Biological Psychology 127 (2017) 46–52

Contents lists available at ScienceDirect

Biological Psychology

journal homepage: www.elsevier.com/locate/biopsycho

Respiratory and hemodynamic contributions to emotion-related pre-syncopal vasovagal symptoms

Johanna M. Harrison[a,*], Philippe T. Gilchrist[b,c], Tiana S. Corovic[a], Curtis Bogetti[a], Yuqing Song[a], Simon L. Bacon[d], Blaine Ditto[a]

[a] Laboratory for Cardiovascular Psychophysiology, Department of Psychology, McGill University, 1205 Ave. Docteur Penfield, Montreal, Quebec, H3A 1B1, Canada
[b] Wolfson College, University of Cambridge, Cambridge CB3 9BB, United Kingdom
[c] MRC/BHF Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Strangeways Research Laboratory, 2 Wort's Causeway, Cambridge, CB1 8RN, United Kingdom
[d] Department of Exercise Science, Concordia University, 7141 Sherbrooke St. West, Montreal, Quebec, H4 B 1R6, Canada

ARTICLE INFO

Keywords:
Vasovagal symptoms
Presyncope
Hypocapnia
Hyperventilation
End-tidal CO_2
Impedance cardiography

ABSTRACT

Vasovagal reactions are conventionally understood as resulting from systemic changes in cardiovascular activity; however, there exists a complementary perspective focused on specific changes in cerebral vasoconstriction associated with hyperventilation-induced hypocapnia. The present study investigated the role of cardiovascular and respiratory activity in self-reported pre-syncopal vasovagal reactions to a surgery video in a sample of 49 healthy women. Participants who indicated more previous real-life episodes of dizziness reported experiencing significantly more symptoms in the laboratory consistent with a vasovagal response. They also showed lower total peripheral resistance and higher pre-ejection period in general, suggesting lower sympathetic nervous system activity. Significant decreases in end-tidal carbon dioxide ($P_{ET}CO_2$) occurred during the surgery video among susceptible participants, without significant increases in respiration rate. Further, participants who experienced reductions from the neutral video in $P_{ET}CO_2$, systolic blood pressure, or both, reported vasovagal symptoms during the surgery video. The results suggest that patterns of respiration associated with decreases in $P_{ET}CO_2$ may contribute to vasovagal symptoms reported in non-clinical groups as well as those with blood-injection-injury phobia and are associated with susceptibility to dizziness.

1. Introduction

Vasovagal reactions can produce a range of distressing symptoms from pre-syncopal weakness, dizziness, and light-headedness to syncope (France, Ditto, France, & Himawan, 2008; Lewis, 1932; Manolis, Linzer, Salem, & Estes, 1990),[1] and are most commonly provoked by emotional events or stimuli (Brignole et al., 2004). For many years, it has been assumed that emotion-related vasovagal responses are the product of large, systemic changes in cardiovascular activity. For better or worse, Lewis (1932) incorporated this idea into the term itself, proposing that a temporary, functional decrease in cerebral blood flow can be produced by the joint effects of vasodilation and vagally-mediated heart rate deceleration on blood pressure. This view has lead many to operationalize blood pressure or heart rate deceleration as indicators of a vasovagal response as opposed to more difficult-to-measure cerebral blood flow. Although this remains accepted practice in many clinical and research settings, recent research suggests that the response is more complex than once thought. For example, building on previous research showing a lack of effect of atropine on the "vasovagal" response (Weissler, Warren, Estes, McIntosh, & Leonard, 1957), more recent studies have generally failed to observe a greater increase in high frequency heart rate variability (Gerlach et al., 2006; Gilchrist & Ditto, 2015; Sarlo, Buodo, Munafò, Stegagno, & Palomba, 2008). Indeed, systemic decreases in blood pressure are not always observed, even in the presence of strong blood donation-related reactions (Ditto, Byrne, & Holly, 2009; Ditto, Gilchrist, & Holly, 2012; Holly, Torbit, & Ditto, 2012).

While these results may indicate heterogeneity in the response (Ritz,

* Corresponding author.
E-mail address: johanna.harrison@mail.mcgill.ca (J.M. Harrison).

[1] To provide clarity to the reader we note that the term pre-syncope (or pre-syncopal symptoms) as it is employed in this manuscript refers to a state or set of symptoms which are consistent with the prodrome of syncope but do not end in loss of consciousness. Though this usage is common in the literature, it is important to note that there exists a debate as to whether the mechanisms involved in a symptomatic reaction that does not end in syncope and one that does are the same (Aydin, Salukhe, Wilke, & Willems, 2010; The Task Force for the Diagnosis and Management of Syncope of the European Society of Cardiology (ESC), 2009).

http://dx.doi.org/10.1016/j.biopsycho.2017.04.011
Received 5 December 2015; Received in revised form 10 April 2017; Accepted 22 April 2017
Available online 26 April 2017

Meuret, & Ayala, 2010), they are also consistent with an emerging complementary perspective focusing on more specific changes in cerebral vasoconstriction, possibly associated with changes in respiratory activity (Folino, 2006). This concept is supported by recent physiological studies of other types of syncopal reactions in individuals undergoing orthostatic tolerance testing or engaged in voluntary hyperventilation. Specifically, a decrease in carbon dioxide (CO_2) induced by hyperventilation can lead to cerebral vasoconstriction, a reduction in cerebral blood flow and syncope when combined with another stressor (Immink, Pott, Secher, & van Lieshout, 2014; Norcliffe-Kaufmann, Kaufmann, & Hainsworth, 2008; Peebles, Ball, MacRae, Horsman, & Tzeng, 2012).

Hyperventilation – a pattern of respiration marked by ventilation which exceeds metabolic demand – can be elicited by breathing too rapidly (increased respiration rate; *RR*, breaths per minute), too deeply (increased tidal volume; V_T, mL), or both (Bott et al., 2009; Brashear, 1983). The term minute ventilation (V'_E) refers to the volume of air inhaled (inhaled V'_E) or exhaled (exhaled V'_E) per minute, where V'_E is directly proportional to both respiration rate and tidal volume as represented by the following equation, $V'_E = V_T \cdot RR$ (George, 2005). The consequence of an increase in minute ventilation is the elimination of CO_2 at a rate greater than it is produced in tissues. This results in decreased arterial partial pressure of CO_2 (hypocapnia) and an increase in the pH of the blood (respiratory alkalosis) (Brashear, 1983; Hornsveld, Garssen, & van Spiegel, 1995; Malmberg, Tamminen, & Sovijarvi, 2000). Hypocapnia produces increased cerebral vascular resistance and decreased cerebral blood flow, known as hypoperfusion (Willie et al., 2012).[2] Capnometry can be used to measure an individual's end-tidal carbon dioxide – the partial pressure of carbon dioxide (CO_2) at the end of an exhaled breath.

