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Effect of pain on autonomic nervous system indices derived from photoplethysmography in healthy volunteers

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Editor's key points

- Photoplethysmography is used in routine perioperative monitoring and may have some utility in assessing pain.
- This study assessed how different photoplethysmographic measures reflect changes in autonomic activity and correlate with pain.
- All measures changed in response to different noxious thermal stimuli, with variable changes related to pain intensity.
- This form of assessing autonomic changes may have utility in both acute and chronic pain assessment.

Background. Photoplethysmographic pulse wave amplitude (PPGA) and heart rate (HR) can be used to measure cold, nociception-induced autonomic responses, or both. The aim of our study was to correlate the intensity of experimental pain to changes in physiological variables reflecting the autonomic nervous system response to pain.

Methods. PPGA, HR, and subjective measurements of pain intensity were measured in 29 healthy male volunteers during two heat stimuli (43°C and 48°C) and the cold pressor test (CPT). Surgical pleth index (SPI), autonomic nervous system state (ANSS), and ANSS index (ANSSi) were calculated using PPGA and HR.

Results. Pain intensity scores increased on the average by 1.6, 3.5, and 8.1 for the 43°C, 48°C, and CPT stimuli, respectively. The pain intensity scores for all three stimuli groups were significantly different from each other ($P<0.001$). All three stimuli changed HR, PPGA, SPI, ANSS, and ANSSi values significantly from their respective baseline values ($P<0.001$ for all). Heat stimuli-induced pain intensity did not correlate with the magnitude of the respective changes in HR, PPGA, SPI, ANSS, and ANSSi. CPT-induced pain intensity correlated with the magnitude of the respective changes in HR, PPGA, SPI, ANSS, and ANSSi. PPGA, ANSSi, ANSS, and SPI differentiated between heat and cold stimuli-induced pain.

Conclusions. All three thermal stimuli produced a significant change in photoplethysmograph-derived parameters. All photoplethysmograph-derived parameters appear to be suitable to study autonomic nervous system activation.

Keywords: autonomic nervous system; heart rate; pain, experimental; pulse plethysmography

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Perioperative assessment of pain is often difficult because of patients' inability to communicate the intensity of their pain. Thus, there is a need for surrogate measures of pain, independent of the patient's participation. Pain stimulates the sympathetic nervous system, which in turn increases heart rate (HR) and causes peripheral vasoconstriction.[1] Photoplethysmography (pulse oximetry) can be used to assess vasomotor tone (vasoconstriction) and HR and, thus, could potentially be used as a surrogate to assess perioperative pain.[2] Photoplethysmography has been used to measure cold pressor test (CPT)-induced peripheral vasoconstriction[1] and nociception during anaesthesia.[3] [4] In experimental pain, the change in HR correlates with intensity and

unpleasantness of pain.[5] [6] However, there is limited information on the ability of photoplethysmography to quantify different intensities and types of pain. In addition to assessment of acute pain, photoplethysmography could be useful in assessing the role of the autonomic nervous system in the development of chronic pain. Also, the effect of psychological methods (relaxation) on pain and stress-induced autonomic nervous system activation could be evaluated.

Photoplethysmography uses light transmission to measure changes in tissue volume. The pulse plethysmographic amplitude (PPGA) of the photoplethysmograph is due to pulsatile changes in tissue volume, mainly arterial blood. During sympathetic activation (vasoconstriction),

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[†] Dr M. Paloheimo sadly died after the paper was accepted for publication.

PPGA decreases. Several parameters using PPGA and HR have been developed in an attempt to measure changes in autonomic nervous system activity in response to nociceptive stimuli. Surgical pleth index (SPI) uses PPGA and HR data from pulse oximetry measurements.[7] SPI was developed for monitoring surgical stress reactions during anaesthesia. Two other parameters using PPGA and HR data, the autonomic nervous system state (ANSS) and ANSS index (ANSSi), have recently been introduced.[4] Nociception-induced sympathetic nervous system activity will increase SPI and ANSSi and decrease PPGA and ANSS.

