Pain Prediction from ECG in Vascular Surgery

Tricia Adjei, Wilhelm von Rosenberg, *Student Member, IEEE*, Valentin Goverdovsky, *Member, IEEE*, Katarzyna Powezka, Usman Jaffer and Danilo P. Mandic, *Fellow, IEEE*

Varicose vein surgeries are routine outpatient procedures, which are often performed under local anaesthesia. The use of local anaesthesia both minimises the risk to patients and is cost effective, however, a number of patients still experience pain during surgery. Surgical teams must therefore decide to administer either a general or local anaesthetic based on their subjective qualitative assessment of patient anxiety and sensitivity to pain, without any means to objectively validate their decision. To this end, we develop a 3-dimensional polynomial surface fit, of physiological metrics and numerical pain ratings from patients, in order to model the link between the modulation of cardiovascular responses and pain in varicose vein surgeries. Spectral and structural complexity features found in heart rate variability signals, recorded immediately prior to 17 varicose vein surgeries, are used as pain metrics. The so obtained pain prediction model is validated through a leave-one-out validation, and achieved a Kappa coefficient of 0.72 (substantial agreement) and an area below a receiver operating curve of 0.97 (almost perfect accuracy). This proof-of-concept study conclusively demonstrates the feasibility of the accurate classification of pain sensitivity, and introduces a mathematical model to aid clinicians in the objective administration of the safest and most cost-effective anaesthetic to individual patients.

***Index Terms*— Pain, Heart Rate Variability, ECG, HF, LF, Permutation Entropy.**

I. Introduction

Modern healthcare systems maintain patient safety as their foremost priority, while acknowledging that clinical procedures must also be cost effective. These requirements are by no means mutually exclusive - for example both patient safety and cost effectiveness are maximised when undergoing surgery under a local or regional anaesthetic, as opposed to a more intensive general anaesthetic. The quantitative assessment of the safety of clinical procedures, under the constraints of patient comfort and economic costs, is however an open and challenging issue.

An indirect way to assess the safety of surgical procedures is through the examination of relevant litigation claims. In a review of 841 anaesthesia related litigation claims against the National Health Service in England, from 1995-2007, it was revealed that local and regional anaesthesia accounted for 8% of anaesthesia related deaths, with complications related to general anaesthesia accounting for the remaining 92% [1]. In addition to loss of life, there are economic implications related to the use of general anaesthesia. For example, in 2010, it was reported that the average cost of general anaesthesia in hip surgery was 40% higher than the corresponding cost of regional anaesthesia [2].

Although these findings are strongly in favour of local and regional anaesthesia, their effectiveness is harder to control, and up to 25% of regionally anaesthetised patients experience pain during surgery [3]. The ability to objectively predict a patient's sensitivity to pain immediately prior to surgery would therefore be invaluable, both in terms of patient safety and economic costs, yet the crucial decision to administer a general or local anaesthetic is often left to the subjective judgement of the presiding clinician.

We therefore set out to identify markers of pain sensitivity from electrocardiograms (ECGs), recorded prior to varicose vein surgery under local anaesthesia, using unobtrusive wearable technology. These findings are then used to build an objective predictive mathematical model of pain, as an aid in surgical decision making. The proposed model is based on the analysis of heart rate variability (HRV) - the most relevant features were found to be the power of the high frequency components, and the structural complexity within the low frequency components of HRV signals. The efficiency of the proposed model is reflected in a kappa coefficient of 0.72 (indicating a substantial agreement) and the area below a receiver operating characteristic (ROC) curve of 0.97 (almost perfect accuracy). To the best of our knowledge, this is the only study to date to achieve such a reliable and accurate prediction of patient pain.

An objective criterion is therefore established to tailor anaesthesia to the psychophysiological profile of individual patients. The eventual more widespread adoption of such a technology promises not only a radically improved

First submitted: 14th March 2017.

T. Adjei, W. von Rosenberg, V. Goverdovsky and D. P. Mandic are with Electrical and Electronic Engineering, Imperial College London, London, SW7 2AZ.
(T. A. email: t.adjei15@imperial.ac.uk, W. R. email: wilhelm.von-rosenberg12@imperial.ac.uk , V. G. email: goverdovsky@imperial.ac.uk, D. P. M. email: d.mandic@imperial.ac.uk).
K. Powezka and U. Jaffer are with St. Mary's Hospital, Praed Street, London, W2 1NY (K. P. email: Katarzyna.Powezka@imperial.nhs.uk, U. J. email: usman.jaffer@icloud.com

experience for day-surgery patients and significant economic savings, but also a dramatic reduction in the number of patients who are unnecessarily administered a potentially harmful general anaesthetic.

II. Pain and the Autonomic Nervous System

Pain. Although the precise mechanisms which control wound pain remain largely unknown [4], the open literature suggests that all three major types of pain (nociceptive, inflammatory and neuropathic) are regulated through the peripheral or central nervous systems [4]. Both the peripheral and central nervous systems regulate the transduction of a noxious stimulus into an electrical impulse, which is then transmitted by nerves to the spinal cord and the brain [5]. Structures within the brainstem, collectively referred to as the limbic system, govern both the perception of pain and the physiological response to pain [5]. It should be noted that numerous other processes, such as the action of hormones, modulate pain intensity during both transmission and perception [5].

In addition to subjectivity, pain prediction is further complicated by the relationship between sex and physiological responses; in particular, the response in young females has been shown to be different from that in males [6]. In their 1996 study, Fillingim and Maixner [7] examined the relationship between resting blood pressure and pain, whereby 23 female and 25 male participants were subjected to ischaemic pain [7]. It was reported that blood pressure values exhibited a significant negative correlation with pain sensitivity in the male subjects only [7]. In 2005, Tousignant-Laflamme *et al*. [8], recorded the heart rates of 19 male and 20 female subjects after the immersion of their hands in hot water [8]. It was found that the change in the heart rates from the males was positively correlated with their subjective pain ratings, whereas the change in the heart rates from the females had a weak negative correlation with their pain ratings [8].

