Role of Heart Rate Variability in Predicting Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis

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Abstract

Introduction **: Early recognition of post-ERCP pancreatitis (PEP) would help deliver an appropriate discharge plan following ERCP. Functioning of the autonomic nervous system can be measured using non-invasive heart rate variability techniques (HRV) and provides quantitative information about the modulation of cardiac vagal and sympathetic activity. Pain evoked sympathetic activation is a well-known phenomenon, as exhibited in those suffering PEP. The aim of this study is to determine if a single post-procedural measurement of HRV identifies those at risk of developing PEP.**

Methods **: A prospective, observational, single-centre cohort study was performed including all patients undergoing either diagnostic or therapeutic ERCP. In addition to standard monitoring electrocardiographic (ECG) signals 4 hours post-ERCP were recorded using a digital ECG.**

Results **: A Total of 115 patients were enrolled over 11 months. PEP occurred in 12 (10.4%) patients. The low frequency (LF)/ high frequency (HF) ratio on HRV was significantly higher in those suffering PEP (median LF/HF 2.58 vs 2.10, p<0.001). It is possible to identify patients at high risk of PEP through HRV analysis where the LF/HF ratio is found to exceed 2.43, with an AUC of 0.827 and combined sensitivity of 83.3 % and specificity of 81.6 % (PPV 42%, NPV 97%).**

Conclusions **: In this first study of HRV analysis in those undergoing ERCP the index of sympathovagal balance (LF/HF) predicted PEP independently of other risk factors. This could lead to the use of post procedural HRV to identify patients suitable for early discharge following ERCP.** (Acta gastroenterol. belg., **2016**, 79, **429-434**).

Key words : heart rate variability, post-endoscopic retrograde cholangiopancreatography pancreatitis.

Introduction

Acute pancreatitis is the most common post-procedural complication following ERCP. Its incidence is reported between 2.1 and 24.4%, with such variability being attributable to heterogeneous patient populations, differing levels of endoscopic expertise, procedural differences, and disparate definitions of post-ERCP pancreatitis (PEP) and its severity (1-12). Whilst most patients develop a mild pancreatitis with rapid and full recovery, a small percentage may follow a severe course with pancreatic necrosis, multiorgan failure, and even death (2,9).

Post-procedural prediction of PEP is known to be difficult with the European Society of Gastrointestinal Endoscopy (ESGE) suggesting testing serum amylase or lipase 2-6 hours after ERCP in patients presenting with pain and who are to be discharged on the day of ERCP[13]. Yet, the distinction between hyperamylasemia with transient abdominal discomfort (TAD) due to post-procedural intestinal distension and PEP remains difficult to establish during the first 24 h after the procedure and as such there is no ideal method of early identification of PEP.

Heart rate variability (HRV) is an indirect estimator of autonomic modulation of the cardiovascular system. Studies of HRV in clinical practice started by establishing the association between HRV and cardiac morbidity (14-15). However, broader applications of HRV have been established. Autonomic dysfunction measured by HRV has since been found to be strongly correlated with morbidity and mortality from diverse diseases (16-19).

Frequency domain HRV analysis decomposes the heart rate intervals data into its frequency components and quantifies them in their relative intensity, termed power. These methods are appropriate for short-term (5min) recordings, hence more clinically applicable when compared to other HRV methods. According to documented standards frequency spectrums are divided into high frequency (HF - 0.15 to 0.4Hz) which indicates cardiac parasympathetic activity ; and low frequency (LF - 0.04 to 0.15Hz) which indicates the aggregate of the cardiac sympathetic nerves and parasympathetic activity of the heart. The low frequency and high frequency ratio (LF/HF) represents the balance between sympathetic and parasympathetic activities (20).

In many disorders changes in HRV may be an early manifestation of the condition and may be useful in quantifying the rate of disease progression and/or the efficacy of therapeutic interventions (19, 21-22).

Pain evoked sympathetic activation is a well-known phenomenon. Previous studies of HRV in patients with acute or chronic pain are consistent to show that in individuals experiencing pain it is associated with lower HF and higher LF, both in absolute and normalized values and higher LF/HF ratios, representing

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Submission date : 12/04/2016
Acceptance date : 31/05/2016

a sympathetic response to stress (23-33). It could be hypothesised that pain related to pancreatic damage caused by ERCP compared to transient post procedural pain is more likely to trigger a shift of the autonomic balance towards sympathetic over activity and therefore may be identified early using non-invasive HRV.