PPGA, SPI, ANSS, and ANSSi responses to different intensities and types of nociceptive stimuli have not been assessed in awake, non-medicated individuals. The aim of our study was to correlate subjective measurements of intensity and unpleasantness of experimental pain to changes in physiological variables reflecting the autonomic nervous system response to pain. In this study, healthy volunteers were exposed to different levels of experimental pain using heat and cold stimuli.

Methods

Healthy males, between 18 and 30 yr of age, were eligible for the study. We excluded individuals who had a history of chronic disease or those taking prescription medications. With approval of the Ethics Committee of the Department of Surgery, Helsinki University Central Hospital, and written informed consent, we enrolled 34 male volunteers into this study.

During the study, subjects rested in a half-sitting position. The temperature of the distal phalanx of the middle finger was measured (Datex-Ohmeda S/5, GE Healthcare, Helsinki, Finland). If the temperature was under 32°C, subjects were given 100–200 ml oral liquid and they were covered with a forced-air warming blanket (Bear Hugger®, Arizant Inc., Eden Prairie, MN, USA). These therapies were performed to prevent peripheral vasoconstriction before the study.

A reusable pulse oximeter sensor (Datex-Ohmeda S/5, GE Healthcare) was placed on the left middle finger for the measurement of HR and plethysmographic pulse wave amplitude (PPGA). These data were recorded electronically and averaged every 10 s using a serial cable and S/5 Collect™ software (GE Healthcare) running on a laptop computer.

Approximately 15 min after application of the monitors and explanation of the different rating scales and heat stimuli (see below), a heat stimulus of 43°C was applied to the inside of the left forearm using a 16×16 mm contact thermode (TSA-II Neurosensory Analyzer, Medoc, Israel). The stimulus started from the baseline temperature of 32°C and increased by 10°C s^{-1}. Temperature was maintained at 43°C for 5 s then decreased by 10°C s^{-1}. This was repeated three times with a time interval of 8 s between the successive peak temperatures. A stronger heat stimulus of 48°C (rate of temperature increase/decrease 5°C s^{-1}, plateau 5 s, interval between peak temperatures 10 s) was applied after a resting period of 5–10 min during which the

measured variables returned to baseline. Subjects rated their pain intensity using the visual analogue scale (VAS) ranging from 0, no pain, to 10, worst pain imaginable.

Approximately 5–10 min after the heat stimuli and after the measured variables had again returned to baseline, a CPT was performed. Subjects immersed their right hand and wrist in a thermostatic bath of $+3^\circ$C ice water (Julabo®, USA). During the cold pain test (CPT), both hands of the subjects were in use and they were not able to use a sliding controller. Therefore, subjects rated their pain intensity verbally at 15 s intervals using a numerical rating scale (NRS) ranging from 0, no pain, to 10, worst pain imaginable. The CPT test lasted for a maximum of 90 s or until maximal tolerated pain. The duration of CPT was recorded.

Pain unpleasantness was recorded after both heat stimuli and CPT using a verbal NRS from 0, not at all unpleasant, to 10, extremely unpleasant.

Data collection and statistical analysis

Data from a previous study[1] were used for power analysis. The PPGA was expressed as the percentage of the baseline, which was 0.51 (0.19) %-units [mean (SD)]. This decreased by 48% in response to CPT. A sample size of 30 subjects was calculated to detect a 0.11%-unit change in amplitude (22%). An α-value of 0.05 and β-1 of 0.8 were assumed.

SPI, ANSS, and ANSSi were calculated after completion of the study using electronically saved pulse oximeter HR and PPGA data. SPI was calculated at GE Healthcare using their proprietary algorithm.[7] ANSS was calculated as the product of HR peak-to-peak interval (ms) and PPGA (%). ANSSi was calculated as $100 - (\text{ANSS}/\text{ANSS}_{max}) \times 90$, where ANSS_{max} is the maximum ANSS for the subject during the study.[4]

Pre-stimulus baseline values were defined as the lowest (HR, ANSSi, SPI) or highest (PPGA, ANSS) values during the 30 s time period immediately before the stimulus. Post-stimulus values were defined as the minimum (PPGA, ANSS) or maximum (HR, ANSSi, SPI) values during the first 120 s after the beginning of the stimulus.

The Mann–Whitney rank-sum test was used for comparisons between different stimuli and between values before and after stimuli. The Spearman rank correlation coefficient was used to analyse correlations between variables. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SigmaStat®, version 3.5 (Systat Software, Inc., Point Richmond, CA, USA).

