected because it corresponds to the time of the distinct secondary redilation observed by Lowenstein and Lowenfeld [13].

Statistical analysis was done using the Student's t-test.

RESULTS

Mean baseline pupil area (BPA) for the normal subjects was 31.9 $\pm$2.0mm^2 (mean$\pm$S.E.). For tropicamide treated subjects mean BPA was 53.9 $\pm$2.6mm^2, and for thymoxamine treated subjects mean BPA was 19.2 $\pm$2.6mm^2. Thus, both drugs produced the expected autonomic block ($p<0.05$).

The reproducibility of the PLR in a single subject is shown in Figure 1. Figure 2 demonstrates a single response with its time differential and illustrates the PLR parameters.

PLR parameters for normal and drug treated subjects are plotted as a function of BPA in Figure 3(a-e) and listed in Table I. For statistical analyses drug-treated groups of subjects were compared only to the subset of normal subjects with comparable baseline pupil area (see Figure 3). Using this comparison tropicamide significantly affected five of the eight PLR parameters, decreasing size of constriction [C(%)], maximum rate of constriction (mrc) and maximum rate of primary redilation (mrdl), and increasing latency of constriction (tc) and percentage recovery [rec(%)]. Magnitude of secondary redilation [d2(%)], time to maximum rate of constriction (tmrc), and time to maximum rate of primary redilation (tmrdl) were unaffected by tropicamide.

Thymoxamine treatment, despite significantly lowering BPA, failed to produce significant differences in any of the

DISCUSSION

In this study we used infrared videopupillometry in combination with pharmacological blockade of the ANS to study the PLR in humans. Baseline pupil area measured after 5 min of adaptation in dim, mesopic, light conditions was similar to that observed by others [4]. The cholinergic antagonist, tropicamide, significantly increased BPA but did not abolish the PLR nor produce the degree of mydriasis obtainable with higher dose tropicamide [21]. These findings suggest that we have induced a partial block of the tonic cholinergic innervation of the pupil. This block probably predominantly affected the cholinergic stimulation of the sphinctor, but conceivably might also include a block of the recently appreciated cholinergic inhibition of the dilator, also resulting in an increase in BPA. The alpha-adrenergic antagonist, thymoxamine, significantly decreased BPA. Since subjects were studied before thymoxamine had time to exert its full effect [25], we assume that the block of the tonic alpha-adrenergic outflow to the pupil was also partial. This block probably predominantly affected the alpha-adrenergic stimulation of the dilator, but might also include a block of alpha-adrenergic inhibition of the sphincter, which would also result in a decrease in BPA.

The effect of autonomic blockade on the PLR was studied, employing a stimulus constant in both intensity and

duration. Since the magnitude of the PLR is a function of BPA, as well as of stimulus intensity and since the pharmacological agents altered BPA, we analyzed the dependence of the PLR parameters on BPA in our control group. While absolute magnitude of constriction is highly dependent on BPA (r=-0.8), the percentage constriction [C(%)] was only moderately correlated with BPA (r=-0.4) within the range of BPAs measured. Therefore C(%) rather than absolute magnitude of constriction is a more appropriate parameter to employ as a measure of constriction in studies in which BPA varies. The maximum rate of constriction, mrc, and the maximum rate of primary redilation, mrdl, were greater at larger BPA (r=0.8 and 0.7 respectively), presumably due to the fact that the absolute magnitude of the PLR was greater while the time to full constriction and the time to the sizable primary redilation remained essentially the same. The two percentage measures, d2(%) and rec(%), were independent of BPA. Of the temporal parameters, only latency was a function of BPA, inversely so, as has been previously observed [1,15]. The values we observed for the PLR parameters (except d2(%), a parameter we devised) were similar to those previously observed [13,17,18].

Since some of the PLR parameters were dependent on BPA, we have compared the data from drug treated subjects with

those from control subjects with a similar BPA (i.e., tropicamide treated subjects with large BPA controls and thymoxamine treated subjects with small BPA controls). It should be noted that for those PLR parameters that were independent of BPA, comparison with the entire control group as well did not alter findings of statistical significance.

Tropicamide affected five of the eight PLR parameters: C(%), mrc, mrdl, tc, and rec(%). The decreases in C% and mrc and the increase in tc represent the well established antagonism by tropicamide of the cholinergic parasympathetic activation of the sphincter pupillae muscle. The decrease in mrdl, a parameter suggested by Lowenstein & Loewenfeld to represent parasympathetic relaxation, was due to the markedly blunted pupillary response in 2 out of the 4 subjects. Unexpectedly, rec(%) was increased in the presence of tropicamide. This observation is not explainable by the Lowenstein & Loewenfeld model of the PLR, in which secondary redilation is attributed to peripheral sympathetic activity. This finding can be explained, however, by invoking the recently demonstrated cholinergic inhibition of the dilator pupillae [28]. If cholinergic inhibition of the dilator is present during the second phase of redilation in the normal PLR, then a cholinergic blocker such as tropicamide would be expected to decrease this inhibition thereby enhancing redilation. Since rec(%) was measured at 5 sec after the

stimulus, we conclude that this cholinergic inhibition of the dilator is present at 5 sec post-stimulus.

Thymoxamine did not significantly affect any of the PLR parameters although it did decrease BPA presumably by blocking tonic alpha-adrenergic tone. The model of Lowenstein & Loewenfeld would have predicted a decrease in d2(%) in the presence of thymoxamine. Since we did not see any change in d2(%), we also looked at the PLR of thymoxamine treated subjects during the time period of 2.6-5.0 sec post-stimulus to see if there were perhaps a later effect of thymoxamine, but none was seen. Rec(%) was also unaffected in thymoxamine treated subjects, further suggesting a minimal or absent contribution by peripheral sympathetic activity (either dilator stimulation or sphincter inhibition) to the redilatory phase of the PLR in man under our experimental conditions.

Lowenstein & Loewenfeld employed a relatively long (1 sec) stimulus, which was not presented in Maxwellian view. Consequently their effective stimulus intensity started to decrease markedly when the pupil constricted at about 300 msec post-stimulus. Nevertheless their stimulus provided a significantly longer input to the CNS compared to our 200 msec stimulus. It is perhaps not surprising then that our findings are not in full agreement with those of Lowenstein & Loewenfeld. We do believe, as others presently do [22,27],

that a Maxwellian view stimulus is the more appropriate one. It is possible that the peripheral sympathetic activity observed by Lowenstein & Loewenfeld is not triggered by a short duration stimulus but only by a more lengthy one. Another possibility is that the secondary redilation observed by Lowenstein & Loewenfeld represents in part an off-response which may have been absent in our experiment or obscured by the overlap of the primary and secondary redilations [2,7].

Since in our study there did not seem to be a role for peripheral sympathetic activity in the secondary redilatory phase, the mechanism of any active redilation remains unknown. One possibility is that all of redilation represents continual parasympathetic relaxation. This latter mechanism would not however appear to explain the often observed abrupt change in the slope of redilation (Figure 1). An alternative hypothesis is that the abrupt change in the rate of redilation reflects an abrupt change in the level of central sympathetic inhibition of the E-W nucleus which is thought to commence during the secondary phase of constriction [13]. A decrease in this central sympathetic inhibition during increased parasympathetic tone would result in a decreased rate of redilation. Indeed Lowenstein & Loewenfeld proposed the mechanism of alternating levels of central sympathetic inhibition to explain the cyclical

changes in pupil area which they observed in excited monkeys in which central sympathetic inhibition was markedly increased.

In the present study we have not investigated the contribution to the PLR of the known beta-adrenergic innervation of the pupil, inhibition of both the sphincter and dilator. It has been reported that the beta-adrenergic blocker timolol does not affect either BPA or the PLR [5,19].

In summary, we have demonstrated the feasibility of employing pupillometry combined with pharmacological blockade to dissect the individual parasympathetic and sympathetic contributions to the PLR in humans. We have found no evidence for peripheral sympathetic activity during secondary redilation, but rather suggest that the redilatory phase represents parasympathetic relaxation, modulated by central sympathetic inhibition and cholinergic inhibition of the dilator.

REFERENCES

1. Alpern M, McCready DW, Jr, Barr L. The dependence of the photopupil response on flash duration and intensity. J Gen Physiol 47:265-278, 1963.

2. Bailey CJ, Guth L. Role of the sympathetic nervous system in the pupillary response to darkness. Experimental Neurology 1:166-170, 1959.

3. Davson H. Physiology of the Eye, 4th ed. New York: Academic Press, 1980.

4. Ellis CJK. The pupillary light reflex in normal subjects. Br J Ophthal 65:754, 1981.

5. Johnson SH, Brubaker RF, Trautman JC. Absence of an effect of timolol on the pupil. Invest Ophthalmol 17:924-926, 1978.

6. Kern R. The adrenergic receptors of the intraocular muscles in man: An in vitro study. Albrecht v Graefes Arch klin exp Ophthal 180:231-248, 1970

7. Kollarits CR, Kollarits FJ, Schuette WH, Whitehouse WC,

Gunkel RD. The pupil dark response in normal volunteers. Current Eye Research 2:255-259, 1983.

8. Lind NA, Shinebourne E. Studies on the development of the autonomic innervation of the human iris. Br J Pharm 38:462P, 1970.

9. Lowenstein O. Clinical diagnosis of disturbances of the central sympathetic system by means of pupillography. Arch Neurol Psychiat 55:682-684, 1946.

10. Lowenstein O. Clinical pupillary symptoms in lesions of the optic nerve, optic chiasm, and optic tract. Arch. Ophthal. 52:385-404, 1954.

11. Lowenstein O. Pupillary reflex shapes and topical clinical diagnosis. Neurology 5:631-644, 1955.

12. Lowenstein O, Friedman ED. Pupillographic studies I. Present state of pupillography: Its method and diagnostic significance. Arch Ophthal 27:969-993, 1942.

13. Lowenstein O, Loewenfeld IE. Mutual role of sympathetic and parasympathetic in shaping of the pupillary reflex to light. Archives of Neurology and Psychiatry 64:341-377,

1950.

14. Lowenstein O, Loewenfeld IE. Effect of physostigmine and pilocarpine on iris sphincter of normal man. Arch Ophthalmol 50:311-318, 1953.

15. Lowenstein O, Loewenfeld IE. Influence of retinal adaptation upon the pupillary reflex to light in normal man. Am J Ophthalmol 51:644-654, 1961.

16. Lowenstein O, Loewenfeld IE. The pupil. In: H Davson (ed.), The Eye. New York: Academic Press, pp. 255-337, 1969.

17. Meyer ME, Ogle KN, Hollenhorst RW, Moyer NJ. Derivative curve in evaluation of pupillary reflex response to light. Exptl Eye Res 8:355-363, 1969.

18. Morgan SS, Hollenhorst RW, Ogle KN. Speed of pupillary light response following topical pilocarpine or tropicamide. Am J Ophthalmol 66:835-844, 1968.

19. Namba K, Utsumi T, Nakajima M. Effect of timolol on the pupillary dynamics under open-loop photic stimulus. Folia Ophthalmol Jpn 31:118-123, 1980.

20. Pfeiffer MA, Cook D, Brodsky J, Tice D, Parrish E, Reenan A, Halter JB, Porte D, Jr. Quantitative evaluation of sympathetic and parasympathetic control of iris function. Diabetes Care 5:518-528, 1982.

21. Pollack SL, Hunt JS, Polse KA. Dose-response effects of tropicamide HCl. Am J Optom Physiol Optics 58:361-366, 1981.

22. Stark L. Neurological Control Systems - Studies in Bioengineering. New York: Plenum Press, 1968.

23. van Alphen GWH. The adrenergic receptors of the intraocular muscles of the human eye. Investigative Ophthalmology 15:502-505, 1976.

24. Velleman PF, Hoaglin DC. Applications, basics, and computing of exploratory data analysis. Boston: Duxbury Press, 1981.

25. Wand M, Grant WM. Thymoxamine hydrochloride: An alpha-adrenergic blocker. Surv Ophthalmol 25:75-84, 1980.

26. Westheimer G. The Maxwellian view. Vision Research 6:669-682, 1966.

27. Yamazaki A, Ishikawa S. Abnormal pupillary responses in myasthenia gravis: A pupillographic study. Brit J Ophthal 60:575-580, 1976.

28. Yoshitomi T, Ito Y, Inomata H. Adrenergic excitatory and cholinergic inhibitory innervations in the human iris dilator. Exp Eye Res 40:453-459, 1985.

Table I. PLR parameters in normals, drug, and comparative normal subgroups.†

Group (n)		C(%)[a]	mrc[a]	mrd1[a]	d2(%)	tc[a]	tmrc	tmrd1	rec(%)
NLs (27)	mean	43.9	43.4	13.2	7.9	0.296	0.515	1.29	83.4
	SE	1.2	2.4	0.7	0.6	0.007	0.007	0.02	1.5
Tropic (4)	mean	9.7**	19.8**	8.1*	7.2	0.330**	0.543	1.195	95.0*
	SE	2.3	3.7	2.2	1.0	0.010	0.017	0.075	2.8
lgNLs (5)	mean	38.5	52.4	15.7	6.1	0.255	0.511	1.283	81.8
	SE	2.7	5.1	1.5	0.7	0.016	0.007	0.054	3.7
Thymox (5)	mean	50.9	34.7	11.2	6.3	0.298	0.493	1.228	86.7
	SE	1.5	5.7	0.8	1.3	0.009	0.014	0.036	2.9
smNLs (11)	mean	46.3	32.7	10.2	8.8	0.306	0.500	1.269	82.8
	SE	1.7	2.3	0.8	1.2	0.010	0.010	0.035	3.0

† Tropicamide compared to large normals (lgNLs), thymoxamine compared to small normals (smNLs).

* $p<0.05$, ** $p<0.01$

[a] These parameters are significantly correlated with baseline pupil area.

Figure 1. A series of pupillary light reflex (PLR) responses from a typical subject. Responses to six 200 msec 1200 cd/m^2 stimuli (S) presented at one minute intervals at time t=0. Pupil area (PA) measured at 20 Hz.

Figure 2. A single PLR response (top) and its time differential (below).

BPA.....mean baseline pupil area over 1 sec prior to flash

tc.....time to constriction (latency)

C(%).....size of constriction (as % of BPA)

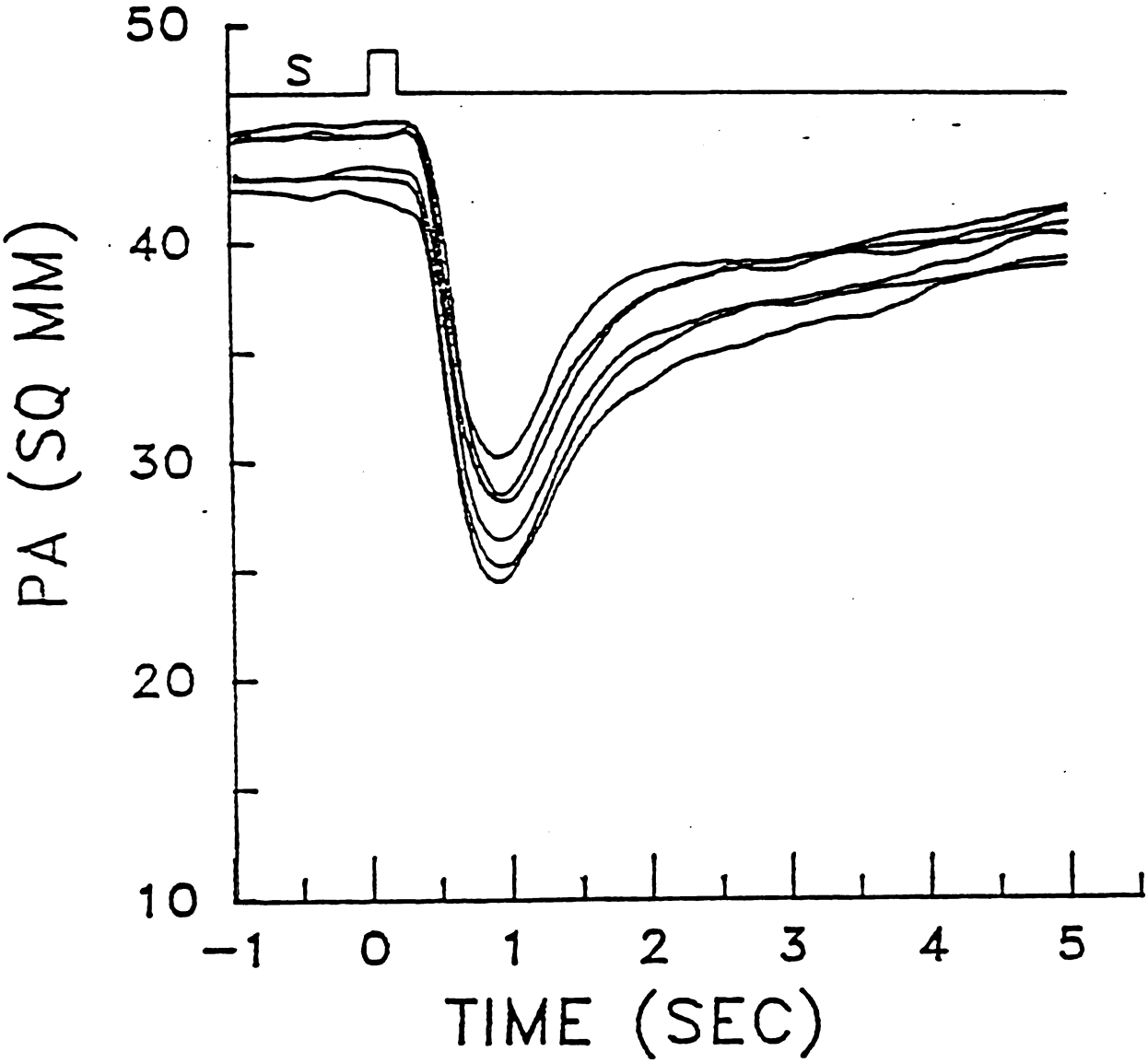
d2(%).....% secondary redilation (% redilation occurring between 2.2-2.6 sec after the stimulus (S)

