

# Psychological traits influence autonomic nervous system recovery following esophageal intubation in health and functional chest pain

A. D. FARMER, \* S. J. COEN, \* † M. KANO, \* † ‡ S. F. WORTHEN, § H. E. ROSSITER, § H. NAVQI, \* S. M. SCOTT, \* P. L. FURLONG § & Q. AZIZ \*

\*Centre for Digestive Diseases, Blizard Institute of Cell & Molecular Science, Wingate Institute of Neurogastroenterology, Barts and the London School of Medicine & Dentistry, Queen Mary University of London, London, UK

†Department of Neuroimaging, Institute of Psychiatry, King's College London, London, UK

‡Behavioural Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan

§Aston Brain Centre, School of Life and Health Sciences, Aston University, Birmingham, UK

## Key Messages

- Esophageal intubation is widely utilized but activates a complex physiological response.
- Herein, we compared a number of validated sympathetic and parasympathetic nervous system parameters in healthy subjects and patients with functional chest pain.
- Oesophageal intubation activates a fight or flight response.
- In future, at least 10 min allowed for the autonomic nervous system to recovery prior to measurements being made.

## Abstract

**Background** Esophageal intubation is a widely utilized technique for a diverse array of physiological studies, activating a complex physiological response mediated, in part, by the autonomic nervous system (ANS). In order to determine the optimal time period after intubation when physiological observations should be recorded, it is important to know the duration of, and factors that influence, this ANS response, in both health and disease. **Methods** Fifty healthy subjects (27 males, median age 31.9 years, range 20–53 years) and 20 patients with Rome III define functional chest pain (nine male, median age of 38.7 years, range

28–59 years) had personality traits and anxiety measured. Subjects had heart rate (HR), blood pressure (BP), sympathetic (cardiac sympathetic index, CSI), and parasympathetic nervous system (cardiac vagal tone, CVT) parameters measured at baseline and in response to per nasum intubation with an esophageal catheter. CSI/CVT recovery was measured following esophageal intubation. **Key Results** In all subjects, esophageal intubation caused an elevation in HR, BP, CSI, and skin conductance response (SCR; all  $p < 0.0001$ ) but concomitant CVT and cardiac sensitivity to the baroreflex (CSB) withdrawal (all  $p < 0.04$ ). Multiple linear regression analysis demonstrated that longer CVT recovery times were independently associated with higher neuroticism ( $p < 0.001$ ). Patients had prolonged CSI and CVT recovery times in comparison to healthy subjects (112.5 s vs 46.5 s,  $p = 0.0001$  and 549 s vs 223.5 s,  $p = 0.0001$ , respectively). **Conclusions** **Implications** Esophageal intubation activates a flight/flight ANS response. Future studies should allow for at least 10 min of recovery time. Consideration should be given to psychological traits and disease status as these can influence recovery.

## Address for Correspondence

Professor Qasim Aziz, PhD, FRCP, The Wingate Institute of Neurogastroenterology, Barts and the London School of Medicine and Dentistry, 26 Ashfield Street, Whitechapel, London E1 2AJ, UK.

Tel: +44 (0)20 7882 2630; fax: +44 (0)20 7882 5640;

e-mail: a.farmer@qmul.ac.uk

Received: 26 June 2013

Accepted for publication: 13 August 2013

**Keywords** anxiety, autonomic nervous system, esophageal intubation, functional chest pain, neuroticism.

## INTRODUCTION

Abnormalities in esophageal sensorimotor function are common, exerting a worldwide burden.<sup>1</sup> These abnormalities may occur in both patients with proven organic disease and also those without obvious structural or biochemical abnormality such as in the functional gastrointestinal disorders (FGID). The underlying pathophysiology of FGID is incompletely understood. Visceral hypersensitivity has been variably demonstrated across a number of FGID, such as functional chest pain<sup>2-4</sup> which is characterized by recurrent unexplained midline chest pain.<sup>5</sup>

Methods used for measuring esophageal sensorimotor function face a number of cardinal limitations. Esophageal function may be influenced by a diverse array of factors including psychological factors and activation of the stress-responsive systems such as the autonomic nervous system (ANS).<sup>6</sup> Moreover, such limitations are compounded by the test technique itself, which invariably involves the *per nasum* or *per oral* introduction of a catheter, of one kind or another, with subsequent esophageal intubation. This process in itself activates a complex stress response, largely mediated by the ANS. Furthermore, many subjects find this process very traumatic and indeed a proportion cannot tolerate this. Hitherto however, the detailed interrogation of this ANS-mediated stress response to esophageal intubation has been hampered by a lack of temporal resolution in many of the surrogate markers of ANS tone, such as those conveyed by power spectral analysis of heart rate variability. This paucity of temporal resolution is further compounded in the literature by significant controversy on the specific interpretation of many proxy measures of ANS tone.<sup>7</sup> Nevertheless, recent advances in autonomic neuroscience technology has led to considerable improvements, this temporal resolution such that validated beat-to-beat parameters of autonomic tone can now be measured.<sup>8</sup> Using these novel measures, Paine *et al.* sought to further define the ANS response to intubation, in a small preliminary group of healthy subjects, broadly demonstrating that sympathetic nervous system (SNS) activation and parasympathetic nervous system (PNS) withdrawal over a total time epoch of 180 s, although this study did not evaluate baseline recovery.<sup>9</sup>

Given that such techniques are so widely used across the study of esophageal sensorimotor function, particularly with the recent observation that auto-

nomous tone may also influence visceral and somatic pain sensitivity in health, a greater understanding of this stress response, and their recovery to baseline using prolonged recordings, is warranted in both health and disease.<sup>10</sup> It is these knowledge gaps that our study aimed to identify the factors that influence this stress response in healthy subjects and patients with functional chest pain. We therefore hypothesized that esophageal intubation activates a fight or flight autonomic response and recovery to baseline maybe different in health and disease.