The notion that hyperventilation may contribute to vasovagal symptoms has existed for many years. In fact, the initial reference to respiration in vasovagal syncope was the seminal Lewis (1932) paper:

"If vasovagal syncope is due to a disturbance of the same central mechanism, respiration should become slow and shallow; but increase appears to be the rule, though it is not invariable…." (Lewis, 1932; p. 875).

Subsequent reference to hyperventilation by Engel and Romano (1947) indicated that they considered it a component of the vasovagal response. However, until recently, aside from observational and case studies (Elmore, Wildman Ii, & Westefeld, 1980; Foulds, 1993; Steptoe & Wardle, 1988; Thyer & Curtis, 1985), the influence of change in respiration preceding emotion-related vasovagal responses was largely unexplored in favour of investigation of cardiovascular indices (Ritz et al., 2010).

Several experimental studies involving Blood-Injection-Injury (BII) phobia patients exposed to a surgery video indicated a significant association between hyperventilation and vasovagal symptoms (Ritz et al., 2010). BII patients have been found to experience increases in minute ventilation and tidal volume irregularity (Ayala, Meuret, & Ritz, 2010; Ritz, Wilhelm, Gerlach, Kullowatz, & Roth, 2005; Ritz, Wilhelm, Meuret, Gerlach, & Roth, 2009), as well as significant hypocapnia – a reduction in mean end-tidal CO_2 below 30 mmHg (Bass & Gardner, 1985) – during exposure and recovery periods (Ayala et al., 2010; Ritz et al., 2005).

The present study is a follow-up to an investigation of physiological activity in young adults susceptible to vasovagal reactions (Gilchrist, Vrinceanu, Beland, Bacon, & Ditto, 2016), as well as studies by other groups who have investigated cardiovascular and respiratory activity associated with vasovagal reactions in susceptible individuals exposed to vasovagal inducing videos (Ayala et al., 2010; Gerlach et al., 2006; Ritz, Meuret, & Simon, 2013; Ritz et al., 2005, 2009; Sarlo et al., 2008). In both the present study and Gilchrist et al. (2016) participants varying in self-reported susceptibility watched a prototypical vasovagal response-inducing video depicting portions of open-heart surgery (Ritz et al., 2005) while measures of cardiovascular activity were obtained. The primary physiological difference observed in the previous experiment was in systolic blood pressure (SBP). Consistent with the results of another study in which we observed evidence of lower sympathetic nervous system activity and greater vasodilation among blood donors who subsequently experienced vasovagal symptoms (Gilchrist & Ditto, 2015), participants with a history of fainting displayed lower SBP even before the surgery video (Gilchrist et al., 2016). However, these previous studies were limited by relatively primitive measures of respiration. Also, while the physiological activity in high-risk participants seemed to "set the stage" for vasovagal symptoms, symptoms were not linked closely with an acute physiological response to the stimulus (either the surgery video or blood donation).

The aim of the present study was to investigate changes in cardiovascular and respiratory measures in a healthy sample exposed to a vasovagal-stimulating surgery video, with a primary focus on end-tidal CO_2 before and during presentation of the video. The relationship between participant tendency towards dizziness and end-tidal CO_2 output, and the capacity of changes in $P_{ET}CO_2$ to predict self-reported vasovagal symptoms during the surgery film were the central questions addressed in the study. It was hypothesized that greater susceptibility to dizziness would be associated with hyperventilation, evidenced by a decline in $P_{ET}CO_2$ during the surgery video. Furthermore, it was predicted that a decline in $P_{ET}CO_2$ levels would be associated with increases in self-reported pre-syncopal symptoms.

2. Method

2.1. Participants

Potential participants between 18 and 35 years old were recruited using posters and online announcements in a university psychology department. Since the large majority of students in this department and corresponding majority of respondents were female, the likelihood of recruiting a very unbalanced sample in regards to sex was high. As a result, for the present purpose, it was decided to recruit a more homogenous sample consisting only of women. Women who reported any history of diabetes, neurological, cardiovascular, or respiratory illness, uncorrected vision or hearing loss, regular medication use, or for whom English was not a first or second language were excluded from the study. To help ensure clear physiological measures, participants were asked to refrain from vigorous physical activity and alcohol consumption the day of the study, and to avoid caffeine and cigarette smoking for four and two hours prior to testing, respectively. No participants withdrew during or following testing. For ethical reasons, precautions were taken to prevent participants from fainting, i.e., they could pause or discontinue the videos. Accordingly, no participants fainted during the study session, thus self-reported vasovagal symptoms represent pre-syncope or near-syncope states that did not continue to loss of consciousness. Data from one participant was excluded for technical reasons. The remaining 49 healthy women were aged 18–29 (M = 20.9, SD = 2.4 years).

2.2. Measures and materials

2.2.1. Video stimuli

As part of a larger protocol that included some other stimuli (not discussed in the present paper) participants watched a neutral control video and a brief documentary of one patient's open-heart surgery. Both were approximately five minutes in duration and presented on a 17-inch computer monitor placed 1 m in front of the participant at approximate eye-level. The neutral control video was a brief documentary of a campus environmental sustainability project that was previously observed to produce no emotional response (Gilchrist et al.,

[2] For more detail on mechanisms in respiratory psychophysiology see Ritz et al. (2002).

2016). The surgery video depicts one patient's experience with open-heart surgery including an initial blood draw, opening the chest with a scalpel and saw, and sewing a coronary artery. While narrated in a non-emotional, educational manner, previous experience with participants in this and other laboratories indicates that most find this and similar surgery videos quite intense and vasovagal symptoms of varying severity are common (Ayala et al., 2010; Ritz et al., 2005; Sarlo et al., 2008; Sarlo, Palomba, Angrilli, & Stegagno, 2002; Steptoe & Wardle, 1988; Vogele, Coles, Wardle, & Steptoe, 2003).

2.2.2. Demographic and medical history questionnaire

A demographic questionnaire requested some medical history information as well as age, height, weight, etc. Most important, participants were asked to rate the frequency with which they fainted or experienced dizziness to the point where they felt they might faint in daily life on separate six-point scales with anchors of "never" and "daily". Most participants (67%) reported no life history of syncope. In contrast, 82% reported that they had experienced previous instances of significant pre-syncopal symptoms (severe dizziness) with differing frequency. Since there was more variability in this measure reflecting susceptibility to vasovagal reactions, it was decided to focus on tendency to experience dizziness as the primary individual difference variable.