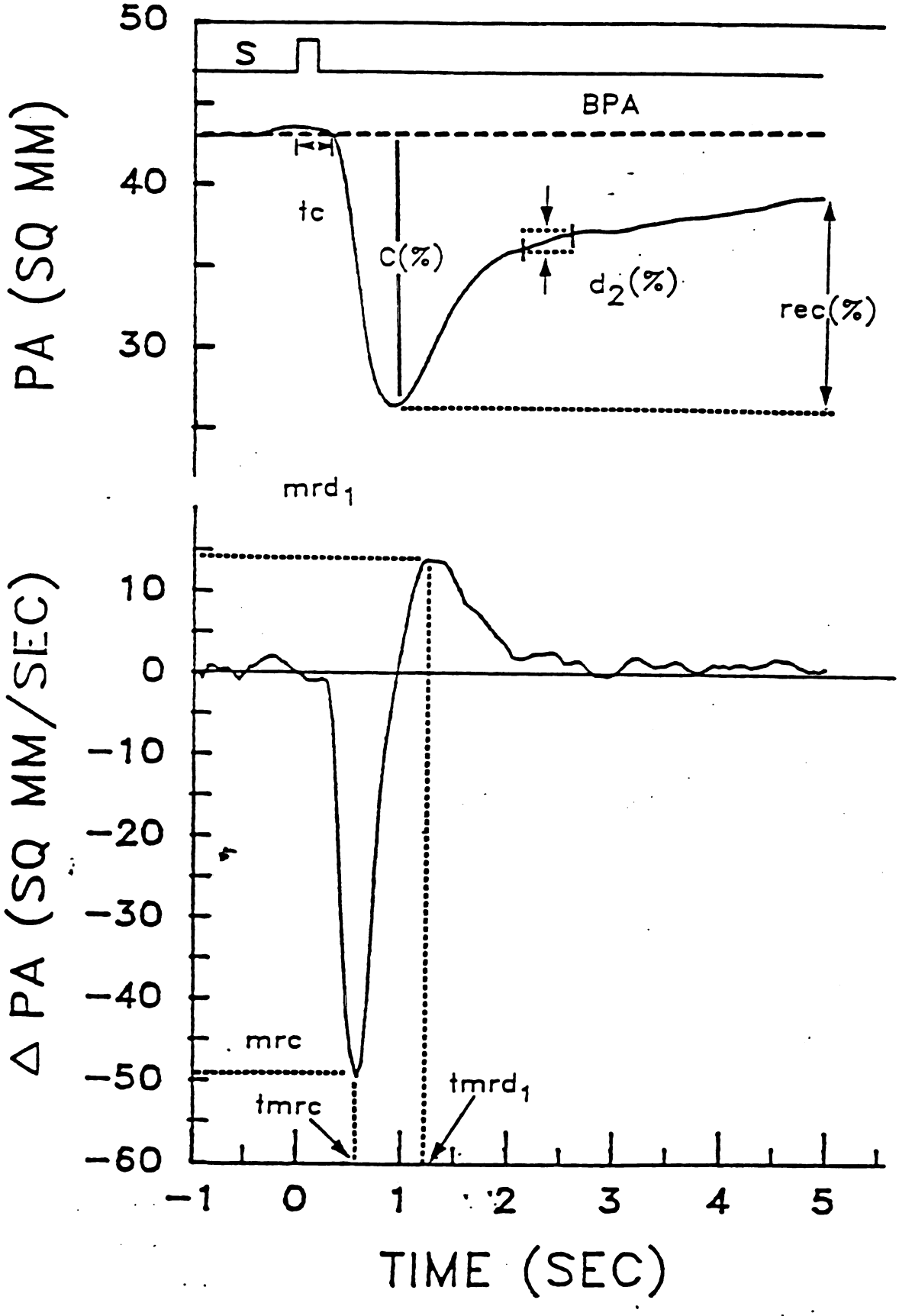
rec(%).....% redilation at 5 sec after the stimulus

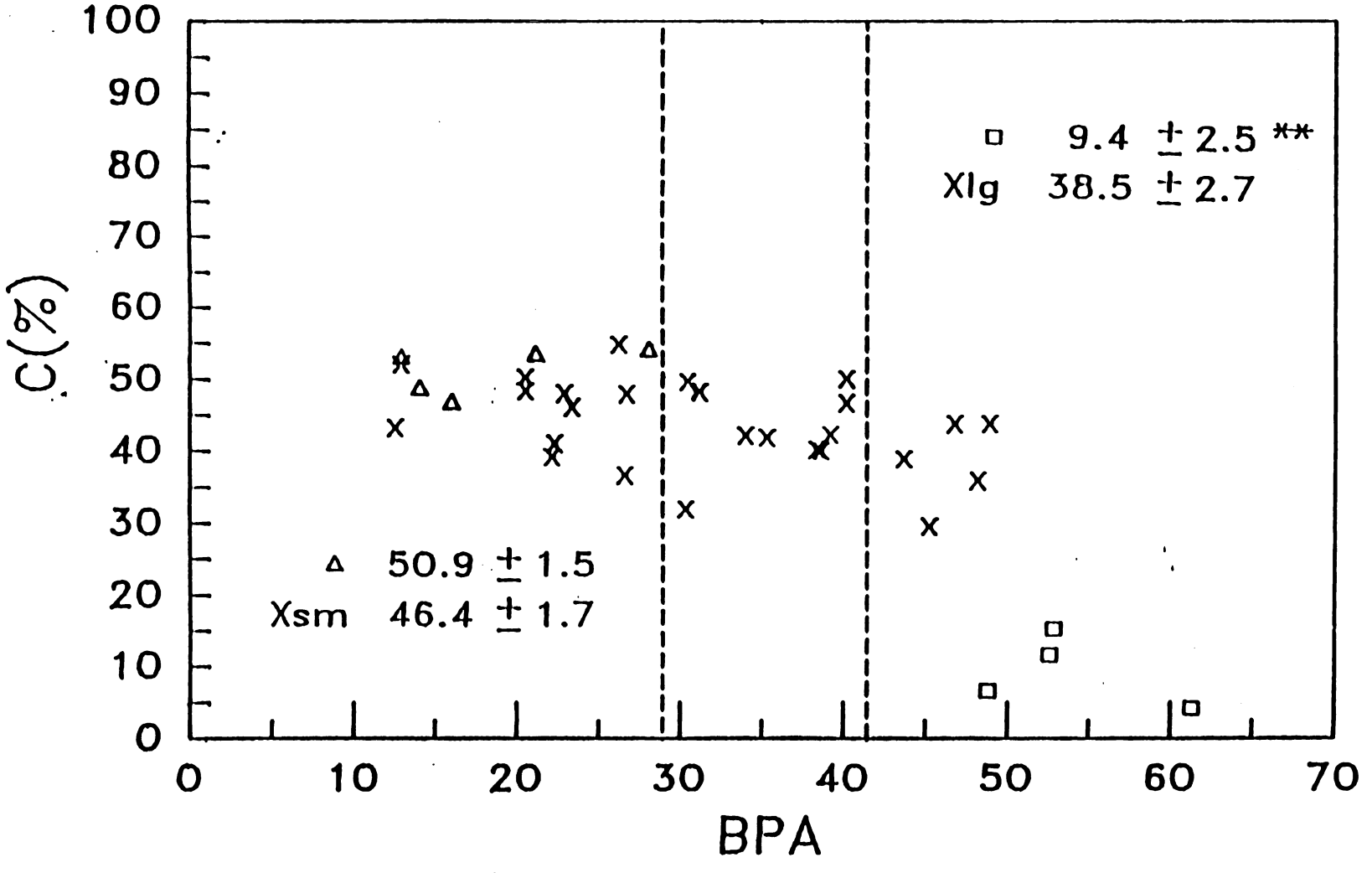
mrc, tmrc.....maximum rate constriction and its time after S

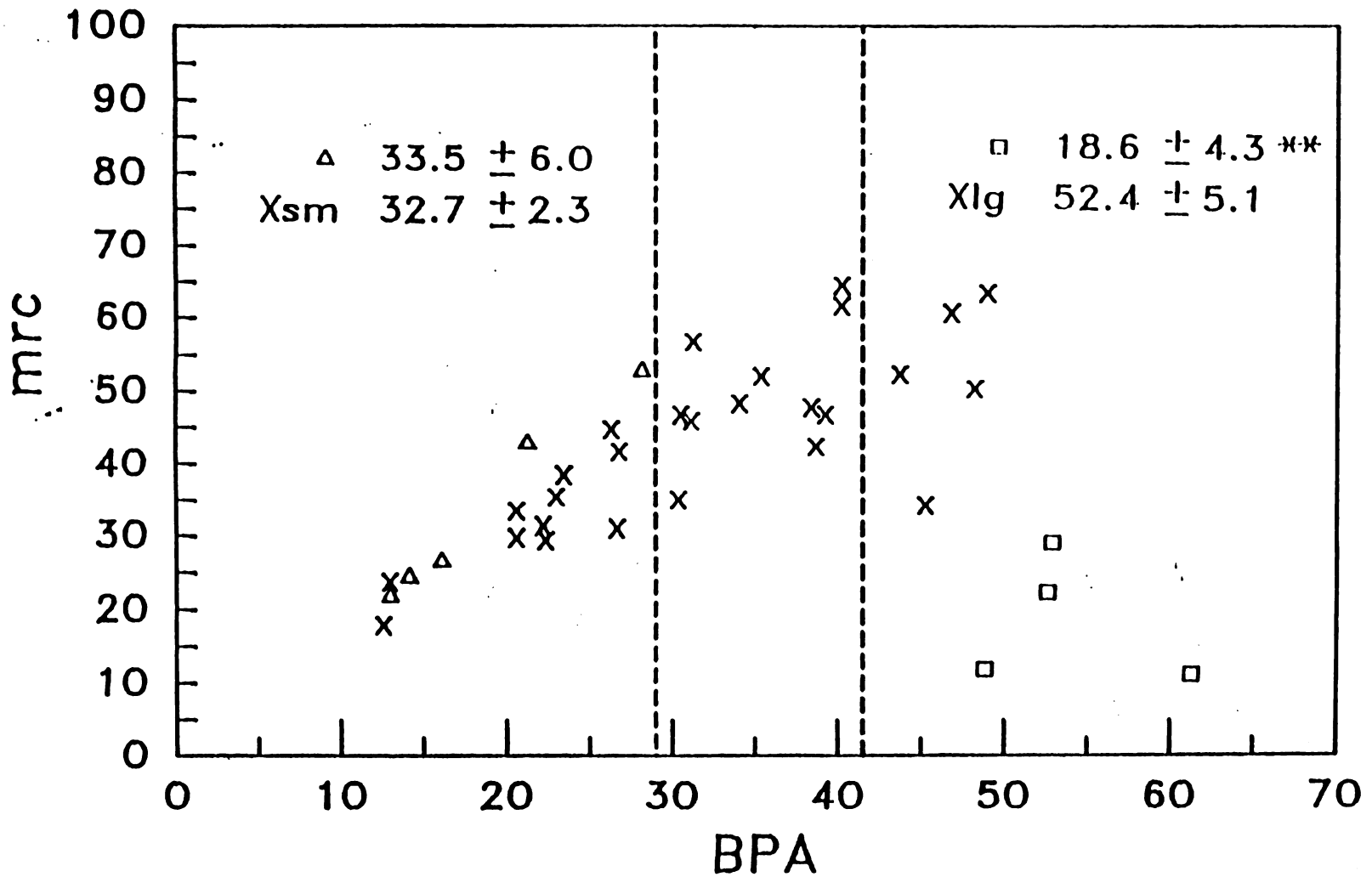
mrdl, tmrdl...maximum rate primary redilation and its time after S

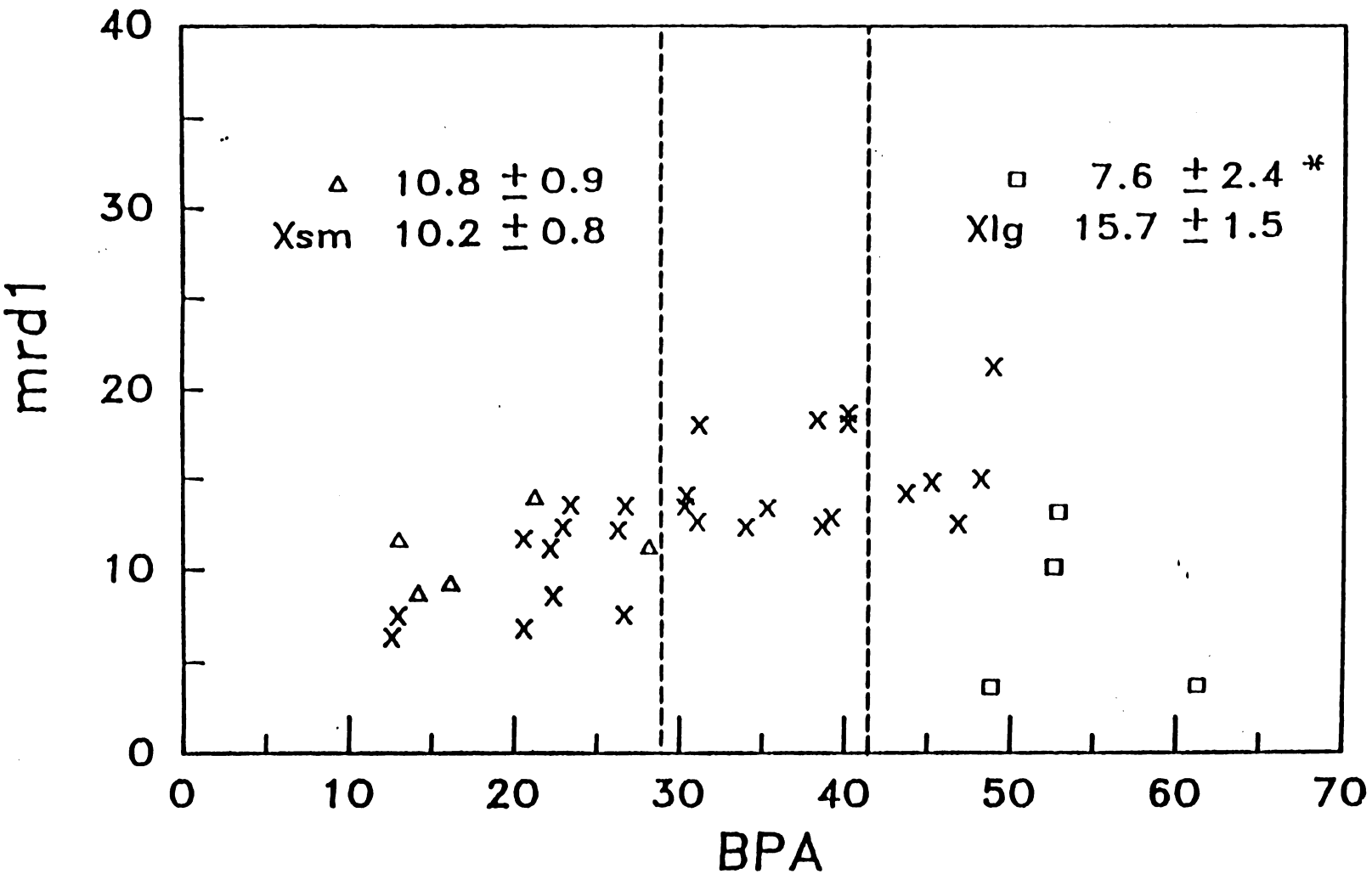
Figure 3 a-e. Five PLR parameters as a function of baseline pupil area (BPA) in normals (X) and after partial parasympathetic (tropicamide □) or sympathetic (thymoxamine △) block. Dotted lines indicate classification of normals into small, medium, and large BPA groups. Small BPA normals (Xsm) were compared to subjects treated with thymoxamine. Large BPA normals (Xlg) were compared to subjects treated with tropicamide (see Table I).

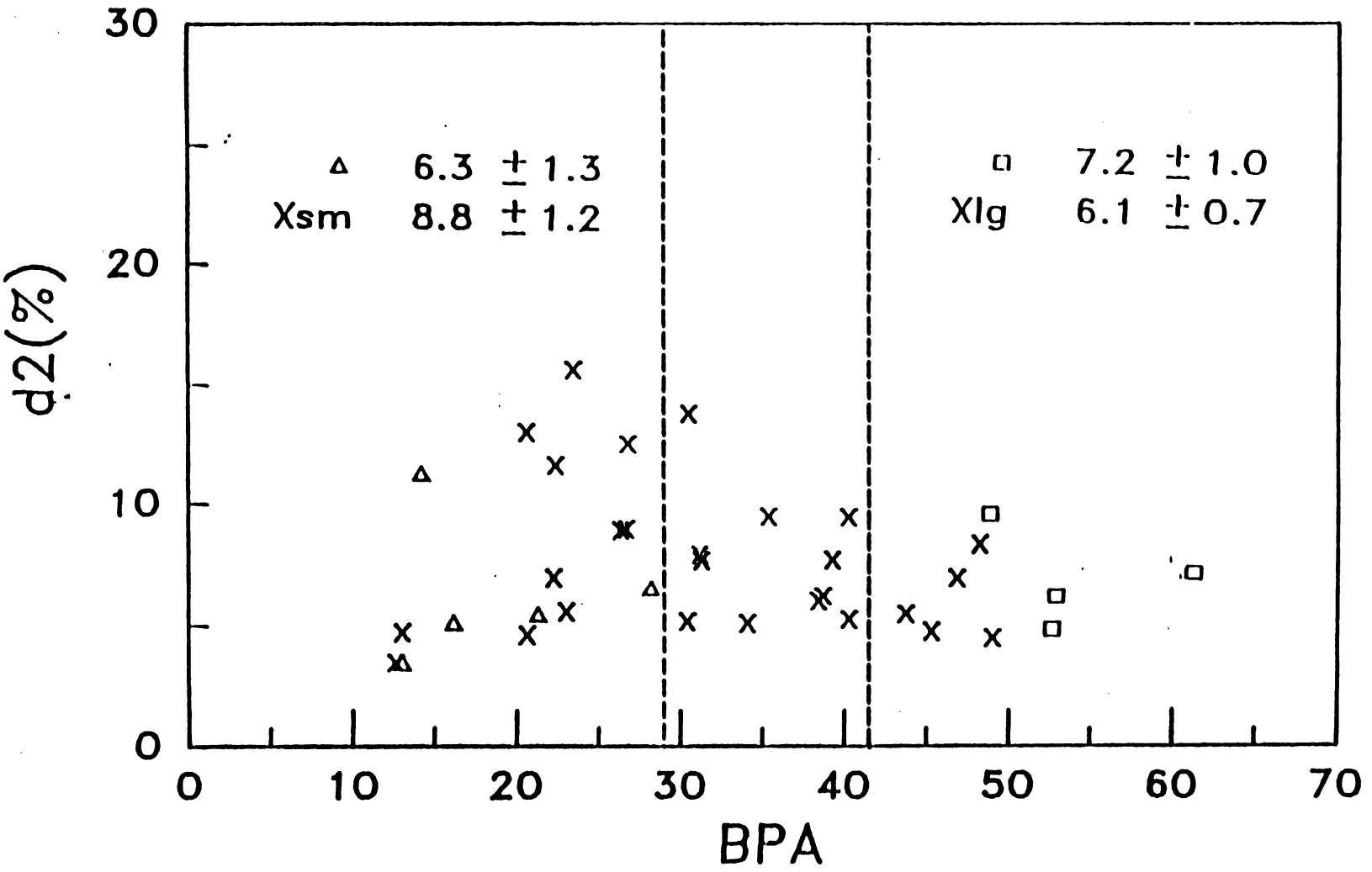

50
S
40
30
20
10
PA (SQ MM)
−1
0
1
2
3
4
5
TIME (SEC)

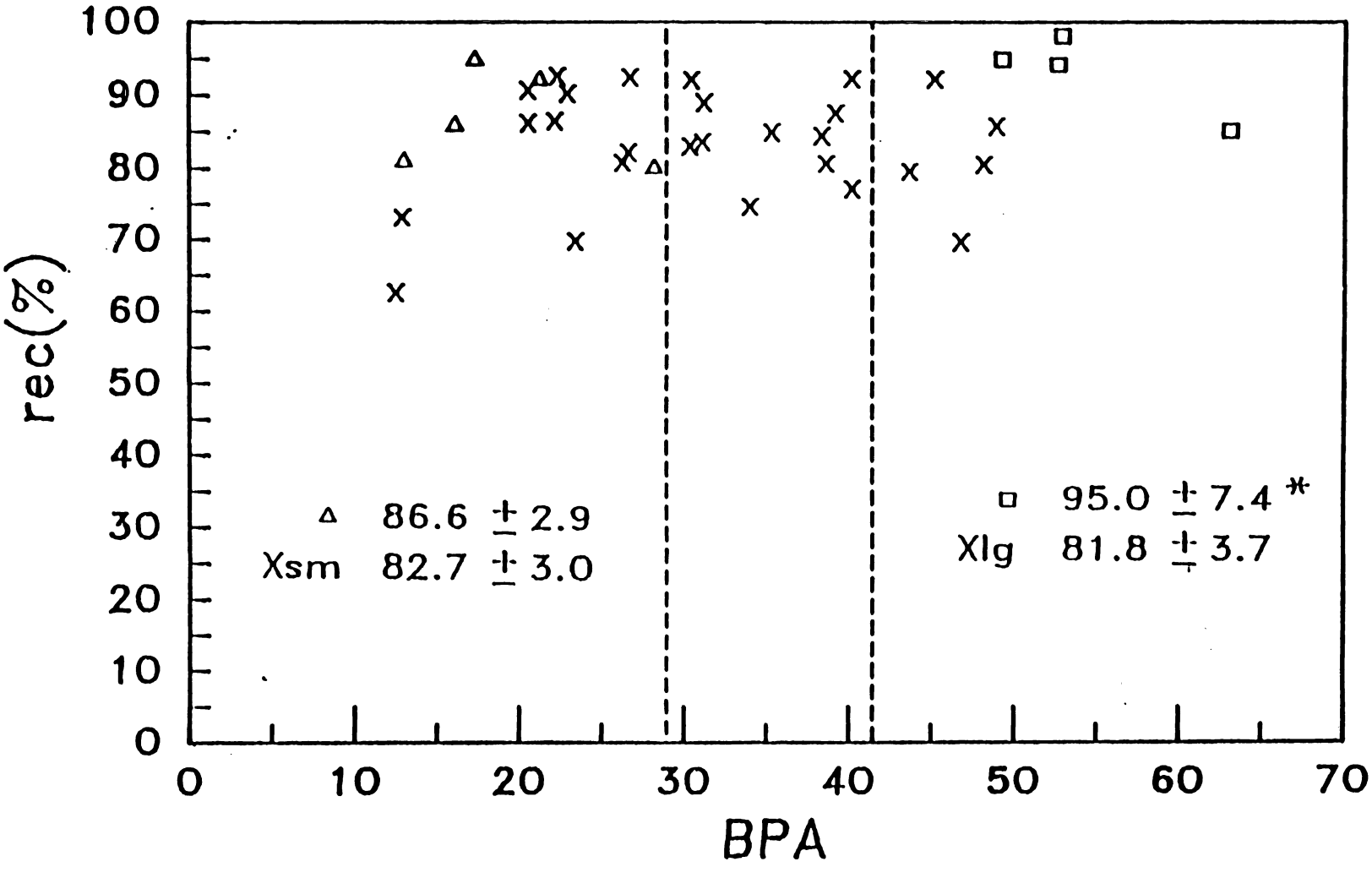

50
S
BPA
40
tc
C(%)
d_2(%)
rec(%)
30
PA (SQ MM)
mrd_1
10
0
−10
−20
−30
−40
mrc
−50
tmrc
$tmrd_1$
−60
Δ PA (SQ MM/SEC)
−1
0
1
2
3
4
5
TIME (SEC)

