A pilot study of preoperative heart rate variability predicting pain during local anesthetic varicose vein surgery

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ABSTRACT

Objective: Local anesthetic endovenous procedures were shown to reduce recovery time, to decrease postoperative pain, and to more quickly return the patient to baseline activities. However, a substantial number of patients experience pain during these procedures. The autonomic nervous system modulates pain perception, and its influence on stress response can be noninvasively quantified using heart rate variability (HRV) indices. The aim of our study was to evaluate whether preoperative baseline HRV can predict intraoperative pain during local anesthetic varicose vein surgery.

Methods: Patients scheduled for radiofrequency ablation were included in the study. They had their electrocardiograms recorded from a single channel of a custom-made amplifier. Each patient preoperatively filled in forms Y-1 and Y-2 of Spielberger's State and Trait Anxiety Inventory, completed the Aberdeen Varicose Vein Questionnaire, and rated anxiety level on a numeric scale. Postoperatively, patients filled in the pain they felt during the procedure on the numeric pain intensity scale. MATLAB software (MathWorks, Natick, Mass) was used to extract R waves and to generate HRV signals, and a mathematical model was created to predict the pain score for each patient.

Results: In multivariable analysis, we looked into correlation between reported patient's pain score (rPPS) and Aberdeen Varicose Vein Questionnaire score, preoperative forms Y-1 and Y-2, preoperative anxiety level, and predicted patient's pain (pPPS) score. Multivariable analysis found association only between rPPS and pPPS. The pPPS was significantly correlated with rPPS ($R = 0.807$; $P < .001$) with accuracy of prediction of 65.2%, which was calculated from R^2 on a linear regression model.

Conclusions: This preliminary study shows that preoperative HRV can accurately predict patients' pain, allowing patients with higher predicted score to have the procedure under general anesthesia. (J Vasc Surg: Venous and Lym Dis 2019;7:382-6.)

Keywords: Pain prediction; HRV; Varicose veins; Local anesthesia

Endovenous thermal ablation, performed either alone or in combination with multiple phlebectomies, is largely carried out under local anesthesia as a day-case procedure. This minimally invasive approach has the advantage of fewer wound complications, less postoperative pain, and a quicker return to baseline activities.[1] However, a sizable proportion of patients still face a considerable amount of intraoperative pain, which can adversely affect the patient's experience.[2] The prospective study cited showed that endovenous ablation is not a painless procedure, with an average pain score of 4. Another paper suggested that up to 25% of patients may experience pain or discomfort during local anesthesia procedures.[3]

Although the specific mechanisms behind the acute wound pain remain largely unknown, it has been suggested that three major types of pain (nociceptive, inflammatory, and neuropathic) are regulated by the peripheral and central nervous systems through the processes of transduction, transmission, modulation, perception, and sensitization.[4] The perception and transmission of pain can be modulated by many factors, including the autonomic nervous system and hormones.[5]

Vagal and sympathetic nervous systems modulate some components of heart rate variability (HRV) through changes in the length of consecutive heart beats (R-R intervals), which are derived from an electrocardiogram.[6] HRV evaluation can be based on time domain analysis and frequency domain analysis. In time domain analysis, HRV parameters are derived from either direct measurement of or differences between the normal-to-normal R-R intervals. In frequency domain analysis, the spectral analysis of HRV aims to separate different frequency components of an entire R-R interval modulation and is usually performed on the basis of short-term

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recordings (minimum of 5 minutes).[7] The Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology recommended that the low-frequency and high-frequency components are best captured within the respective frequency bands of 0.04 to 0.15 Hz and 0.15 to 0.4 Hz.[8] HRV is composed of high-frequency and low-frequency components that reflect parasympathetic and sympathetic influence of the autonomic nervous system on the heart, respectively. There is a general opinion that the ratio between low- and high-frequency components of the heart rate is a measure of balance of sympathovagal activity.[7]

Given the fact that the autonomic nervous system influences pain perception, HRV may be a novel tool to predict intraoperative pain in patients undergoing local anesthetic procedures. Therefore, if intraoperative pain could be accurately predicted, this would help patients make better informed decisions and would allow a more personalized approach to patient care.

ARTICLE HIGHLIGHTS

- **Type of Research:** Prospective pilot study evaluating preoperative heart rate variability (HRV) to predict pain during local anesthetic varicose vein surgery
- **Key Findings:** Predicted pain scores derived from analysis of preoperative HRV correlated with intraprocedural pain reported by the patient after local anesthetic varicose vein surgery ($R = 0.807$; $P < .001$).
- **Take Home Message:** Preoperative HRV analysis can possibly be used to identify patients who may experience higher levels of pain during varicose vein surgery with local anesthesia, perhaps allowing patients and physicians to better choose or suggest anesthetic techniques for varicose vein surgery.