2.2.3. Blood donation reaction inventory (BDRI)

Vasovagal symptoms within the session, including symptoms of dizziness, lightheadedness and weakness, were measured using the Blood Donation Reaction Inventory (BDRI). On this well-validated survey, participants specified on six-point scales the degree to which they experienced symptoms from "not at all" to "an extreme degree" (France et al., 2008; Meade, France, & Peterson, 1996). The BDRI has high internal consistency (Cronbach's $\alpha = 0.93–0.96$) and has been shown to correspond with phlebotomist ratings of donor reactions (France et al., 2008; France, France, Roussos, & Ditto, 2004; France, Rader, & Carlson, 2005).

2.2.4. Medical fears survey-short form (MFS-SF)

The MFS-SF (Olatunji et al., 2012) was used to assess fears (on a four-point scale from "no fear or concern" to "intense fear") associated with five subscales: injections and blood draws, sharp objects, examination and symptoms, blood, and mutilation. The short version of the MFS has strong psychometric properties, having comparable convergent/discriminant validity and subscales highly correlated with the original (Olatunji et al., 2012).

2.3. Apparatus

2.3.1. Blood pressure

Measurements of systolic and diastolic blood pressure (SBP, DBP) were obtained using an Accutorr Plus™ (Datascope Corp., Montvale, NJ, USA) oscillometric monitor with a cuff attached to the upper non-dominant arm. One discrete measurement was recorded during the last 30 s of each condition.

2.3.2. Impedance cardiography and electrocardiogram

A Biopac® MP150 system (Biopac Systems Canada, Montreal, QC, Canada) sampling at 1000 Hz was used to obtain continuous electrocardiogram (ECG) and impedance cardiography data. The ECG, used to derive heart rate (HR), was obtained with electrodes attached on the lower ribcage. The impedance signal was obtained using a tetrapolar configuration of spot electrodes. One recording and one current electrode were attached 3 cm apart on the dorsal surface of the base of the neck. A similar pair of electrodes were attached over the spine at the level of the xiphoid process. The impedance signal was used to derive measures of stroke volume (SV), cardiac output (CO), total peripheral resistance (TPR), and pre-ejection period (PEP). PEP is the interval between electrical stimulation of the heart and the opening of the aortic valve, and is considered a good noninvasive measure of cardiac sympathetic activity (Burgess, Penev, Schneider, & Van Cauter, 2004; Newlin & Levenson, 1979).

2.3.3. Capnometry

Repeated measurements of respiration rate (RR) and end-tidal CO_2 ($P_{ET}CO_2$) in 5 s windows were obtained using an Oridion Microcap™ Plus capnometer (Covidien, Mansfield, MA, USA). Disposable Smart Capnoline Plus™ lines were used allowing sampling of air expired from the mouth as well as nose.

2.4. Procedure

Upon arrival at the laboratory, the participant was seated in a testing room that could be observed through a one-way mirror. They provided written informed consent for the experiment. The consent form included brief descriptions of all study procedures, including physiological measures and the nature of the videos to be presented; no deception was used in the study. The participant was notified of their right to withdraw at any time. The physiological recording equipment was connected, after which they completed the demographic and medical history questionnaire and the MFS-SF. They were then asked to sit quietly for five minutes while resting physiological activity was recorded. Afterward, the neutral control video was presented followed by some other activities, including the surgery video, all separated by five-minute recovery periods.

The participant was asked to watch the videos in their entirety and refrain from averting their gaze. After the surgery film they rated the experience of vasovagal symptoms by completing the BDRI. At the end of the study, all participants were reimbursed $20 CAD for their time. The McGill University Research Ethics Board approved all procedures.

2.5. Data reduction and analysis

The primary dependent variables in the study were cardiovascular and respiratory measures. The primary independent variables were Condition (baseline, neutral video, surgery video) and Susceptibility to Dizziness (treated as continuous variable). Although preliminary regression analyses showed no significant associations between order of stimulus presentation and any predictor variables, as a precaution, order was retained as a model covariate to account for any variance that could be attributed to time differences between the presentation of the neutral and surgery videos in all analyses. To score the impedance-based cardiovascular measures, a 30 s artifact-free segment approximately 1 min to 30 s before the end of each condition was selected. Values of HR, SV, CO, TPR, and PEP were calculated using Biopac AcqKnowledge® software according to current standards (Sherwood et al., 1990). For each physiological measure except blood pressure, average values during the baseline condition, neutral video, and surgery video were obtained, as well as maximum and minimum values. Given the focus on the inhibitory vasovagal response and the sometimes fast-moving nature of the response, statistical analyses reported below focused on the minimum values for HR, SV, CO, TPR, and $P_{ET}CO_2$, and the maximum values of PEP (since lower sympathetic nervous system (SNS) activity is associated with longer PEP) and RR (given its association with hyperventilation). Since just one discrete measure of SBP and DBP were obtained during each period the average and minimum values could not be distinguished and only these values were analyzed.

Correlations and linear regression were used to examine possible associations between Susceptibility to Dizziness and other demographic and behavioural variables. The primary analyses were repeated measures General Linear Models (GLM, to accommodate a continuous independent variable) (Cohen, Cohen, West, & Aiken, 2002), i.e., 3 Condition (baseline, neutral video, surgery video) x Susceptibility to

Dizziness (treated as continuous) GLMs. This approach was used to prevent the loss of variance in the continuous IV (Susceptibility to Dizziness) that would result from dichotomizing participants into groups (MacCallum, Zhang, Preacher, & Rucker, 2002). Greenhouse–-Geisser (GG) corrected p-values are reported along with uncorrected degrees of freedom, and GG epsilon (ε), where Mauchly's test of sphericity indicated a violation of the assumption of sphericity. Post-hoc analyses of significant main effects of the repeated-measures variable were conducted with Bonferroni adjustment for multiple comparisons. Parameter estimates were used to evaluate significant between-subjects effects (regression line slope and intercept for continuous independent variables). Follow-up ANOVAs using change scores between levels of the repeated measure were used to evaluate significant interactions between Condition and Susceptibility to Dizziness. Partial eta squared (η_p^2) statistics were reported for effect size estimates as it is a commonly used statistic that accommodates multivariate designs and excludes systematic variance which is not associated with the effect being measured (Tabachnick & Fidell, 2007).

Finally, multiple linear regression models were used to examine the capacity of the decrease in $P_{ET}CO_2$ (using calculated change scores) to predict pre-syncopal vasovagal symptoms. In addition to overall results, the Results section presents data from an individual participant who reported and displayed significant pre-syncopal symptoms.