A 2008 study by Schlereth and Birklein examined whether the context of pain can affect physiological responses [9]; it was found that fear in response to an immediate threat increases pain thresholds, whereas anxiety, when anticipating a threat, decreases pain thresholds [10]. In summary, though many studies have investigated the physiology of pain, to date, the accurate prediction of pain has not been realised. This study however, achieves pain prediction.

Autonomic Nervous System. A key part of the physiological reaction to pain are the responses of the sympathetic and parasympathetic components of the autonomic nervous system [8]. The sympathetic nervous system (SNS) is associated with the energisation of the body, whereas the parasympathetic nervous system (PNS) is associated with the conservation of energy in the body; for example, the activity of the SNS causes an increase in heart rate and blood pressure [11]. Short term SNS activation has been suggested to supresses pain [9]; for instance, SNS activation releases the hormone norepinephrine, which is known to attenuate pain [5]. A study from 2002 investigated the relationship between the hormone cortisol, and pain, in 65 subjects [6] (cortisol is also released after SNS activation). A negative correlation between pain ratings and resting cortisol levels was reported to be statistically significant in the 31 male subjects only, although cortisol levels increased in both the male and female subjects following the onset of pain [6]. It was therefore concluded that the modulating effect of the SNS on pain may only occur in males [6]. A 2002 review on the effect of sex hormones on the autonomic control of the cardiovascular system suggested that oestrogen hormones enhance parasympathetic activity in females [12]. Given that female oestrogen levels naturally vary throughout the menstrual cycle, the effect of oestrogen on pain is also expected to vary throughout the menstrual cycle [6]. To this end, our study excluded pre-menopausal women from the patient cohort.

The assessment of the SNS and PNS activities is therefore a pre-requisite for objective pain prediction, and it has become widely accepted, though not without some controversy [13], that the low frequency (LF) and high frequency (HF) power spectral components of HRV signals can reflect the activities of the SNS and PNS respectively [14]. The *Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology* recommend that the LF and HF components are best captured within the respective frequency bands of 0.04-0.15 Hz and 0.15-0.4 Hz [14]. However, a conclusive interpretation of the activities within both bands is increasingly the subject of ongoing research [15].

It is important to highlight that the interpretation of the LF component in HRV is complex [13], as the LF component has been suspected to reflect modulation of both the SNS and PNS [14]. It has also been widely reported that HRV, and so its LF and HF components, is influenced by respiration [16]. The use of paced breathing has therefore been recommended to minimise the influence of respiration on HRV [16]. The range for typical respiratory frequencies is reported to coincide with the HF band [17], whereas slow breathing has been shown to produce respiratory frequencies which coincide with the LF band [16]. However, the use of paced breathing is not realistic in real-world applications. Next, it has been suggested that frequencies within the LF band can be modulated by the myogenic contraction of smooth muscles in blood vessels [17]. The relaxation and contraction of the muscles in blood vessels increases and decreases blood pressure, respectively [17]. This further confounds the interpretation of the activity within the LF band, as a decrease in blood pressure is typically associated with parasympathetic activity, and would be expected to produce changes in the HF band only. Nonetheless, it is therefore evident that the activities within LF and HF components of HRV signals are of physiological significance.

In our work, special emphasis is placed on utilising LF and HF to model the complex link between HRV and quantitative levels of pain.

III. Materials and Methods

A. Patients and Surgery

Data from 16 varicose vein surgery patients were analysed in this study. Seventeen ECGs were recorded from 9 male patients aged 54.8 ± 16.3 years, and 7 female patients aged 60 ± 9 years, during varicose vein surgeries, between August 2015 and October 2016. Two ECGs were recorded from one male patient on two separate occasions. Due to the retrospective nature of the data analysis, it was not possible to determine whether the female patients were pre- or post-menopausal. Therefore, only women aged 49 years or older were included in the data analysis, as the mean age for natural menopause in the UK was 48 in 2011 [18].

The recording protocol consisted of an initial period of rest, which varied between 14 minutes and 67 minutes, a period of surgery, which varied between 19 minutes and 50 minutes, and a final rest period after surgery, which varied between 5 minutes and 60 minutes. The ECGs were recorded from a single channel of a custom made portable data logger at a sampling frequency of 1000 Hz, with electrodes placed on the torso; to ensure the faithful acquisition of pain-related HRV dynamics, the breathing of patients was not paced.

The surgical procedures performed were either the ablation or avulsion, or both the ablation and avulsion of long saphenous varicose veins. Skin punctures were performed using 0.5 ml of 1% lidocaine, and ultrasound was used to correctly place a catheter in the affected vein. A tumescent anaesthetic containing 360 ml of 0.9% sodium chloride and 40 ml of 1% lidocaine with adrenaline (at a concentration of 5 micrograms/ml) was infiltrated through the affected vein. An additional 10 ml of 1% lidocaine was subcutaneously administered at the site of the skin incisions.

All recordings took place in hospitals within the Imperial College Healthcare Trust, London, with full consent from the participating patients. Ethics approval for physiological sensing was granted by the Joint Research Office at Imperial College London (reference ICREC_12_1_1).

Prior to surgeries, all patients completed standard state and trait anxiety questionnaires, respectively known as Form Y1 and Form Y2 [19], in order to establish the agreement between the state and trait anxiety measures and the perceived level of pain. The minimum anxiety scores from these questionnaires is 20, and the maximum is 80 [19]. Following the surgeries, patients were asked to rate their pain on a scale of 1 to 10, where 10 indicates extreme pain. Pain scores of 7 or greater were defined as high; a predicted score of 7 is therefore defined as the threshold at which the clinicians will administer general anaesthesia to a patient.

B. Data Analyses

1) Pre- processing

All analyses were performed in the MATLAB programming environment. Our own custom software, introduced in [20], was used to extract R-waves and generate HRV signals, which were then interpolated at a sampling frequency of 4 Hz.

2) Spectral Analysis

The powers within the LF and HF bands in all HRV signals were computed, and were normalised by the power within the considered 0.04-0.5 Hz band, using the formulas

$$Normalised\ LF = \frac{LF_P}{N_P} \quad (1)$$

$$Normalised\ HF = \frac{HF_P}{N_P} \quad (2)$$

where LF_p and HF_p are the respective powers in the LF and HF bands, and N_p is the power in the whole of the 0.04-0.5 Hz band.