## MATERIALS AND METHODS

### Subjects

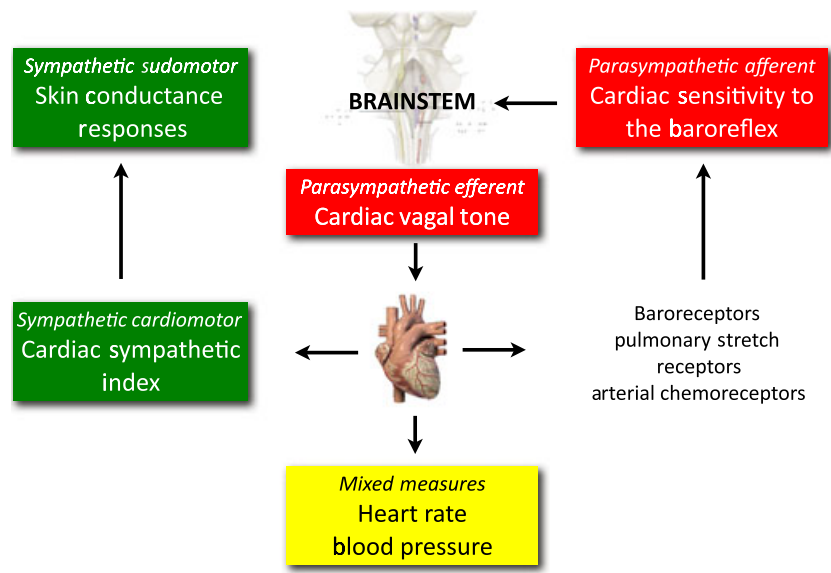
Twenty functional chest pain patients, defined according to the Rome III criteria, and 50 healthy subjects took part in the study.<sup>5</sup> Patients were identified from the gastrointestinal physiology database at the Royal London Hospital and healthy subjects were recruited from the residents of the surrounding geographical area. Within 12 months of the study, all patients had a negative cardiac evaluation (either a negative exercise tolerance test or coronary angiogram) with normal esophageal motility demonstrated on high-resolution manometry, normal 24 h pH-metry and a normal esophago-gastro-duodenoscopy with normal biopsies from the mid and distal esophagus. All subjects were naïve to the experimental protocol but received written information beforehand and provided written informed consent. Females were studied in the follicular phase of their menstrual cycle. Subjects were excluded if they were taking any analgesics, centrally acting medications or those influencing autonomic responses. Current smokers were asked not to smoke for 24 h before the study. Subjects were asked to refrain from alcohol consumption for 24 h prior to the study. All subjects were screened for sub-clinical anxiety and depression using the validated Hospital Anxiety and Depression Scale and healthy subjects were excluded if their scores exceeded 7 on either scale.<sup>11</sup> All subjects were screened for co-morbid chronic pain disorders. As several measures in the study were questionnaire based, those who exceeded a self-deception score, as assessed by the Weinberger Adjustment Inventory, were excluded from the analysis thus ensuring response integrity.<sup>12</sup> These studies were approved by the East London and the City Ethics Committee 2 (Ref: 08/H0703/47, permission date February 2010). All subjects were naïve to the study protocol.

### Personality & anxiety measures

The validated Big Five Inventory (BFI) was used to measure the personality traits of neuroticism (BFI-N) and extroversion (BFI-E).<sup>9</sup> State (STAI-S) and trait (STAI-T) anxiety was assessed using the validated State-Trait Anxiety Inventory.<sup>13</sup> These specific measures were chosen based on our previous studies.<sup>9,14</sup>

### Esophageal intubation & visceral pain induction

Subjects were intubated *per nasum* with an esophageal catheter (Sandhill Scientific, Oxford, UK), without local anesthetic, so that its distal tip was positioned 34 cm *ab nares*. The catheter was



**Figure 1** A schematic summary of the autonomic measures used in this study.

secured using adhesive tape (Micropore, 3M; Healthcare, Bracknell, UK) applied to the subject's nose, upper lip, and face to minimize any displacement during the study.

## Autonomic nervous system measures

The ANS measures used in this study are summarized in Fig. 1.

**Blood pressure** Digital arterial blood pressure (BP) was measured non-invasively using the validated photoplethysmographic technique (Portapres, Amsterdam, The Netherlands).<sup>15,16</sup>

**Skin conductance responses** Skin conductance is a putative sympathetic 'emotional sudomotor' measure responsive within milliseconds to threatening stimuli.<sup>17</sup> Skin on the distal digit pulp of the right index and ring fingers was wiped with water and allowed to dry. In each subject, skin conductance electrodes were then attached and the skin conductance level was zeroed using a commercially available bioamp (Powerlab, ADInstruments, Oxford, UK). The mean skin conductance response (SCR) was extracted and analyzed off-line.