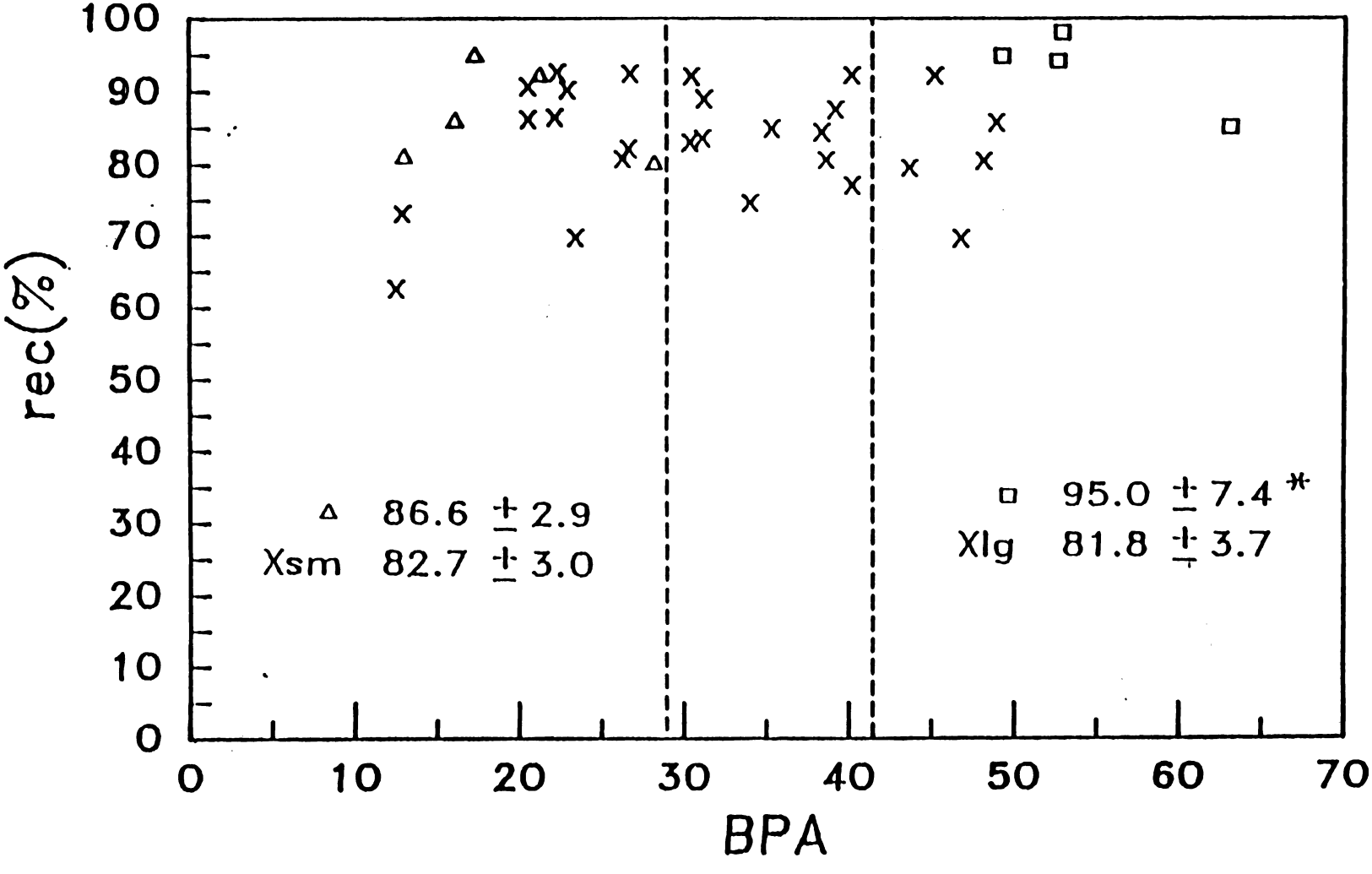

100
90
80
70
60
50
40
30
20
10
0
C(%)
0
10
20
30
40
50
60
70
BPA
△ 50.9 ± 1.5
Xsm 46.4 ± 1.7
□ 9.4 ± 2.5 **
Xlg 38.5 ± 2.7


100
90
80
70
60
50
40
30
20
10
0
mrc
0
10
20
30
40
50
60
70
BPA
△ 33.5 ± 6.0
Xsm 32.7 ± 2.3
□ 18.6 ± 4.3 **
Xlg 52.4 ± 5.1


40
30
20
10
0
mrd1
△ 10.8 ± 0.9
Xsm 10.2 ± 0.8
□ 7.6 ± 2.4 *
Xlg 15.7 ± 1.5
0
10
20
30
40
50
60
70
BPA


30
20
10
0
d2(%)
Δ 6.3 ± 1.3
Xsm 8.8 ± 1.2
□ 7.2 ± 1.0
Xlg 6.1 ± 0.7
0
10
20
30
40
50
60
70
BPA


100
90
80
70
60
50
40
30
20
10
0
rec(%)
0
10
20
30
40
50
60
70
BPA
△ 86.6 ± 2.9
Xsm 82.7 ± 3.0
□ 95.0 ± 7.4 *
Xlg 81.8 ± 3.7


100
90
80
70
60
50
40
30
20
10
0
rec(%)
0
10
20
30
40
50
60
70
BPA
Δ 86.6 ± 2.9
Xsm 82.7 ± 3.0
□ 95.0 ± 7.4 *
Xlg 81.8 ± 3.7

CHAPTER 2.

Alterations in autonomic function in patients with arthritis and fibrositis

SUMMARY

Chapter 2. Analysis of autonomic function in patients with arthritis and fibrositis

Despite considerable evidence of an interrelationship between the autonomic nervous system (ANS) and clinical pain, it has been difficult to establish reliable patterns of autonomic dysfunction characteristic of specific pain syndromes. This difficulty may be due in part to the homeostatic function of the ANS, which ensures that transient changes in peripheral levels of autonomic activity are returned to baseline levels, over time, to keep physiological variables (e.g. heart rate, blood pressure) within an optimal range. Thus, in order to reveal autonomic abnormalities in patients with clinical pain, it may be necessary to monitor autonomic function during maneuvers that further perturb the ANS (dynamic testing), in order to detect disturbances in the regulatory processes that maintain homeostasis. Another possible explanation for this difficulty in establishing autonomic dysfunction is that most studies of ANS function have employed patients with mixed or unspecified diagnoses. Thus, if pain syndromes are associated with specific patterns of autonomic dysfunction, significant findings may have been missed. In the current study, we used dynamic tests of ANS function, including

heart rate and skin conductance responses during mental arithmetic and the valsalva maneuver, and the response of the pupil to light flash (pupillary light reflex, PLR), to study autonomic function in two groups of patients with chronic pain: one with inflammatory arthritis and the other with primary fibrositis (i.e. "psychogenic rheumatism").

In patients with arthritis, compared to normals, we observed altered autonomic function was observed in pupillary, cardiovascular, and sudomotor systems. Altered autonomic function comprised: (1) smaller baseline pupil size, and smaller amplitude and rate of constriction of the PLR; (2) elevated resting heart rate and a diminished bradycardia during the valsalva maneuver; and (3) greater increase in skin conductance during mental arithmetic. Our previous observation of a similar pattern, altered cardiovascular and sudomotor responses, in patients with postoperative pain suggests similar ANS involvement in patients with pain consistent with demonstrable tissue pathology, irrespective of type or duration of the tissue pathology.

In patients with fibrositis we observed fewer autonomic changes than in patients with arthritis or postoperative pain. The only signs of altered autonomic function in these patients were an elevated resting heart rate and a diminished PLR response. Changes in the resting heart rate

and the PLR may reflect a combination of pain, chronicity, and psychological disturbance.

These data reveal distinct patterns of altered autonomic response in patients with arthritis and fibrositis affecting both resting autonomic tone and reactions to perturbations. We draw several inferences regarding the relative contributions of the parasympathetic and sympathetic limbs of the ANS to these alterations. In both groups of patients, the pupillary data suggest concurrent increases in both absolute parasympathetic tone and absolute sympathetic tone. The elevated resting heart rate, also observed in both patient groups, indicates relative tonic sympathetic dominance (increased tonic SNS activity or decreased tonic PNS activity). The decreased bradycardia observed during the valsalva maneuver demonstrates impaired cardiovascular parasympathetic reactivity in the arthritis patients. Finally, the mental arithmetic task revealed enhanced sudomotor reactivity in the patients with arthritis. If these autonomic changes reflect a contribution of the ANS to pain, then the induction of specific alterations in the ANS may have therapeutic potential. In conclusion, these studies demonstrate autonomic alterations in two groups of patients with chronic pain. In combination with other data such as medical history and psychological pain measures, autonomic function testing may help to

distinguish organic from "functional" pain and to elucidate the relative contributions of physiological and psychological factors in different clinical pain syndromes.

INTRODUCTION

There is considerable clinical and experimental evidence demonstrating an interrelationship between pain and the autonomic nervous system (ANS). For example, acute pain can be associated with increased heart rate, increased skin conductance, and increased pupil size [20,68,71,77]. In addition, there are chronic pain syndromes with characteristic localized or generalized autonomic abnormalities, such as reflex sympathetic dystrophies [16,33,41,65,69], migraine headache [2,5,18,19,26,80], phantom limb pain [35,51], mitral valve prolapse [12,28,31], and Guillain-Barre syndrome [25,60]. However, attempts to demonstrate reliable patterns of autonomic dysfunction in other chronic pain syndromes for the most part have not been successful [21,68]. The lack of positive findings in other studies of chronic pain patients might have been due in part to the use of static measures of parameters affected by the ANS, rather than the use of maneuvers [21,73]. This is because the homeostatic function of the ANS maintains the controlled physiological parameters within a narrow range so that dynamic maneuvers must be used to detect disturbances in the regulatory processes that maintain homeostasis. Another possible explanation for this failure to detect autonomic dysfunction is that most studies of ANS function have employed patients with mixed or unspecified diagnoses.

If pain syndromes are associated with specific patterns of autonomic dysfunction, a significant finding might have been missed since comparisons were not made between distinct etiologic entities. A few studies of homogeneous groups of patients with pain have reported autonomic dysfunction. Localized autonomic dysfunction (increased skin conductance) in areas of pain have been demonstrated in patients with painful neck injuries [62]. Also, in recent studies in which autonomic maneuvers were employed, generalized autonomic abnormalities have been demonstrated in patients with fractured limbs [48] and in patients with chronic low back pain [14]. We have recently used the approach of employing several physiological maneuvers perturbing several parameters affected by the ANS ("autonomic maneuvers"), and demonstrated specific abnormalities of autonomic function in postoperative dental pain [34,55].

Patients with arthritis have also been reported to demonstrate autonomic dysfunction. Diminished sweating responses have been observed in patients with arthritis following intradermal nicotine [37] or following hot water baths at 44 degrees C [7]. Recent studies of cardiovascular function in patients with rheumatoid arthritis have found elevated resting heart rates and decreased heart rate responses to horizontal to vertical tilt [44] and to the valsalva maneuver [22]. There is evidence for autonomic

dysfunction in experimental arthritis in rats as well [15].

Patients with fibrositis, a chronic pain syndrome in which patients report musculoskeletal discomfort with specific sites of increased tenderness, have no demonstrable tissue pathology [8,11,38,66,82], in contrast to the marked inflammatory process at the sites of pain in inflammatory arthritis [32]. Patients with fibrositis have also been suspected to have autonomic dysfunction [30,61,70,81]. However, there have been no studies of autonomic function in patients with fibrositis.

In this study we have measured the response of multiple autonomic parameters to dynamic autonomic maneuvers in order to compare autonomic function in patients with inflammatory arthritis to those with fibrositis. We found autonomic abnormalities in both patient groups. These abnormalities in patients with demonstrable organic cause (arthritis) were distinct from those in patients without a demonstrable cause (fibrositis).

METHODS

Subjects

The study population included 38 normal subjects, 19 patients with inflammatory arthritis, and 17 patients with primary fibrositis. All subjects signed a consent form approved by the local institutional review board before participating in the study. All patients included reported pain at the time of study.

Demographic and medication data are listed in Table I. There were sex and age differences in the composition of the groups, which were considered in the statistical analyses (see below).

Exercise level is known to affect cardiovascular autonomic function [3,63,64]. In our study, however, exercise was an insignificant factor, since self-reports of exercise level did not correlate significantly with heart rate in the normal group, and since exercise levels did not significantly differ among the groups ($Chi^2(4)=3.53$, n.s.).

Twenty of the patients were taking medications with known or suspected autonomic effects. In order to reduce these effects, patients were requested to abstain from these medications if possible for twelve hours prior to testing.

Experimental procedures

Autonomic measures were obtained while subjects were

seated in an adjustable chair in a small (6'x7') sound-attenuated experimental room. Pupillary measurements were obtained after five minutes of adaptation to a constant dim ambient light level (0.3 foot-candles) provided by a single 40W red incandescent bulb mounted overhead. During pupillometry the subject looked with one eye into an optical device in which a small red bulb was placed optically at infinity in order to eliminate accommodation effects. The other eye was illuminated by a low intensity infrared light and photographed with an infrared sensitive video camera. Following pupillometry, subjects performed mental arithmetic and the valsalva maneuver according to instructions given via audio tape recorder. These maneuvers, each consisting of baseline, task, and recovery periods, were separated by a five minute break.

Parameters measured

Pupil area was measured at 20 Hz with an infrared pupillometer (Micromeasurements Inc., Berkeley, CA.), which uses microcomputer-controlled tracking to compensate for minor head and eye movements.

Heart period, monitored by surface electrodes attached to the chest, was converted to beat-to-beat heart rate (HR). Skin resistance was measured by the application of a constant small current (0.5 microamps) between two Ag-AgCl

disk electrodes (0.5 sq.cm.) attached to the volar surface of the second phalanx on the second and third digits of the non-dominant hand. An electrode paste consisting of a sodium chloride electrolyte in a neutral ointment cream medium [27] was used. Skin resistance was monitored at 1 Hz and averaged over five second intervals to yield tonic level before mathematical conversion to conductance units (micromhos). Finger pulse volume was measured by an infrared photoplethysmograph attached to the distal phalanx of the fourth digit of the non-dominant hand. Respiration was monitored by a thermistor probe placed near the nostril to allow for interpretation of fluctuations of heart rate secondary to sinus arrhythmia [39].

Pupil area, heart period, and skin resistance were recorded in real time and stored by a PDP-8 computer. Pupil area measurements were also viewed simultaneously on a storage oscilloscope, in order to rule out artifactual and noisy responses at the time of collection. Oscilloscope traces of finger pulse volume and respiratory responses obtained during the valsalva maneuver were photographed in order to provide a record of the peripheral pulse decrement associated with the maneuver.

Maneuvers performed

a. Pupillary light reflex

The light stimulus for the PLR was a 200 msec square-wave pulse of collimated white light (1200 candelas/sq.m.) generated by a glow modulator tube (Sylvania R-1131C). The light beam was focused to a width of 2 mm. in the plane of the pupil (Maxwellian view), to provide an open-loop stimulus that remains constant regardless of pupillary response, since the pupil size is always greater than stimulus size containing the entire stimulus [67,75]. The duration of the stimulus was chosen to be shorter than the latency of pupillary constriction [23] to further ensure elimination of variation in effective stimulus intensity caused by pupillary constriction during the flash. Starting shortly before a trial, the subject looked at the red fixation light which was coaxial to the stimulus. The subject pressed a button to begin each period of recording of pupil area which continued until five seconds after the stimulus was delivered. Length of the prestimulus interval was varied in order to reduce possible effects of flash anticipation on the pupillary response. Twelve responses were obtained at one minute intervals.

b. Mental arithmetic

During and for one minute prior to the mental arithmetic task, heart period and skin resistance were

continuously monitored. The task consisted of one minute of serial subtractions of seven starting from one thousand. Subjects were requested to speak their answers loudly and as rapidly as possible.

c. Valsalva maneuver

After one minute of breathing to a count (7.5 breaths/min), subjects performed the valsalva maneuver by blowing into a hand-held respirometer and holding a pressure of 30 cm. of water for 25 sec at mid-inspiration. A 20-gauge syringe needle in the respirometer tubing provided a small leak so that subjects could not hold the pressure merely by holding inflated cheeks with a closed glottis, but needed to maintain elevated intrathoracic pressure. Before measurements of the response were taken, subjects practiced in order to become familiar with the maneuver. Subjects were observed during measurement to assure that they held the desired pressure. The maneuver was considered adequately performed if a consistent one-third decrease in finger pulse volume occurred during the tachycardic stage.