The normalisation was performed using the 0.04-0.5 Hz band instead of the full band, as the physiological explanation for powers below 0.04 Hz is questionable in short recordings [14]. In addition, as mean heart rate is usually at least 1 Hz, and can be defined as the sampling frequency of HRV, the Nyquist theorem states that the meaningful information in HRV signals will be contained below 0.5 Hz [21]. A 5-minute sliding window was used for the analysis, in accordance with the recommendations in [14], with a 1 second increment.

3) Non-linear Analysis

The complexity loss theory states that constraints on a physiological system, such as illness or age, reduce the inherent structural complexity within the system, which is manifested as a reduction in entropy [22,23]. We therefore employed structural complexity analysis, performed through the permutation entropy method, to examine the change in structural complexity in HRV in response to pain. The LF and HF components of HRV were obtained through band-pass filtering the HRV signals by respective LF and HF finite impulse response filters of order 3000, using the Blackman-Harris window. The pass-bands for the LF and HF filters were 0.04-0.15 Hz and 0.15-0.4 Hz respectively, in accordance with the frequency ranges recommended in [14]. The complexity within the LF and HF components of the HRV signals was analysed using the robust permutation entropy method. Permutation entropy uses partitions, formed by comparing data-points to their neighbours, to create symbols; the entropy is defined as the source entropy of the relative frequency of each symbol [24]. We used the permutation entropy formulation from [25], whereby, a time series of *N* points,

$$x(i)_{i=1}^{N} \quad (3)$$

is embedded to create vectors, $X(i)$,

$$X(i) = [x(i), x(i+\tau), x(i+2\tau) \ldots, x[i+(m-1)\tau] \quad (4)$$

where m is the embedding dimension, and τ the time delay.

The elements in $X(i)$ are then ranked into ascending order,

$$x[i+(j_1-1)\tau] \leq x[i+(j_2-1)\tau] \leq \cdots \leq x[i+(j_m-1)\tau] \quad (5)$$

where j is the time index of each element (note that if $x[i+(j_1-1)\tau] = x[i+(j_2-1)\tau]$, the vectors are

ordered according to their time index). The time indices are then used to map each re-ordered vector onto a symbol,

$$A(i) = [j_1, j_2, \dots, j_m] \quad (6).$$

The relative frequency of every unique symbol, is then found as P_i, and the permutation entropy, PE, is computed as the Shannon entropy of the k relative frequencies,

$$PE(m) = \sum_{i=1}^{k} P_i \ln P_i \quad (7).$$

To enable the comparison of the PE computed from signals of different lengths, PE can be normalised as follows,

$$normPE = \frac{PE(m)}{\ln(m!)} \quad (8)$$

where $0 \leq normPE \leq 1$, and $normPE = 0$ defines a completely regular or chaotic signal [25].

The normalised permutation entropies for the LF and HF components of HRV are respectively denoted by LFPE and HFPE, and were computed within 5-minute sliding windows, with a 1 second increment. The embedding dimension of m=5 was found to be sufficiently large to fully capture the dynamics within the signal, while ensuring that the number of data points in $x(i)$ did not exceed $m!$, as recommended in [24]. The time delay of τ=1 is recommended to preserve the original temporal relationship between data-points. The values m=5, and a τ=1 were therefore employed to compute the PE.

To summarise, the signal features used in the subsequent modelling were the normalised LF powers, normalised HF powers, LFPE values, and HFPE values; these were segmented to create epochs of data pertaining to the pre-surgery rest period, the surgery, and the post-surgery rest period.

C. *Model Fits*

The analysis parameters were the subjective Y1 and Y2 scores from the questionnaires, and the objective parameters from the pre-surgery period, of the mean of the normalised LF powers, the mean of the normalised HF powers, the mean of the LFPE values and the mean of the HFPE values. Linear regressions and polynomial surface fits (PSFs) were created independently, based on the above analysis parameters, and the self-reported pain scores from patients were used for training to classify patients into low- and high-pain predicted categories. The independence of the PSFs and linear regressions ensures a full exploration of the linearity, degree of coupling, and/or nonlinearity of the physiology of pain.

For rigour, the linear regression models were created though an iterative approach, whereby the input parameter with the least significant contribution was successively removed until the resulting linear regression was based only on the parameter with the most significant contribution. In total, six linear regression models were created; the best performing model is defined as the model with the highest accuracy.

An empirical evaluation was also employed to determine the optimal nonlinear PSF. This consisted of evaluating the quadratic, cubic and quartic polynomials derived from assigning the above computed parameters as either the abscissa or the ordinate. The optimal fit was found to be of order-2 in the in the abscissa, and order-3 in the ordinate, (the polynomial is described in equations 9 to 12, where x and y represent the abscissa and ordinate, respectively),

$$PSF = f(x, y) \quad (9)$$

$$f(x, y) = \underline{\theta}^T \underline{X} \quad (10)$$

where, $$\underline{X} = [1, x, y, x^2, xy, y^2, x^2y, xy^2, y^3] \quad (11)$$

and the polynomial coefficients are given in $\underline{\theta}$,

$$\underline{\theta} = [\theta_0, \theta_1, \theta_2, \theta_3, \theta_4, \theta_5, \theta_6, \theta_7, \theta_8] \quad (12).$$

For simplicity, the normalised LF and HF powers will be denoted by LF and HF in the remainder of this paper.

D. *Statistical Analyses*

The accuracies of the proposed linear regressions and surface fits were evaluated using a leave-one-out (LoO) validation, that is, every model for the pain score prediction of a given patient was created without the patient's data. The consistencies of the polynomial surface fits created through the LoO validation were evaluated using the Wilcoxon rank-sum test, which established whether the model coefficients from a given LoO computation came from a distribution with the same median as that of the coefficients from the other LoO computations.

The predicted pain scores from the LoO validation were then defined as binary, i.e. high or low pain sensitivity, and performances were evaluated with the following standard metrics: (i) Kappa coefficients and (ii) receiver operating characteristic (ROC) curves.