**Heart rate, cardiac vagal tone, and cardiac sensitivity to the baroreflex** Skin was firstly prepared by light exfoliation to reduce impedance and improve signal (Nuprep, DO Weaver & Co, Aurora, CO, USA) in areas for standard three-lead electrocardiogram (ECG) placement (right and left sub-clavicular and cardiac apex). Electrocardiogram electrodes (Ambu Blue Sensor P, Baltorpbakken, Denmark) were then placed in these areas. Electrocardiogram was acquired at 5 KHz using a commercially available biosignals acquisition system (Neuroscope™, Medifit Instruments, Enfield, UK). The R wave is the first upward deflection above the electrical baseline on the ECG and the part of the QRS complex that represents ventricular depolarization. The Neuroscope has an in-built R-wave detection algorithm, which features accuracy to the nearest millisecond, from which the R-R interval and heart rate are derived. The Neuroscope also measures brainstem PNS efferent activity, known as cardiac vagal tone (CVT), in real time is measured on a validated linear vagal scale (LVS), where 0 represents full atropinization.<sup>8</sup> The

Neuroscope also incorporates beat-to-beat R-R interval and mean BP into an algorithm on a 10-second cycle, calculating cardiac sensitivity to the baroreflex (CSB), an indirect measure of parasympathetic afferent activity.<sup>18</sup> These measures are described in detail elsewhere,<sup>9,10</sup> but in contrast to traditional measures, such as power spectral analysis of heart rate variability, are validated for time epochs of less than 1 min.<sup>9</sup> It is well-documented that following a stressor, vagal tone plays a major role in restoring HR to baseline values.<sup>19</sup>

**Cardiac sympathetic index** R-R interval data were extracted from the Neuroscope recordings and was hand edited removing any missed, or extra beats, as these can result in large artifacts. Following this, the R-R data were re-formatted and entered into the Cardiac Metric program for the calculation of the validated Toichi's Cardiac Sympathetic Index (CSI).<sup>20,21</sup> CSI is a ratio of R-R intervals and therefore has no units.

**Autonomic nervous system recovery times** Given that HR is a mixed measure of ANS tone, we utilized CSI and CVT as surrogate markers of SNS and PNS recovery, which was defined by the point at which it returned to baseline for at least 30 s. Autonomic parameters were recorded according to internationally agreed guidelines.<sup>22</sup>

## Protocol

All subjects were studied in the afternoon (from 1400 to 1600 h) in a quiet, temperature controlled (20–22 °C) laboratory. Subjects completed the questionnaires and were reclined at 45° on a bed. After attachment of ANS recording equipment, baseline data was acquired for 15 min. Baseline ANS data were derived from the middle 5 min of the recording. Subjects were then intubated with the esophageal catheter, allowed to rest for up to 30 min during which they had continuous ANS monitoring.

## Statistical analysis

Data distribution was analyzed using the D'Agostino–Pearson omnibus K2 normality test.<sup>23</sup> Results of quantitative data are

presented either as median with interquartile ranges (IRQ) for non-normally distributed data, or mean  $\pm$  SD and range for parametric data. For quantitative data, differences between the groups were assessed using the Student's *t*-test in case of parametric data and using the Wilcoxon matched-pairs test in case of non-parametric data. Correlational analyses were performed using Spearman's ( $r_s$ ) coefficient. Multiple linear regression analysis was used to assess the association of CSI and CVT recovery time as the dependent variable and age, gender, personality traits as the independent variables. All tests were two-tailed, and  $p < 0.05$  was adopted as the statistical criterion. Analyses were performed using proprietary software (GraphPad Prism 5, La Jolla, CA, USA and SPSS 18, IBM, New York, NY, USA).

## RESULTS

### Subjects characteristics

Twenty functional chest pain patients (nine male, median age of 38.7 years, range 28–59 years) and 50 subjects (27 males, median age 31.9 years, range 20–53 years) were recruited to the study. One patient (male, aged 28.4 years) did not complete the study, he exceeded the self-deception score. All subjects were Caucasian. All other subjects completed and tolerated the study well.

### Psychological characteristics

In healthy subjects, the mean personality scores were as follows:- BFI-N - 3.6 (IRQ 2.1–4.7), BFI-E - 3.5 (IRQ 2.5–4.9), and the anxiety scores were STAI-S - 33 (IRQ 26.5–40) and STAI-T - 37 (IRQ 30.5–45). Big Five Inventory-N correlated positively with STAI-S ( $r_s = 0.79$ ,  $p < 0.0001$ ) and STAI-T ( $r_s = 0.44$ ,  $p < 0.0001$ ) but negatively with BFI-E ( $r_s = -0.5$ ,  $p = 0.0001$ ). Patients had higher BFI-N (4.8 [IRQ 4.2–4.9] vs 3.6 [IRQ 2.1–4.7],  $p < 0.0001$ ), STAI-S (43 [IRQ 38–45] vs 33 [IRQ 26.5–40],  $p < 0.0001$ )

and STAI-T (45 [IRQ 40–47] vs 37 [IRQ 30.5–45],  $p = 0.003$ ) in comparison to controls.

### Autonomic parameters at baseline and in response to intubation

In all subjects, all autonomic parameters displayed significant changes in response to intubation. Esophageal intubation resulted in an elevation of HR, systolic blood pressure (SBP), mean blood pressure (MBP), diastolic blood pressure (DBP), CSI, and SCR with a concomitant decrease of CVT and CSB. Significant differences in baseline heart rate, CVT, and CSI between patients and controls were noted. Similarly, differences were also observed in CVT and CSI between patients and controls in response to esophageal intubation, see Table 1.

### Autonomic nervous system recovery times

The CSI median recovery time was 56 s (IRQ 36–81.5 s). The CVT median recovery time was 331 s (IRQ 170.5–544 s). Cardiac sympathetic index and CVT recovery time positively correlated ( $r_s = 0.81$ ,  $p < 0.0001$ ), see Fig. 2.