Results

Data from 29 subjects of the original 34 were analysed. These subjects were 24 (18–28) (mean, range) yr old and their BMI ranged from 20 to 28. Five volunteers were excluded from analysis. Three subjects were excluded due to technical failure, one for inability to report pain intensity adequately, and one for unexplained resting tachycardia.

Pain intensity and unpleasantness scores after the three different stimuli are shown in Figure 1A. The pain intensity and unpleasantness scores of all three groups were significantly
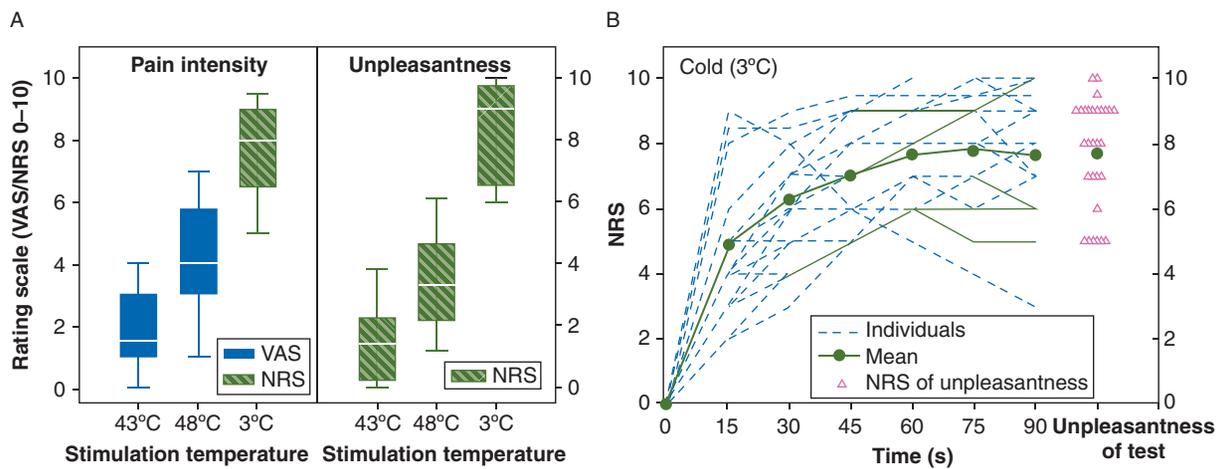
Fig 1 (A) Box plot showing pain intensity and unpleasantness produced by 43°C and 48°C heat stimuli, and CPT in 29 volunteers. The end of the boxes presents the 25th and 75th percentiles, with a line at the median and error bars define 10th and 90th percentiles. The pain intensity and unpleasantness for all three stimuli were significantly different from each other ($P<0.001$). For the CPT, the NRS value at the time of withdrawal of the hand from water is shown. (B) Pain intensity during CPT and the unpleasantness of the test in 29 volunteers. The subjects immersed their right hand and wrist into +3°C water for as long as they could tolerate it but no longer than 90 s. Dotted lines represent individual subjects and the continuous line indicates the mean value.

Table 1 Mean (SD) values of HR, PPGA, SPI, ANSS, and ANSSi before and after 43°C and 48°C heat stimuli, and cold-water immersion in 29 volunteers. All three thermal stimuli produced significant changes in HR, PPGA, SPI, ANSS, and ANSSi compared with baseline ($P<0.001$ for all)