This study aims to investigate the association of autonomic dysfunction and PEP 4 hours post-procedure measured through non-invasive HRV analysis in patients who have undergone ERCP.

The research was undertaken as part of the third year of the MSc in Surgical Sciences or Edinburgh Surgical Sciences Qualification www.essq.rcsed.ac.uk

Patients and Methods

A prospective, observational, single-centre cohort study was performed in the General Surgery Department with Endoscopy Unit of the Kiev Regional Hospital (Ukraine). Consecutive patients admitted for therapeutic or diagnostic ERCP between March 2014 and June 2015 were included in the study.

Intraoperative sedation included midazolam and fentanyl. Relaxation of duodenum was maintained with intravenous buscopan. Some cases were carried out with administration of local anaesthetic agent (lidocaine). Per rectal diclofenac was used routinely with an aim of PEP's prophylaxis. Selection of additional measures for PEP's prophylaxis was at the discretion of the endoscopist who performed the procedure.

As the measurement of heart rate variability has been shown to be affected by the factors listed below, patients who had any of the conditions provided below were excluded from the study: chronic or acute heart failure, diabetes mellitus, heart transplant, cardiomyopathies, cardiac arrhythmia or presence of a cardiac pacemaker, use of medications which were reported to cause alteration of autonomic balance (calcium channel blockers, anti-arrhythmic agents, beta-adrenergic blockers), and patients who had general anesthesia during the procedure. Patients were also excluded if they were unable to give informed consent.

Patient characteristics were recorded for the following variables: age, sex, history of prior acute pancreatitis (prior AP), presence or absence of sphincter of Oddi dysfunction (SOD), presence or absence of bilirubin elevation, body mass index (BMI). SOD was suspected based on Rome III criteria (34).

After the procedure, all patients remained in hospital overnight and were monitored in the ward. Venous blood samples were collected 24h after the procedure for amylase measurement. Analgesic requirements were satisfied in accordance with WHO analgesic ladder.

Local Central Ethics Committee approval was obtained for the study. All patients were provided with an information sheet and signed a study consent form prior to inclusion. This study involved no additional risk to patients other than non-invasive cardiac imaging.

HRV measurement

In addition to the Hospital's standard post-ERCP monitoring patients underwent non-invasive measurement using electrocardiographic (ECG) monitoring equipment. ECG signals 4 hours post-ERCP were recorded at the bedside using a digital ECG measurement device (Cardio CE Bt ; XAI Medical, Kharkov, Ukraine) with subjects supine according to the standards developed by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (Task Force) (20). Normal beat intervals were identified from lead II ECG recordings by the device's software. All artifacts and ectopic beats were removed in accorance with the guidelines outlined by the Task Force. The power spectrum of the beat-to-beat intervals was generated using fast Fourier transformation using the device's software.

Clinical outcomes

The primary outcome of the study was the presence of PEP. The diagnosis of PEP required both of (i) abdominal pain that persisted for at least 24 hours, and (ii) a serum amylase level measured 24 hours after the procedure that was more than three times the upper limit of the normal range (9). The severity of PEP was assessed in accordance with Cotton's criteria (9).

Statistical Analysis

All patients were assigned an individual anonymous patient number and data was analyzed using SPSS (Version 15) (SPSS, Chicago, IL, USA) on completion of the recruitment period.

Categorical data (age (<60yr old or >60yr old), sex, presence or absence of suspected SOD, prior

AP, billirubinaemia, body mass index (BMI) <30 or >30) was compared using Fisher's exact test. Non-parametric continuous variables LF, HF, LF/HF were reported as median (interquartile range) and compared between groups using Mann-Whitney U analysis. HRV variables were assessed to have statistically significant difference in values between PEP and non-PEP. A p-value <0.05 was considered significant. Factors with a p value <0.06 according to Fisher's exact test were included in a multivariate (logistic regression) analysis. Regression analysis was performed to assess the association of LF/HF with PEP, adjusting for age, sex, presence of SOD. Goodness-of-fit for the final multivariate model was assessed by the 2-log likelihood criterion. The performance of LF/HF for predicting post-operative outcomes was further analyzed using receiver operating characteristics (ROC) and the area under the curve (AUC) was calculated.