Data reduction and analysis

a. Pupillary light reflex

For each pupillary response a smoothed curve [72] of pupil area vs. time and its time differential curve (velocity) were analyzed using parameters similar to those employed by Lowenstein and Loewenfeld [49]: baseline pupil

area (BPA), latency of constriction (tc); magnitude of constriction [C(%)]; maximum rate of constriction and its time (mrc, tmrc); maximum rate of primary redilation and its time (mrdl, tmrdl); and percentage recovery [rec(%)] (Figure 1).

b. Mental arithmetic: Skin conductance

Figure 2 illustrates skin conductance (SC) baseline and response measures. Baseline skin conductance was defined as the mean of the one minute period immediately prior to starting the tape recorder which provided task instructions. The skin conductance response measure was defined as the maximum five second mean value of skin conductance observed during the task (including the instructions).

c. Mental arithmetic: Heart rate

Figure 3 illustrates a typical heart rate (HR) response during the performance of mental arithmetic. Baseline (resting) heart rate was taken as the mean heart rate over a ten-second period before task instructions began. Heart rate response was defined as the mean heart rate of the ten-second period containing the fastest beat-to-beat heart rate during the mental arithmetic task (maxHR). In all subjects this occurred during the 60 seconds of continuous subtraction.

d. Valsalva maneuver: Skin conductance

Figure 4 illustrates a typical skin conductance

response during the valsàlva maneuver. Baseline skin conductance for the maneuver was defined to be the minimum ten second mean skin conductance attained during the minute immediately preceding task instructions. The skin conductance response to the maneuver was defined to be the maximum five second mean skin conductance recorded during the task, whether during instructions or during the strain.

e. Valsalva maneuver: Heart rate

Figure 5 illustrates a typical heart rate response during the valsalva maneuver. Premaneuver baseline was defined as the mean heart rate over three respiratory cycles immediately preceding the breath holding and strain portion of the maneuver. Two measures of heart rate response to the maneuver were obtained: the minimum beat-to-beat heart rate observed within 30 seconds immediately following release of straining (minHR) and the valsalva ratio (Vratio), the ratio of maximum beat-to-beat heart rate during the strain to the minimum heart rate attained after the release.

f. Statistical analyses

Data were analyzed using either the analysis of variance, followed by pair-wise multiple comparisons using Fisher's "protected t" procedure when appropriate [13], or the analysis of covariance (ANCOVA), in order to control for pre-existing group differences in sex, baseline level, or age [13,26]. All measured parameters were tested for sex

differences, but only the baseline skin conductance level in the mental arithmetic task revealed a significant difference, which has been reported previously [40,54]. Therefore group comparisons for skin conductance responses were performed using analysis of covariance to control for sex. In the normal group the following PLR parameters were significantly correlated with BPA: magnitude of constriction [C(%)], maximum rate of constriction (mrc), and maximum rate of primary redilation (mrdl). Analyses of these parameters were therefore performed by ANCOVA with BPA as a covariate, and all tabled mean values represent covariance adjusted means. Since in the normal group the maximum rates of constriction (mrc) and redilation (mrdl) were also significantly correlated with age (negatively), age was included as a covariate in the ANCOVA in order to compare mrc and mrdl among groups. Since the maximum skin conductance values were significantly correlated with age and with the baseline skin conductance level, data analyses of skin conductance variables were performed by ANCOVA with age and baseline skin conductance as covariates. Since heart rate responses were significantly correlated with age and baseline heart rate, heart rate comparisons between groups were made by ANCOVA with age and baseline heart rate as covariates.

RESULTS

Pupillary Function

BPA was significantly smaller in the arthritis group compared to normal ($p<.05$). The fibrositis group did not differ significantly from normal (Table II).

The percentage pupillary constriction and the rate of constriction in response to light flash in the arthritis group and the fibrositis group were less than in normals, but the patient groups did not differ from each other.

No differences were found for the other PLR parameters: latency (tc), maximum rate of primary redilation (mrdl), time to maximum rate of constriction (tmrc), time to maximum rate of primary redilation (tmrdl), and percentage recovery [rec(%)].

Electrodermal function

Mental arithmetic

No significant differences in baseline skin conductance were found between groups (Table III), and all three groups showed a significant increase in skin conductance during the performance of mental arithmetic. The maximum skin conductance attained was greater in the arthritis group than in the normal group, while the fibrositis group did not

Valsalva maneuver

All three groups showed the expected increase in skin conductance during the early tachycardic phase of the valsalva maneuver. There were no significant differences in the maximum skin conductance attained (Table III).

Cardiovascular function

Mental arithmetic

Both patient groups had elevated baseline heart rates compared to normal (Table IV). Performance of mental arithmetic significantly increased heart rate in all three groups. There were no differences between groups in the maximum heart rate attained during mental arithmetic.

Valsalva maneuver

All three groups manifested bradycardia immediately following the release of the valsalva maneuver. The arthritis group was found to have a significantly diminished bradycardic response compared to the normal group ($p<.05$), while the fibrositis group did not differ from normal (Table IV). Although the mean valsalva ratio did not differ among the groups, the proportion (6/17=.35) of patients with arthritis with valsalva ratios less than 1.50 (generally considered abnormal [9,45]) was significantly larger than

that of the normal group (2/30=.07) (Chi^2=4.43, $p<.05$). The proportion of abnormally low valsalva ratios in the fibrositis group (4/17=.24) did not differ significantly from the normal group (Chi^2=1.46).

DISCUSSION

We employed dynamic autonomic maneuvers (the pupillary light reflex, the valsalva maneuver, and the stress of mental arithmetic) involving multiple parameters controlled by the ANS (pupillary size, skin conductance, and heart rate) to compare patients having two distinct clinical pain syndromes: arthritis, a disease with demonstrable tissue inflammation, and fibrositis, a pain syndrome with no demonstrable histopathological explanation.

A diminished baseline pupil area and a decreased pupillary constrictive response were seen in the arthritis group. Decreased BPA indicates a relatively increased parasympathetic tone. This relative increase could represent the summation of any combination of the following: (1) increase in tonic parasympathetic activity, (2) decrease in tonic sympathetic activity, and (3) decrease in tonic central sympathetic inhibition of the Edinger-Westphal nucleus [50]. The observed reductions in percentage constriction, C(%), and maximum rate of constriction, mrc, imply reduced parasympathetic reactivity in the arthritis group. Both the relative increase in parasympathetic tone and the decrease in parasympathetic reactivity observed in the arthritis group can be explained by a concurrent elevation of absolute parasympathetic tone and absolute

central sympathetic tone. In this case, BPA as well as C(%) and mrc could be decreased, because elavated central sympathetic tone strongly inhibits pupillary constriction [50]. Hyperactivity in both limbs of the ANS during stress or pain has previously been reported [29,57,58,74].

With respect to normals, BPA in the fibrositis group was unchanged, but C(%) and maximum rate of pupillary constriction (mrc) were decreased. These findings can be explained by the same alteration proposed for the arthritis group, namely increases in both absolute parasympathetic and central sympathetic tone, but relatively less of the latter, so that BPA remained unchanged while the dynamic measure (PLR constriction) was affected.

Baseline heart rate was elevated in both arthritis and fibrositis groups, consistent with previous reports for patients with arthritis [22,44]. Four patients with fibrositis reported taking tricyclic antidepressants, which have known anticholinergic effects that might have contributed to this observation by elevating heart rate [4]. When these four patients were excluded from the analysis, however, baseline heart rate remained elevated in the fibrositis group. Heart rate and exercise levels did not correlate in our normal group, and indeed the baseline heart rate in our normal group (70.7 BPM) does not represent high levels of physical conditioning. Therefore, the elevated

resting heart rates we observed in both patient groups suggest a relatively decreased parasympathetic tone, since resting heart rate in man is controlled primarily by the parasympathetic nervous system [47,56].

The smaller bradycardic response upon release of the valsalva maneuver in the arthritis group indicates reduced parasympathetic reactivity, since the vagus nerve is known to mediate the bradycardic response [24]. While one could argue that the arthritis patients were less able to perform the maneuver effectively, poor performance is an unlikely explanation for the result, because we observed all subjects during the maneuver to assure that they held the correct pressure, and excluded subjects with inadequate decreases in finger pulse volume from the analysis. Dynamic cardiovascular function (reactivity) was normal in the fibrositis group.

During performance of mental arithmetic, all groups attained similar baseline-adjusted maximum heart rates, suggesting that cardiovascular sympathetic reactivity to psychological stress [6] is unaltered in arthritis or fibrositis. We also compared the groups by expressing the increase in heart rate as a percentage of the resting heart rate and found the same lack of influence of arthritis or fibrositis. This contrasts with a previous study [34], in which we found a diminished heart rate response during

mental arithmetic in preoperative and postoperative patients compared to normals. Thus cardiovascular sympathetic reactivity may be affected by subacute but not chronic pain.

Although Riley & Richter [62] reported areas of reduced skin resistance (i.e. increased skin conductance) corresponding to body areas that were painful, the tonic (baseline) levels of skin conductance did not differ among the three groups in our study, despite painful inflammation of the joints of the fingers near the site of skin conductance measurement in many of the arthritis patients. While the increase in skin conductance in the fibrositis group during the stress of mental arithmetic did not differ from normal, the enhanced skin conductance response of the arthritis group during the stress of mental arithmetic demonstrates an increased reactivity in the cholinergic sympathetic sudomotor system in patients with arthritis. This result is particularly interesting considering reports of impaired sweating responses in arthritis patients following hot water immersion [7] or intradermal injection of nicotine [37], which induces local sweating through an axon reflex. Perhaps the sudomotor response to local stimulation uses different peripheral mechanisms than the response to mental stress, which operates through central neural circuits.

We found that the maximum skin conductance attained

during the valsalva maneuver was similar in patient and normal groups. This contrasts both with the result of the mental arithmetic task in this study and with our previous finding of a dampened electrodermal response during the valsalva maneuver in dental patients with postoperative pain [55]. The latter contrast may reflect differences in duration or type of pain experienced by patients with subacute (postoperative) or chronic (rheumatic) conditions. The former contrast, however, between the valsalva maneuver and mental arithmetic, suggests that skin conductance responses to the valsalva maneuver and to mental arithmetic have different mechanisms. Deep breathing is known to be a potent stimulus for the skin conductance response [54]; the effective stimulus for the skin conductance response during the valsalva maneuver probably comprises a mixture of psychological and physiological factors. In fact, for future studies, we recommend use of more uniform types of stimuli (e.g. standard noise, Von Frey hair, or light flash) to test the cholinergic sympathetic sudomotor system, since the amount of stress induced by mental arithmetic can vary widely across individuals, depending on such unmeasured factors as motivation and educational level.

These data reveal different patterns of altered autonomic response in patients with arthritis and fibrositis affecting both resting autonomic tone and reactions to

perturbations. These findings indicate the presence of generalized autonomic changes in these patients, since they were observed in multiple parameters and not just in the area of pain. To draw inferences regarding the relative parasympathetic and sympathetic contributions to these alterations requires examination of the relationships among the three response modalities measured. The elevated resting heart rates observed in both arthritis and fibrositis groups suggests relative tonic cardiovascular sympathetic dominance (increased sympathetic tone and/or decreased parasympathetic tone). As we have argued previously, the pupillary data suggest hyperactivity in both limbs of the ANS. It is known that both parasympathetic and sympathetic activity can be elevated under conditions of stress and pain [29,57,58,72]. In the arthritis group, we have found evidence for increased SNS reactivity (increased skin conductance response during mental arithmetic) and decreased PNS reactivity as well (decreased bradycardia during the valsalva maneuver). The latter is consistent with the "Law of Initial Values" [76], e.g. if parasympathetic activity is already elevated, a stimulus such as the blood pressure overshoot following release of the valsalva maneuver can evoke only a relatively small further increase in neural output.

Comparison of the response patterns in the current data from patients with chronic pain to the patterns previously

observed in patients with subacute (postoperative dental) pain [34,55] suggests that these conditions are characterized by distinct autonomic concomitants. In comparing the response patterns of postoperative pain and stress to those of preoperative stress, Naifeh et al. [55] postulated a specific link between pain and electrodermal activity and between stress and cardiovascular activity. As in the postoperative dental pain group in that study, reactivity in the arthritis group in this study was altered in both electrodermal and cardiovascular systems. Since in both postoperative and arthritis patient groups, the pain was related to clearly demonstrable physiological pathology, the presence of similar autonomic reaction patterns in these two groups is consistent with the hypothesis that characteristic autonomic abnormalities are associated with pain due to demonstrable histochemical pathology. In contrast to the patterns of abnormal autonomic activity seen in the patients with pain of clearly pathophysiologic origin, sudomotor and cardiovascular reactivity was normal in the fibrositis group. Although there is evidence that psychological disorders are common in the fibrositis syndrome [1,59,78], reactions of the fibrositis group also differed from those of the preoperative dental (stress) group, at least in the cardiovascular and sudomotor systems. Whether these two groups have similar activity in the

pupillary system is unknown, since pupillary light reflex measurements have yet to be obtained in preoperative or postoperative patients. Perhaps pupillary reactivity, significantly affected in both arthritis and fibrositis, may be useful to index the affective component of chronic pain [see Chapter 3].

In this study we have evaluated autonomic function in two types of pain, i.e. pain of organic etiology (inflammatory arthritis) and pain of functional etiology (primary fibrositis). Why might we expect ANS function to be altered in these patients? Based upon the known effect of increased nociceptive input on the ANS, changes in ANS function in patients with arthritis are expected to increase resting sympathetic tone. Since in fibrositis there is no demonstrable ongoing process activating nociceptive afferents, this peripheral effect, increasing sympathetic tone, would be expected to be diminished or absent. In fact, we did observe fewer abnormalities in ANS function in the fibrositis group. The abnormalities that were present in the fibrositis group might be expected on the basis of the known affective disorder which accompanies fibrositis [1,59,78]. Since it is known that there are ANS abnormalities in affective disorders [17,43], fibrositis might be expected to be accompanied by alterations in central autonomic activity. However, since chronic pain, on an organic basis, also leads

to a similar affective disorder [68], changes in central autonomic function might very well be similar in our two pain groups. Indeed all of the abnormalities we found in patients with fibrositis were also present in the patients with arthritis. The present study cannot, however, distinguish between peripheral nociceptive and central affective explanations of the observed abnormalities in the two patient groups.

This research has several implications for future studies of the role of the ANS in clinical pain. Clearly, to study the interrelationship between the ANS and clinical pain requires the measurement of multiple autonomic parameters, both under resting conditions and during maneuvers known to perturb them. To interpret the parasympathetic and sympathetic activity underlying measured levels of autonomic parameters, it must be considered that both arms of the ANS can be increased by stress or pain, to different degrees. The inclusion of the PLR can be a particularly valuable addition to cardiovascular and sudomotor tests in the assessment of ANS function, since changes at particular times reflect activity in the different branches of the ANS, and the PLR is unaffected by the level of effort of the subject. Measurement of several autonomic parameters is important because of the "fractionation" [42] of autonomic responses (i.e. ANS

activity in different organs is not homogeneous).

In summary we have found several signs of altered autonomic function in patients with arthritis and fibrositis, including both resting autonomic tone and autonomic ractivity (reactions to perturbations). These findings confirm previous suggestions of altered autonomic function in these patients [7,37,44]. In addition, these data further implicate the ANS in clinical pain, and support the hypothesis of response sterotypy [42,68], that there are autonomic response patterns unique to different clinical pain conditions. Further studies may reveal more and even subtler alterations in the ANS during pain. Such studies may also reveal possible roles for the ANS in contributing to the maintenance of chronic pain syndromes. If the observed autonomic alterations in pain reflect a contribution of the ANS to pain, then the induction of specific alterations in the ANS may have therapeutic potential. In fact, in a recent clinical trial, regional infusion of guanethidine (which depletes norepinephrine and produces a temporary sympathectomy in the treated limb) in patients with severe rheumatoid arthritis, produced dramatic reductions in pain and inflammation [46]. Other methods of altering ANS functioning, such as biofeedback, may also prove useful in these and other pain conditions [10], particularly when abnormal parameters can be rationally identified, and the

production of the desired alterations can be verified. Despite the prevailing view that autonomic measures are not useful to study clinical pain [68,79], we have now demonstrated autonomic alterations in two groups of patients with chronic pain as well as in a group of patients with postoperative pain. We believe that well-designed studies will reveal that autonomic alterations are intimately related to clinical pain. In combination with other data such as medical history and psychological pain measures, autonomic function testing may help to distinguish "organic" from "functional" pain and to elucidate the relative contributions of physiological and psychological factors in different clinical pain syndromes.

REFERENCES

1. Ahles, T.A., Yunus, M.B., Riley, S.D., Bradley, J.M., and Masi, A.T. (1984): Psychological factors associated with the primary fibromyalgia syndrome. Arthritis Rheum, 27:1101-1106.
2. Anthony, M. (1981): Biochemical indicies of sympathetic activity in migraine. Cephalalgia, 1:83-89.
3. Astrand, P.O., and Rodahl, K. (1977): Textbook of work physiology. McGraw-Hill, New York.
4. Baldessarini, R.J. (1980): Drugs and the treatment of psychiatric disorders. In: The Pharmacological Basis of Therapeutics, edited by Gilman, A.G., Goodman, L.S., and Gilman, A., pp. 56-90. MacMillan, New York.
5. Balottin, U., Arisi, D., Frigo, G.M., and Lanzi, G. (1983): Iris adrenergic sensitivity and migraine in pediatric patients. Headache, 23:32-33.
6. Bannister, R. (1983): Testing autonomic reflexes. In: Autonomic Failure, edited by Bannister, R. Oxford Univ Press, Oxford.
7. Bennett, P.H., and Scott, J.T. (1965): Autonomic neuropathy in rheumatoid arthritis. Ann Rheum Dis, 24:161-168.
8. Bennett, R.M. (1981): Fibrositis: Misnomer for a

common rheumatic disorder. Western J Med, 134:405-413.

9. Bennett, T., Farquhar, I.K., Hosking, D.J., and Hampton, J.R. (1978) Assessment of methods for estimating autonomic nervous control of the heart in patients with diabetes. Diabetes, 27:1167-1174.

10. Blacker, H.M. (1980): Volitional sympathetic control. Anesth Analg, 59:785-788.

11. Campbell, S.M., Clark, S., Tindall, E.A., Forehand, M.E., and Bennett, R.M. (1983): Clinical characteristics of fibrositis I. A "blinded" controlled study of symptoms and trigger points. Arthritis Rheum, 26:817-824.

12. Coghlan, H.C., Irwin, P.K., Cowley, M.J., Copley, D.P., Gillis, D.R., and James, T.N. (1976): Abnormal heart rate response in mitral valve prolapse syndrome: Results with valsalva and tilt testing (abstr). Clin Res, 25:45A.

13. Cohen, J., and Cohen, P. (1975): Applied Multiple Regression/Correlation Analysis for the Behavioral Sciences. Lawrence Earlbaum, Hillsdale, NJ.

14. Collins, G.A., Cohen, M.J., Naliboff, B.D., and Schandler, S.L. (1982): Comparative analysis of paraspinal and frontalis EMG, heart rate, and skin conductance in chronic low back pain patients and normals to various postures and stress. Scand J Rehab

Med, 14:39-46.

15. Colpaert, F.C., and van der Hoogen, R.H.W.H. (1983): Ventilatory response to adjuvant arthritis in the rat. Life Sci, 32:957-963.

16. Cronin, K.D., and Kirsner, R.L.G. (1982): Diagnosis of reflex sympathetic dysfunction: Use of the skin potential response. Anaesthesia, 37:848-852.

17. Dawson, M.E., Schell, A.M., and Catania, J.J. (1977): Autonomic correlates of depression and clinical improvement following electroconvulsive shock therapy. Psychophysiology, 14:569-578.

18. Downey, J.A., and Frewin, D.B. (1972): Vascular responses in the hands of patients suffering from migraine. J Neurol Neurosurg Psychiat, 35:258-263.

19. Drummond, P.D. (1982): Extracranial and cardiovascular reactivity in migrainous subjects. J Psychosom Res, 26:317-331.

20. Dudley, D.l., Masuda, M., Martin, C.J., and Holmes, T.H. (1965): Psychophysiological studies of experimentally induced action oriented behavior. J Psychosom Res, 9:209-221.

21. Ebersold, M.J., Laws, E.R., and Albers, J.W. (1977): Measurements of autonomic function before, during, and after transcutaneous stimulation in patients with chronic pain and in control subjects. Mayo Clin Proc,

52:228-232.

22. Edmonds, M.E., Jones, T.C., Saunders, W.A., and Sturrock, R.D. (1979): Autonomic neuropathy in rheumatoid arthritis. Br Med J, 2:173-175.

23. Ellis, C.J.K. (1981): The pupillary light reflex in normal subjects. Br J Ophthal, 65:754-760.

24. Ewing, D.J. (1978): Cardiovascular reflexes and autonomic neuropathy. Clin Sci Molec Med, 55:321-327.

25. Fagius, J., and Wallin, B.G. (1983): Microneurographic evidence of excessive sympathetic outflow in the Guillain-Barre syndrome. Brain, 106:589-600.