	43°, mean (SD)	48°, mean (SD)	Cold, mean (SD)	Statistical comparisons of variables between three thermal stimuli
HR				
Before	68.1 (10.6)	67.5 (11.3)	67.1 (10.8)	Cold compared with 43°C, $P<0.05$
After	83.3 (13.4)	83.5 (12.7)	91.7 (17.3)	No statistical difference between 43°C and 48°C
PPGA				
Before	9.3 (3.1)	8.7 (2.6)	7.9 (2.8)	Cold compared with 43°C and 48°C, $P<0.05$ for both
After	3.1 (1.3)	2.6 (1.5)	1.4 (0.9)	No statistical difference between 43°C and 48°C
ANSS				
Before	8.3 (3.0)	7.9 (3.0)	7.1 (3.0)	Cold compared with 43°C and 48°C, $P<0.05$ for both
After	2.5 (1.1)	2.1 (1.3)	1.0 (0.6)	No statistical difference between 43°C and 48°C
ANSSi				
Before	23.3 (13.7)	27.2 (14.4)	34.7 (15.9)	Cold compared with 43°C and 48°C, $P<0.05$ for both
After	78.1 (7.4)	80.0 (10.4)	89.8 (5.7)	No statistical difference between 43°C and 48°C
SPI				
Before	24.1 (5.8)	23.6 (8.5)	24.9 (11.8)	Significantly different between all three stimuli, $P<0.001$
After	66.8 (11.8)	71.7 (13.0)	87.2 (9.1)	

different from each other ($P<0.001$), CPT producing the most intense pain and unpleasantness. Twenty-four volunteers kept their hand in the cold water for 90 s during the CPT (Fig. 1B). The remaining five volunteers withdrew their hand at 25, 41, 60, 75, and 89 s after the beginning of the CPT.

All three stimuli (43°C, 48°C, and CPT) increased HR, ANSSi, and SPI values and decreased PPGA and ANSS values significantly ($P<0.001$ for all) compared with the pre-test baseline values (Table 1). Changes in the PPGA after all three stimuli are shown for each volunteer in Figure 2.

Post-stimulus HR values were significantly different between the 43°C heat stimulus test and CPT ($P<0.001$, Table 1). Post-stimulus PPGA, ANSS, and ANSSi values did not differ between the two heat stimuli tests but were significantly different between the CPT and the heat stimuli tests ($P<0.001$). The post-stimulus SPI values were significantly different between all three tests ($P<0.001$). Figure 3 illustrates the time course of changes in HR and ANSSi values during all three stimuli in one volunteer. Changes in HR, PPGA, SPI, and ANSSi values immediately before and for 2
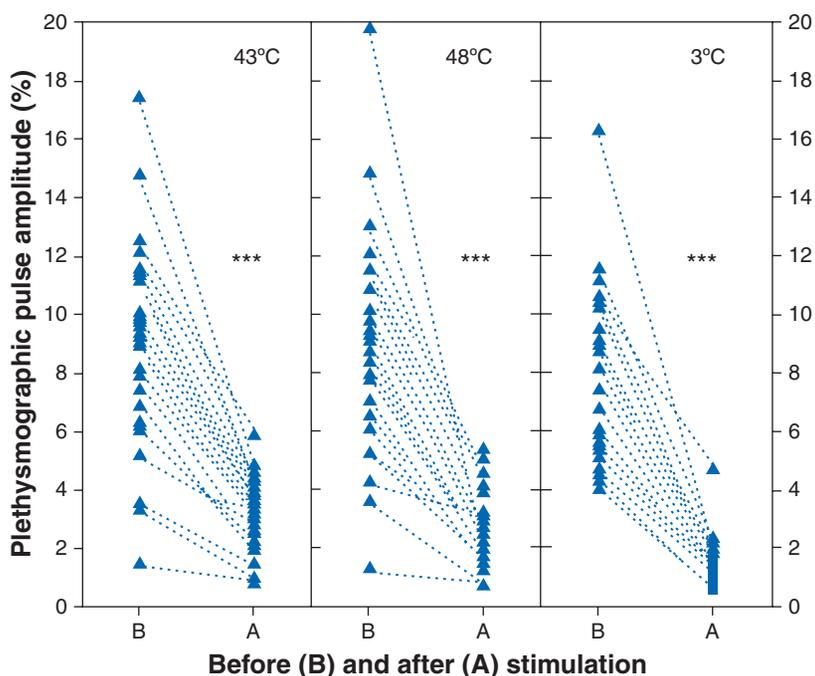
Fig 2 Changes in the PPGA after 43°C and 48°C heat stimuli, and CPT in 29 volunteers.
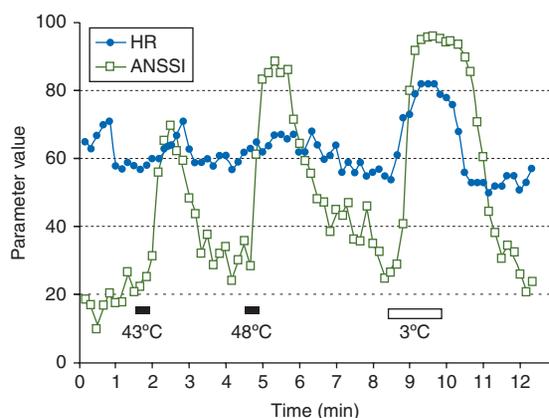
Fig 3 Changes in HR and ANSSi during three thermal stimuli (43°C and 48°C, CPT) in one subject.