METHODS

Ethical approval for physiologic sensing was granted by the Imperial College, London Joint Research Office (reference ICREC_12_1_1) and the Imperial College Healthcare Trust Clinical Governance Department.

A verbal consent to participate was obtained from consecutive patients scheduled for a day-case radiofrequency endovenous ablation with multiple phlebectomies between August 2015 and October 2016 under local anesthesia. Given the retrospective nature of data analysis and because of the confounding effect of menstrual cycle phase on HRV, the female group was divided into two subgroups: presumed premenopausal, younger than 49 years; and presumed postmenopausal, aged 49 years and older, as 49 years is the median age of natural menopause in the United Kingdom.[9]

Electrocardiograms were recorded before, during, and after the procedure to establish the baseline of the HRV of each patient. Periprocedural tracing correlated with the changes during the procedure as we recorded exact timings of beginning of ablation and start of phlebectomies. For model creation, we analyzed only preoperative electrocardiography recordings.

Electrocardiography signals were recorded preoperatively for 20 minutes during the surgical procedure and for 10 minutes after the operation, using a custom-made portable amplifier. Also, preoperatively, patients were asked to complete forms Y-1 and Y-2 of Spielberger's State and Trait Anxiety Inventory (STAI), to report their anxiety level on a numeric scale (0, no anxiety; 10, extreme anxiety), and to complete the Aberdeen Varicose Vein Questionnaire (AVVQ).[10] Form Y-1 of the STAI consists of 20 statements that ask individuals to describe how they feel at a particular moment. Form Y-2 of the STAI consists of 20 statements that instruct individuals to describe how they generally feel. All answers are marked from 1 to 4 according to the key given with the statements.[11]

All varicose vein procedures were carried out using a standardized technique. No patient was given sedation or oral benzodiazepine before or during the procedure or took oral analgesia on the day of surgery. Each patient underwent above-knee long saphenous vein radiofrequency ablation with calf phlebectomies under tumescent anesthesia (360 mL of saline with 40 mL of 1% lignocaine and 1:200 000 norepinephrine). Tumescent fluid was administered using a 21-gauge needle and pump in the plane along the long saphenous vein. The number of calf phlebectomies varied from two to five, which was the maximum number tolerated by the patient.

Immediately after the procedure, patients were asked to report the pain they experienced during the procedure on a numeric pain intensity scale (reported patient's pain score [rPPS]; 0, no pain; 10, extreme pain). Pain scores of 7 or higher were considered by us a cutoff point for higher and lower pain.

Mathematical model. Anonymized electrocardiography data were analyzed using MATLAB software (R2015b_win64; MathWorks, Natick, Mass) to create a mathematical model for predicting patients' pain (predicted patient's pain score [pPPS]). The mathematical model of HRV is based on analysis of all components within low- and high-frequency bands in R-R intervals. These components were computed from recorded electrocardiograms using MATLAB software. Analyzed components included normalized high- and low-frequency powers and permutation entropy values in low and high frequencies. All these objective parameters from preoperative electrocardiograms as well as subjective Y-1 and Y-2 forms were subsequently used to create linear regressions and polynomial surface fit models. Their accuracies were evaluated using a leave-one-out

validation, which means that every model for the prediction of pain score of a given patient was created without the patient's data.

Custom software was used to extract R waves and to generate HRV signals. Low- and high-frequency bands in all HRV signals were computed and normalized by the power within the considered 0.04- to 0.5-Hz band. A permutation entropy method was employed to examine the change in structural complexity in HRV in response to pain. The signal features from HRV used in subsequent modeling included normalized low-frequency powers, normalized high-frequency powers, low-frequency permutation entropy values, and high-frequency permutation entropy values. These objective parameters from the presurgical period and the subjective Y-1 and Y-2 scores from the questionnaires were used to create a polynomial surface fit model. The accuracy of the proposed polynomial surface fit was evaluated using a leave-one-out validation, which means that every model for the pain score prediction of a given patient was created without the patient's data. The final prediction model revealed that normalized high frequency (the power in the high-frequency component of HRV divided by the total power of HRV) and low-frequency permutation entropy (the permutation entropy of the low-frequency component of HRV) provided accurate pain prediction. A negative correlation was found between normalized high frequency, low-frequency permutation entropy, and pain score.[12]

Statistics and power calculation. Statistical analysis was conducted using the Statistical Package for the Social Sciences (version 21; IBM Corp, Armonk, NY). Variables are presented as median and interquartile range (IQR). Significance was taken at the 95% level. Power calculations were not required for this feasibility study.