26. Fanciullacci, M. (1979): Iris adrenergic impairment in idiopathic headache. Headache, 19:8-13.

27. Fowles, D.C., Christie, M.J., Edelberg, R., Grings, W.W., Lykken, D.T., and Venables, P.H. (1981): Publication requirements for electrodermal measurements. Psychophysiology, 18:232-239.

28. Gaffney, F.A., Karlsson, E.S., Campbell, W., Schutte, J.E., Nixon, J.V., Willerson, J.T., and Blomqvist, C.G. (1979): Autonomic dysfunction in women with mitral valve prolapse syndrome. Circulation, 59:894-901.

29. Gellhorn, E. (1967): Principles of autonomic-somatic integration. Univ Minnesota Press, Minneapolis.

30. Good, M.G. (1950): The role of skeletal muscles in the

pathogenesis of disease. Acta Med Scand, 138:285-292.

31. Gravanis, M.B., and Campbell, W.G. (1982): The syndrome of prolapse of the mitral valve: An etiologic and pathogenic enigma. Arch Pathol Lab Med, 106:369-374.

32. Guilliland, B.C., and Mannik, M. (1983): Rheumatoid arthritis. In: Harrison's Principles of Internal Medicine, edited by Petersdorf, R.G., Adams, R.D., Braunwald, E., Isselbacher, K.J., and Martin, J.D., pp. 1977-1994. McGraw-Hill, New York.

33. Guntheroth, W.G., Chakmakjian, S., Brena, S., Ricketts, H.J., and Wiederhielm, C.A. (1971): Posttraumatic sympathetic distrophy. Am J Dis Child, 121:511-514.

34. Heller, P.H., Perry, F., Naifeh, K.H., Gordon, N.C., Wachter-Shikura, N., and Levine, J.D. (1984): Cardiovascular autonomic response during clinical pain and stress. Pain, 18:33-40.

35. Howe, J.F. (1983): Phantom limb pain - A re-afferentation syndrome. Pain, 15:101-107.

36. Huitema, B.E. (1980): The Analysis of Covariance and Alternatives. John Wiley & Sons, New York.

37. Kalliomaki, J.L., Saarimaa, H.A., and Tiovanen, P. (1963): Axon reflex sweating in rheumatoid arthritis. Ann Rheum Dis, 22:46-49.

38. Kaplan, H., and Brooke, M.H. (1971): Histochemical study of muscle in rheumatic disease. Arthritis Rheum, 14:168-169.

39. Katona, P.G., and Jih, F. (1975): Respiratory sinus arrythmia: Non-invasive measure of parasympathetic control. J App Physiol, 39:801-805.

40. Kawahata, A. (1960): Sex differences in sweating. In: Essential problems in climatic physiology, edited by Yoshimura, H., Ogata, K., and Itoh, S., pp. 169-184. Nankodo, Kyoto.

41. Kleinert, H.E., Cole, N.M., Wayne, L., Harvey, R., Kutz, J.E., and Atasoy, E. (1973): Post-traumatic sympathetic dystrophy. Ortho Clin N Am, 4:917-927.

42. Lacey, J.I., Kagan, J., Lacey, B.C., and Moss, H.A. (1963): Situational determinants and behavioral correlates of autonomic response patterns. In: Expression of the Emotions in Man, edited by Knapp, P., pp. 161-196. International Univ. Press, New York.

43. Lader, M.H. (1980): The psychophysiology of anxiety. In: Handbook of Biological Psychiatry, vol. 2, edited by Van Praag, H.M., pp. 225-247, Marcel Dekker, New York.

44. Leden, I., Eriksson, A., Lilja, B., Sturfelt, G., and Sundkvist, G. (1983): Autonomic nerve function in rheumatoid arthritis of varying severity. Scand J

Rheum, 12:166-170.

45. Levin, A.B. (1966): A simple test of cardiac function based upon the heart rate changes induced by the valsalva maneuver. Am J Cardiol, 18:90-99.

46. Levine, J.D., Fye, K., Heller, P., Basbaum, A.I., and Whiting-O'Keefe, Q. (1986): Clinical response to intravenous guanethidine in patients with rheumatoid arthritis. J Rheumatol, In Press.

47. Levy, M.N. (1971): Sympathetic-parasympathetic interactions in the heart. Circ Res, 29:437-445.

48. Little, R.A., and Stoner, H.B. (1983): Effect of injury on the reflex control of pulse rate in man. Circ Shock, 10:161-171.

49. Lowenstein, O., and Loewenfeld, I.E. (1950): Mutual role of sympathetic and parasympathetic in shaping of the pupillary reflex to light. Arch Neurol Psychiat, 64:341-377.

50. Lowenstein, O., and Loewenfeld, I.E. (1969): The pupil. In: The Eye. Vol 3: Muscular Mechanisms, edited by Davson, H., pp. 255-337. Academic Press, New York.

51. Marsland, A.R., Weekes, J.W.N., Adkinson, R.L., and Leong, M.G. (1982): Phantom limb pain: A case for beta blockers? Pain, 12:295-297.

52. Mayer, S.E. (1980): Neurohumoral transmission and the autonomic nervous system. In: The Pharmacological

Basis of Therapeutics, edited by Gilman, A.G., Goodman, L.S., and Gilman, A., pp. 56-90. MacMillan, New York.

53. Melzack, R., and Wall, P.D. (1983): The Challenge of Pain. Basic Books, New York.

54. Montagu, J.D., and Coles, E.M. (1966): Mechanism and measurement of the galvanic skin response. Psych Bull, 65:261-279.

55. Naifeh, K.H., Heller, P.H., Perry, F., Gordon, N.C., and Levine, J.D. (1983): Altered electrodermal responsivity associated with clinical pain. Pain, 16:277-283.

56. Obrist, P.A. (1981): Cardiovascular Psychophysiology: A Perspective. Plenum, New York.

57. Obrist, P.A., Gaebelein, C.J., Teller, E.S., Langer, A.W., Grignolo, A., Light, K.C., and McCubbin, J.A. (1978): The relationship among heart rate, carotid dP/dt, and blood pressure in humans as a function of the type of stress. Psychophysiology, 15:102-115.

58. Obrist, P.A., Wood, D.M., and Perez-Reyes, M. (1965): Heart rate during conditioning in humans: Effects of UCS intensity, vagal blockade, and adrenergic block of vasomotor activity. J Exp Psychol, 70:32-442.

59. Payne, T.C., Leavitt, F., Garron, D.C., Katz, R.S., Golden, H.E., Glickman, P.B., and Vanderplate, C.

(1982): Fibrositis and psychologic disturbance. Arth Rheum, 25:213-217.

60. Persson, A., and Solders, G. (1983): R-R variations in Guillain-Barre syndrome: A test of autonomic dysfunction. Acta Neurol Scand, 67:294-300.

61. Reynolds, M.D. (1983): The development of the concept of fibrositis. J Hist Med, 38:5-35.

62. Riley Jr., L.H., and Richter, C.P. (1975): Uses of the electrical skin response method in the study of patients with neck and upper extremity pain. Johns Hopkins Med J, 137:69-74.

62. Scheuer, J., and Tipton, C.M. (1977): Cardiovascular adaptations to training. Ann Rev Physiol, 39:221-257.

63. Shephard, R.J. (1982): Physiology and Biochemistry of Exercise. Praeger, New York.

64. Shumacker, H.B., and Abramson, D.I. (1949): Posttraumatic vasomotor disorder. Surg Gynec Obstet, 88:417-434.

65. Smythe, H.A. (1979): Non-articular rheumatism and psychogenic musculoskeletal syndromes. In: Arthritis and Allied Conditions, edited by McCarty, D.J., pp. 881-891. Lea and Febinger, Philadelphia.

66. Stark, L. (1968): Neurological control systems - Studies in bioengineering. Plenum Press, New York.

67. Sternbach, R.A. (1968): Pain: A Psychophysiological

Analysis. Academic Press, New York.

68. Sunderland, S. (1968): Nerves and Nerve Injuries. Livingstone, Edingburgh.

69. Travell, J. (1949): Basis of multiple uses of local block of somatic trigger areas (procaine infiltration and ethyl chloride spray). Miss Vall Med J, 71:13-21.

70. Uematsu, S., and Long, D.M. (1976): Thermography in chronic pain. In: Medical Thermography: Theory and Clinical Applications, edited by Uematsu, S., pp. 52-68. Brentwood, Los Angeles.

71. Velleman, P.F., and Hoaglin, D.C. (1981): Applications, basics, and computing of exploratory data analysis. Duxbury Press, Boston.

72. Wenger, M.A. (1966): Studies of autonomic balance: A summary. Psychophysiology, 2:173-186.

73. Wenger, M.A., Clemens, T.L., and Cullen, T.D. (1962): Autonomic functions in patients with gastrointestinal and dermatological disorders. Psychosom Med, 24:267-273.

74. Westheimer, G. (1966): The Maxwellian view. Vis Res, 6:669-682.

75. Wilder, J. (1950): The law of initial values. Psychosom Med, 12:392.

76. Wolf, S., and Hardy, J.D. (1941): Studies on pain: Observations on pain due to local cooling and on

factors involved in the "cold pressor" effect. J Clin Invest, 20:521-533.

77. Wolfe, F., Cathey, M.A., Kleinheksel, S.M., Amos, S.P., Joffman, R.G., Young, D.Y., and Hawley, D.J. (1984): Psychological status in primary fibrositis and fibrositis associated with rheumatoid arthritis. J Rheum, 11:500-506.

78. Wolff, B.B. (1980): Measurement of human pain. In: Pain, edited by Bonica, J.J. Raven Press, New York.

79. Wolff, H.G. (1963): Headache and Other Head Pain, New York.

80. Yunus, M.B. (1984): Primary fibromyalgia syndrome: Current concepts. Comp Therapy, 10:21-28.

81. Yunus, M.B., Masi, A.T., Calabro, J.J., Miller, K.A., and Feigenbaum, S.L. (1981): Primary fibromyalgia (fibrositis): Clinical study of 50 patients with matched normal controls. Sem Arth Rheum 11:151-171.

Table I. Demographic variables.

	Normal	Arthritis	Fibrositis
Number	38	19	17
Mean age (±SE)	34.1 ±1.6	46.5 ±3.4	43.8 ±3.0
Sex (M/F)	22/16	5/14	0/17
Exercise levels*:			
None	12	7	5
Moderate	12	9	5
Vigorous	14	3	7
Medications:			
#meds/# in group	3/38	19/19	15/17
Known to affect ANS:			
Antiarrhymic (quinidine)	0	1	0
Antihistamine	1	0	0
Antipsychotic (thioridazine)	0	1	0
Beta-blocker	0	1	0
Bronchodilator	0	1	0
Ca++ channel blocker	0	1	0
Codeine	0	1	3
Digitalis	0	1	0
Psychotropic (lithium)	0	1	0
Sedative (benzodiazapine)	0	2	2
Theophylline	0	0	1
Tricyclic antidepressants	0	0	4
May affect ANS			
"Allergy meds"	0	0	1
H2 blocker (Rantidine, Tagamet)	0	1	2
Not known to affect ANS			
Antibiotic	0	0	1
Antimetabolic (allopurinol)	0	1	0
Estrogens, BCP	1	1	1
Cromolyn	0	0	1
Nonsteroidal anti-inflammatory agents	1	16	6
Remittive antiarthritics	0	9	0
L-thyroxin	0	3	0

*Exercise levels were determined on the basis of self-report. The vigorous category included subjects who reported 4 or more hours per week of exercise sufficient to obtain a cardiovascular training effect [3,61,62].

Table II. Pupillary autonomic function. Mean (SEM) baseline pupil area (BPA) in sq.mm., percent constriction [C(%)], maximum rates of constriction (mrc) and redilation (mrdl) in sq.mm./sec.

group	N	BPA	C(%)[1]	mrc[2]	mrdl[1]
Normal	38	32.3 (1.5)	43.8 (1.0)	41.2 (1.8)	12.5 (0.7)
Arthritis	19	26.1* (2.0)	37.8** (1.7)	36.3* (2.4)	11.0 (0.8)
Fibrositis	17	33.4 (2.0)	38.6** (2.3)	36.1* (2.3)	9.8** (0.9)

* Significant difference vs. normal, $p<.05$
** Significant difference vs. normal, $p<.01$

[1]BPA as covariate
[2]Age and BPA as covariates

Table III. Electrodermal Autonomic Function. Mean (SEM) skin conductance values in micromhos (microSiemens).

Group	Baseline SC[1]	Mental arithmetic maxSC[2]	Valsalva maneuver maxSC[2]
Normal	1.76 (0.2)	3.51 (0.4)	3.91 (0.5)
Arthritis	1.25 (0.2)	4.77* (0.6)	3.82 (0.5)
Fibrositis	1.70 (0.3)	3.25 (0.7)	2.35 (0.4)

* Significant difference vs. normal, $p<.05$

[1]Sex and age as covariates
[2]Sex, age and baseline SC as covariates

Table IV. Cardiovascular autonomic function. Mean heart rates in beats per minute (SEM).

Group	Baseline[1]	Mental arithmetic max[2]	Mental arithmetic min[2]	Valsalva maneuver Vratio[2]
Normal	70.7 (2.0)	95.5 (3.3)	54.9 (1.5)	2.01 (.07)
Arthritis	80.2** (2.2)	92.5 (4.1)	62.7** (2.1)	1.69 (.07)
Fibrositis	84.4** (3.5)	92.6 (3.5)	56.0 (2.8)	1.84 (.14)

** Significant difference vs. normal, $p<.01$

[1]Age as covariate
[2]Age and baseline heart rate as covariates

Figure 1. Typical pupillary light reflex (PLR) response (top) and its time differential (below) showing measured parameters.

BPA.....mean baseline pupil area over 1 sec prior to flash

tc.....time to constriction (latency)

C(%).....size of constriction (as % of BPA)

rec(%).....% redilation at 5 sec after the stimulus

mrc,tmrc....maximum rate constriction and time after S

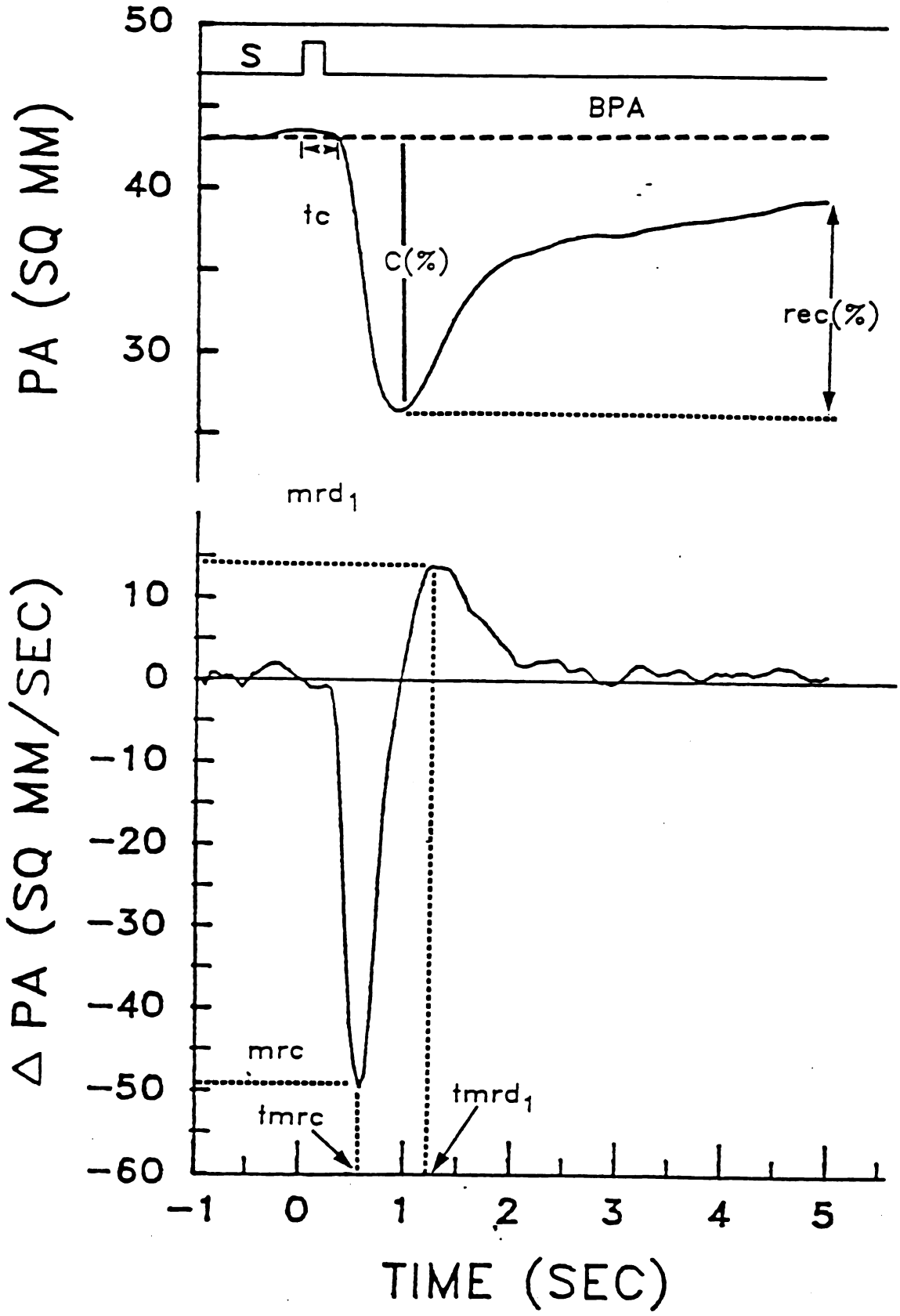
mrdl,tmrdl..maximum rate primary redilation and time S

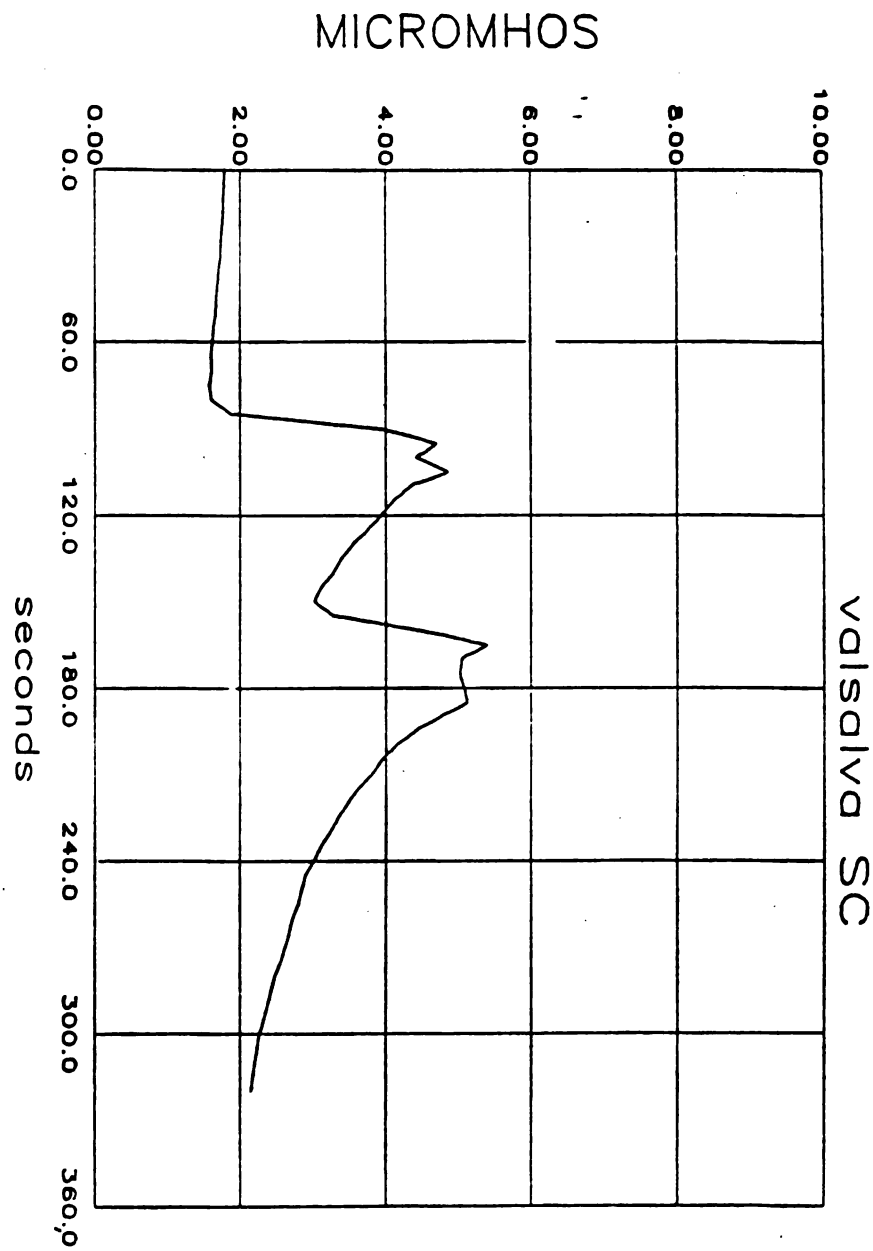
Figure 2. Typical skin conductance (SC) response during mental arithmetic.