The Kappa coefficient is commonly used to evaluate the performance of a classifier, and indicates the level of agreement between two 'observers' [26], i.e., the level of agreement between the actual pain score and the predicted pain score. Ranging from -1 to 1, a coefficient of -1 suggests systematic disagreement, a coefficient of 0 suggests agreement due to chance, and a coefficient of 1 suggests perfect agreement [26]. The Kappa coefficient is therefore a measure of precision [26], and was used to evaluate the agreement of the predicted pain scores with the scores stated by patients.

In addition, ROC curves can be used to indicate the accuracy of a diagnostic test [27]. The area under a ROC curve (AUC) quantifies the accuracy of a diagnostic test; a combination of a high true positive rate and a low false positive rate is reflected in an AUC close to unity, whereas an AUC of 0.5 suggests an accuracy owing to chance [27]. To create a ROC curve, true positive rates are plotted against false positive rates, as the cut-off threshold of a diagnostic test is varied [27].

In summary, the optimal linear regression or polynomial surface fit will have the highest accuracy, and the Kappa coefficient will indicate its precision. The Kappa coefficients

and AUCs from all linear regressions and polynomial surface fits are given in Table V in the appendix.

IV. Results

In all the subsequent analyses, a statistical significance level of 0.05 was employed, and statistically significant *p*-values are shown in bold. All results are shown to two significant digits.

Linear Regression model 4 (see Table V in the appendix for all linear regressions) yielded the highest AUC from the linear regression analyses, at 0.78; the *p*-values for the parameters in the regression are shown in Table I. The LFPE parameter was found to contribute most significantly to the prediction of pain in every linear regression examined.

Table I. Statistical results from Linear Regression 4.

Model	Parameters	*P*-value	Kappa Coefficient	ROC AUC
Linear Regression 4	LF	0.22	0.45	0.78
	LFPE	**0.0019**		
	Y2	**0.025**		

Table II shows the statistical results from PSF 21, which produced a Kappa coefficient of 0.72 and an AUC of 0.97; the first parameter listed in the table, LFPE, is the abscissa, and the second parameter, HF, is the ordinate. In total, 30 surface fits were created using all possible combinations of the parameters.

Table II. Statistical results from PSF 21.

Model	Parameters	Kappa coefficient	ROC AUC
Polynomial Surface Fit 21	LFPE	0.72	0.97
	HF		

The mean coefficients and standard deviations computed from the 17 LoO computations of PSF 21 are shown in Table III.

Table III. Mean coefficients and standard deviations from PSF 21.

Coefficient	Mean	Standard Deviation
θ_0	4.0	0.15
θ_1	1.3	0.27
θ_2	-0.94	0.24
θ_3	1.5	0.30
θ_4	0.70	0.53
θ_5	1.3	0.42
θ_6	3.0	0.50
θ_7	-6.3	1.0
θ_8	0.24	0.19

The statistical results from the Wilcoxon rank-sum test are shown in Table VII in the appendix. No significant differences were found between the surface fits from the 17 LoO computations.

Figure 1 shows PSF 21, created using data from all patients.

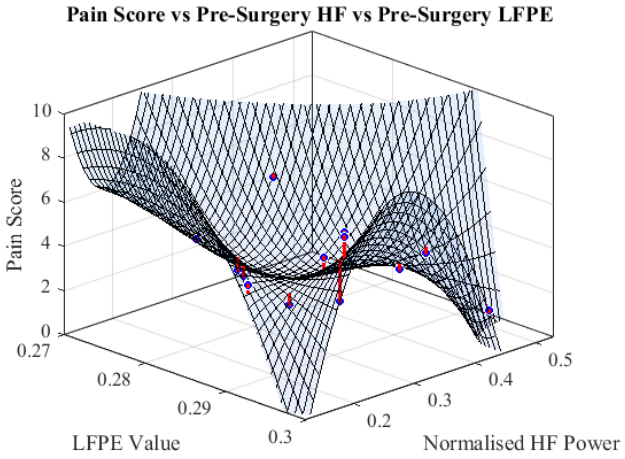

Figure 1. Polynomial surface fit 21. The red lines indicate the distance between each data point and the surface fit.

Table IV summarises the classification results from PSF 21, showing that low pain was correctly predicted in 11/11 cases while high pain was correctly predicted in 4/6 cases (many of the patients who experienced high pain complained of a sharp pulling/pushing pressure). The true negative rate of 100% (low pain prediction) demonstrates the feasibility of objective pain prediction from HRV, while the result for high pain indicates that a larger-scale study is needed to fine tune the parameters of the highly nonlinear pain prediction polynomial. Figure 2 shows the agreement between the pain scores predicted by PSF 21 and those stated by the patients.

Table IV. Confusion matrix of prediction results from PSF 21.

	Low pain stated	High pain stated
Low pain predicted	11	2
High pain predicted	0	4

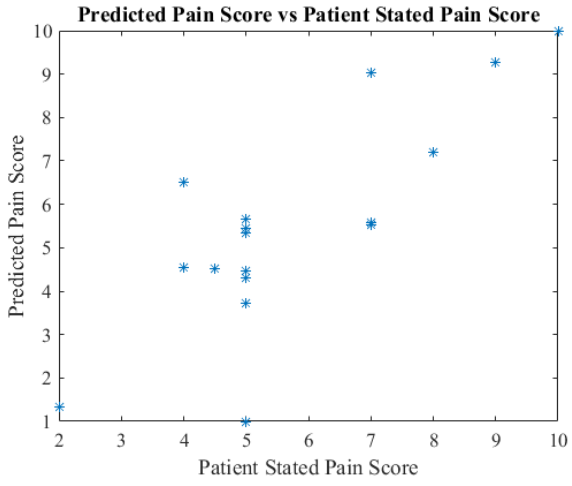

Figure 2. Agreement between the predicted pain scores from PSF 21 and the pain scores stated by patients.