min after the beginning of CPT are illustrated in Figure 4. In some individuals, HR and PPGA started to change before the CPT (Fig. 4).

The intensity of pain produced by the CPT but not by 43°C or 48°C heat stimuli, correlated with the magnitude of change in HR, PPGA, SPI, ANSS, and ANSSi ($P<0.05$ for all). The unpleasantness scores produced by CPT correlated with the magnitude of change in SPI ($P<0.05$) but not with HR, PPGA, ANSS, or ANSSi. With increasing pain intensity of the stimulus, the ANSSi also increased (Fig. 5). ANSSi did not differ between the two heat stimuli. However, ANSSi was

significantly higher after the cold stimulus than after the two heat stimuli ($P<0.001$).

Discussion

In the present study, healthy volunteers were exposed to three different noxious stimuli. These stimuli resulted in three significantly different subjective reports of pain intensity and unpleasantness. All three stimuli increased HR, ANSSi, and SPI values and decreased PPGA and ANSS values compared with baseline. However, most of these parameters could differentiate only between the strongest stimulus (CPT) and the two more moderate stimuli but not between the moderate and mild stimuli. The intensity of the relatively mild pain produced by the two heat stimuli (43 and 48°C) did not correlate with the magnitude of change in HR, PPGA, ANSS, ANSSi, or SPI while the CPT induced more intense pain that correlated with the magnitude of changes in all measured physiological variables.

ANSSi increased with increasing intensity of the painful stimulus. The mildly painful and unpleasant heat stimulus of 43°C produced a large change in ANSSi compared with baseline. The stronger and more painful stimulus of 48°C increased ANSSi slightly more when compared with the low-intensity stimulus. The change in ANSSi before and after the heat stimuli was significant for both temperatures, but there was no statistically significant difference in the magnitude of the ANSSi response between the two stimuli. This may be due to the fact that any stimulus increasing arousal activated the autonomic nervous system. ANSSi was able to