### Sympathetic nervous system recovery times

Univariate correlational analysis demonstrated significant associations with BFI-N and STAI-S ( $r_s = 0.7$ ,  $p < 0.0001$  and  $r_s = 0.68$ ,  $p < 0.0001$ , respectively). Multiple linear regression analysis was used to assess the association of CSI recovery time as the dependent variable and age, gender and the personality traits of BFI-N, BFI-E, STAI-S, and STAI-T as the independent

**Table 1** Comparison of autonomic variables at baseline and in response to esophageal intubation

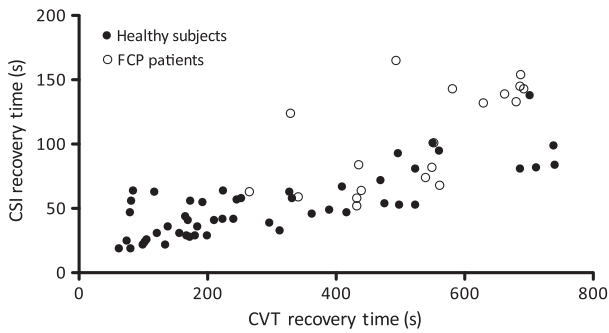
Autonomic parameters		Baseline			Intubation		
		Controls	Patients	<i>p</i> -value	Controls	Patients	<i>p</i> -value
Mixed ANS measures	HR (bpm)	68.2 $\pm$ 11.5	74.2 $\pm$ 8.3	0.04*	77.7 $\pm$ 12.3	83.4 $\pm$ 11.9	0.08
	SBP (mmHg)	125.5 $\pm$ 18.7	123.7 $\pm$ 15.3	0.7	141.7 $\pm$ 18.7	146 $\pm$ 28.2	0.46
	MBP (mmHg)	80.9 $\pm$ 15	83.4 $\pm$ 13.8	0.52	93.4 $\pm$ 17.7	100.5 $\pm$ 20.7	0.15
	DBP (mmHg)	58.7 $\pm$ 14.5	63.3 $\pm$ 14.3	0.23	69.1 $\pm$ 15.3	77.3 $\pm$ 17.7	0.06
PNS measures	CVT (LVS)	8.1 (5.7–11.3)	4.7 (3.3–6.8)	0.0002*	6.0 (4.3–7.2)	3.6 (2–4.4)	0.0008*
	CSB( $\Delta$ RR/ $\Delta$ mmHg)	6.0 (4.5–8.3)	4.2 (3.6–6.2)	0.02*	3.0 (1.8–5.6)	2.5 (1.4–4.6)	0.25
SNS measures	CSI	2 $\pm$ 0.9	2.7 $\pm$ 0.6	0.002*	2.4 $\pm$ 0.9	2.9 $\pm$ 0.5	0.02*
	SCR ( $\mu$ S)	3.1 $\pm$ 2.8	4.2 $\pm$ 1.4	0.1	13.9 $\pm$ 8.6	18.3 $\pm$ 10.8	0.07

HR, SBP, MBP, DBP, CSI, and SCR were parametrically distributed and thus data are expressed as mean  $\pm$  SD. CVT and CSB were non-parametric and therefore data are expressed as median and IRQ.

HR, heart rate; CSI, cardiac sympathetic index; SCR, skin conductance response; CVT, cardiac vagal tone; CSB, cardiac sensitivity to the baroreflex; IRQ, interquartile range; SNS, sympathetic nervous system; PNS, parasympathetic nervous system; ANS, autonomic nervous system.

\*Significant values.





**Figure 2** The correlation between cardiac sympathetic index (CSI) and cardiac vagal tone (CVT) recovery demonstrating that whilst CSI recovery times were shorter than CVT, there was a positive correlation between them – patients are denoted by circles and healthy subjects by dots ( $r = 0.81$ ,  $p < 0.0001$ ).

variables and did not demonstrate any significant independent associations.

### Parasympathetic nervous system recovery times

Univariate correlational analysis demonstrated significant associations between CVT recovery with BFI-N and STAI-S ( $r_s = 0.87$ ,  $p < 0.0001$  and  $r_s = 0.73$ ,  $p < 0.0001$ , respectively). Multiple linear regression analysis was used to assess the association of CVT recovery time as the dependent variable with age, gender and the personality traits of BFI-N, BFI-E, STAI-S, and STAI-T as the independent variables. The overall model

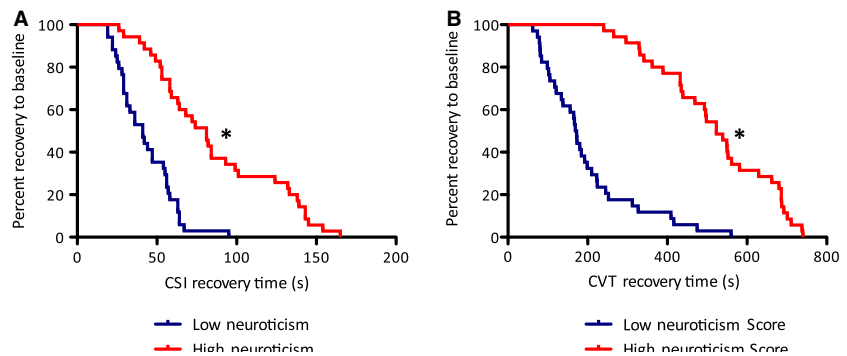
fit was  $R^2 = 0.77$ . Only BFI-N was independently associated with longer CVT recovery times following esophageal intubation ( $\beta = 133.5$ , SE 17.6,  $t = 7.6$ ,  $p = 0.0001$ , 95% confidence interval 98.3–168.7).