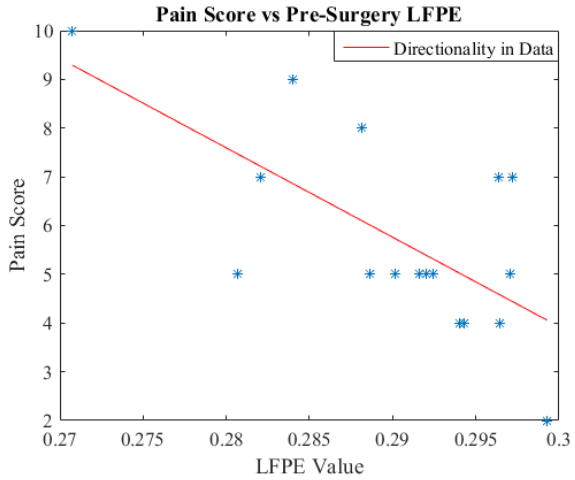

Figure 3. Relationship between reported pain score and pre-surgery LFPE.

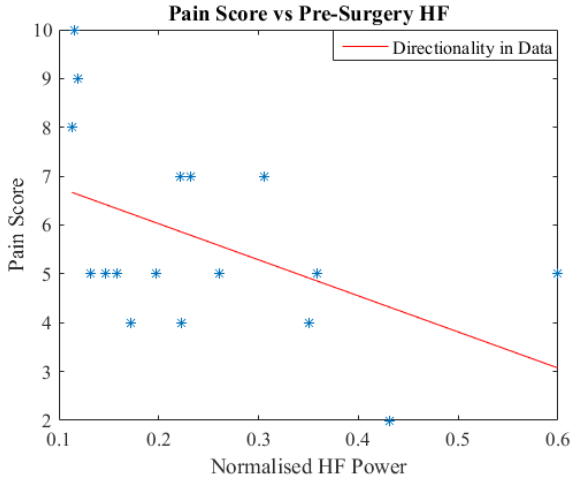

Figure 4. Relationship between reported pain score and pre-surgery HF.

V. DISCUSSION

The results have demonstrated that pain in surgery can be predicted from ECG, recorded prior to surgery. Our results show conclusively that the optimal prediction was achieved from a nonlinear polynomial surface fit, using LFPE and HF, as demonstrated by a very high area under a ROC curve of 0.97. Upon closer inspection of PSF 21, the pain scores had negative correlations with both LFPE and HF (see Figs. 3 and 4, in which the red lines indicate the principal directionality in the data). The negative correlation between LFPE and pain score indicates greater pain intensity with decreased structural complexity within the low frequency component of HRV. In accordance with the complexity loss theory, low complexity within the low frequency component of HRV is indicative of a reduced adaptivity (in the system, or systems, contributing to the LF band) to physiological and environmental changes [23]. Therefore, despite the disagreement over the origins of the contributions to the LF band (i.e. the SNS alone, or both the SNS and PNS [13], or both autonomic and myogenic activity [17]), the negative correlation between LFPE and pain indicates that increased pain sensitivity is the result of poor physiological adaptivity/responsiveness. This theory is supported by [6], in which high resting levels of cortisol, a key hormonal component of the SNS response to stress, were reported to correlate with low pain ratings.

Furthermore, findings in [9] established that prolonged anxiety decreased pain thresholds, therefore, the anxiety in patients who were extremely nervous before surgery would have placed constraints upon the physiological systems related to pain, leading to reduced structural complexities.

In accordance with the widely accepted hypothesis thatthe dominant contributor to the power in the HF band is the activity of the PNS, the negative correlation between HF and pain score indicates that those with high PNS tone perceived less pain. However, given the negative correlation between LFPE and pain, and that other studies have found that markers of high SNS tone, are correlated with reduced pain sensitivity (known as a hypoalgesia effect) [6,7], it can be concluded that hypoalgesia is not the result of the specific action of either nervous system. Instead, both nervous systems must share a common feature which has a hypoalgesic effect. One such feature shared by both nervous systems is activation from baroreceptors [28].

Baroreceptors in the venae cavae and atria of the heart detect low blood pressure and activate the SNS, whereas baroreceptors located in the aortic arch of the heart and the carotid sinus in the neck, detect high blood pressure and activate the PNS [28]. The hypoalgesic effects of either a dominant SNS or PNS are therefore likely to be the result of baroreceptor activation. This is particularly relevant as it has been found that individuals with higher resting blood pressures experience greater hypoalgesia than those with normal resting blood pressures [7]. The hypoalgesic effects of baroreceptors are well documented and it is reported that the stimulation of baroreceptors triggers a release of opioids and reduces cerebral arousal [29]. Hence, if baroreceptor activation is the primary cause of the varying levels of hypoalgesia experienced by the patients in this study, the computed HF values from the patients could indicate levels of baroreceptor activation.

The positive correlation between LFPE and HF is also informative. High HF power accompanied by high structural complexity within the LF band could indicate, a decreased determinism in the activity of the SNS as PNS tone increases. However, as other studies report strong negative correlations between indicators of SNS tone and pain [6,7], it can be concluded that if LF was an indicator of sympathetic tone alone, it would have performed exceptionally well in the prediction of pain. In this study, LF was not a strong predictor of pain, thus indicating that it does not solely reflect the activity of the SNS. The positive correlation between LFPE and HF therefore provides support for the theory that LF also contains contributions from the PNS [30], as increases in LFPE are likely to reflect a shift of PNS contributions from the LF band further into the HF band. Furthermore, the varying performances of LF and HF in the prediction of pain indicate that LF and HF do not have a strictly linear relationship.

The results from this study have also highlighted that responses from subjective qualitative measures of state anxiety, such as questionnaires, are of limited use in the prediction of pain sensitivity. This could be due to repressors within the patient cohort, that is, those who deny being in a stressed state [31]. The presence of repressors undermines the use of questionnaires as these patients understate their anxiety. Future attempts to predict pain using the responses to anxiety questionnaires will therefore have to consider the presence of repressors.

Limitations. The main limitation of this study is the relatively small size of the patient cohort, 16 in total, which may have affected the extrapolations of the surface fit. In addition, we were not able to determine the extent to which respiration influenced the power within the HF band, due to a lack of respiratory data in a form which would permit its extraction from the heart rate data. The lack of data related to myogenic activity also prevents an investigation into myogenic influences on HRV, and the retrospective nature of the analyses means that it was not possible to confirm which female patients were pre- or post- menopausal. The study cohort may therefore have included pre-menopausal females.