841
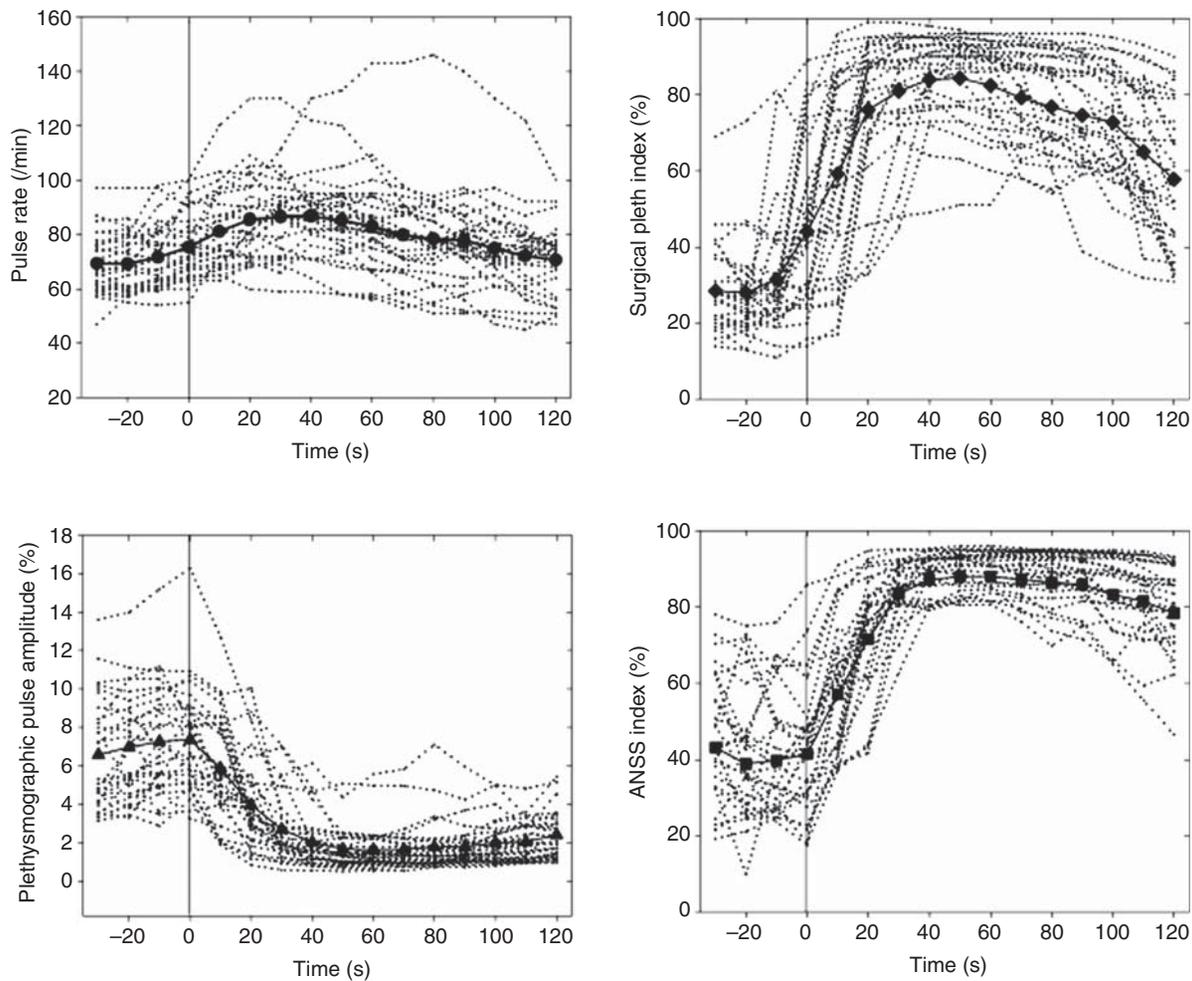
Fig 4 Changes in HR, PPGA, SPI, and ANSSi during CPT in 29 healthy volunteers. Dotted lines indicate the individual subjects and the continuous line shows the mean values.
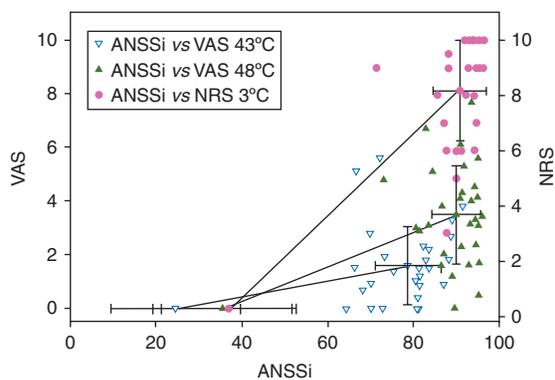
Fig 5 ANSSi and pain intensity (VAS/NRS) before and after thermal stimuli in 29 healthy volunteers. The difference between ANSSi at 43°C and 48°C was not statistically significant. ANSSi was significantly greater after CPT than after the 48°C heat stimulus (*P*<0.001).

differentiate the painful stimulus of the CPT from both less painful heat stimuli.

Several studies have evaluated the use of photoplethysmography-derived parameters to assess peri-operative autonomic nervous system activity.[4][7][8] Clinical interest in this area has been driven by lack of reliable non-invasive monitors to assess perioperative pain and analgesia. Surgery-induced perioperative stress response increases autonomic nervous system activity resulting in peripheral vasoconstriction. Photoplethysmography quantitates changes in tissue volume, that is, vasoconstriction/vasodilation. Pulse oximeters are photoplethysmoghraphs that are routinely used during surgery and thus, seem like ideal monitors to measure autonomic nervous system activity. However, previous studies have reported conflicting results.[4][7][8] This may, in part, be due to different experimental conditions. Most studies have used anaesthetic and analgesic drugs, which attenuate the perioperative stress response to varying degrees. To eliminate drug-induced confounding factors, we studied awake, non-medicated healthy

volunteers. Our study is also unique in using several different intensities of experimental pain and in studying several different parameters derived from the photoplethysmography.