### Stratification of sympathetic and parasympathetic nervous system recovery times by neuroticism

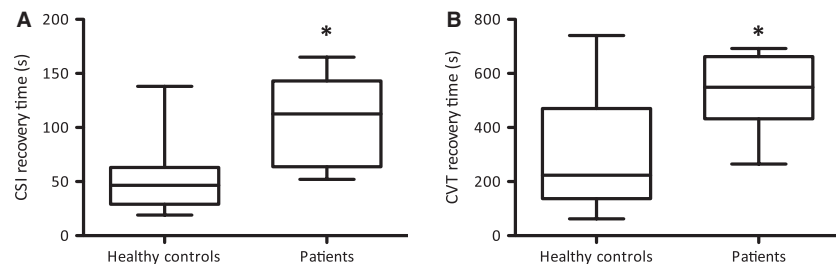
In order to dichotomize BFI-N into those with low and high scores, the raw scores were first converted into Z-scores and then into T-scores (mean 50, SD  $\pm 10$ ), a method similar to that described by Zobel *et al.* and McCleery *et al.*<sup>24,25</sup> The mean and SD for the low BFI-N group was  $40.9 \pm 3.9$  and  $58.9 \pm 4.9$  for the high BFI-N group. From this dichotomization, Kaplan–Meier curves were constructed based on CSI and CVT recovery times for each of the two groups of BFI-N, see Fig. 3. The mean CSI recovery time for the high BFI-N group was  $86.4 \pm 39.8$  s vs  $42.7 \pm 17.7$  s in the low BFI-N group ( $p < 0.0001$ ). The mean CVT recovery time for the high BFI-N group was  $521.1 \pm 145.3$  s vs  $196.1 \pm 120.6$  s in the low BFI-N group ( $p < 0.0001$ ).

### Stratification of sympathetic and parasympathetic nervous system recovery times by health or disease status

Cardiac sympathetic index and CVT recovery were stratified according to health ( $n = 50$ ) or functional



**Figure 3** Kaplan–Meier curves illustrating the proportion of cardiac sympathetic index (CSI) recovery (A) and cardiac vagal tone (CVT) recovery (B) in high and low neuroticism groups. Log rank (Mantel–Cox) tests for CSI ( $\chi^2 31.6$ , df 1) and CVT ( $\chi^2 55$ , df 1) demonstrated statistical significance at  $p < 0.0001$  (\*).



**Figure 4** Box & Whiskers plots (error bars indicating minimum and maximum values) of cardiac sympathetic index (A) and cardiac vagal tone (B) recovery times. \* $p < 0.0001$ .

chest pain ( $n = 19$ ) with results shown in Fig. 4. The median CSI recovery time for healthy subjects was 46.5 s (IRQ 29–63) vs 112.5 s (IRQ 63.7–165) for patients,  $p = 0.0001$ . The median CVT recovery time for healthy subjects was 223.5 s (IRQ 137–470.5) vs 549 s (IRQ 432–662) for patients,  $p = 0.0001$ .

## DISCUSSION

In this study, we have demonstrated that esophageal intubation induces SNS activation and PNS withdrawal. The recovery of PNS tone to baseline was preceded by that of the SNS tone. Interestingly, in the univariate analysis both SNS and PNS recovery times were positively correlated with neuroticism and state anxiety scores. In the multiple linear regression analysis, longer PNS tone recovery times were independently associated with neuroticism scores. Furthermore, when dichotomizing according to personality traits and disease status, our data also suggest important differences in SNS and PNS recovery.

The ANS is a hierarchically controlled, bidirectional, body–brain interface that integrates afferent bodily inputs and central motor outputs for homeostatic and emotional processes. The pattern of ANS response we observed to esophageal intubation was, in part, what might be reasonably expected in a typical ‘fight-flight’ defense response. Nevertheless, it is striking to note that PNS withdrawal significantly outlasted the SNS activation. This prolonged PNS withdrawal could represent what Thayer and Friedman term cardiac ‘disinhibition’ related to the ‘threat appraisal’.<sup>26</sup> The widely held belief among cognitive neuroscientists is that the default response to any threat, in this case esophageal intubation, is activation of sympatho-excitatory circuits in preparation for action. This activation is likely to be related to the phenomenon of ‘negativity bias’ such that negative/threatening information being processed is more likely to display a degree of preponderance over the positive.<sup>27,28</sup> Taken from the evolutionary/survival outlook, this represents an adaptive response that ‘errs’ on the side of caution. However, the continued chronic perception of threat is considered to be maladaptive, as it is associated with dysregulation endocrine and autonomic output, in addition to cognitive decline.<sup>29,30</sup> Thus, in response to, as the subject’s perception of threat decreases after intubation has taken place, presumably due to the very nature of the study, reflected in earlier normalization of sympatho-excitatory influences before those PNS influences.<sup>31</sup>

Nevertheless, this does not adequately explain the causal factors of the prolongation of the recovery of

PNS tone to baseline. Until recently, it had been the generally accepted opinion that visceral pain was largely mediated by spinal afferents, with the primary function of vagal afferents being the transmission of interoceptive information from the periphery to central structures. However, three emerging strands of pre-clinical and clinical evidence have postulated as to the role of the vagus nerve in modulating nociception, particularly from the viscera. Firstly, electrical physiological studies have demonstrated that electrical or chemical stimulation of vagus nerve can activate spinothalamic tract neurons.<sup>32</sup> Secondly, in animal models, Chen *et al.* demonstrated that topical application of local anesthetic to sub-diaphragmatic vagal afferents increased pain thresholds<sup>33</sup> and more recently Furuta *et al.* observed that following vagotomy colonic pain thresholds were decreased.<sup>34</sup> Thirdly, a recent small open-label Phase I/II trial of vagus nerve stimulation in patients with fibromyalgia reported improvements in pain measures.<sup>35</sup> By amalgamating these strands of evidence, it is possible to conjecture that the prolonged recovery of CVT that we observed in this study was in fact a compensatory antinociceptive response to esophageal intubation. As it is reasonably well-established that those subjects who have higher neuroticism and anxiety scores demonstrate heightened pain sensitivity,<sup>10,36</sup> it is possible to speculate that the higher neuroticism and anxiety subjects had a prolonged antinociceptive CVT response due to heightened pain sensitivity in this group *ab initio*.