3. Results

3.1. Psychological correlates of susceptibility to dizziness

There were no significant associations between Dizziness Susceptibility and age or body mass index, though it significantly predicted self-reported vasovagal symptoms (BDRI score) during the surgery video ($R^2 = 0.095$, $F(1, 45) = 4.71$, $p < 0.05$). To better understand the dizziness variable, pairwise correlations were conducted between it and all Medical Fear Survey-short form (MFS-SF) items. The strongest correlation by far ($r = 0.45$, $p < 0.001$) was between frequency of dizziness and the participant's rating of the fear they experience "having blood drawn from your arm". Correspondingly, participants' scores on the MFS injection subscale significantly predicted their self-reported dizziness tendency ($R^2 = 0.16$, $F(1.45) = 8.65$, $p < 0.01$).

3.2. Physiological correlates of susceptibility to dizziness

Repeated-measures GLMs were conducted for each physiological variable over three Conditions (baseline, neutral video, surgery video), where Susceptibility to Dizziness was treated as a continuous independent variable.

3.2.1. Cardiovascular measures

The GLM of $HR_{(min)}$ produced a significant main effect of Condition, $F(2, 78) = 52.56$, $p < 0.001$, $\eta_p^2 = 0.57$. In general, $HR_{(min)}$ dropped significantly from the Baseline condition to the Neutral video, and decreased further during the Surgery video (Fig. 1). Similarly, for SBP, there was a significant main effect of Condition, ($\varepsilon = 0.88$), $F(2, 86) = 11.00$, $p < 0.001$, $\eta_p^2 = 0.20$, where SBP decreased significantly from baseline to both the Neutral and the Surgery video (Fig. 1). The patterns of physiological variables over conditions can been seen in Table 1.

There were no significant effects in the analyses of DBP, $SV_{(min)}$, and $CO_{(min)}$. However, there was a significant main effect of Dizziness Susceptibility on $TPR_{(min)}$, $F(1, 40) = 4.85$, $p < 0.01$, $\eta_p^2 = 0.10$. In general, as dizziness tendency increased, $TPR_{(min)}$ decreased throughout the study, as indicated by negative correlation between $TPR_{(min)}$ and Dizziness Susceptibility in each condition. This lower $TPR_{(min)}$ is indicative of lower SNS activity and vascular tone associated with greater dizziness susceptibility.

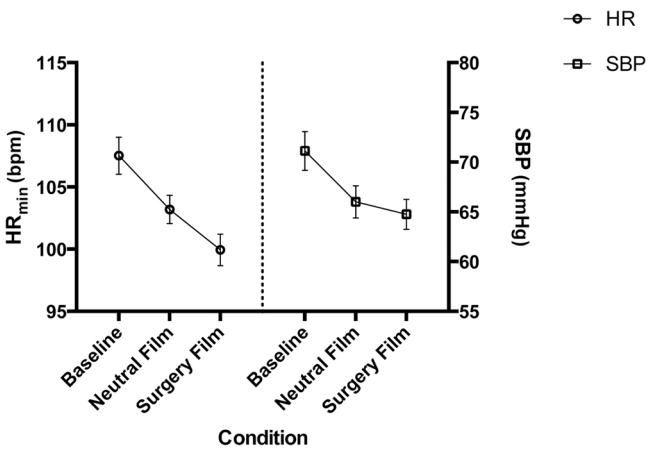

Fig. 1. Mean participant heart rate and systolic blood pressure during baseline, neutral and surgery videos.

Table 1
Estimated marginal means (M) corrected for susceptibility to dizziness and order with standard deviation (SD).

Physiological Measure	Units	Baseline M (SD)	Neutral M (SD)	Surgery M (SD)
Respiratory				
$P_{ET}CO_{2(min)}$	mmHg	33.4[a] (4.6)	33.6[b] (3.4)	31.9[c] (2.60)
$RR_{(max)}$	breaths/min	23.1[a] (3.4)	22.4[a] (3.2)	21.3[a] (6.2)
Cardiovascular				
$SBP_{(mean)}$	mmHg	107.9[a] (10.8)	103.8[b] (8.9)	102.8[b] (8.4)
$DBP_{(mean)}$	mmHg	65.1[a] (8.6)	64.6[a] (7.6)	63.13[a] (8.2)
$HR_{(min)}$	beats/min	70.7[a] (12.4)	65.2[b] (9.4)	61.2[c] (10.5)
$PEP_{(max)}$	ms	349.9[a] (242.9)	315.3[a] (261.4)	302.5[a] (232.6)
$SV_{(min)}$	ml/beat	28.9[a] (14.8)	32.9[a] (14.5)	32.4[a] (29.3)
$CO_{(min)}$	l/min	2.2[a] (1.1)	2.4[a] (1.1)	2.5[a] (1.9)
$TPR_{(min)}$	dynes*s/cm^5	1070.3[a] (529.3)	1194.2[a] (652.9)	1140.3[a] (683.4)

Note. Column means without common superscript are significantly different ($p < 0.05$.).

The notion of lower sympathetic activity was also supported by a significant main effect of Dizziness Susceptibility on $PEP_{(max)}$, $F(1, 38) = 7.35$, $p < 0.01$, $\eta_p^2 = 0.16$. Positive correlations between dizziness tendency and $PEP_{(max)}$ indicated that, in general, participants who reported greater dizziness tendency had higher $PEP_{(max)}$ in all conditions.

While there were no significant effects on respiration rate, the GLM of $P_{ET}CO_{2(min)}$ produced a significant Dizziness Susceptibility x Condition interaction effect ($\varepsilon = 0.83$), $F(2, 84) = 3.93$, $p < .05$, $\eta_p^2 = 0.09$. Between the neutral and surgery video, for each unit of increase in participant Susceptibility to Dizziness the drop in $P_{ET}CO_{2(min)}$ increased by a factor of 1.42 ($\beta = -1.42$, $F(1, 46) = 5.72$, $p < 0.05$, $\eta_p^2 = 0.11$). The regression equation estimated a decrease between the neutral and surgery videos in $P_{ET}CO_{2(min)}$ in the range of hypocapnia if susceptibility to dizziness was greater than the mean (Bass & Gardner, 1985; Ritz et al., 2010), (Fig. 2) .

A secondary series of analyses was conducted where fainting history was entered as an additional covariate to address the possibility that the effects of susceptibility to dizziness may have differed depending on fainting history. However, this produced no changes in significant results.