RESULTS

Demographic data. Forty-nine patients were submitted to the study. We excluded 20 patients because of corrupted recordings, which means that R-R intervals could not have been clearly differentiated and extracted to be analyzed. The data from the remaining 29 patients were analyzed: 10 men (34.5%), 12 premenopausal women (41.4%), and 7 postmenopausal women (24.1%). Their median age was 49 years (mean, 48.8 ± 14.9 years). Total AVVQ scores ranged from 3.2 to 34.9 (median, 12.75; IQR, 6.66-18.20). Preoperative questionnaire scores varied from 22 to 61 (median, 38; IQR, 31-50) for form Y-1 and from 25 to 60 (median, 36; IQR, 30-40.5) for form Y-2 (Table I). Preoperative anxiety level scores ranged from 0 to 9 (median, 5; IQR, 3-7). The rPPS ranged from 2 to 10 (median, 5; IQR, 4.75-7.5; Table II).

Multivariable analysis and linear regression. We have performed multivariable analysis to assess which of the analyzed parameters of preoperative Y-1 and Y-2 scores, preoperative anxiety level, AVVQ score, and pPPS were statistically associated with rPPS. As there were multiple factors that could potentially influence the level of intraoperative pain, we chose multivariable analysis and not univariate. Statistical analysis showed that AVVQ scores were not associated with rPPS. The result of multivariable analysis was that only pPPS demonstrated a statistically significant association with rPPS (Pearson correlation coefficient, $R = 0.807$; $P < .001$) for men and postmenopausal women. After including premenopausal women, this association was less significant (Pearson correlation coefficient, $R = 0.451$; $P = .014$; Fig). Linear regression showed that accuracy (R^2) of pPPS was 65.2% (0.652) for men and postmenopausal women ($P < .001$), whereas after including premenopausal women (all 29 patients), the accuracy (R^2) of pPPS was 20.4% (0.204; $P = .014$). The data were within normal distribution. Spearman rank correlation coefficient for men and postmenopausal women was 0.657 ($P = .004$). After including premenopausal women (all 29 patients), Spearman rank correlation coefficient was 0.375 ($P = .045$).

Table I. Form Y-1 and form Y-2 scores

	Sex		
	Postmenopausal women, mean	Men, mean	Premenopausal women, mean
Preoperative Y-1 (total score)	37.71	38.70	41.42
Preoperative Y-2 (total score)	36.43	38.80	35.00

DISCUSSION

The complexity of pain, defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage," and the importance of its correlation with psychological factors have been formally recognized since 1979.[13] Age and sex are considered major determinants of HRV, and its response to mental stress

Table II. Demographics summary

	Sex		
	Postmenopausal women, mean	Men, mean	Premenopausal women, mean
Age, years	60.00	54.80	37.50
AVVQ score	20.3	13.06	11.41
rPPS	6.29	5.35	6.17
pPPS	5.48	5.51	5.83

AVVQ, Aberdeen Varicose Vein Questionnaire; *pPPS,* predicted patient's pain score; *rPPS,* reported patient's pain score.