Future studies will examine the correlation between the information in the LF band and the level of pain during the actual surgery. Also, further analyses will be undertaken to realise PSF 21 through recurrent neural networks [32], allowing future studies to explore machine learning and deep network frameworks. An investigation into the performances of other established structural complexity measures, such as Fuzzy Entropy [33] and Multivariate Multiscale Entropy [34] would also be of interest.

VI. Conclusions

Surgery under local anaesthesia is both safer and more cost effective than surgery under general anaesthesia, yet, it is not unusual for locally anaesthetised patients to experience pain during surgery. To this end, we set out to investigate the feasibility of pain prediction in varicose vein surgeries, based on electrocardiograms recorded before surgery. To our knowledge, this is the first such study, and could profoundly affect how clinicians determine the patients who are best suited to general anaesthesia.

The results show, conclusively, that it is feasible to predict patient pain, and hence determine if a patient requires general anaesthesia. The most accurate predictions have been obtained using a polynomial surface fit of order-2 in the abscissa and order-3 in the ordinate. The respective abscissas and ordinates are the permutation entropies computed from the LF components of HRV signals, and the power in the HF components of HRV signals. A leave-one-out validation using 17 electrocardiograms has resulted in a true negative rate of 100%, a Kappa coefficient of 0.72 (substantial agreement) and an area under a ROC curve of 0.97 (almost perfect accuracy).

VII. Appendix

Table V evaluates the statistical results from the iterative refinement of six linear regressions to predict patient pain. Significant *p*-values are shown in bold.

The results from the polynomial surface fits created using all combinations of LF, HF, LFPE, HFPE, the Y1 and the Y2 questionnaire scores are shown in Table VI.

The results from the Wilcoxon rank-sum test of the polynomial coefficients computed from the LoO validation are shown in Table VII. The lack of significant *p*-values amongst the results indicates the consistency of the surface fit coefficients computed from the LoO validation.

Table V. Statistical results from the linear regression models.

Model	Parameters	*P*- value	Kappa Coefficient	ROC AUC
Linear Regression 1	LF	0.28	0.63	0.64
	HF	0.32		
	LFPE	**0.015**		
	HFPE	0.53		
	Y1	0.93		
	Y2	0.21		
Linear Regression 2	LF	0.25	0.33	0.74
	HF	0.29		
	LFPE	**0.0037**		
	HFPE	0.50		
	Y2	**0.024**		
Linear Regression 3	LF	0.22	0.23	0.74
	HF	0.32		
	LFPE	**0.0017**		
	Y2	**0.018**		
Linear Regression 4	LF	0.22	0.45	0.78
	LFPE	**0.0019**		
	Y2	**0.025**		
Linear Regression 5	LFPE	**0.00036**	0.27	0.74
	Y2	**0.024**		
Linear Regression 6	LFPE	**0.0032**	0.44	0.64

Table VI. Precision and accuracy of all 30 polynomial surface fits.

Model	Parameters	Kappa coefficient	ROC AUC
Polynomial Fit 1	LF HF	0.28	0.69
Polynomial Fit 2	LF LFPE	0.16	0.73
Polynomial Fit 3	LF HFPE	-0.61	0.09
Polynomial Fit 4	LF Y1	0.23	0.45
Polynomial Fit 5	LF Y2	-0.2	0.45
Polynomial Fit 6	HF LFPE	0.56	0.83
Polynomial Fit 7	HF HFPE	-0.55	0.12
Polynomial Fit 8	HF Y1	0.23	0.45
Polynomial Fit 9	HF Y2	-0.03	0.45
Polynomial Fit 10	LFPE HFPE	0.06	0.58
Polynomial Fit 11	LFPE Y1	0.33	0.64
Polynomial Fit 12	LFPE Y2	0.16	0.52
Polynomial Fit 13	HFPE Y1	0.44	0.81
Polynomial Fit 14	HFPE Y2	-0.03	0.55
Polynomial Fit 15	Y1 Y2	0.09	0.27
Polynomial Fit 16	HF LF	0.48	0.86
Polynomial Fit 17	LFPE LF	0.48	0.79
Polynomial Fit 18	HFPE LF	-0.11	0.43
Polynomial Fit 19	Y1 LF	0.23	0.45
Polynomial Fit 20	Y2 LF	-0.03	0.42
Polynomial Fit 21	LFPE HF	0.72	0.97
Polynomial Fit 22	HFPE HF	-0.29	0.4
Polynomial Fit 23	Y1 HF	0.23	0.48
Polynomial Fit 24	Y2 HF	0.06	0.43
Polynomial Fit 25	HFPE LFPE	-0.11	0.59
Polynomial Fit 26	Y1 LFPE	0.16	0.62
Polynomial Fit 27	Y2 LFPE	0.06	0.55
Polynomial Fit 28	Y1 HFPE	0.44	0.79
Polynomial Fit 29	Y2 HFPE	-0.29	0.32
Polynomial Fit 30	Y2 Y1	-0.11	0.37

Table VII. Statistical *p*-values computed from the Wilcoxon rank-sum test, assessing the consistency of the surface fit coefficients from the LoO validation of PSF 21.

		Coefficient *p*- values								
		θ_0	θ_1	θ_2	θ_3	θ_4	θ_5	θ_6	θ_7	θ_8
Leave-One-Out Validation Computation	**1**	0.59	0.82	0.82	0.59	0.24	0.35	1	0.71	0.35
	2	0.47	0.47	0.35	0.24	0.24	0.94	0.35	0.35	0.94
	3	0.35	0.94	0.59	1	1	0.59	0.59	0.71	0.47
	4	0.94	0.35	1	0.71	0.94	0.47	0.82	0.94	0.59
	5	0.82	0.12	0.35	0.35	0.71	0.24	0.47	0.47	0.47
	6	0.12	0.59	0.24	0.12	0.82	0.12	0.12	0.24	0.82
	7	0.82	0.82	0.82	0.94	0.12	0.59	0.94	0.94	0.94
	8	0.94	0.59	0.47	0.71	0.47	0.47	0.94	1	0.82
	9	0.7	0.35	0.71	0.59	0.12	0.24	0.24	0.12	0.12
	10	0.71	0.12	0.47	0.94	0.59	0.71	0.71	0.59	0.71
	11	0.24	0.24	0.59	0.82	0.47	0.12	0.59	0.59	0.35
	12	0.24	0.71	0.94	0.47	0.35	0.71	0.82	0.82	0.59
	13	0.47	0.24	0.12	0.24	0.82	0.94	0.24	0.12	0.12
	14	0.12	0.47	0.24	0.12	0.94	0.35	0.12	0.24	1
	15	0.59	0.71	0.71	0.47	0.59	0.82	0.35	0.47	0.24
	16	1	1	0.94	0.82	0.35	1	0.71	0.82	0.71
	17	0.35	0.94	0.12	0.35	0.71	0.82	0.47	0.35	0.24

REFERENCES

[1] T. M. Cook, L. Bland, R. Mihai and S. Scott, "Litigation related to anaesthesia: An analysis of claims against the NHS in England 1995–2007", *Anaesthesia*, vol. 64, no. 7, pp. 706-718, Jul. 2009.