Results

During the fifteen month study period a total of 134 patients had ERCP, of which 115 patients were

included in the study. 2 patients were excluded due to a history of type I diabetes >5 years, 3 were excluded due to a history of type II diabetes >5 years, 5 patients were excluded due to cardiac morbidity, and 9 patients did not undergo HRV analysis due to unavailability of the measuring device. 109 patients had therapeutic ERCP. Choledocholithiasis was the main indication for therapeutic ERCP. Therapeutic procedures mostly included removal of common bile duct (CBD) stones. Diagnostic ERCP including brush cytology was performed in 6 patients.

PEP occurred in 12 patients (10.4%) being of mild severity in 7 (6.08%) patients and moderate severity in 5 (4.35%) patients. There were no severe forms of PEP or deaths in this series. Clinical characteristics of the patients are demonstrated in Table 1. Females were more likely to suffer PEP when compared to males (2 (4%) vs. 10 (15.4%), p=0.048). Patients aged <60yr and patients with a history of previous acute pancreatitis had a higher incidence of PEP (27.3% vs 5.9% and 27.3% vs 8.7% respectively) although this was not significant (p value = 0.055).

The distribution of LF, HF, and LF/HF is demonstrated in Table 2. The median postprocedural LF/HF measure was significantly higher in patients who had PEP than in those who did not (median LF/HF 2.58 vs. 2.10,

Table 1. — **Case mix and post-ERCP pancreatitis event**

		Total cohort (n= 115)	PEP (%)	P value*
Sex	Male	50	2 (4%)	0.048
	Female	65	10 (15.4%)	
Age	<60 yr old	47	8 (17%)	0.055
	>60 yr old	68	4 (5.9%)	
Prior AP	Present	11	3 (27.3%)	0.055
	Absent	104	9 (8.7%)	
Elevated bilirubin	Present	99	12 (12.1%)	0.141
	Absent	16	0	
Suspected SOD	Present	12	3 (25%)	0.081
	Absent	103	9 (8.7%)	
BMI<30kg/m2	Present	26	4 (15.4%)	0.348
	Absent	89	8 (9%)	

The likelihood of PEP was significantly higher in females (p=0.048). PEP was also more likely in the presence of SOD, Prior AP, and in those <60yr old, although this was not significant. *Analyses were determined using Fisher's Exact Test. AP – Acute Pancreatitis, SOD – Sphincter of Oddi Dysfunction, BMI – Body Mass Index.

Table 2. — **Clinical details and HRV analysis in post-ERCP patients**

	Patient characteristic	Patient number N=	LF/HF median, interquartile range	P value	LF median, interquartile range	P value	HF median, interquartile range	P value
Sex	Male	50	2.1300; 1.80 – 2.47	0.685	904; 373.75 - 1779.50	0.821	516; 183.75-845.75	0.993
	Female	65	2.1700; 1.86 – 2.39		995; 412.00-1732.00		387; 195.50-833.00	
Age	<60 yr old	47	2.2500; 1.82-2.50	0.304	1745; 1128.00-2094.00	p<0.001	843; 584.00-962.00	p<0.001
	>60 yr old	68	2.1250; 1.85-2.31		462; 334.5-968.85		218; 165.00-493.00	
Prior AP	Present	11	2.5000; 1.88-2.84	0.248	457; 286.00-1541.00	0.112	176; 112.00-698.00	0.054
	Absent	104	2.1600; 1.84-2.35		1022; 410.50-1804.50		533; 202.50-843.50	
Elevated bilirubin	Present	99	2.1700; 1.84-2.55	0.077	995; 405.00-1745.00	0.518	532; 189.00-843.00	0.728
	Absent	16	1.9550; 1.85-2.18		512; 376.50-1593.75		291; 204.50-768.25	
PEP	Present	12	2.5800; 2.45-2.84	p<0.001	1261; 315.75-2006.75	0.96	455; 117.00-729.50	0.382
	Absent	103	2.1000; 1.82-2.3		878; 405.00-1729.00		498; 198.00-843.00	
BMI<30kg/m2	Present	26	2.2800; 1.83-2.57	0.156	1002; 438-1604	0.883	532; 198.00-825.75	0.676
	Absent	89	2.1200; 1.84-2,34		931; 390.50-1756.00		371; 191.00-855.00	
Suspected SOD	Present	12	2.0350; 1.72-2,74	0.791	935; 301.25-1588.25	0.564	351; 182.00-827	0.684
	Absent	103	2.1600; 1.85-2.42		931; 405.00-1767.00		532; 193.00-843.00	

Patient characteristics by LF, HF, LF/HF reveal significant differences in LF/HF levels in patients that had PEP (p<0.001) when analyzed using Mann-Whitney U test.

p<0.001) (Table 2). The median LF/HF was also higher in patients with hyperbilirubinaemia although this was not statistically significant (2.17 vs. 1.95, p=0.077). The median levels of LF and HF were significantly higher in those <60 years old (median LF 1745 vs 462, p<0.001; median HF 843 vs 218, p<0.001). There was no difference in LF or HF with regards any other patient characteristic.