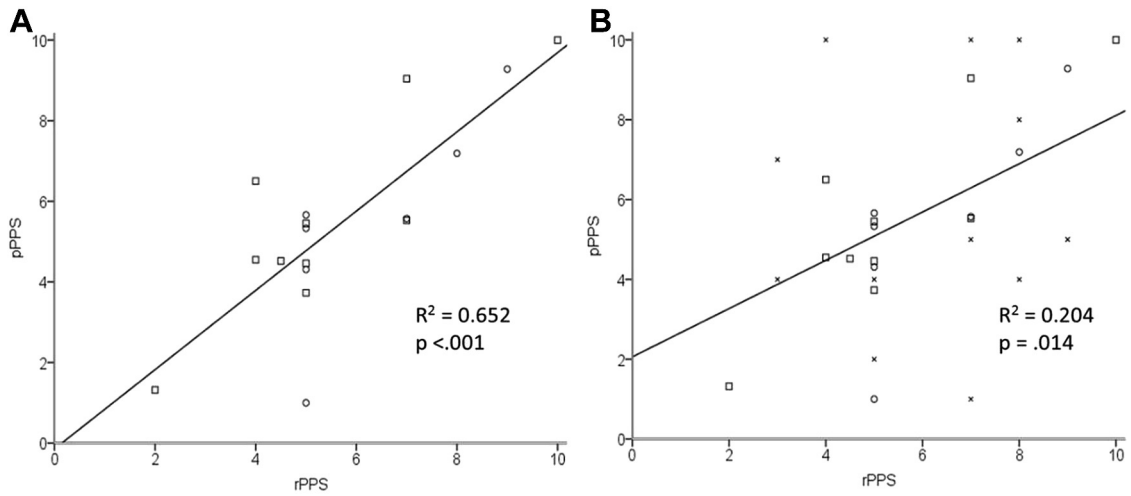

Fig. A, Scatter graph of predicted patient's pain score (*pPPS*) vs reported patient's pain score (*rPPS*) for men (□) and postmenopausal women (○). **B,** Scatter graph of pPPS vs rPPS for men (□), premenopausal women (*x*), and postmenopausal women (○).

has been well documented in the literature.[14-16] One piece of research focused on the relationship between anxiety and pain perception confirmed a moderate correlation between rated anxiety and rated pain perception during the shock trials. However, only approximately 34% of variance could be explained on the basis of anxiety level alone.[17] Another study examined whether physiologic responses to the pain could be affected by its context. It was found that fear in response to an immediate threat increases pain threshold, whereas anxiety, when expecting a threat, decreases the threshold.[18,19] It proves that patients' pain perception depends on many different variables: psychological, hormonal, and neurologic.

To the best of our knowledge, this is the first study that shows that preoperatively recorded HRV can accurately predict the level of pain experienced by men and presumed postmenopausal women during local anesthesia procedures, whereas for presumed premenopausal women, this association is weaker. The question about menopausal status was not included in the demographic data collection sheet as we have relied on the paper[9] that on the basis of a large-scale population study showed median age of menopause as 49 years. Given the inability to ascertain which phase of the menstrual cycle the presumed premenopausal women were in during the procedure, the inaccurate pain prediction in that group of patients is possibly explained by the fact that pain perception differs between the phases of the menstrual cycle; women in different menstrual cycle phases were shown to have greater parasympathetic activity during the follicular phase compared with the luteal phase.[20] One review assessing the influence of sex hormones on the autonomic control of the cardiovascular system suggested that estrogen enhances parasympathetic activity in women.[20] Low estrogen levels in postmenopausal women are suspected to be one of the factors that may lead to exacerbation of pain perception.[21] Higher peripheral nervous system activity has been shown to have an inhibitory effect on pain modulation in men, whereas this relationship was not found in women.[22] Sex-related differences weaken with age and diminish around the time of menopause, which may suggest a potential hormonal influence on the autonomic nervous system.[23]

The negative correlation between the HRV and the predicted pain score suggests that those with higher parasympathetic tone perceived less pain.[12] Another limitation to our study is that some recordings were corrupted as a result of hardware issues in our new custom-made recording device, which have subsequently been fixed. Although this study is limited by a relatively small sample size, we report strong correlation between pPPS and rPPS for men and women aged 49 years and older (presumed postmenopausal). The true negative rate of 100% (low pain prediction) demonstrates the feasibility of objective pain prediction from HRV for men and presumed postmenopausal women (aged 49 years and older).[12] A further large-scale study will focus on the assessment of premenopausal women, evaluating the usefulness of our proposed tool in selecting patients for local anesthetic procedures and identifying those who will benefit from additional analgesic strategies. In addition, objective HRV measures may be superior to subjective qualitative measures of anxiety in predicting intraoperative pain.

The AVVQ was filled in by patients before the procedure, and scores were highest for postmenopausal women and lowest for premenopausal in women, whereas scores for men were slightly higher than those for premenopausal women. We are unable to explain why there should be a difference between these groups

of patients in total AVVQ scores as performed procedures and numbers of phlebectomies were similar. We consider it might be related to their interpretation of their symptoms. A larger prospective study will probably help us find the explanation for such a difference, especially with postoperative AVQQ.

CONCLUSIONS

Preoperative HRV analysis can accurately predict intraoperative pain in men and in women aged 49 years and older (presumed postmenopausal). However, preoperative HRV is less accurate in prediction of intraoperative pain in women younger than 49 years (presumed premenopausal). Our study included 29 analyzable patients, which is a small cohort; but in our opinion, it shows that our hypothesis might be the correct one. To evaluate clinical usefulness of the proposed method in selecting patients who would benefit from regional or general anesthesia, a large-scale prospective study is required.