Esophageal intubation is widely utilized in experimental and clinical studies across a diverse array of disciplines. These techniques have become increasingly refined with the passage of time from simple manometry and balloon inflation, to the barostat to multimodal techniques combined with high-resolution imaging. Whilst there is little doubt that this considerable body of work has added significantly to our knowledge of esophageal physiology and sensorimotor mechanisms in health and disease, the very act of intubation remains a fundamental physiological limitation and arguably a barrier to large-scale recruitment to studies. To date, to the best of our knowledge, there is an absence of agreement regarding the time that should be left between intubation and commencement of any intervention or measurement. Thus, it should not come as any surprise that within the present literature, there is considerable variation and therefore could be a source of potential confounder affecting many areas of interest including, but not limited to, GI tract physiological, visceral pain, and functional neuroimaging studies. A considerable proportion of studies do not report the length of time

between intubation and the application of a stimulus.<sup>37–40</sup> However, a number of studies, however, report a rest period of between 0 and 15 min<sup>36,41,42</sup> yet others a period greater than 15 min.<sup>43,44</sup> Thus given this degree of difference, standardization is warranted, particularly when considering balloon distension studies. This consideration has particular salience in functional chest pain as esophageal hypersensitivity to balloon distension, first described in 1986 by Richter *et al.* and subsequently confirmed by others, is considered to be a pathophysiological feature in this disorder.<sup>2,45</sup> However, this hypersensitivity has insufficient specificity and sensitivity for routine diagnostic use in clinical practice which maybe due to the lack of the aforementioned standardization.<sup>2,45,46</sup> Moreover, as a wider implication, given the resources and cost required for conducting research studies, particularly with respect to functional neuroimaging, the ability to delineate and stratify recovery times following esophageal intubation presents a number of advantages. For example, these include the potential for increasing throughput of participants by not waiting for excessive periods following intubation but not at the expense of introducing confounders by not leaving enough time. Based on the data presented herein, the measurement of personality traits, through the use of validated questionnaires, may allow an individualized approach to subjects, in health and disease, when considering recovery times in paradigm design and in standard operating procedures for esophageal manometry.

Thus, our results may have important ramifications in the routine clinical practice of esophageal manometry. It has recently been demonstrated that peristaltic dysfunction within the esophagus may be associated with vagal hyper-reactivity<sup>47</sup> yet, to date, neither the American Neurogastroenterology and Motility Society, the European Society of Neurogastroenterology and Motility<sup>48</sup> nor the American Gastroenterological Association<sup>49</sup> have made recommendations regarding the rest periods following intubation. It is also likely that the British Society of Gastroenterology's guidelines of a 5–10 min rest period before measurements are taken may be insufficient for some individuals, particularly those who have heightened anxiety or neuroticism.<sup>50</sup> Furthermore, it is likely that thought should be given to the type, and indeed caliber, of esophageal catheter that measurements are taken with. For instance, given the increasingly widespread adoption of high-resolution esophageal pressure topography, differences in catheter design may also influence ANS recovery.

This study is not without its limitations. Whilst the number of subjects we studied is reasonably large for

this type of study, whether such results are applicable to larger cohorts of healthy subjects and other FGID remains to be seen. In addition, we acknowledge that some of the differences we have observed in ANS recovery could be due to purely psychological differences between healthy subjects and patients with functional chest pain, given its defining feature is chronic visceral pain, it is possible that there are important neurobiological differences in autonomic reactivity, and thus recovery, in response to stress.<sup>51</sup> We also readily acknowledge that we have not studied every single personality and anxiety factors that may influence ANS response to intubation, for instance measures such as depression or coping, we adopted a pragmatic approach examining those which are amongst the most widely studied by other groups. Whether these results are also applicable to the *per oral* route of esophageal intubation is uncertain, although it is likely that the *per nasum* route activates a similar heightened stress response. Finally, we have not stratified groups according to previous experience of esophageal intubation. In this study, all patients had previously undergone esophageal intubation at esophageal manometry yet this previous experience was variable amongst healthy subjects and therefore could potentially have contributed to the elevated STAI-S seen in the former. Nevertheless, STAI-S was not independently associated with prolonged ANS recovery times in the multiple linear regression analysis. In addition, whether the measurement of cardiotropically derived autonomic parameters accurately reflects gut-specific autonomic tone remains an area of considerable controversy within the field and, in our opinion, to date remains a central unanswered question.

In conclusion, esophageal intubation activates a complex ANS response whose recovery is influenced by personality traits and disease status. In future research and clinical studies, these differences should be controlled for when defining rest periods during protocol design. Whether such differences are applicable to wider patients groups, such as those with a FGID other than functional chest pain, is uncertain and warrants further investigation. As an overall recommendation, based on these data, we would suggest a rest period of 10 min between esophageal intubation and the acquisition of data.

## ACKNOWLEDGMENTS

This research/ADF was funded by a Medical Research Council project grant. Medical Research Council grant number – MGAB1A1R.

## FUNDING

Medical Research Council grant number – MGAB1A1R.