In a logistic regression model using PEP as the outcome and LF/HF as a covariate, adjusting for additional risk factors of age, sex and history of prior AP was explored (Table 3). This had no effect on reducing the statistical significance of LF/HF as a predictor of PEP. LF/HF remained a highly significant predictor of PEP (p<0.001), with an odds ratio of 14.882 (95% CI 2.863-77.366). There was no evidence of multicollinearity issues or lack of fit. The Hosmer-Lemeshow goodness of fit test was not significant at the 0.05 significance level and the C-statistic was 0.850 (Table 3). It should, however, be borne in mind that the sample size here is generally considered too small for a multivariate analysis.

All patients who experienced PEP had LF/HF >2.3. None of the patients who experienced PEP had a LF/HF ratio that was either normal or <2.3. Although, it has to be noted that patients who were event free had a LF/HF ranging in a wide amplitude between 1.20-3.40.

The optimal cut-off point for prediction of PEP was examined using ROC curve analysis (Figure 1).

The ROCs of 4h LF/HF level after the ERCP showed good test performance. A post procedural LF/HF ratio of 2.43 had the best combined sensitivity (83.3 %) and specificity (81.6 %), with an AUC of 0.827 (SE 0.045, 95 % CI; 0.739-0.915, p<0.001), a positive predictive value (PPV) of 42%, and a negative predictive value (PPN) of 97% (Figure 1).

Discussion

The prediction and early identification of PEP is challenging. Patient physiological characteristics and co-morbidities, procedural features, and post-procedural factors are all influential in the pathogenesis of PEP, however there is no ideal method of identifying those that will develop PEP. Current blood tests, such as amylase and lipase levels are inconsistent and do not aid sufficiently in clinical decision-making on whether patients can be safely discharged on the day of procedure.

This was the first prospective study to have demonstrated a correlation between post-procedural HRV frequency domain measurement (LF/HF) and incidence of PEP. The results of this pilot study suggest that it is possible to identify patients at high risk of PEP through HRV analysis where the LF/HF ratio is found to exceed 2.43, with an AUC of 0.827 and combined sensitivity of 83.3 % and specificity of 81.6 % (PPV 42%, NPV 97%).

This suggests that the LF/HF ratio is a good predictor of PEP irrespective of clinical risk factors.

From this study LF/HF cannot be considered completely discriminatory, as there were several cases when LF/HF was raised in the absence of PEP, due to other reasons (including transient abdominal pain). In reverse, patients with a 'normal' LF/HF have an extremely low chance of PEP. Thus, although several limitations this study demonstrates that a high LF/HF ratio is a predictor of PEP. However, of greater importance, a low LF/HF is highly indicative of an uneventful post-procedural period.

The lack of cases of severe PEP in the studied population have not allowed investigation of the ability of HRV to stratify severities of PEP which is something that could be looked at in the future research. As

Table 3. — **Logistic regression model of LF/HF and PEP correcting for age, sex, and prior AP.**

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
							Lower	Upper
Age(1)	1.322	.750	3.103	1	.078	3.749	.862	16.313
Sex(1)	1.671	.880	3.605	1	.058	5.318	.947	29.852
Step 1[a] PriorAP(1)	1.287	.872	2.181	1	.140	3.622	.656	19.990
LF_HF	2.700	.841	10.307	1	.001	14.882	2.863	77.366
Constant	-10.672	2.528	17.825	1	.000	.000		

a. Variable(s) entered on step 1: Age, Sex, prior AP, LF_HF.

Log-Likelihood =54.076
Hosmer and Lemeshow Test

Step	Chi-square	df	Sig.
1	3.359	7	.850

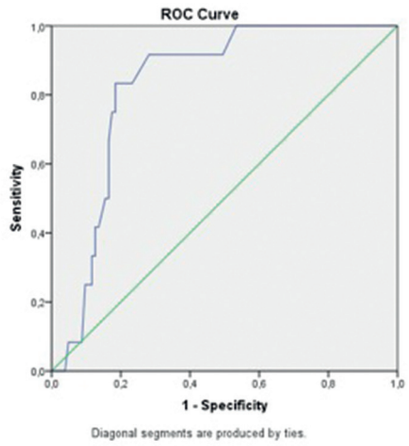

Figure 1 — ROC curve: LF/HF and PEP. 0,827 (SE 0.045, 95 % CI; 0.739-0.915, p<0.001). Test Result Variable: LF/HF

timely and accurate evaluation of severity is of major importance, it would be prudent to assess discriminative ability of HRV for different severities of PEP.