AUTHOR CONTRIBUTIONS

Conception and design: UJ, NS, DM
Analysis and interpretation: KP, TA, WR, PN, VG, DM
Data collection: KP
Writing the article: KP
Critical revision of the article: TA, WR, PN, VG, NS, DM, UJ
Final approval of the article: KP, TA, WR, PN, VG, NS, DM, UJ
Statistical analysis: KP
Obtained funding: DM
Overall responsibility: KP

REFERENCES

1. Siribumrungwong B, Noorit P, Wilasrusmee C, Attia J, Thakkinstian A. A systematic review and meta-analysis of randomised controlled trials comparing endovenous ablation and surgical intervention in patients with varicose veins. Eur J Vasc Endovasc Surg 2012;44:214-23.
2. Roots MT, Borger van der Burg BL, Wever JJ. Pain perception during and after VNUS ClosureFAST procedure. Phlebology 2011;26:209-12.
3. Aitkenhead A. Injuries associated with anaesthesia. A global perspective. Br J Anaesth 2005;95:95-109.
4. Arroyo-Novoa CM, Figueroa-Ramos MI, Miaskowski C, Padilla G, Stotts N, Puntillo KA. Acute wound pain: gaining a better understanding. Adv Skin Wound Care 2009;22:373-80.
5. Moffat R, Rae CP. Anatomy, physiology and pharmacology of pain. Anaesth Intensive Care Med 2010;12:12-5.
6. Milicevic G. Low to high frequency ratio of heart rate variability spectra fails to describe sympatho-vagal balance in cardiac patients. Coll Antropol 2005;29:295-300.
7. Buijs RM, Swaab DF, editors. Handbook of clinical neurology, 3rd series. Autonomic nervous system, vol 117. Amsterdam: Elsevier; 2013.
8. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. Eur Heart J 1996;17:354-81.
9. Pokardi A, Iversen L, Hannaford P. Factors associated with age of onset and type of menopause in a cohort of UK women. Am J Obstet Gynecol 2011;205:34.e1-13.
10. Garatt A. Aberdeen Varicose Vein Questionnaire. Health Services Research Unit. Department of Public Health, Medical School University of Aberdeen; 1996.
11. Spielberger C. State-Trait Anxiety Inventory for Adults, Self-Evaluation Questionnaire, STAI form Y-1 and form Y-2. Redwood City, Calif: Mind Garden; 1977.
12. Adjei T, von Rosenberg W, Goverdovsky V, Powezka K, Jaffer U, Mandic DP. Pain prediction from ECG in vascular surgery. IEEE J Transl Eng Health Med 2017;5:2800310.
13. International Association for the Study of Pain, Subcommittee on Taxonomy. Pain terms: a list with definitions and notes on usage. Pain 1979;6:249-52.
14. Kim D, Koo H, Wooil L, Kim M. Application and limitation of frequency domain, LF/HF component in heart rate variability as an acute stress index [paper 128]. Proceedings of the International Conference on Biomedical Engineering and Systems; Prague, Czech Republic; August 14-15, 2014.
15. Salahuddin L, Cho J, Jeong MG, Kim D. Ultra short term analysis of heart rate variability monitoring mental stress in mobile settings. Conf Proc ITEEE Eng Med Biol Soc 2007;2007:4656-9.
16. Schubert C, Lambertz M, Nelesen RA, Bardwell W, Choi JB, Dimsdale JE. Effects of stress on heart rate complexity—a comparison between short-term and chronic stress. Biol Psychol 2009;80:325-32.
17. Weisenberg M, Aviram O, Wolf Y, Rapaheli N. Relevant and irrelevant anxiety in the reaction to pain. Pain 1984;20:371-83.
18. Schlereth T, Birklein F. The sympathetic nervous system and pain. Neuromolecular Med 2008;10:141-7.
19. Rhudy JL, Meagher MW. Fear and anxiety: divergent effects on human pain thresholds. Pain 2000;84:65-75.
20. Dart AM, Du XJ, Kingwell BA. Gender, sex hormones and autonomic nervous control of the cardiovascular system. Cardiovasc Res 2002;53:678-87.
21. Tousignant-Laflamme Y, Marchand S. Autonomic reactivity to pain throughout the menstrual cycle in healthy women. Clin Auton Res 2009;19:167-73.
22. Nahman-Averbuch H, Dayan L, Sprecher E, Hochberg U, Brill S, Yarnitsky D, et al. Sex differences in the relationship between parasympathetic activity and pain modulation. Physiol Behav 2016;154:40-8.
23. Gordan R, Gwathmey JK, Xie L. Autonomic and endocrine control of cardiovascular function. World J Cardiol 2015;7:204-14.

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