[2] A. Chakladar and S. M. White, "Cost estimates of spinal versus general anaesthesia for fractured neck of femur surgery", *Anaestheia*, vol. 65, no. 8, pp. 810-814, May 2010.

[3] A. R. Aitkenhead, "Injuries associated with anaesthesia. A global perspective", *British Journal of Anaesthesia*, pp. 95-109, May 2005.

[4] C. M. Arroyo-Novoa, M. I. Figueroa- Ramos, C. Miaskowski, G. Padilla, N. Stotts and K. A. Puntillo, "Acute wound pain: Gaining a better understanding", *Advances in Skin & Wound Care*, vol. 22, no. 8, pp. 373-830, Aug. 2009.

[5] R. Moffat and C. P. Rae, "Anatomy, physiology and pharmacology of pain", *Anaesthesia & Intensive Care Medicine*, vol. 12, no. 1, pp. 12-15, Jan. 2011.

[6] M. al'Absi, K. L. Petersen and L. E. Wittmers, "Adrenocortical and hemodynamic predictors of pain perception in men and women", *Pain*, vol. 96, no. 1, pp. 197-204, Mar. 2002.

[7] R. B. Fillingim and W. Maixner, "The influence of resting blood pressure and gender on pain responses", *Psychomatic Medicine*, vol. 58, no. 4, pp. 326-332, Jul./Aug. 1996.

[8] Y. Tousignant-Laflamme, P. Rainville and S. Marchand, "Establishing a link between heart rate and pain in healthy subjects: A gender effect", *The Journal of Pain*, vol. 6, no. 6, pp. 341-347, Jun. 2005.

[9] T. Schlereth and F. Birklein, "The sympathetic nervous system and pain". *Neuromolecular Medicine*, vol. 10, no. 3, pp. 141-147, Sept. 2008.

[10] J.L. Rhudy, and M.W. Meagher, "Fear and anxiety: divergent effects on human pain thresholds", *Pain*, vol. 84 no. 1, pp. 65-75, Jan. 2000.

[11] F. Figueroa- Fankhanel, "Measurement of stress", *Psychiatric Clinics of North America*, vol. 37, no. 4, pp. 455-487, Dec. 2014.

[12] A. M. Dart, X. J. Du and B.A. Kingwell, "Gender, sex hormones and autonomic nervous control of the cardiovascular system", *Cardiovascular Research*, vol. 53, no. 3, pp. 678-687, Feb. 2002.

[13] G. E. Billman, "The LF/HF ratio does not accurately measure cardiac sympatho-vagal balance", *Frontiers in Physiology*, vol. 4, no. 26, article 26, Feb. 2013.

[14] 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", *European Heart Journal*, vol. 17, no. 3, pp. 354-381, March 1996.

[15] W. von Rosenberg, T. Chanwimalueang, T. Adjei, U. Jaffer, V. Goverdovsky and D. P. Mandic, "Resolving Ambiguities in the LF/HF Ratio: LF-HF Scatter Plots for the Categorization of Mental and Physical Stress", *Frontiers in Physiology*, 2017.

[16] T. E. Brown, L.A. Beightol, J. Koh and D.L. Eckberg, "Important influence of respiration on human RR interval power spectra is largely ignored", *Journal of Applied Physiology*, vol. 75, no. 5, pp. 2310-2317, Nov. 1993.

[17] D. A. Kenwright, A. Bahraminasab, A. Stefanovska and P. V. E. McClintock, "The effect of low-frequency oscillations on cardio-respiratory synchronization", *The European Physical Journal B*, vol. 65, no. 3, Jun. 2008, pp. 425-433.

[18] A. J. Pokoradi, L. Iversen, P. C. Hannaford, "Factors associated with age of onset and type of menopause in a cohort of UK women", *American Journal of Obstetrics and Gynecology*, vol. 205, no. 1, pp. 34.e1-34.e13, Feb. 2011.

[19] C. D. Spielberger, "State- Trait Anxiety Inventory for Adults (Forms Y1 and Y2): Manual", Menlo Park: Mind Garden Inc. 1983, 2015.

[20] T. Chanwimalueang, W. von Rosenberg and D. P. Mandic, "Enabling R-peak detection in wearable ECG: Combining matched filtering and Hilbert Transform", in *Proceedings of the IEEE International Conference on Digital Signal Processing*, Singapore, 2015, pp. 134-138.

[21] T. Kuusela, "Methodological Aspects of Heart Rate Variability Analysis". In Kamath M. V., Watanbe M. A. and Upton A. R. M. (eds.) *Heart Rate Variability (HRV) Signal Analysis: Clinical Applications*. Thousand Oaks: Sage Publications, 2004, pp. 9-42.

[22] A. L. Goldberger, C.- K. Peng and L. A. Lipsitz, "What is physiologic complexity and how does it change with aging and disease?", *Neurobiology of Aging*, vol. 23, no. 1, pp. 23-26, Jan. 2002.

[23] D. E. Vaillancourt and K. M. Newell, "Changing complexity in human behavior and physiology through aging and disease" *Neurobiology of Aging*, vol. 23, no. 1, pp. 1-11, Jan. 2002.

[24] C. Bandt and B. Pompe, "Permutation entropy- a natural complexity measure for time series", *Physical Review Letters*, vol. 88, no. 17, pp. 1-5, Apr. 2002.