The measurement of HRV is cheap and widely available, and could be easily incorporated with other clinical parameters to generate a new prognostic model of PEP. There was no statistically significant difference between LF and HF between PEP and non-PEP group. This observation demonstrates that the shift towards the dominance of sympathetic or parasympathetic input into autonomic activity cannot be estimated by measurement of LF increases or HF decreases in isolation.

As this is a pilot study it was not possible to carry out a power calculation, but based on these results a power calculations using a cut-off of 2.43 and a pancreatitis rate of 10% a validation study of this kind would require to recruit at least 2000 patients to achieve precision of 0.05 with 95% confidence level, requiring at least a multicenter if not a national study-which may be a limitation. In the study, only the presence or absence of PEP was recorded, based on Cottons' definition criteria, with such vagueness of the end-point potentially providing another limitation. However, as adoption of Cotton's criteria for the recognition of PEP has been practiced among many research studies and remains to be the end-point for future research, it has therefore been decided to be acceptable to use as an end-point in this study.

Another limitation is the large exclusion criteria for the study which includes cardiac arrhythmia, use of a cardiac pacemaker and use of drugs that have the potential to alter HRV. This may limit the applicability of HRV to a broader spectrum of patients. However as cardiac arrhythmias, cardiac pacing, and techniques of general anesthesia were not common in the studied cohort none of the patients were excluded from our study for this reason. At the same time performing ERCP on patients with severe cardiac comorbidity would under normal conditions be an indication for an inpatient admission regardless of HRV analysis.

Drugs that were routinely used in the studied cohort of patients (fentanyl, midazolam, buscopan, lidocaine and diclofenac) were unlikely to provide meaningful source of bias by altering HRV measures as none of them were reported to have sympathetic activation effect (35-37)

Nevertheless, before the results are validated on the population with different routine sedation and anaesthetic techniques, they may not be directly applicable and transferable to other ERCP populations.

Another limitation is that the study did not take into account and take record of administration of post-procedural analgesia. Clearly, the effect of various analgesic agents (most importantly opiod analgesia) on HRV modulation should be studied in future.

This might be a small limitation of the results if the PEP-prophylaxis strategy exercised in the study does not represent strategy of other institutions - assuming NSAIDS or pancreatic stents may influence frequency of PEP occurrence but have no effect on HRV modulation.

At present, there is no consensus or local hospital protocol in Ukraine on prophylaxis and management of post-ERCP pancreatitis. The official statement of the ESGE is currently being used to guide clinician in managing PEP[13]. Placement of a 5-Fr prophylactic pancreatic stent in high risk patients is routinely performed at Kiev's region but this practise varies between institutions depending on the availability of the stent locally. None of the patients in the studied cohort were subjected to prophylactic pancreatic stent. Regardless risk of PEP, all patients received diclofenac only (administered per rectum) post-procedural. Sublingual administration of glyceryl trinitrate was not a routine practise of PEP's prophylaxis at Kiev Regional Hospital.

This study is the first to explore the role of HRV in PEP patients. It opens a window for future research in the area of PEP's prognosis. Investigation of the predictive quality of time domain methods of HRV, measurement of time and frequency domain methods during various time periods after ERCP, and application of long-term measurements (4 h and above) could be considered in future studies. If reproduced and further investigated, these findings could alter currently applied post-ERCP discharge strategies, hence enhancing the cost-effectiveness of ERCP interventions for diagnostic and therapeutic means.

In conclusion, despite the limitations described above, results from the study suggest that patients diagnosed with PEP in accordance with Cotton criteria had sympathetic activation 4 h after ERCP, identified by HRV analysis. It was confirmed that a single short-term measurement of frequency domain HRV parameter (LF/HF ratio) within 4 hours after ERCP may predict PEP, and more importantly identify those that are very unlikely to suffer PEP. Further validation in prospective studies is warranted, however incorporating LF/HF

into known prognostic scales might give rise to a better outcome predictor for patients with suspected PEP.

Disclosures

Authors have nothing to disclose.

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