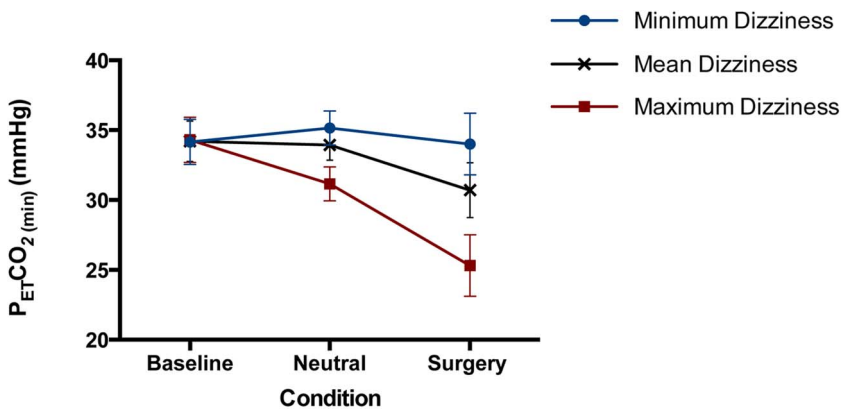

Fig. 2. End-tidal carbon dioxide ($P_{ET}CO_2$) output of participants during baseline condition, neutral and surgery videos as evaluated at maximum, minimum and mean of participant susceptibility to dizziness ratings according to regression equation from each Condition. Error bars represent SEM.

Similarly, a parallel set of analyses was conducted using mean values obtained during each of the three conditions (Baseline, Neutral Video, Surgery Video) to compare with the results of minimum values. With one important exception, the pattern of results was identical. For example, there was a clear main effect of condition on heart rate, $F(2, 80) = 4.88$, $p < 0.05$ related to a significant decrease in HR from baseline during the neutral video and a further significant decrease during the surgery video (M = 78.7 vs. 75.7 vs. 70.0 bpm). The main difference was the absence of a significant Dizziness Susceptibility x Condition interaction in the GLM of average end-tidal CO_2 during the periods.

3.3. Prediction of vasovagal symptoms from physiological response

The decrease in $P_{ET}CO_{2(min)}$ during the surgery video was consistent with the idea that hyperventilation plays a role in the dizziness and other vasovagal symptoms that some experience in such circumstances. To examine the capacity of the decrease in $P_{ET}CO_{2(min)}$ to predict self-reported vasovagal symptoms, change scores were calculated by subtracting the neutral video value from the surgery value and used in a regression equation to predict BDRI score. To compare the relative ability of decrease in $P_{ET}CO_{2(min)}$ and blood pressure to predict BDRI, SBP during the neutral video was subtracted from SBP during the surgery video and these values were also added to the regression equation along with the interaction effect and the baseline values of these change scores, i.e., the neutral video values. The results of the regression indicated the predictors explained 17.8% of the variance ($R^2 = 0.18$, $F(5,43) = 3.071$, $p < 0.05$) in reported vasovagal symptoms during the surgery video.

Interestingly, the interaction effect of change in $P_{ET}CO_{2(min)}$ and SBP significantly predicted BDRI score ($\beta = -.47$, $t(43) = -2.78$, $p < 0.01$) due to the fact that participants who did *not* experience a decrease in either SBP or $P_{ET}CO_{2(min)}$ reported no vasovagal symptoms on the BDRI ($M = 0$), whereas those who experienced a drop in SBP, $P_{ET}CO_{2(min)}$, or both during the surgery video all reported symptoms (M = 2.6, 2.4, and 2.4, respectively). While the sample was not large enough for detailed sub-group analyses, this suggests that both systemic and local (cerebral) vascular effects may play a role in emotion-related vasovagal reactions.

3.4. Case example

Another limitation of the study related to sample size is that few participants displayed overt signs of a vasovagal reaction. Combined with the fact that cardiovascular change was modest, this raises the possibility that the physiological responses and symptoms elicited by the surgery video were more a reflection of some other state such as panic or disgust than vasovagal reactions. This idea will be discussed in more detail in the Discussion section. However, one participant in particular exhibited overt symptoms exclusively during the surgery video including strong flushing, fidgeting, and placing her fist over her mouth. The research assistant intervened by stopping the video and giving the participant some fruit juice; she did not vomit or faint, though this video has elicited several brief faints in other studies in this laboratory. The participant's self-report results also suggested a pre-syncopal vasovagal response. Her report of faintness, dizziness, light-headedness, and weakness (BDRI score) was 9 of possible a 16. Although she said that she had never actually fainted before, she indicated a common tendency to experience dizziness – 4 on a 0–5 scale. Her MFS rating of the fear she experiences during blood draws was also high – 3 on a 0–3 scale. At the same time, her blood pressure during the experiment was 107/76, 104/70, and 105/72 mmHg during the baseline, neutral video, and surgery video conditions, respectively. Similarly, her heart rate remained stable between the neutral (M = 62 bpm) and surgery videos (M = 62 bpm). In contrast, the RR and $P_{ET}CO_2$ signals (Fig. 3) revealed signs of hyperventilation, including a notice-

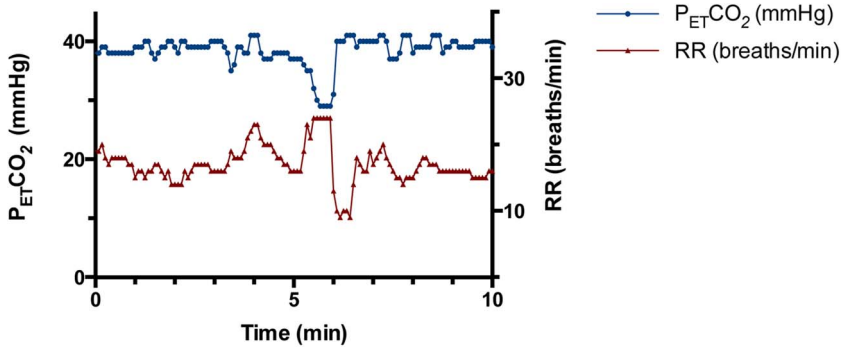

Fig. 3. Case example shows near simultaneous decrease in end-tidal carbon dioxide ($P_{ET}CO_2$) and increase in respiration rate (RR).

able increase in respiration rate from an already high value at the beginning of the surgery video (her average RR during the baseline and neutral video conditions was 18.3 and 16.1 breaths/min), and a significant drop in $P_{ET}CO_2$.