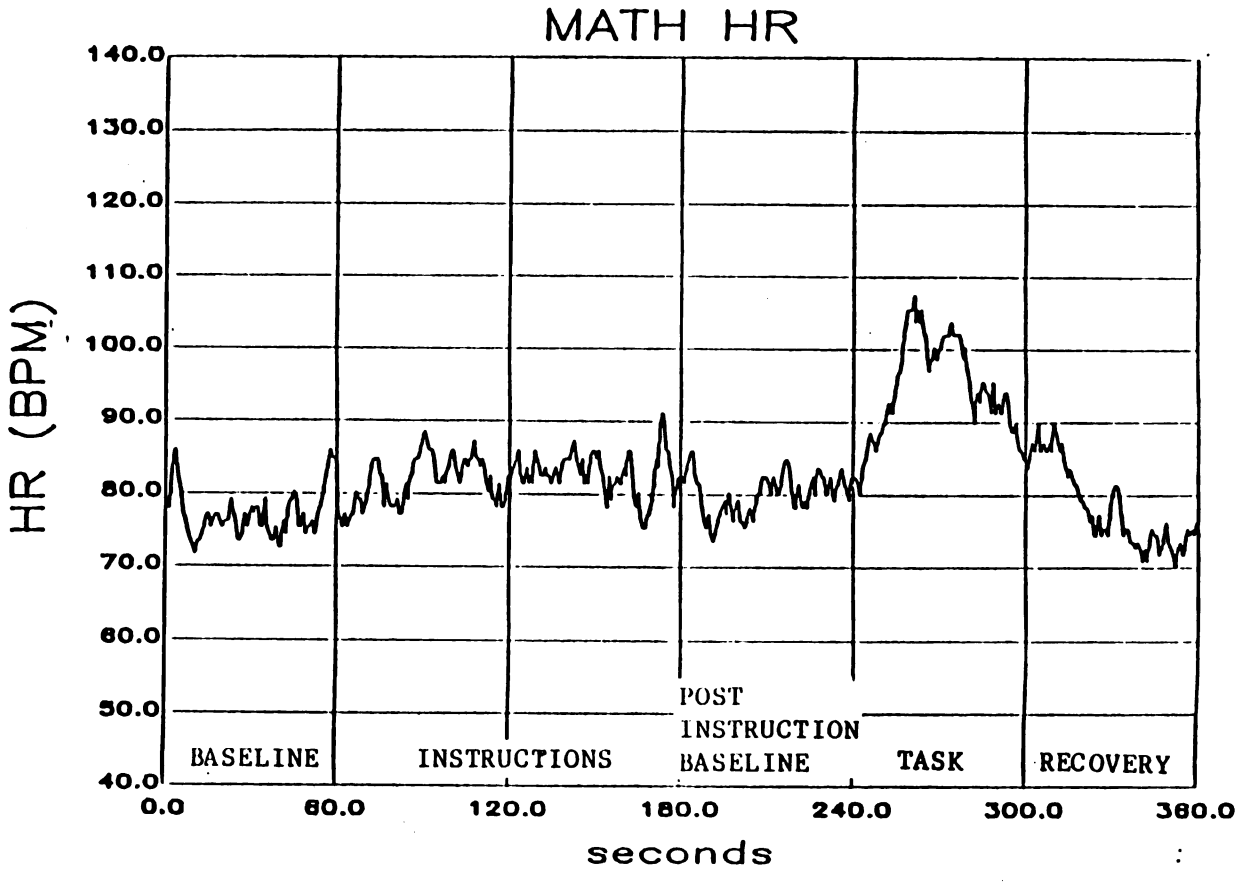
Figure 3. Typical heart rate (HR) response during mental arithmetic.

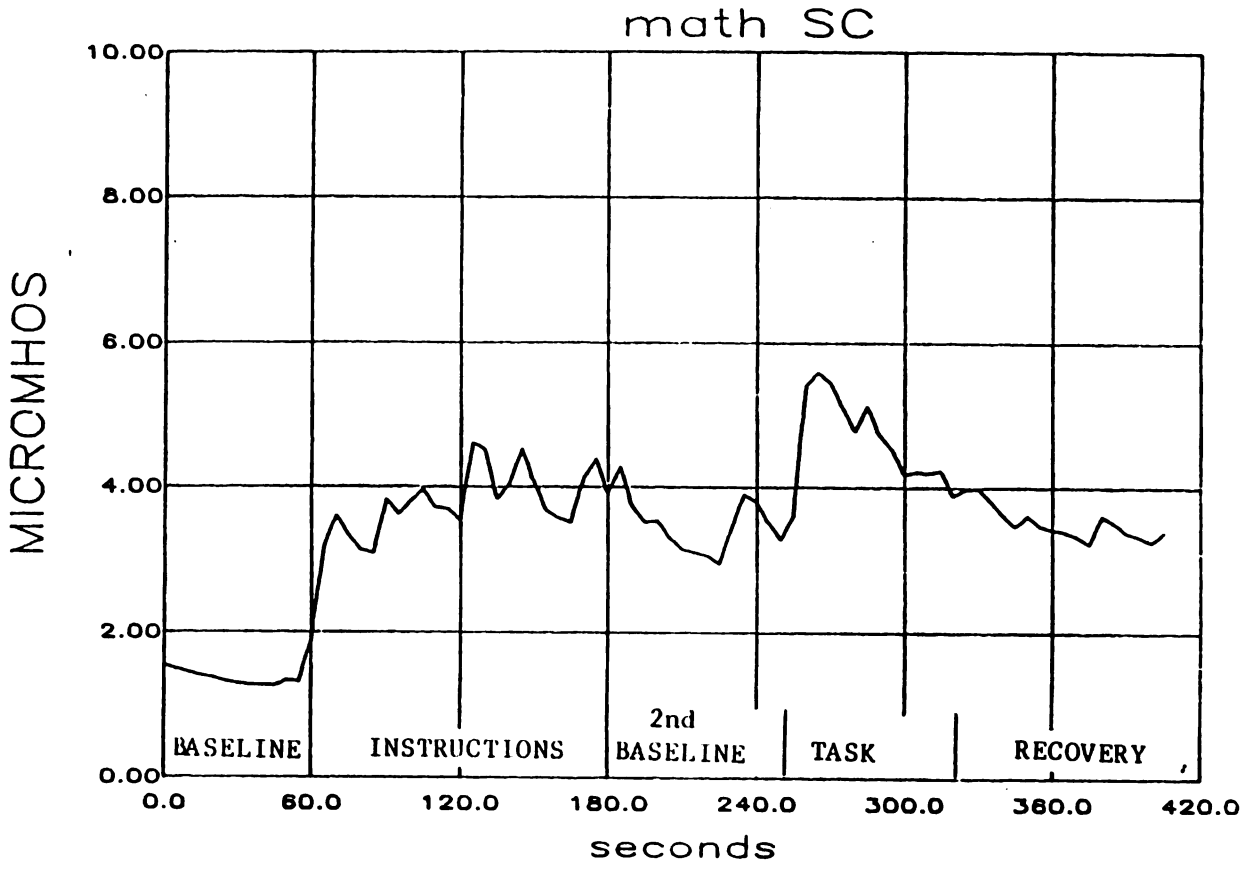
Figure 4. Typical skin conductance (SC) response during valsalva maneuver.

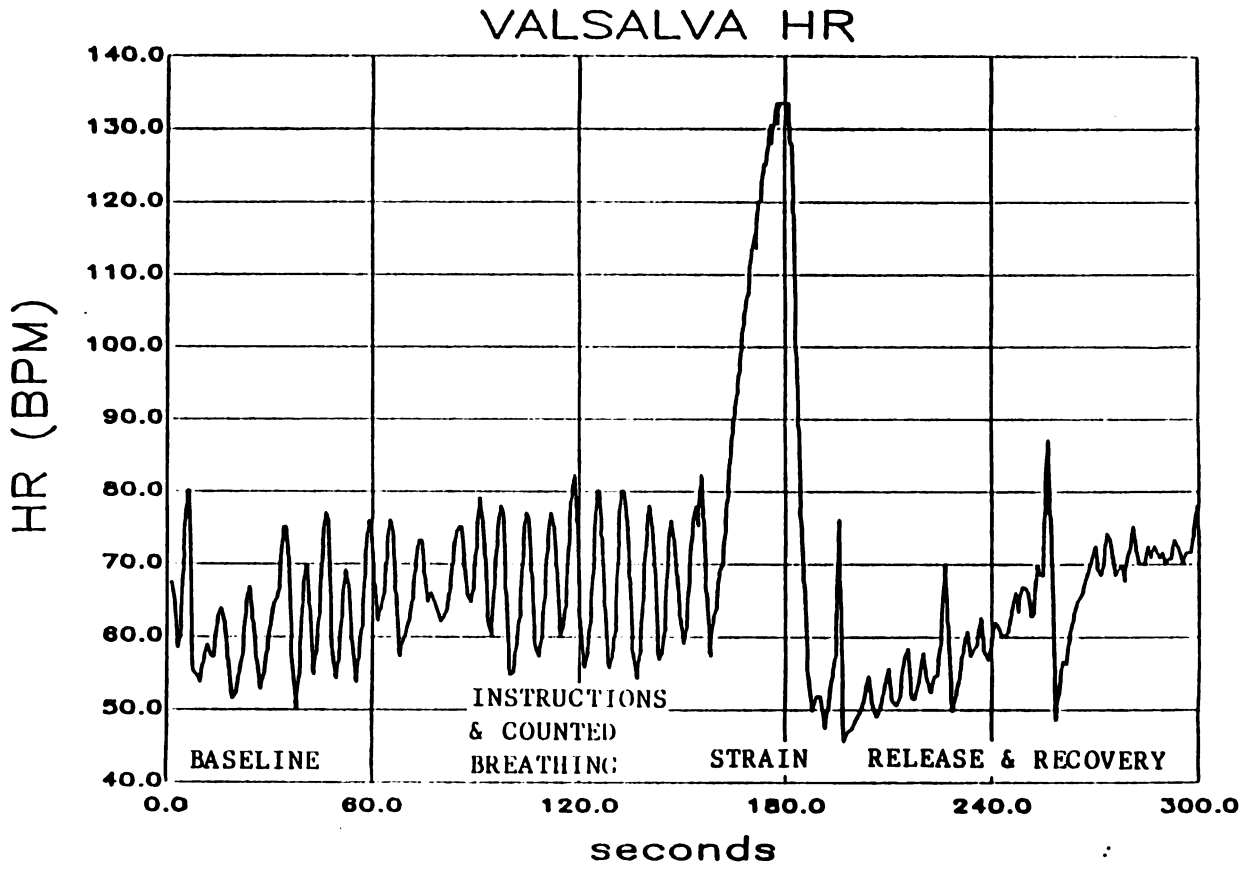
Figure 5. Typical heart rate (HR) response during valsalva maneuver.


50
S
BPA
40
tc
C(%)
rec(%)
30
PA (SQ MM)
mrd1
10
0
-10
-20
-30
-40
mrc
-50
tmrc
tmrd1
-60
Δ PA (SQ MM/SEC)
-1
0
1
2
3
4
5
TIME (SEC)


MICROMHOS
0.00
2.00
4.00
6.00
8.00
10.00
0.0
60.0
120.0
180.0
240.0
300.0
360.0
seconds
valsalva SC


MATH HR
HR (BPM)
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
BASELINE
INSTRUCTIONS
POST
INSTRUCTION
BASELINE
TASK
RECOVERY
0.0
60.0
120.0
180.0
240.0
300.0
360.0
seconds


math SC
MICROMHOS
10.00
8.00
6.00
4.00
2.00
0.00
BASELINE
INSTRUCTIONS
2nd BASELINE
TASK
RECOVERY
0.0
60.0
120.0
180.0
240.0
300.0
360.0
420.0
seconds


VALSALVA HR
HR (BPM)
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
0.0
60.0
120.0
180.0
240.0
300.0
seconds
BASELINE
INSTRUCTIONS & COUNTED BREATHING
STRAIN
RELEASE & RECOVERY

CHAPTER 3.

Correlations between multiple pain measures in patients with arthritis and fibrositis

SUMMARY

Chapter 3. Correlations between multiple pain measures in patients with arthritis and fibrositis

There is no clear relationship between a patient's description of pain (intensity or quality) and the amount of demonstrated histochemical pathology. In order to elucidate any relationship between pain descriptions and etiology, we administered two established measures of pain to 18 patients with inflammatory arthritis and 17 patients with primary fibrositis ("psychogenic rheumatism"). The measures used were the visual analog scale (VAS), a simple measure of pain intensity, and the McGill Pain Questionnaire (MPQ), a multidimensional measure of sensory and affective components of pain as well as of intensity.

The two groups of patients were readily distinguishable on the basis of their pain descriptions. The patients with arthritis, despite their significantly greater demonstrable pathology, reported significantly less "sensory" pain and less pain on a significant number of additional measures. In patients with arthritis, we observed large positive correlations between many of the scores on the different pain measures, thus lending credence to the hypothesis that these scores indeed measure pain secondary to tissue injury. In the fibrositis group, one with little demonstrable

histochemical pathology, significantly lower and paradoxically even negative correlations were found between scores on the different measures. Thus the degree of correlation between pain measures was distinct for fibrositis and inflammatory arthritis. A possible explanation for the low correlation between measures in patients with fibrositis is that their pain is extremely labile, perhaps because it is truly "psychogenic", i.e. entirely due to a perceptual disorder and not driven by a peripheral cause (e.g. inflammation), or because their pain is indeed due to some (minimal) injury, but with a labile central component which exaggerates pain. Also the lability could be due to pain secondary to transient events such as increases in muscle tone and readily reversible anatomical events such as nerve traction. In any case, the application of these pain measures, which have been validated in research with patients with demonstrable pathology, does not seem to adequately measure the experience of patients with fibrositis. This disparity among pain measures must be kept in mind in the study of patients with fibrositis and other pain syndromes in which overt tissue pathology is not apparent, and in fact it appears that new measures need to be developed.

INTRODUCTION

There is no clear relationship between type or extent of injury and a patient's description of pain. For example, it is not uncommon to find extensive injury or pathology with little or no pain [40,58], and intense pain in the absence of detectable organic pathology or injury [36]. While this lack of correlation may in part reflect the operation of well known physiological factors such as endogenous pain inhibitory circuits [3] and psychological influences such as cultural stereotypy and affective state [4,7,8,55,65], it may also reflect that clinical pain is multidimensional, with complex sensory-discriminative and affective-motivational components [36].

There is considerable controversy over how to measure clinical pain most effectively. In clinical pain, as opposed to experimental pain, the cause of the pain cannot be quantified. Another reason for the difficulty in measuring pain is that there is no uniform definition for subjective sensations [4,61]. The usual procedure for establishing reliability has been to measure pain repeatedly in patients whose pain is not expected to vary [51]. The validity of pain measures has been defined either by calibrating the measures during experimental pain while employing known intensities of noxious stimuli [45] or by examining

correlations between different pain measures [5,11,35]. However, the extent to which experimental pain measures are applicable to clinical pain is unclear [4,54,61]. Studies which have used multiple measures of pain have reported widely varying correlations. Since major types of pain measures (behavioral, physiological, subjective) often do not correlate well [15,16,43], they may be measuring different aspects of the pain experience. In a similar way, it is unclear to what extent measurements between individuals with different pain syndromes or even individuals with the same syndrome can be compared.

Subjective pain reports are nevertheless the current gold standard for any studies involving pain [23]. Pain magnitude or intensity has been most commonly measured, using pain rating scales with adjectives and numbers to represent pain. Adjective scales, such as the four word scale described by Keele [24], consist of a list of adjectives, usually arranged along a continuum, from which patients select one or more that describe their pain experience. These scales are easy to use, and have been used in numerous studies of pain [4,21,27]. They have been strongly criticised, however, particularly for their unidimensionality (usually magnitude alone) and lack of sensitivity (too few adjectives) [22]. Numerical scales have been used to quantify pain intensity in a way similar to

adjective scales. Even scales with many numbers may not be more sensitive, however, since there is evidence that humans can only discriminate approximately seven levels of pain intensity [41,61]. Another drawback of numerical scales is that they produce uneven distributions, suggesting that some numbers are preferred over others independently of the variable measured [52].

A method allowing much greater sensitivity than adjective or numerical scales is the visual analog scale (VAS; see Appendix 1) [9,22]. A continuous line with verbal anchors at each end, the VAS is a form of cross-modality matching in which patients indicate their pain intensity by marking a length on the line proportional to their pain. The VAS appears to have high reliability and validity [51] and is in widespread use both clinically and experimentally.

The recognition that the various qualities of pain are independently important led to the attempt to measure these qualities separately. One approach has been to combine several adjective scales. Melzack and his colleagues [37,39] used factor analysis to derive 20 different adjective scales, each representing a different quality of pain, to produce the McGill Pain Questionnaire (MPQ; see Appendix 2). The MPQ provides separate pain intensity measures on postulated sensory, affective, and evaluative dimensions of pain [37]. The MPQ also includes a five point numbered

adjective scale and a body diagram which allows patients to provide specific information regarding the location and distribution of their pain. Numerous studies have supported the reliability and validity of the MPQ in various clinical pain populations [25,46,50]. Furthermore, the MPQ has been able to discriminate among patients with various pain conditions on the basis of word choice patterns [12].

While many other measures of pain have been developed, the VAS and the MPQ are the most well established and appropriate for the study of chronic pain in humans. Objective techniques, such as measurement of nonverbal pain behaviors and physiological parameters, have been used, especially for special purposes (e.g. rehabilitation) or populations (e.g. children or patients with known autonomic disorders such as migraine headache). A recent addition to subjective techniques has been a verbal measure based on cross-modality matching, in which subjects estimate the magnitude of pain implied by pain descriptors by adjusting a response continuum on another modality, such as handgrip force, time duration, or loudness, in order to produce a "ratio scale of pain descriptors" [18]. Although proponents claim that these techniques produce relatively bias-free ratio scales, this claim has been challenged on technical grounds [20], and these scales have yet to be validated with chronic pain populations.