PPGA is a measure of the pulsatile component of a photoplethysmogram. PPGA has been reported to decrease (as a result of vasoconstriction) in response to noxious perioperative stimuli such as skin incision, tetanus, or tracheal intubation.[4] [9] [10] These stimulus-induced decreases in PPGA can be attenuated or eliminated by increasing doses of narcotics or by reducing stimulus intensity. Most previous studies have used either different stimuli or different anaesthetic and narcotic doses. These varying experimental conditions make it difficult to draw conclusions on the sensitivity of PPGA to detect changes in autonomic nervous system activity. Our results in unmedicated volunteers suggest that PPGA changes significantly in response to even a mild noxious stimulus, but that it has limited specificity to differentiate between different pain intensities.

Several indices that incorporate both PPGA and HR data were developed to improve the sensitivity of photoplethysmography to assess perioperative autonomic nervous system activity.[4] [7] SPI was developed by Datex-Ohmeda (now GE Healthcare). Although the algorithm is proprietary, available literature discloses that about two-third of the input comes from PPGA data and one-third from HR data. SPI also includes averaging and learning algorithms. Paloheimo and colleagues[4] developed ANSS and ANSSi after years of clinical experimentation with these parameters. ANSSi calculation also changes over time, as ANSSmax is a dynamic variable. In this study, ANSSi was calculated after the study, keeping ANSSmax constant for each subject. Previous studies have shown that both SPI and ANSSi are able to detect changes in autonomic nervous system activity in response to intraoperative nociceptive stimuli.[4] [10] [11] However, the ability of these parameters to differentiate between different stimulus intensities has not been well documented. In the present study, both SPI and ANSSi showed significant changes after all three thermal stimuli. PPGA, ANSSi, ANSS, and SPI differentiated between the pain intensities caused by heat and cold stimuli while HR did not. Only SPI differentiated between the two heat stimuli. Both ANSSi and ANSS responded in a dose-dependent manner to increasing pain intensities. However, both measures are very sensitive to any sensory or emotional stimuli, which make them difficult to use in everyday clinical monitoring of awake patients.

In a previous study[8] of awake patients with postoperative pain, SPI differentiated pain intensities of ≤ 5 and > 5 on the numerical pain rating scale (0–10), whereas it was unable to differentiate lower pain intensities of ≤ 3 and > 3. SPI did not change significantly after administration of fentanyl.[8] Thus, ANSS seems to be the most sensitive of the parameters and ANSSi (open algorithm) seems to be equal to SPI (protected algorithm).

In our experimental model, the autonomic nervous system activation behaved almost like a binary variable (on, off). Even a mild stimulus caused a significant change in all

measured parameters. Even though some of the parameters detected a statistical difference between different pain stimuli, the actual effects were clinically insignificant. For example, the mild and moderate heat stimuli decreased PPGA by 67% and 70%, respectively, while the stronger CPT stimuli decreased PPGA only by an additional 12%. Similarly, SPI increased by 279% and 313% after the mild and moderate stimuli, respectively, and by 348% after the CPT stimuli. These large changes in responses to even mild stimuli may in part explain why the different parameters were unable to differentiate between all three stimuli, even though the pain VAS scores were significantly different.

PPGA responses may depend on baseline experimental conditions. PPGA is significantly decreased in cold extremities, by anxiety and by discomfort, all common in perioperative patients. Baseline peripheral vasoconstriction will reduce the sensitivity of PPGA and its derived variables to detect autonomic nervous system activation. This may complicate the use of PPGA and its derived variables in awake patients. In order to minimize some of these confounding variables, we kept our volunteers well hydrated, warm, and as comfortable as possible as evidenced by the relatively high baseline PPGA values. The open periphery was confirmed by continuous temperature monitoring of a finger in the pulse oximeter hand.