4. Discussion

The present results are consistent with a number of previous studies of the psychophysiology of emotion-related vasovagal reactions. For example, the importance of vasodilation was highlighted by Sarlo et al. (2008), who found greater decreases in TPR among participants with BII phobia in response to a surgery video. Our results revealed that participants who reported greater susceptibility to dizziness generally had higher $PEP_{(max)}$ and lower $TPR_{(min)}$ throughout the study, suggesting reduced sympathetic activation and lower vascular tone. The findings are also consistent with results of our previous laboratory experiment (Gilchrist et al., 2016) and naturalistic study of blood donors (Gilchrist & Ditto, 2015). In the blood donor study, donors who subsequently experienced vasovagal symptoms had lower TPR even before they arrived at the donation chair, similar to the present results.

While susceptibility to dizziness in the present study was associated with some systemic cardiovascular measures, the results suggest an additional influence of reduced arterial CO_2. Participants prone to dizziness displayed a significant decrease in $P_{ET}CO_{2(min)}$ during the surgery video, often to the level of hypocapnia. Likewise, participants who experienced decreases from the neutral video in $P_{ET}CO_{2(min)}$, systolic blood pressure or both, reported symptoms consistent with a vasovagal response during the surgery video.

Similarly, several studies have found that BII phobics exposed to a surgery video often experience hypocapnia that is associated with measures of hyperventilation and vasovagal symptoms (Ayala et al., 2010; Ritz et al., 2013, 2005, 2009).

Interestingly, individuals with orthostatic intolerance also often exhibit hyperventilation-related decreases in $P_{ET}CO_2$ during postural change which appears to contribute to pre-syncopal symptoms and syncope, as well as reduced cerebral blood flow (Carey, Eames, Panerai, & Potter, 2001; Lagi, Cencetti, Corsoni, Georgiadis, & Bacalli, 2001; Norcliffe-Kaufmann et al., 2008; Novak et al., 1998; Porta, Casucci, Castoldi, Rinaldi, & Bernardi, 2008). Finally, such findings are in line with physiological studies that have shown a reduction in CO_2 can trigger both local cerebral vasoconstriction (Claassen, Zhang, Fu, Witkowski, & Levine, 2007) and vasodilation in the periphery (Norcliffe-Kaufmann et al., 2008).

While we did not find a significant effect of dizziness susceptibility on respiration rate, several studies of BII phobics have found evidence of decreased $P_{ET}CO_2$ without a significant increase in RR (Ayala et al., 2010; Ritz et al., 2013, 2009). In these cases, tidal volume and minute ventilation, but not respiration rate, were associated with vasovagal symptoms. Although measures of respiratory activity in the present study were limited to respiration rate and $P_{ET}CO_2$, given the relationship between hypocapnia and respiration patterns, it is likely that additional assessment of breathing patterns may have yielded some indication of hyperventilation, specifically, increases in tidal volume or minute ventilation (Ritz et al., 2002, 2010). In general, the present study extends the literature by suggesting that associations among hyperventilation, $P_{ET}CO_2$, and susceptibility to dizziness are not limited to individuals with especially strong fears of blood and injury.

That said, the study had a number of limitations. A significant methodological limitation was the limited measurement of blood pressure at discrete time points rather than continuous blood pressure monitoring. While a common procedure, this reduced ability to detect transient change in blood pressure if resolved before the oscillometric reading. Similarly, participants rated their symptoms immediately following, not during, the surgery video when symptoms may have abated; also since the ratings referred to their experiences during the video, they could not be compared to physiological activity in the post-video period.

Relatedly, the use of minimum (for HR, SV, CO, TPR, and $P_{ET}CO_2$) and maximum (for PEP and RR) values in the primary analyses of the continuously measured physiological variables had both advantages and disadvantages. In contrast to blood pressure, this allowed the analyses to reflect possibly phasic fast-moving levels of the physiological variables that contribute to vasovagal symptoms. On the other hand, by definition, minimum/maximum values are less representative of typical levels during a period and thus need to be viewed with caution.

Further limitations of the study were the modest all-female sample and the retrospective self-report questionnaires used to gather participant history. While the use of only women may limit the generalizability of the findings to women, in view of evidence suggesting women are more likely to experience emotion-related vasovagal reactions (France et al., 2005; Newman, 2004; Newman, Pichette, Pichette, & Dzaka, 2003), they remain important both in terms of expanding understanding the possible role of respiration in vasovagal responses in general and the nature of vasovagal responses in a group at elevated risk. As far as the retrospective assessment of susceptibility to dizziness and related characteristics, this could be improved if participants were asked to record vasovagal symptoms prospectively. Nevertheless, the fact that ratings of susceptibility to dizziness predicted laboratory measures supports their validity to some degree.

Finally, perhaps the most important limitation relates the modest cardiovascular responses observed in the study. Despite the use of a stimulus commonly used to elicit vasovagal responses, it is possible that the results are more a reflection of some non-vasovagal state such as panic or disgust that lead to hyperventilation. Rather than suggesting that hyperventilation is one mechanism of the effects of vasovagal reactions, the results may point to the importance of hyperventilation in determining individual differences in susceptibility to dizziness without any particular connection to the vasovagal process. Regardless of the issue of vasovagal responses, dizziness and lightheadedness are symptoms of hyperventilation in general (Meuret, 2010).

This problem cannot be resolved easily with the current results and will be an important focus for future research, in part due to the treatment implications. For example, is respiration control a useful strategy to reduce vasovagal reactions, or just specific instances of hyperventilation? Based on previous findings indicating that respiratory mechanisms can contribute to vasovagal symptoms in BII phobics, respiration control seems like a potentially useful strategy to reduce risk for vasovagal responses in individuals with especially strong fears of blood and injury. However, it is unclear whether it would help individuals like those in the present non-clinical “susceptible” group if they were presented with a stronger real-life vasovagal stimulus such as blood donation. It will be useful to clarify this issue given that respiratory dysregulation is behaviorally targetable.

Acknowledgements

This research was supported by a grant from the Canadian Institutes of Health Research (#133459) (B.D.). Fellowship support for the first author and second authors was provided by Les Fonds de la recherche en santé du Quebec.

References

Ayala, E. S., Meuret, A. E., & Ritz, T. (2010). Confrontation with blood and disgust stimuli precipitates respiratory dysregulation in blood-injection-injury phobia. *Biological Psychology*, *84*(1), 88–97. http://dx.doi.org/10.1016/j.biopsycho.2010.02.004.

Aydin, M. A., Salukhe, T. V., Wilke, I., & Willems, S. (2010). Management and therapy of vasovagal syncope: A review. *World Journal of Cardiology*, *2*(10), 308–315. http://dx.doi.org/10.4330/wjc.v2.i10.308.

Bass, C., & Gardner, W. N. (1985). Respiratory and psychiatric abnormalities in chronic symptomatic hyperventilation. *British Medical Journal (Clinical Research Edition)*, *290*(6479), 1387–1390 Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1415586/.