[25] C. Bian, Q. Chang, M. D. Y. Qianli and S. Qinghong, "Modified permutation-entropy analysis of heartbeat dynamics", *Physical Review E*, vol. 85, no. 2, pp. 1-7, Feb. 2012.

[26] A. J. Viera and J. M Garrett, "Understanding nterobserver agreement: The Kappa statistic", *Family Medcine*, vol. 37, no. 5, pp. 360-363, May 2005.

[27] A. K. Akobeng, "Understanding diagnostic tests 3: Receiver operating characteristic curves", *Atca Paediatrica*, vol. 96, no. 5, pp. 644-647, Mar. 2007.

[28] R. Gordon, J. K. Gwathmey and L.-H. Xie, "Autonomic and endocrine control of cardiovascular function", *World Journal of Cardiology*, vol. 7, no. 4, pp. 204-214, Apr. 2015.

[29] T. G. Pickering, "Pain and blood pressure", *The Journal of Clinical Hypertension*, vol. 5, no. 5, pp. 359-361, Sept. 2003.

[30] D. C. Randall, D. R. Brown, R. M. Raisch, J. D. Yingling and W. C. Randall, "SA nodal parasympathectomy delineates autonomic control of heart rate power spectrum", *American Journal of Physiology-Heart and Circulatory Physiology*, vol. 260, no. 3, pp. H985-H988, Mar. 1991,

[31] L. B. Myers and N. Derakshan, "The repressive coping style and avoidance of negative affect". In I. Nyklíček, L. Temoshok and A. Vingerhoets (ed.) *Emotional Expression and Health: Advances in Theory, Assessment and Clinical Applications*. New York: Taylor and Francis, 2004, pp. 171-186.

[32] D. P. Mandic and J. A. Chambers, *Recurrent Neural Networks for Prediction: Learning Algorithms, Architectures, and Stability*. Wiley Series in Adaptive and Learning Systems for Signal Processing, Communications, and Control. Chichester: John Wiley & Sons, 2001.

[33] M. U. Ahmed, T. Chanwimalueang, S. Thayyil, and D. P. Mandic, "A multivariate multiscale fuzzy entropy algorithm with application to uterine EMG complexity analysis," *Entropy*, vol. 19, no. 2, pp. 1-18, Jan. 2017.

[34] M. U. Ahmed and D. P. Mandic, "Multivariate Multiscale Entropy," *IEEE Signal Processing Letters*, vol. 19, no. 2, pp. 91-95, Jan. 2012.

Tricia Adjei was awarded an M.Eng. degree in medical engineering from the University of Surrey, Guildford, UK, in 2014, and is currently studying a PhD within the Department of Electrical and Electronic Engineering at Imperial College London, UK. She is researching the modelling and quantification of physiological stress.

She was employed as a research engineer at the medical device company Oxehealth Ltd, UK, from 2014 to 2015.

Wilhelm von Rosenberg (M'15) received the B.Sc. degree in physics from Heidelberg University, Heidelberg, Germany, in 2012, which included an exchange year with the University of Delhi, New Delhi, India, and the M.Sc. degree in physics from Imperial College London, London, U.K., in 2013. He is currently pursuing the Ph.D. degree with the Department of Electrical and Electronic Engineering. His research focuses on the propagation of

neural and cardiac signals through body tissues, mobile vital signs and EEG recordings, and the quantification of mental and physical stress from biosignals.

Valentin Goverdovsky (M'13) received the M.Eng. degree in electronic engineering and the Ph.D. degree in communications from Imperial College London, U.K.

He is currently a Rosetrees Fellow with the Department of Electrical and Electronic Engineering, Imperial College London. His research interests are primarily in the areas of biomedical instrumentation, analog integrated circuits, and radio frequency communications. He is currently involved in the development of wearable biosensing platforms, such as the novel in-the-ear sensing concept for 24/7 monitoring of brain and body functions in the context of traumatic brain injury. He received the Eric Laithwaithe Award for excellence in research.

Katarzyna Powezka was born in Poland in 1979. She was awarded an MD degree in 2004, and the title of Specialist in General Surgery in 2014.

She has been working in the UK since 2014, first at Wexham Park Hospital and then at Imperial College Healthcare NHS Trust. She has been working in the Vascular Department since Aug 2015, being involved in clinical work as well as in research projects.

Usman Jaffer was born in London in 1974. He completed a BSc in Biomedical Sciences from King's College London. He then undertook a period of basic cardiovascular research in the University of JW Goethe in Frankfurt, Germany. He then pursued a Medical career degree from the University of the Punjab. On his return to the UK he undertook another period of lab based research in Cardiovascular Biology at King's College London before commencing his House Officer postings at Addenbrooke's Hospital, Cambridge. He continued medical training on the Cambridge surgical training rotation before coming to Imperial College where he undertook two consecutive Masters programmes in Surgical Sciences and Medical Ultrasound. His interest in medical education led him to undertake a Postgraduate Certificate in Medical Education from the University of Dundee by correspondence.

He currently works with his team at Imperial College NHS Trust, working on simulation and assessment tools for treating medical emergencies and performing medical ultrasound, wearable sensor technology for stress anxiety assessment and assessment of effective team working, ischaemia reperfusion injury in peripheral vascular disease, and various quality improvement initiatives in healthcare.

Danilo P. Mandic (F'13) is currently a Professor of Signal Processing with Imperial College London, London, U.K., where he has been involved in the area of nonlinear adaptive and biomedical signal processing. He has been a Guest Professor with the Katholieke Universiteit Leuven, Leuven, Belgium, and a Frontier Researcher with RIKEN, Tokyo. His publication record includes two research monographs, Recurrent Neural Networks for Prediction (West Sussex, U.K.: Wiley, 2001) and Complex-Valued Nonlinear Adaptive Filters: Nocircularity, Widely Linear, and Neural Models (West Sussex, U.K.: Wiley, 2009), an edited book Signal Processing for Information Fusion (New York: Springer, 2008), and over 400 publications in signal and image processing.

He is a member of the London Mathematical Society. He has produced award winning papers and products from his collaboration with industry, and has received the President's Award for excellence in postgraduate supervision at Imperial College.