A small number of studies have used both the VAS and the MPQ and have reported enormous variability in the correlations between them [48,49,56,59]. Correlations between the VAS and subscales of the MPQ for instance have varied from r=.16 for women in labor [49] to r=.65 for gall bladder surgery patients [56]. Correlations between the VAS and verbal descriptor scales (such as the Present Pain Intensity of the MPQ) range even further, from r=.29 for episiotomy patients [48] to r=.87 for a mixed group of patients with "organic" pain [62]. It has been suggested on the basis of research with headache patients that concordance between pain measures may become attenuated as chronicity increases [32,44]. Other evidence suggests that pain reports become more diffuse as psychological disturbance increases [2,28]. It is plausible then, that the degree of correlation between multiple pain measures is related to the etiology of different pain syndromes.

In this study we attempted to elucidate any relationship between pain reports and etiology by applying these two subjective pain measures, the VAS and the MPQ, to study patients with pain secondary to known inflammation (arthritis) or with pain but little or no demonstrable histochemical pathology (primary fibrositis). Inflammatory arthritis includes several common diseases characterized by painful swollen joints, due to inflammatory processes

producing tissue damage in the synovial lining of the affected joints [19]. Primary fibrositis is a painful rheumatic syndrome characterized by the presence of diffuse musculoskeletal pain, sleep disorders, and "trigger points", specific focal areas of tenderness within muscle without detectable organic pathology [6,63]. A recent study which employed a modified version of the MPQ and a 100 point numerical scale to study patients with fibrositis and patients with rheumatoid arthritis, did not clearly distinguish between them [30]. Unfortunately, since the MPQ was significantly modified in the Leavitt et al. study (the number of words was increased by nine, and all words were presented in random order), the reliability and validity of their pain measures are unknown. For this study, we have decided to analyze VAS and MPQ scores and to correlate them in patients with arthritis and fibrositis since their pain scores and the correlations between them may yield insight into the relationship between injury and pain and into the poorly understood clinical pain syndrome of fibrositis. This approach provides a number of comparisons between two groups of patients with chronic pain: etiology (more and less demonstrable histochemical pathology), pain levels (two intensity scales and two component subscales), and consistency of pain descriptions (correlations among pain scales and subscales).

METHODS

Patients were recruited from the Arthritis Clinic at the University of California, San Francisco (UCSF) and from the private practices of San Francisco Bay Area physicians. The study population included 19 patients with inflammatory arthritis and 17 patients with primary fibrositis. Mean ages (±SE) for the patient groups, 46.5 (±3.4) for the arthritis group and 43.8 (±3.0) for the fibrositis group, did not differ significantly. The experimental protocol was approved by the UCSF Committee on Human Research.

Ratings of pain intensity were obtained using a Visual Analog Scale (VAS; see Appendix 1). Patients were requested to place a single vertical mark across a 10 cm. horizontal line with the words "no pain" at the left end and "worst pain ever" at the right end, at a point corresponding to their present level of pain intensity. The scale was scored by measuring the distance in centimeters from the "no pain" mark to the patient's mark.

Multidimensional ratings of pain were obtained in the same session using a one page version of the McGill Pain Questionnaire (MPQ; see Appendix 2) [37]. Patients were asked to locate their pain on a body diagram, to choose pain descriptor words within 20 categories consisting of 2-6 words, and to indicate present pain intensity on a scale

from 0 to 5. The descriptor word lists were read aloud to the patients with the instruction that they choose not more than one word from each category that described their present pain. Dictionary definitions of the word descriptors were supplied to the patients upon request. Separate sensory, affective, and total Pain Rating Index (PRI) scores were obtained using the "weighted-rank method" described by Melzack et al. [38], in which the rank score of each chosen descriptor is multiplied by a weighting factor to correct for differences between categories in implied pain intensity, as determined by factor loadings in the original factor analysis of these words [39]. Separate scores for the evaluative component of pain, as described by Melzack [37], have not been included, since recent studies have indicated that the affective and evaluative descriptors cannot be reliably distinguished [29].

Statistical comparisons between mean pain ratings were made by t-test. Product-moment correlations were calculated between pain scales for each patient group. Comparisons between correlations were made using Fisher's z-transformation [13].

RESULTS

Mean pain ratings of 18 patients with inflammatory arthritis and 17 patients with primary fibrositis on the Visual Analog Scale (VAS) and McGill Pain Questionnaire (MPQ) are listed in Table I. The arthritis group reported less pain than the fibrositis group on all six pain scales, and significantly less pain by t-test on the sensory scale of the MPQ (PRI-S) ($p<.05$).

Correlations for the arthritis group between the VAS and MPQ subscales are displayed in Table II. The VAS correlated highly with the Present Pain Intensity (PPI) scale of the MPQ, which is a similar horizontal line intensity scale ($r=.76$, $p<.01$). The VAS did not correlate significantly, however, with either the sensory, affective or total adjective scales of the MPQ (PRI-S, PRI-A, PRI-T, respectively). These MPQ subscales correlated very highly with each other, but none correlated significantly with PPI, the MPQ pain intensity measure.

Correlations for the fibrositis group between the VAS and MPQ subscales are displayed in Table III. In this group, pain intensity as measured with the VAS did not correlate with any of the MPQ subscales. The sensory, affective and total subscales correlated significantly with each other (although less so than in the arthritis group).

Surprisingly, the MPQ measure of pain intensity (PPI) correlated strongly in a negative direction with the sensory subscale score (PRI-S) for the fibrositis group (Figure 1).

Correlations in the arthritis group were significantly higher (Fisher's z-transformation) than in the fibrositis group for VAS vs. PPI ($p<.05$), PRI-S vs. PRI-T ($p<.01$), and PRI-A vs. PRI-T ($p<.01$). Comparison of correlations in the arthritis group against those of the fibrositis group for PRI-S vs. PRI-A approached but did not attain significance at the .05 level ($p=.06$).

DISCUSSION

In this study we examined multiple measures of pain and the correlations between them in patients with substantial organic pathology (arthritis) and with minimal or no organic pathology (fibrositis).

The pain measures clearly distinguished the arthritis and fibrositis groups. The patients with arthritis, despite their relatively greater pathology, reported significantly less "sensory" pain and less pain on a significant number of additional measures, demonstrating that in fact these measures do not simply reflect the degree of pathology. The arthritis group also used significantly fewer word descriptors to describe their pain. Although one might have anticipated higher affective scores in the fibrositis group, since psychological disturbance is reported to be prevalent in these patients [1,42,60], neither the affective scores nor the ratio of the sensory to the affective scores differed between the groups. These findings are in agreement with those of Leavitt et al. [29], who found that patients with fibrositis chose significantly more pain descriptive words than did patients with rheumatoid arthritis, and that the patients with fibrositis reported higher pain scores on both sensory and affective scales than patients with rheumatoid arthritis, though not significantly so. Several

studies have reported that psychological disturbance (or affective distress) is associated with diffuse pain language, such as the use of more sensory and affective words to describe pain of similar intensity [2]. In contrast, the particular words chosen on the MPQ did not distinguish well between arthritis and fibrositis patients in either the Leavitt et al. study or in our study. The most distinguishing characteristic between the two groups in the Leavitt et al. study was the more widespread and diffuse pain distribution reported by the fibrositis patients. We also found more widespread and diffuse pain in the fibrositis patients in our study, as indicated by their responses on the body diagrams of the MPQ. We noted a more striking difference between the groups, however, when we examined the correlations between pain scales.

The pattern of correlations between the various pain measures differed remarkably between the arthritis and fibrositis groups (Tables II and III). In patients with arthritis, we observed large positive correlations between scores on many of the different pain measures, thus lending credence to the hypothesis that these scores are indeed measuring pain secondary to tissue injury. In the fibrositis group, one with little demonstrable histochemical pathology, significantly lower and even negative correlations were found between scores on the different pain measures. The

correlation between the VAS and the Present Pain Intensity (PPI) scale of the MPQ was very high for the arthritis group, but was insignificant for the fibrositis group. For the arthritis group, intercorrelations of the Pain Rating Index scales (PRI: Sensory, Affective, and Total) were significantly higher than those for the fibrositis group.

This observation of relatively higher correlations in the arthritis group is consistent with numerous studies which support the reliability and validity of both the VAS and the MPQ. Reliability is determined by the extent to which a measure expected to remain constant is repeatable. Revill et al. [51] found the VAS to be highly reliable with repeated use by women in labor. Reliability for the MPQ has also been claimed on the basis of repeated administrations within given populations. Melzack [37] reported consistency of word choices on the MPQ in cancer patients over days ranged from 50 to 100%. Due to the subjective nature of pain [36], validity depends upon convergence of various measures of the same or similar constructs [14]. Levine et al. [34] reported that for 95% of successive pain measurements in oral surgery patients, changes in VAS ratings agreed with verbal self-reports of change (pain increased, decreased, or remained the same). In Melzack's original report on the MPQ [37], correlations between the PPI and PRI subscales ranged from .29 to .49. Melzack in fact acknowledged that the PPI

was more labile than the other indices and more susceptible to influence by variables other than the sensory dimensions of pain. Therefore, it remains unclear whether these various scales are measuring the same entity. The remarkably high correlations found in this study between the PRI scales for the arthritis group (from .85 to .95) suggest a high degree of consistency between different dimensions of pain in patients with clear organic pathology. Van Buren and Kleinknecht [57] reported similarly high correlations between these scales (ranging to r=.78) in a study of postextraction dental pain.

The strong negative correlation between sensory and intensity measures (PRI-S vs. PPI) in the fibrositis group at first glance seemed bizarre, so we plotted a scattergram to determine if this result might be artifactual (Fig. 1). Clearly, the pain ratings of the fibrositis patients were extremely inconsistent and variable. Perhaps this is a manifestation of the previously mentioned widespread and diffuse nature of pain as reported by fibrositis patients. For whatever reason, the low and variable correlations seen in this study reflect the difficulty in measuring pain both reliably and validly in these patients. A possible explanation for the low correlation between measures in patients with fibrositis is that their pain is extremely labile, perhaps truly "psychogenic", i.e. entirely due to a

perceptual disorder and not driven by an external cause (e.g. inflammation), or that their pain is due to some (minimal) injury, but with a labile central component which exaggerates pain. Also the lability could be due to pain secondary to transient events such as increases in muscle tone and readily reversible anatomical events such as nerve traction. In any case, pain measures which have been validated in research with patients with demonstrable pathology do not seem to adequately measure the experience of patients with fibrositis. Another factor possibly contributing to the variability in pain measures in patients with fibrositis is that these patients may have unusual difficulty in perceiving their internal state [26,32,53]. If so, these patients would score relatively poorly on tests of proprioception and interoception.

The fact that the patterns of inter-scale correlations were quite different for the fibrositis and arthritis groups is consistent with the literature, since correlations between measures vary widely depending upon the types of pain populations studied [48,49,56,59,62]. While this wide variation may be due in part to a continuing need for improvement in pain measurement, we suggest that patterns of inter-correlations between pain measures may provide important information relative to the perception processes of patients with pain.

While the field of pain measurement has advanced greatly with the introduction of multidimensional measures of pain, such as the MPQ, further research in this area is clearly needed. Controversy remains about both the number and the nature of the dimensions that need to be specified. Melzack and his colleagues, arguing that pain in humans can be characterized by sensory, affective and evaluative dimensions, developed the MPQ, using factor analysis of pain-related adjectives, to provide objective measures of these dimensions [37,39]. The necessary and sufficient dimensions for characterizing different pain syndromes may differ. There is evidence that as many as seven dimensions may be required to describe chronic low back pain [29]. The most appropriate dimensions for arthritic or fibrositic pain are unknown.

In summary, we found that the correlations among multiple measures of pain were consistently higher in a group of patients with demonstrable tissue pathology (arthritis) and were lower and more variable in a group of patients with little or no demonstrable tissue pathology (fibrositis). We have proposed that this difference reflects the etiology of the pain. This disparity among pain measures must be kept in mind in the study of patients with fibrositis and other pain syndromes in which overt tissue pathology is not apparent; in fact it appears that new

measures need to be developed. The efficacy of pain measurement, of course, depends on its application. For many clinical and research purposes, a simple metric of pain intensity may be adequate. For the purpose of understanding the physiological mechanisms and the psychological processes underlying different aspects of pain, measurement of different aspects or dimensions of pain may be necessary. Usefulness of pain constructs (e.g. the affective component) will be greatly increased if they can be found to correlate with objective measures which have high validity. The addition of autonomic measures, as we have done in a companion study (Chapter 2), and behavioral measures in future studies, such as facial expression [31] voice analysis [33], and movement patterns [47], may thus contribute to the understanding of pain both in the laboratory and in the clinic.

REFERENCES

1. Ahles, T.A., Yunus, M.B., Riley, S.D., Bradley, J.M., and Masi, A.T. (1984): Psychological factors associated with the primary fibromyalgia syndrome. Arthritis Rheum, 27:1101-1106.
2. Atkinson, J.H., Kremer, E.F., and Ignelzi, R.J. (1982): Diffusion of pain language with affective disturbance confounds differential diagnosis. Pain, 12:375-384.
3. Basbaum, A.I., and Fields, H.L. (1978): Endogenous pain control mechanisms: Review and hypothesis. Ann Neurol, 4:451-462.
4. Beecher, H.K. (1959): Measurement of Subjective Responses. Oxford University Press, New York.
5. Campbell, D.T., and Fiske, D.W. (1959): Convergent and discriminant validation by the multitrait-multimethod matrix. Psych Bull, 56:81-85.
6. Campbell, S.M., Clark, S., Tindall, E.A., Forehand, M.E., and Bennett, R.M. (1983): Clinical characteristics of fibrositis I. A "blinded" controlled study of symptoms and trigger points. Arthritis Rheum, 26:817-824.
7. Carlen, P.L., Wall, P.D., Nadvorna, H., and Steinbach, T. (1978): Phantom limbs and related phenomena in

recent traumatic amputations. Neurology, 28:211-217.

8. Clark, W.C., and Clark, S.B. (1980): Pain responses in Nepalese porters. Science, 209:410-412.

9. Clarke, P.R.F., and Spear, F.G. (1964): Reliability and sensitivity in the self-assessment of well-being. Bull Br Psychol Soc, 17:55.

10. Crockett, D.J., Prkachin, K.M., and Craig, K.D. (1977): Factors of the language of pain in patient and volunteer groups. Pain, 4:175-182.

11. Downie, W.W., Leatham, P.A., Rhind, V.M., Wright, V., Branco, J.A., and Anderson, J.A. (1978): Studies with pain rating scales. Ann Rheum Dis, 37:378-381.

12. Dubuisson, D., and Melzack, R. (1976): Classification of clinical pain descriptions by multiple group discriminant analysis. Exp Neurol, 51:480-487.

13. Ferguson, G.A. (1966): Statistical analysis in Psychology and Education. McGraw-Hill, New York.

14. Fiske, D.W. (1982): Convergent-discriminant validation in measurements and research strategies. In: Forms of Validity in Research, edited by Brinberg, D., and Kidder, L.H. Jossey-Bass, San Francisco.

15. Fordyce, W.E. (1976): Behavioral methods for chronic pain and illness. C.V. Mosby, St. Louis.

16. Fordyce, W.E., Lansky, D., Caslyn, D.A., Shelton, J.L., Stolov, W.C., and Rock, D.L. (1984): Pain

measurement and pain behavior. Pain, 18:53-69.

17. Garner, W.R., Hake, H.W., and Ericksen, C.W. (1956): Operationism and the concept of perception. Psych Rev, 63:149-159.

18. Gracely, R.H., McGrath, P., and Dubner, R. (1978): Ratio scales of sensory and affective verbal pain descriptors. Pain, 5:5-10.

19. Guilliland, B.C., and Mannik, M. (1983): Rheumatoid arthritis. In: Harrison's Principles of Internal Medicine, edited by Petersdorf, R.G., Adams, R.D., Braunwald, E., Isselbacher, K.J., and Martin, J.D., pp. 1977-1994. McGraw-Hill, New York.

20. Hall, W. (1981): On "Ratio scales of sensory and affective verbal pain descriptors". Pain, 11:101-107.

21. Hardy, J.D., Wolf, S., and Goodell, H. (1952): Pain Sensations and Reactions. Williams & Wilkins, Baltimore.

22. Huskisson, E.C. (1974): Measurement of pain. Lancet, 2:1127-1131.

23. IASP Subcommittee on Taxonomy (1979): Pain terms: A list with definitions and notes on usage. Pain, 6:249-252.

24. Keele, K.D. (1948): The pain chart. Lancet, ii:6-8.

25. Kremer, E., and Atkinson, J.H. (1981): Pain measurement: Construct validity of the affective

dimension of the MPQ with chronic benign pain patients. Pain, 11:93-100.

26. Kremer, E., and Atkinson, J.H. (1983): Pain language as a measure of affect in chronic pain patients. In: Pain measurement and assessment, edited by Melzack, R. Raven Press, New York.

27. Lasagna, L., Mosteller, F., von Felsinger, J.M., and Beecher, H.K. (1954): A study of the placebo response. Am J Med, 16:770.

28. Leavitt, F., and Garron, D.C. (1979): Psychological disturbance and pain report differences in both organic and non-organic low back pain patients. Pain, 7:187-195.

29. Leavitt, F., Garron, D.C., Whisler, W.W., and Sheinkop, M.B. (1978): Affective and sensory dimensions of back pain. Pain, 4:273-281.

30. Leavitt, F., Katz, J., Golden, H.E., Glickman, P.B., and Layfer, L.F. (1986): Comparison of pain properties in fibromyalgia patients and rheumatoid arthritis. Arthritis Rheum 29:775-781.

31. LeResche, L. (1982): Facial expression in pain: A study of candid photographs. J Nonverbal Behav, 7:46-56.

32. Lethem, J., Slade, P.D., Troup, J.D.G., and Bentley, G. (1983): Outline of a fear-avoidance model of

exaggerated pain perception - I. Behav Res Ther, 21:401-408.

33. Levine, J.D., and Gordon, N.C. (1982): Pain in prelingual children and its evaluation by pain-induced vocalization. Pain, 14:85-93.

34. Levine, J.D., Gordon, N.C., Jones, R.T., and Fields, H.L. (1978): The narcotic antagonist naloxone enhances clinical pain. Nature, 272:826-827.

35. McGuire, D.B. (1984): The measurement of clinical pain. Nursing Res, 33:152-156.

36. Melazack, R., and Wall, P.D. (1982): The Challenge of Pain. Basic Books, New York.

37. Melzack, R. (1975): The McGill Pain Questionnaire: Major properties and scoring methods. Pain, 1:277-299.

38. Melzack, R., Katz, J., and Jeans, M.E. (1985): The role of compensation in chronic pain: Analysis using a new method of scoring the McGill Pain Questionnaire. Pain, 23:101-112.

39. Melzack, R., and Torgeson, W.S. (1971): On the language of pain. Anesthesiology, 34:50-59.

40. Melzack, R., Wall, P.D., and Ty, T.C. (1982): Acute pain in an emergency clinic: Latency of onset and descriptor patterns. Pain, 14:33-43.

41. Miller, G.A. (1956): The magical number seven, plus or minus two: Some limits on our capacity for processing

information. Psych Rev, 63:811-97.

42. Payne, T.C., Leavitt, F., Garron, D.C., Katz, R.S., Golden, H.E., Glickman, P.B., and Vanderplate, C. (1982): Fibrositis and psychologic disturbance. Arthritis Rheum, 25:213-217.

43. Philips, C., and Hunter, M. (1981): Pain behavior in headache sufferers. Behav Anal Modif, 4:257-266.

44. Philips, C., and Jahanshahi, M. (1985): The effects of persistent pain: The chronic headache sufferer. Pain, 21:163-176.

45. Price, D.D., McGrath, P.A., Ratii, A., and Buckingham, B. (1983): The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. Pain, 17:45-56.

46. Prieto, E.J., Hopson, L., Bradley, L.A., Byrne, M., Geisinger, K.F., Midax, D., and Marchisello, P.J. (1980): The language of low back pain: Factor structure of the McGill Pain Questionnaire. Pain, 8:11-19.

47. Prkachin, K.M., Currie, N.A., and Craig, K.D. (1983): Judging nonverbal expressions of pain. Canad. J. Behav. Sci., 15:409-421.