Bott, J., Blumenthal, S., Buxton, M., Ellum, S., Falconer, C., Garrod, R., & White, J. (2009). Guidelines for the physiotherapy management of the adult, medical,

spontaneously breathing patient. *Thorax*, *64*(Suppl. (1)), i1–52. http://dx.doi.org/10.1136/thx.2008.110726.
Brashear, R. E. (1983). Hyperventilation syndrome? *Lung*, *161*(5), 257–273.
Brignole, M., Alboni, P., Benditt, D. G., Bergfeldt, L., Blanc, J.-J., Thomsen, P. E. B., & Wieling, W. (2004). Guidelines on management (diagnosis and treatment) of syncope – Update 2004. *The Task Force on Syncope, European Society of Cardiology*, *25*(22), 2054–2072. http://dx.doi.org/10.1016/j.ehj.2004.09.004.
Burgess, H. J., Penev, P. D., Schneider, R., & Van Cauter, E. (2004). Estimating cardiac autonomic activity during sleep: impedance cardiography, spectral analysis, and Poincare plots. *Clinical Neurophysiology*, *115*(1), 19–28. http://dx.doi.org/10.1016/S1388-2457(03)00312-2.
Carey, B. J., Eames, P. J., Panerai, R. B., & Potter, J. F. (2001). Carbon dioxide, critical closing pressure and cerebral haemodynamics prior to vasovagal syncope in humans. *Clinical Science (London)*, *101*(4), 351–358. http://dx.doi.org/10.1042/cs1010351.
Claassen, J. A., Zhang, R., Fu, Q., Witkowski, S., & Levine, B. D. (2007). Transcranial Doppler estimation of cerebral blood flow and cerebrovascular conductance during modified rebreathing. *Journal of Applied Physiology (1985)*, *102*(3), 870–877. http://dx.doi.org/10.1152/japplphysiol.00906.2006.
Cohen, J., Cohen, P., West, S. G., & Aiken, L. S. (2002). *Applied multiple regression/correlation analysis for the behavioral sciences*. Mahwah: Lawrence Erlbaum Associates.
Ditto, B., Byrne, N., & Holly, C. (2009). Physiological correlates of applied tension may contribute to reduced fainting during medical procedures. *Annals of Behavioral Medicine*, *37*(3), 306–314. http://dx.doi.org/10.1007/s12160-009-9114-7.
Ditto, B., Gilchrist, P., & Holly, C. (2012). Fear-related predictors of vasovagal symptoms during blood donation: it's in the blood. *Journal of Behavioral Medicine*, *35*(4), 393–399. http://dx.doi.org/10.1007/s10865-011-9366-0.
Elmore, R. T., Wildman Ii, R. W., & Westefeld, J. S. (1980). The use of systematic desensitization in the treatment of blood phobia. *Journal of Behavior Therapy and Experimental Psychiatry*, *11*(4), 277–279. http://dx.doi.org/10.1016/0005-7916(80)90071-3.
Engel, G. L., & Romano, J. (1947). Studies of syncope: IV. Biologic interpretation of vasodepressor syncope. *Psychosomatic Medicine*, *9*(5), 288–294. http://dx.doi.org/10.1016/0002-8703(48)90429-3.
Folino, A. F. (2006). Cerebral autoregulation in neurally mediated syncope: victim or executioner? *Heart*, *92*(6), 724–726. http://dx.doi.org/10.1136/hrt.2005.069179.
Foulds, J. (1993). Cerebral circulation during treatment of blood-injury phobia: a case study. *Behavioural and Cognitive Psychotherapy*, *21*(02), 137–146.
France, C. R., France, J. L., Roussos, M., & Ditto, B. (2004). Mild reactions to blood donation predict a decreased likelihood of donor return. *Transfusion and Apheresis Science*, *30*(1), 17–22. http://dx.doi.org/10.1016/j.transci.2003.08.014.
France, C. R., Rader, A., & Carlson, B. (2005). Donors who react may not come back: analysis of repeat donation as a function of phlebotomist ratings of vasovagal reactions. *Transfusion and Apheresis Science*, *33*(2), 99–106. http://dx.doi.org/10.1016/j.transci.2005.02.005.
France, C. R., Ditto, B., France, J. L., & Himawan, L. K. (2008). Psychometric properties of the Blood Donation Reactions Inventory: a subjective measure of presyncopal reactions to blood donation. *Transfusion*, *48*(9), 1820–1826. http://dx.doi.org/10.1111/j.1537-2995.2008.01831.x.
George, R. B. (2005). *Chest medicine: Essentials of pulmonary and critical care medicine*. Philadelphia, PA: Lippincott Williams & Wilkins.
Gerlach, A. L., Spellmeyer, G., Vogele, C., Huster, R., Stevens, S., Hetzel, G., & Deckert, J. (2006). Blood-injury phobia with and without a history of fainting: disgust sensitivity does not explain the fainting response. *Psychosomatic Medicine*, *68*(2), 331–339. http://dx.doi.org/10.1097/01.psy.0000203284.53066.4b.
Gilchrist, P. T., & Ditto, B. (2015). Sense of impending doom: Inhibitory activity in waiting blood donors who subsequently experience vasovagal symptoms. *Biological Psychology*, *104*(0), 28–34. http://dx.doi.org/10.1016/j.biopsycho.2014.11.006.
Gilchrist, P. T., Vrinceanu, T., Beland, S., Bacon, S. L., & Ditto, B. (2016). Disgust stimuli reduce heart rate but do not contribute to vasovagal symptoms. *Journal of Behavior Therapy and Experimental Psychiatry*, *51*, 116–122. http://dx.doi.org/10.1016/j.jbtep.2016.01.005.
Holly, C. D., Torbit, L., & Ditto, B. (2012). Applied tension and coping with blood donation: A randomized trial. *Annals of Behavioral Medicine*, *43*(2), 173–180. http://dx.doi.org/10.1007/s12160-011-9315-8.
Hornsveld, H., Garssen, B., & van Spiegel, P. (1995). Voluntary hyperventilation: The influence of duration and depth on the development of symptoms. *Biological Psychology*, *40*(3), 299–312.
Immink, R. V., Pott, F. C., Secher, N. H., & van Lieshout, J. J. (2014). Hyperventilation, cerebral perfusion, and syncope. *Journal of Applied Physiology*, *116*(7), 844–851 Retrieved from http://jap.physiology.org/content/116/7/844.abstract, http://jap.physiology.org/content/jap/116/7/844.full.pdf.