## CONFLICTS OF INTEREST

No conflicts of interest

## REFERENCES

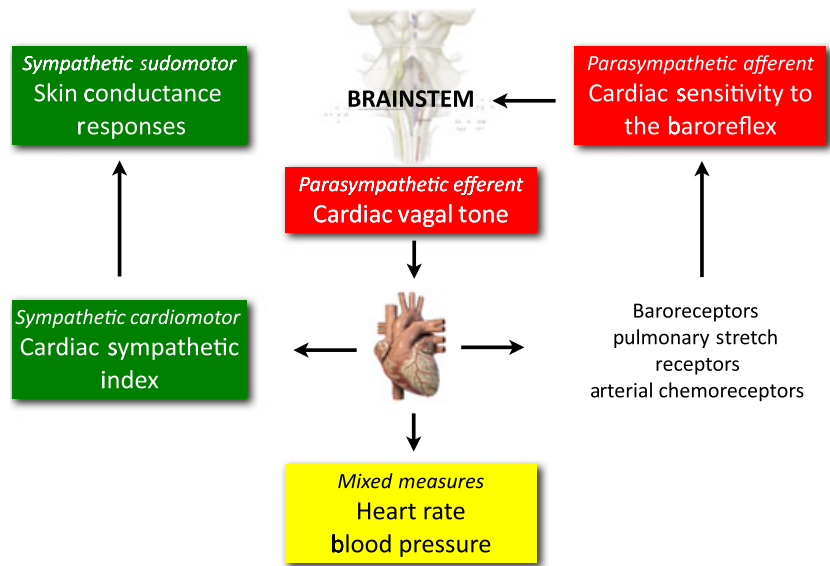
- 1 Giamberardino MA. *Visceral Pain: Clinical, Pathophysiological and Therapeutic Aspects*. Oxford: Oxford University Press, 2009.
- 2 Rao SS, Gregersen H, Hayek B, Summers RW, Christensen J. Unexplained chest pain: the hypersensitive, hyper-reactive, and poorly compliant esophagus. *Ann Intern Med* 1996; **124**: 950–8.
- 3 Wingate DL. The irritable bowel syndrome. *Gastroenterol Clin North Am* 1991; **20**: 351–62.
- 4 Bouin M, Plourde V, Boivin M *et al.* Rectal distention testing in patients with irritable bowel syndrome: sensitivity, specificity, and predictive values of pain sensory thresholds. *Gastroenterology* 2002; **122**: 1771–7.
- 5 Drossman DA. *Rome III: The Functional Gastrointestinal Disorders*, 3rd edn. McLean, VA: Degnon Associates, 2006.
- 6 Farmer AD, Aziz Q. Visceral pain hypersensitivity in functional gastrointestinal disorders. *Br Med Bull* 2009; **91**: 123–36.
- 7 Reyes del Paso GA, Langewitz W, Mulder LJ, van Roon A, Duschek S. The utility of low frequency heart rate variability as an index of sympathetic cardiac tone: a review with emphasis on a reanalysis of previous studies. *Psychophysiology* 2013; **50**: 477–87.
- 8 Julu PO. A linear scale for measuring vagal tone in man. *J Auton Pharmacol* 1992; **12**: 109–15.
- 9 Paine P, Kishor J, Worthen SF, Gregory LJ, Aziz Q. Exploring relationships for visceral and somatic pain with autonomic control and personality. *Pain* 2009; **144**: 236–44.
- 10 Farmer AD, Coen SJ, Kano M *et al.* Psychophysiological responses to pain identify reproducible human clusters. *Pain* 2013; doi: 10.1016/j.pain.2013.05.016.
- 11 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; **67**: 361–70.
- 12 Weinberger DA, Schwartz GE, Davidson RJ. Low-anxious, high-anxious, and repressive coping styles: psychometric patterns and behavioral and physiological responses to stress. *J Abnorm Psychol* 1979; **88**: 369–80.
- 13 Spielberger CD. *Manual for the State/Trait Anxiety Inventory (Form Y): (Self Evaluation Questionnaire)*. Palo Alto: Consulting Psychologists Press, 1983.
- 14 Paine P, Worthen SF, Gregory LJ, Thompson DG, Aziz Q. Personality differences affect brainstem autonomic responses to visceral pain. *Neurogastroenterol Motil* 2009; **21**: 1155–e98.
- 15 Benarroch EE, Opfer-Gehrking TL, Low PA. Use of the photoplethysmographic technique to analyze the Valsalva maneuver in normal man. *Muscle Nerve* 1991; **14**: 1165–72.
- 16 Eckert S, Horstkotte D. Comparison of Portapres non-invasive blood pressure measurement in the finger with intra-aortic pressure measurement during incremental bicycle exercise. *Blood Press Monit* 2002; **7**: 179–83.
- 17 Cacioppo JT, Tassinary LG, Bertson GG. *Handbook of Psychophysiology*, 3rd edn. Cambridge: Cambridge University Press, 2007.
- 18 Julu PO, Cooper VL, Hansen S, Hainsworth R. Cardiovascular regulation in the period preceding vasovagal syncope in conscious humans. *J Physiol* 2003; **549**: 299–311.
- 19 Goldberger JJ, Le FK, Lahiri M, Kannankeril PJ, Ng J, Kadish AH. Assessment of parasympathetic reactivation after exercise. *Am J Physiol Heart Circ Physiol* 2006; **290**: H2446–52.
- 20 Cook EW 3rd, Miller GA. Digital filtering: background and tutorial for psychophysicists. *Psychophysiology* 1992; **29**: 350–67.
- 21 Toichi M, Sugiura T, Murai T, Sengoku A. A new method of assessing cardiac autonomic function and its comparison with spectral analysis and coefficient of variation of R-R interval. *J Auton Nerv Syst* 1997; **62**: 79–84.
- 22 Heart rate variability standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation* 1996; **93**: 1043–65.
- 23 D'Agostino RB, Stephens MA. *Goodness-of-fit Techniques*. New York: M. Dekker, 1986.
- 24 Zobel A, Barkow K, Schulze-Rauschenbach S *et al.* High neuroticism and depressive temperament are associated with dysfunctional regulation of the hypothalamic-pituitary-adrenocortical system in healthy volunteers. *Acta Psychiatr Scand* 2004; **109**: 392–9.
- 25 McCleery JM, Goodwin GM. High and low neuroticism predict different cortisol responses to the combined dexamethasone–CRH test. *Biol Psychiatry* 2001; **49**: 410–5.
- 26 Thayer JF, Friedman BH. Stop that! Inhibition, sensitization, and their neurovisceral concomitants. *Scand J Psychol* 2002; **43**: 123–30.
- 27 Cacioppo JT, Gardner WL. Emotion. *Annu Rev Psychol* 1999; **50**: 191–214.
- 28 Herry C, Bach DR, Esposito F *et al.* Processing of temporal unpredictability in human and animal amygdala. *J Neurosci* 2007; **27**: 5958–66.
- 29 McEwen BS, Sapolsky RM. Stress and cognitive function. *Curr Opin Neurobiol* 1995; **5**: 205–16.
- 30 Seeman TE, Crimmins E. Social environment effects on health and aging: integrating epidemiologic and demographic approaches and perspectives. *Ann N Y Acad Sci* 2001; **954**: 88–117.
- 31 Thayer JF, Sternberg E. Beyond heart rate variability: vagal regulation of allostatic systems. *Ann N Y Acad Sci* 2006; **1088**: 361–72.
- 32 Chandler MJ, Zhang J, Foreman RD. Vagal, sympathetic and somatic sensory inputs to upper cervical (C1–C3) spinothalamic tract neurons in monkeys. *J Neurophysiol* 1996; **76**: 2555–67.
- 33 Chen SL, Wu XY, Cao ZJ *et al.* Subdiaphragmatic vagal afferent nerves modulate visceral pain. *Am J Physiol Gastrointest Liver Physiol* 2008; **294**: G1441–9.
- 34 Furuta S, Matsumoto K, Horie S, Suzuki T, Narita M. Subdiaphragmatic vagotomy induces a functional change in visceral Adelta primary afferent fibers in rats. *Synapse* 2012; **66**: 369–71.
- 35 Lange G, Janal MN, Maniker A *et al.* Safety and efficacy of vagus nerve stimulation in fibromyalgia: a phase I/II proof of concept trial. *Pain Med* 2011; **12**: 1406–13.