Anticipation of the painful stimulus affects pain and related physiological reactions.[12] [13] A previous study showed that physiological responses to painful stimuli are stronger with low predictability of the stimulus. From our clinical experience, we know that moderate intensity auditory stimuli can change ANSS in lightly anaesthetized patients. The present data indicate that in some volunteers, anticipation of the cold stimulus produced changes in HR and PPGA before CPT, suggesting that the activation of autonomic nervous system had both an emotional and a physical component. Interestingly, the mean SPI seemed to change, even though the mean HR and PPGA remained stable immediately before CPT and between 60 and 90 s. Because chronic pain involves autonomic nervous system activation and has both strong emotional and physical components, these methods should be explored to study the development of chronic pain, and potential drug and psychological therapies in patients suffering from chronic pain.

Our study has several limitations. We placed the pulse oximeter probe on the finger, a location known to have a high density of adrenoceptors and highly reactive to autonomic nervous system activation. Thus, we cannot comment on potential responses from other monitoring sites. We studied awake subjects in order to eliminate drug-induced confounding variables. Our results may not be applicable to subjects under different experimental conditions. We only studied males and, thus, cannot comment on potential effects in females. After dropouts, we studied 29 subjects, which is fewer than the 30 subjects suggested by original power calculations. Finally, we did not randomize the order of the noxious stimuli because it was not feasible in our experimental setup.

In conclusion, we used three different noxious stimuli that produced significantly different pain intensity and unpleasantness VAS scores. All three stimuli produced a significant change in all parameters derived from the photoplethysmograph. All parameters that were derived from the photoplethysmography signal appear to be suitable to study autonomic nervous system activation. These methods may provide exciting possibilities for clinical research regarding, for example, individual differences in reactions to pain and analgesics. The relationship between overall central nervous system sensitivity and autonomic nervous system responses to pain stimuli could be studied in patients suffering from chronic pain.

References

1 Awad AA, Ghobashy MAM, Ouda W, *et al.* Different responses of ear and finger pulse oximeter waveform to cold pressor test. *Anesth Analg* 2001; **92**: 1483–6

2 Paloheimo MPJ, Penttinen M. ANS-spot and autonomic system stability during general anaesthesia—a new pain indicator. *Br J Anaesth* 2004; **93**: 489–90P

3 Korhonen I, Yli-Hankala A. Photopletysmography and nociception. *Acta Anaesthesiol Scand* 2009; **53**: 975–85

4 Paloheimo MPJ, Sahanne S, Uutela KH. Autonomic nervous system state: the effect of general anaesthesia and bilateral tonsillectomy after unilateral infiltration of lidocaine. *Br J Anaesth* 2010; **104**: 587–95

5 Colloca L, Benedetti F, Pollo A. Repeatability of autonomic responses to pain anticipation and pain stimulation. *Eur J Pain* 2006; **10**: 659–65

6 Rainville P, Bao QV, Chrétien P. Pain-related emotions modulate experimental pain perception and autonomic responses. *Pain* 2005; **118**: 306–18

7 Huiku M, Uutela K, van Gils M, *et al.* Assessment of surgical stress during general anaesthesia. *Br J Anaesth* 2007; **98**: 447–55

8 Ledowski T, Ang B, Schmarbeck T, Rhodes J. Monitoring of sympathetic tone to assess postoperative pain: skin conductance vs surgical stress index. *Anaesthesia* 2009; **64**: 727–31

9 Luginbühl M, Rüfenacht M, Korhonen I, Gils M, Jacob S, Petersen-Felix S. *Br J Anaesth* 2006; **96**: 323–29

10 Kallio H, Linberg LI, Majander AS, Uuutela KH, Niskanen ML, Ploheimo MPJ. Measurement of surgical stress in anaesthetized children. *Br J Anaesth* 2008; **101**: 383–9

11 Wennervirta J, Hynynen M, Koivusalo A-M, Uutela K, Huiku M, Vakkuri A. Surgical stress index as a measure of nociception/antinociception balance during general anesthesia. *Acta Anaesthesiol Scand* 2008; **52**: 1038–45

12 Oka S, Chapman CR, Kim B, *et al.* Predictability of painful stimulation modulates subjective and physiological responses. *J Pain* 2010; **11**: 339–46

13 Porro CA, Baraldi P, Pagnoni G, *et al.* Does anticipation of pain affect cortical nociceptive systems? *J Neurosci* 2002; **22**: 3206–14