48. Reading, A.E. (1980): A comparison of rating scales. J Psychosom Res, 24:119-124.

49. Reading, A.E. (1982): A comparison of the McGill Pain

Questionnaire in chronic and acute pain. Pain, 13:185-192.

50. Reading, A.E. (1983): The McGill Pain Questionnaire: An appraisal. In: Pain Measurement and Assessment, edited by Melzack, R. Raven Press, New York.

51. Revill, S.I., Robinson, J.O., Rosen, M., and Hogg, M.I.J. (1976): The reliability of a linear analogue for evaluating pain. Anesthesia, 31:1191-1198.

52. Scott, J., and Huskisson, E.C. (1976): Graphic representation of pain. Pain, 2:175-184.

53. Smythe, H.A. (1979): 'Fibrositis' as a disorder of pain modulation. Clin Rheum Dis, 5:823-832.

54. Sternbach, R.A. (1968): Pain: A Psychophysiological Analysis. Academic Press, New York.

55. Sternbach, R.A., and Tursky, B. (1965): Ethnic differences among housewives and psychophysical and skin potential responses to electric shock. Psychophysiology, 1:241-246.

56. Taenzer, P. (1983): Postoperative pain: Relationships among measures of pain, mood, and narcotic requirements. In: Pain Measurement and Assessment, editied by Melzack, R. Raven Press, New York.

57. Van Buren, J., and Kleinknecht, R.A. (1979): An evaluation of the McGill Pain Questionnaire for use in dental pain assessment. Pain, 6:23-33.

58. Wall, P.D. (1979): On the relation of injury to pain. Pain, 6:253-264.

59. Walsh, T.D., and Leber, B. (1983): Measurement of chronic pain: Visual analog scales and McGill Melzack Pain Questionnaire compared. In: Pain Measurement and Assessment, edited by Melzack, R. Raven Press, New York.

60. Wolfe, F., Cathey, M.A., Kleinheksel, S.M., Amos, S.P., Joffman, R.G., Young, D.Y., and Hawley, D.J. (1984): Psychological status in primary fibrositis and fibrositis associated with rheumatoid arthritis. J Rheum, 11:500-506.

61. Wolff, B.B. (1980): Measurement of human pain. In: Pain, edited by Bonica, J.J. Raven Press, New York.

62. Woodforde, J.M., and Merskey, H. (1972): Some relationships between subjective measures of pain. J Psychosom Res, 16:173-178.

63. Yunus, M., Masi, A.T., Calabro, J.J., Miller, K.A., and Feigenbaum, S.L. (1981): Primary fibromyallgia (fibrositis): Clinical study of 50 patients with matched normal controls. Sem Arth Rheum, 11:151-171.

64. Zarkowska, E., and Philips, H.C. (1986): Recent onset vs. persistent pain: Evidence for a distinction. Pain, 25:365-372.

65. Zborowski, M. (1952): Cultural components in responses to pain. J Soc Issues, 8:16-30.

Table I. Pain ratings on Visual Analog Scale (VAS) and McGill Pain Questionnaire (MPQ) subscales for two groups of chronic pain patients (Mean ±SE).

	Arthritis	Fibrositis	
VAS	3.1 ± 0.5	4.5 ± 0.4	
PPI	1.8 ± 0.2	2.1 ± 0.3	
PRI-S	9.4 ± 1.4	14.5 ± 1.4	*p<.05
PRI-A	4.3 ± 1.3	5.6 ± 1.0	
PRI-E	2.1 ± 0.3	2.3 ± 0.3	
PRI-T	19.2 ± 3.5	25.5 ± 2.4	
A/S	.38 ± .07	.38 ± .06	

Abbreviations:

VAS = Visual Analog Scale
MPQ = McGill Pain Questionnaire, with PPI & PRI subscales
PPI = Present Pain Index (5 point scale from MPQ)
PRI-S = Pain Rating Index - Sensory
PRI-A = Pain Rating Index - Affective
PRI-E = Pain Rating Index - Evaluative
PRI-T = Pain Rating Index - Total
A/S = ratio of Affective to Sensory scores

Table II. Correlations between pain rating scales in 18 patients with inflammatory arthritis.

	VAS	PPI	PRI-S	PRI-A	PRI-T
VAS	1				
PPI	.76**	1			
PRI-S	.17	.21	1		
PRI-A	.26	.24	.85**	1	
PRI-T	.24	.25	.95**	.95**	1

Abbreviations:

VAS = Visual Analog Scale
PPI = Present Pain Index (5 point scale from MPQ)
PRI-S = Pain Rating Index - Sensory
PRI-A = Pain Rating Index - Affective
PRI-T = Pain Rating Index - Total

** $p<.01$

Table III. Correlations between pain rating scales in 17 patients with primary fibrositis.

	VAS	PPI	PRI-S	PRI-A	PRI-T
VAS	1				
PPI	.21	1			
PRI-S	.09	-.61**	1		
PRI-A	-.01	-.14	.51*	1	
PRI-T	.32	-.29	.64**	.69**	1

Abbreviations:

VAS = Visual Analog Scale
PPI = Present Pain Index (5 point scale from MPQ)
PRI-S = Pain Rating Index - Sensory
PRI-A = Pain Rating Index - Affective
PRI-T = Pain Rating Index - Total

* $p<.05$
** $p<.01$

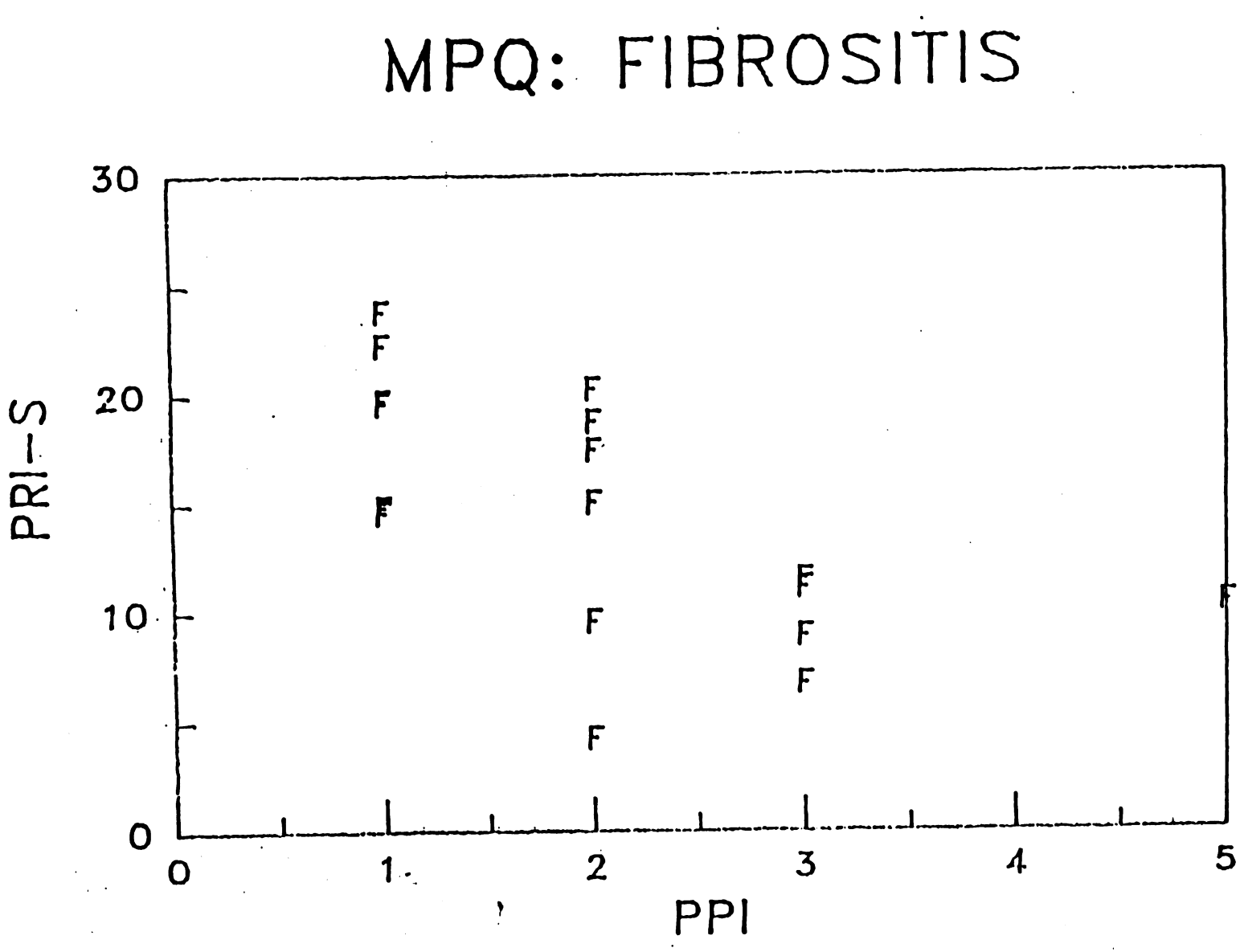
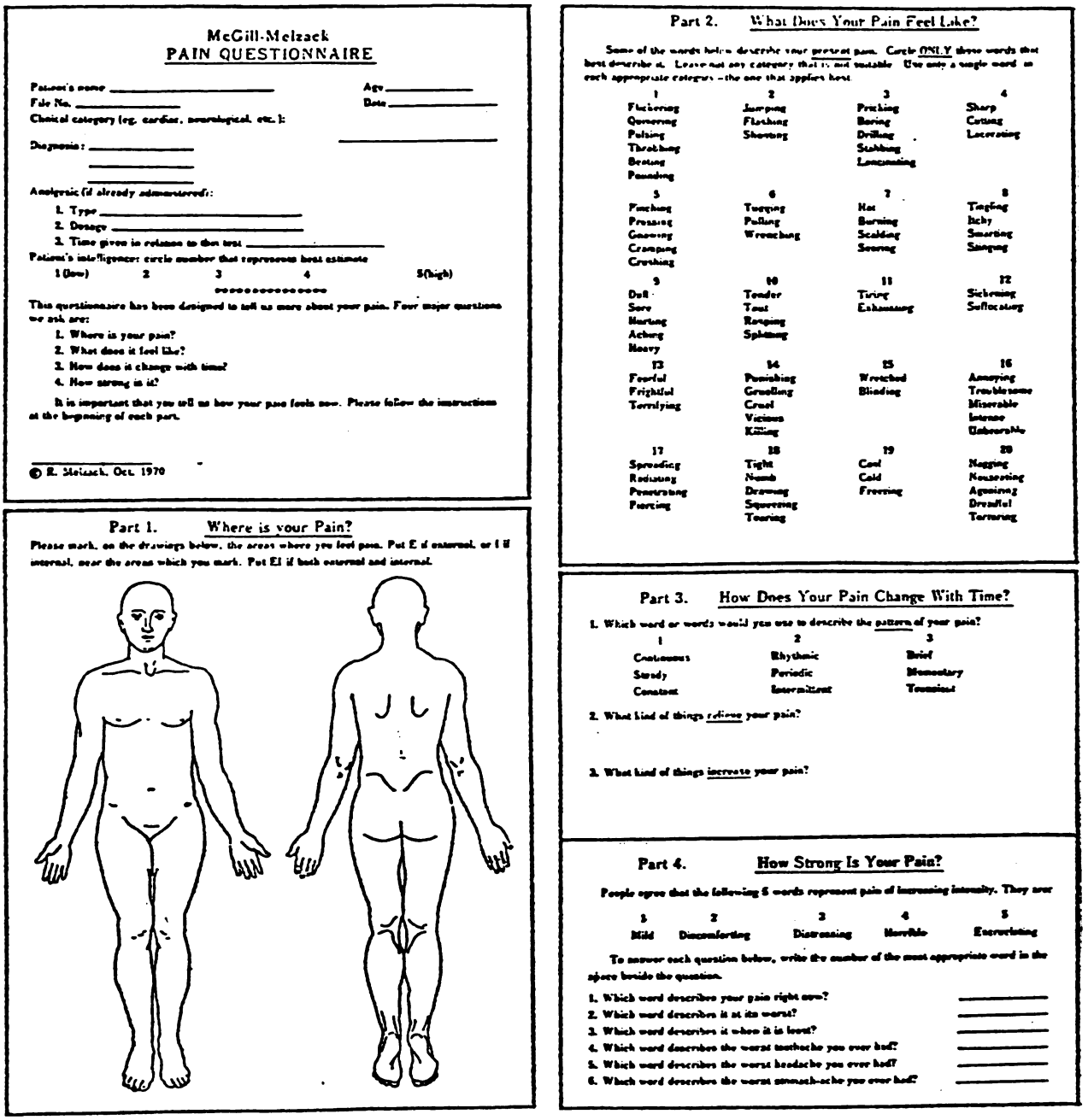


Figure 1. Scattergram showing the relationship between scores on the Present Pain Index (PPI) and the Pain Rating Index - Sensory (PRI-S) of the MPQ for 17 patients with primary fibrositis. Each symbol ("F") represents a single patient's score.

Please place a mark on this line, which represents how much discomfort (pain) you now feel on a scale from the worst pain you have ever experienced to no pain.

APPENDIX 1. The Visual Analog Scale.



McGill-Melzack
PAIN QUESTIONNAIRE

Patient's name _____ Age _____
File No. _____ Date _____
Clinical category (eg. cardiac, neurological, etc.): _____
Diagnosis: _____
Analgesic (if already administered):
1. Type _____
2. Dosage _____
3. Time given in relation to this test _____
Patient's intelligence: circle number that represents best estimate
1 (low) 2 3 4 5 (high)

This questionnaire has been designed to tell us more about your pain. Four major questions we ask are:
1. Where is your pain?
2. What does it feel like?
3. How does it change with time?
4. How strong is it?

It is important that you tell us how your pain feels now. Please follow the instructions at the beginning of each part.

© R. Melzack, Oct. 1970

Part 1. Where is your Pain?

Please mark, on the drawings below, the areas where you feel pain. Put E if external, or I if internal, near the areas which you mark. Put EI if both external and internal.

Part 2. What Does Your Pain Feel Like?

Some of the words below describe your present pain. Circle ONLY three words that best describe it. Leave out any category that is not suitable. Use only a single word in each appropriate category - the one that applies best.

1	2	3	4
Flickering	Jumping	Pricking	Sharp
Quivering	Flashing	Boring	Cutting
Pulsing	Shooting	Drilling	Lacerating
Throbbing		Stabbing	
Beating		Lancinating	
Pounding			
5	6	7	8
Pinching	Tugging	Hot	Tingling
Pressing	Pulling	Burning	Itchy
Gnawing	Wrenching	Scalding	Smarting
Cramping		Searing	Stinging
Crushing			
9	10	11	12
Dull	Tender	Tiring	Sickening
Sore	Taut	Exhausting	Suffocating
Hurting	Rasping		
Aching	Splitting		
Heavy			
13	14	15	16
Fearful	Punishing	Wretched	Annoying
Frightful	Grueling	Blinding	Troublesome
Terrifying	Cruel		Miserable
	Vicious		Intense
	Killing		Unbearable
17	18	19	20
Spreading	Tight	Cool	Nagging
Radiating	Numb	Cold	Nauseating
Penetrating	Drawing	Freezing	Agonizing
Piercing	Squeezing		Dreadful
	Tearing		Torturing

Part 3. How Does Your Pain Change With Time?

1. Which word or words would you use to describe the pattern of your pain?

1	2	3
Continuous	Rhythmic	Brief
Steady	Periodic	Momentary
Constant	Intermittent	Transient

2. What kind of things relieve your pain?

3. What kind of things increase your pain?

Part 4. How Strong Is Your Pain?

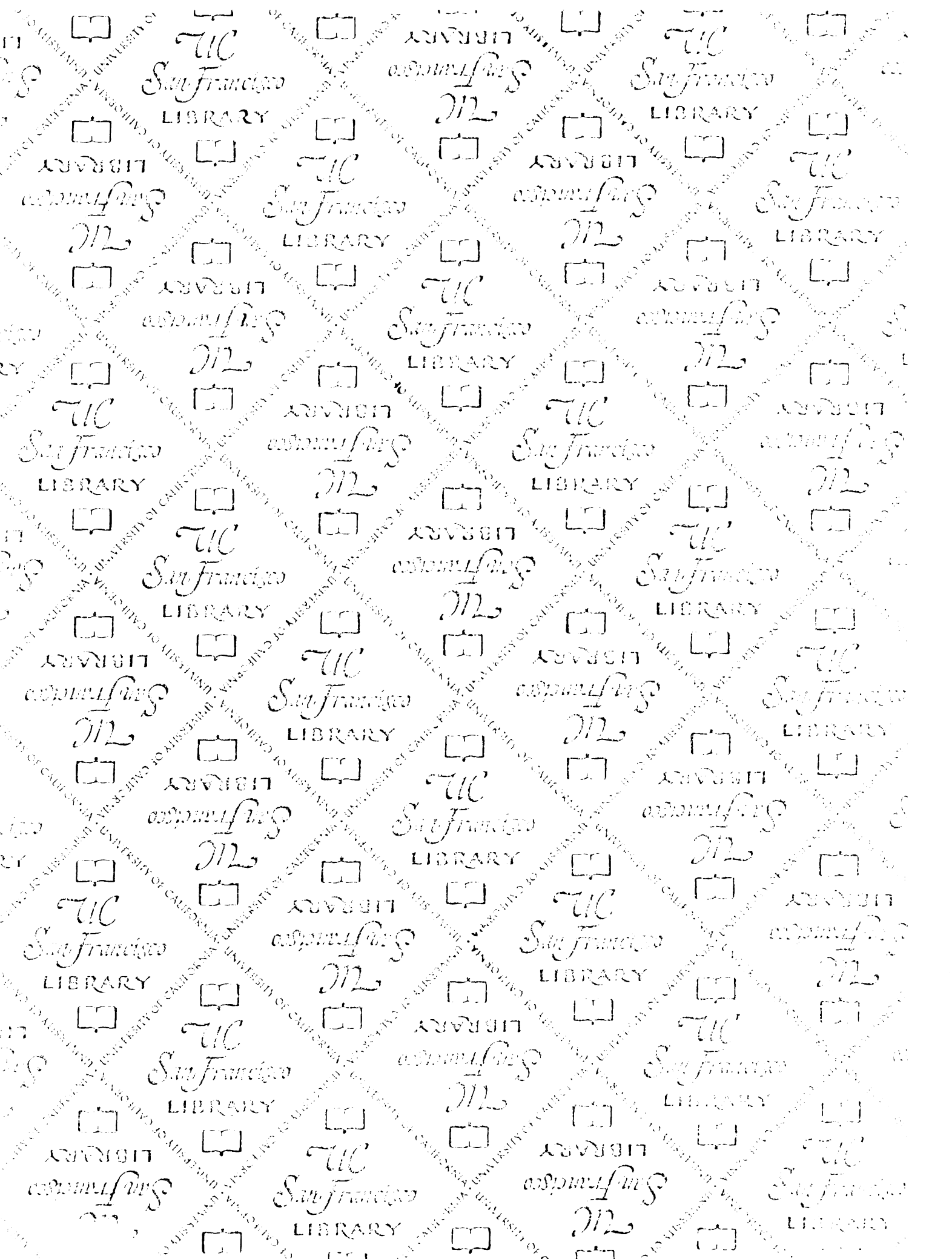
People agree that the following 5 words represent pain of increasing intensity. They are:

1	2	3	4	5
Mild	Discomforting	Distressing	Horrible	Excruciating

To answer each question below, write the number of the most appropriate word in the space beside the question.

1. Which word describes your pain right now? _____
2. Which word describes it at its worst? _____
3. Which word describes it when it is least? _____
4. Which word describes the worst toothache you ever had? _____
5. Which word describes the worst headache you ever had? _____
6. Which word describes the worst stomach-ache you ever had? _____

APPENDIX 2. The McGill Pain Questionnaire.


UC
San Francisco
LIBRARY