- 36 Sharma A, Van Oudenhove L, Paine P, Gregory L, Aziz Q. Anxiety increases acid-induced esophageal hyperalgesia. *Psychosom Med* 2010; **72**: 802–9.
- 37 Andreollo NA, Thompson DG, Kendall GP, Earlam RJ. Responses of the upper esophageal sphincter and esophageal body to graded intraluminal distension. *Braz J Med Biol Res* 1987; **20**: 165–73.
- 38 Kendall GP, Thompson DG, Day SJ, Garvie N. Motor responses of the oesophagus to intraluminal distension in normal subjects and patients with oesophageal clearance disorders. *Gut* 1987; **28**: 272–9.
- 39 Smout AJ, DeVore MS, Dalton CB, Castell DO. Cerebral potentials evoked by oesophageal distension in patients with non-cardiac chest pain. *Gut* 1992; **33**: 298–302.
- 40 Lu HC, Hsieh JC, Lu CL *et al*. Neuronal correlates in the modulation of placebo analgesia in experimentally-induced esophageal pain: a 3T-fMRI study. *Pain* 2010; **148**: 75–83.
- 41 Rao SS, Patel RS. How useful are manometric tests of anorectal function in the management of defecation disorders? *Am J Gastroenterol* 1997; **92**: 469–75.
- 42 McMahon BP, Frokjaer JB, Kunwald P *et al*. The functional lumen imaging probe (FLIP) for evaluation of the esophagogastric junction. *Am J Physiol Gastrointest Liver Physiol* 2007; **292**: G377–84.
- 43 Galeazzi F, Luca MG, Lanaro D *et al*. Esophageal hyperalgesia in patients with ulcerative colitis: role of experimental stress. *Am J Gastroenterol* 2001; **96**: 2590–5.
- 44 Remes-Troche JM, Attaluri A, Chahal P, Rao SS. Barostat or dynamic balloon distention test: which technique is best suited for esophageal sensory testing? *Dis Esophagus* 2012; **25**: 584–9.
- 45 Richter JE, Barish CF, Castell DO. Abnormal sensory perception in patients with esophageal chest pain. *Gastroenterology* 1986; **91**: 845–52.
- 46 Nasr I, Attaluri A, Hashmi S, Greger-H, Rao SS. Investigation of esophageal sensation and biomechanical properties in functional chest pain. *Neurogastroenterol Motil* 2010; **22**: 520–6, e116.
- 47 Amarasiri DL, Pathmeswaran A, Dassanayake AS, de Silva AP, Ranasinha CD, de Silva HJ. Esophageal motility, vagal function and gastroesophageal reflux in a cohort of adult asthmatics. *BMC Gastroenterol* 2012; **12**: 140.
- 48 Murray JA, Clouse RE, Conklin JL. Components of the standard oesophageal manometry. *Neurogastroenterol Motil* 2003; **15**: 591–606.
- 49 Pandolfino JE, Kahrilas PJ, American Gastroenterological Association. AGA technical review on the clinical use of esophageal manometry. *Gastroenterology* 2005; **128**: 209–24.
- 50 Bodger K, Trudgill N. *Guidelines for Oesophageal Manometry and pH Monitoring [New edn]*. Bodger K, Trudgill N, eds. Great Britain: British Society of Gastroenterology, 2006.
- 51 Farmer AD, Kano M, Coen SJ, Aziz Q. Psychophysiological responses to oesophageal stimulation in functional chest pain: a case control study. *Gut* 2011; **60**: A153.

# Graphical Abstract

The contents of this page will be used as part of the graphical abstract of html only. It will not be published as part of main.



The psychological trait of neuroticism retards autonomic recovery following esophageal intubation in health and functional chest pain.