Lagi, A., Cencetti, S., Corsoni, V., Georgiadis, D., & Bacalli, S. (2001). Cerebral vasoconstriction in vasovagal syncope: Any link with symptoms? A transcranial Doppler study. *Circulation*, *104*(22), 2694–2698.
Lewis, T. (1932). A lecture on vasovagal syncope and the carotid sinus mechanism. *British Medical Journal*, *1*(3723), 873–876 Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2520889/, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2520889/pdf/brmedj07387-0001.pdf.
MacCallum, R. C., Zhang, S., Preacher, K. J., & Rucker, D. D. (2002). On the practice of dichotomization of quantitative variables. *Psychological Methods*, *7*(1), 19–40. http://dx.doi.org/10.1037/1082-989X.7.1.19.
Malmberg, L. P., Tamminen, K., & Sovijarvi, A. R. (2000). Orthostatic increase of respiratory gas exchange in hyperventilation syndrome. *Thorax*, *55*(4), 295–301 Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1745734/pdf/v055p00295.pdf.
Manolis, A. S., Linzer, M., Salem, D., & Estes, I. I. I. N. A. M. (1990). Syncope: current diagnostic evaluation and management. *Annals of Internal Medicine*, *112*(11), 850–863. http://dx.doi.org/10.7326/0003-4819-112-11-850.
Meade, M. A., France, C. R., & Peterson, L. M. (1996). Predicting vasovagal reactions in volunteer blood donors. *Journal of Psychosomatic Research*, *40*(5), 495–501.
Meuret, A. E. (2010). *Hyperventilation the corsini encyclopedia of psychology*. John Wiley Sons, Inc.
Newlin, D. B., & Levenson, R. W. (1979). Pre-ejection period: Measuring beta-adrenergic influences upon the heart. *Psychophysiology*, *16*(6), 546–553.
Newman, B. H., Pichette, S., Pichette, D., & Dzaka, E. (2003). Adverse effects in blood donors after whole-blood donation: A study of 1000 blood donors interviewed 3 weeks after whole-blood donation. *Transfusion*, *43*(5), 598–603.
Newman, B. H. (2004). Adjusting our management of female blood donors: The key to an adequate blood supply. *Transfusion*, *44*(4), 591–596. http://dx.doi.org/10.1111/j.0041-1132.2004.04014.x.
Norcliffe-Kaufmann, L. J., Kaufmann, H., & Hainsworth, R. (2008). Enhanced vascular responses to hypocapnia in neurally mediated syncope. *Annals of Neurology*, *63*(3), 288–294. http://dx.doi.org/10.1002/ana.21205.
Novak, V., Spies, J. M., Novak, P., McPhee, B. R., Rummans, T. A., & Low, P. A. (1998). Hypocapnia and cerebral hypoperfusion in orthostatic intolerance. *Stroke*, *29*(9), 1876–1881. http://dx.doi.org/10.1161/01. str.29.9.1876.
Olatunji, B. O., Ebesutani, C., Sawchuk, C. N., McKay, D., Lohr, J. M., & Kleinknecht, R. A. (2012). Development and initial validation of the medical fear survey-short version. *Assessment*, *19*(3), 318–336. http://dx.doi.org/10.1177/1073191111415368.
Peebles, K. C., Ball, O. G., MacRae, B. A., Horsman, H. M., & Tzeng, Y. C. (2012). Sympathetic regulation of the human cerebrovascular response to carbon dioxide. *Journal of Applied Physiology (1985)*, *113*(5), 700–706. http://dx.doi.org/10.1152/japplphysiol.00614.2012.
Porta, C., Casucci, G., Castoldi, S., Rinaldi, A., & Bernardi, L. (2008). Influence of respiratory instability during neurocardiogenic presyncope on cerebrovascular and cardiovascular dynamics. *Heart*, *94*(11), 1433–1439. http://dx.doi.org/10.1136/hrt.2006.114223.
Ritz, T., Dahme, B., Dubois, A. B., Folgering, H., Fritz, G. K., Harver, A., & Van de Woestijne, K. P. (2002). Guidelines for mechanical lung function measurements in psychophysiology. *Psychophysiology*, *39*(5), 546–567 10.1017.s0048577202010715.
Ritz, T., Wilhelm, F. H., Gerlach, A. L., Kullowatz, A., & Roth, W. T. (2005). End-Tidal pCO2 in blood phobics during viewing of emotion- and disease-related films. *Psychosomatic Medicine*, *67*(4), 661–668. http://dx.doi.org/10.1097/01.psy.0000170339.06281.07.
Ritz, T., Wilhelm, F. H., Meuret, A. E., Gerlach, A. L., & Roth, W. T. (2009). Do blood phobia patients hyperventilate during exposure by breathing faster, deeper, or both? *Depression and Anxiety*, *26*(2), E60–E67. http://dx.doi.org/10.1002/da.20466.
Ritz, T., Meuret, A. E., & Ayala, E. S. (2010). The psychophysiology of blood-injection-injury phobia: Looking beyond the diphasic response paradigm. *International Journal of Psychophysiology*, *78*(1), 50–67. http://dx.doi.org/10.1016/j.ijpsycho.2010.05.007.
Ritz, T., Meuret, A. E., & Simon, E. (2013). Cardiovascular activity in blood-injection-injury phobia during exposure: Evidence for diphasic response patterns? *Behaviour Research and Therapy*, *51*(8), 460–468. http://dx.doi.org/10.1016/j.brat.2013.03.011.
Sarlo, M., Palomba, D., Angrilli, A., & Stegagno, L. (2002). Blood phobia and spider phobia: Two specific phobias with different autonomic cardiac modulations. *Biological Psychology*, *60*(2–3), 91–108. http://dx.doi.org/10.1016/S0301-0511(02)00030-3.
Sarlo, M., Buodo, G., Munafò, M., Stegagno, L., & Palomba, D. (2008). Cardiovascular dynamics in blood phobia: Evidence for a key role of sympathetic activity in vulnerability to syncope. *Psychophysiology*, *45*(6), 1038–1045. http://dx.doi.org/10.1111/j.1469-8986.2008.00713.x.
Sherwood, A., Allen, M. T., Fahrenberg, J., Kelsey, R. M., Lovallo, W. R., & van Doornen, L. J. P. (1990). Methodological guidelines for impedance cardiography. *Psychophysiology*, *27*(1), 1–23. http://dx.doi.org/10.1111/j.1469-8986.1990.tb02171.x.
Steptoe, A., & Wardle, J. (1988). Emotional fainting and the psychophysiologic response to blood and injury: Autonomic mechanisms and coping strategies. *Psychosomatic Medicine*, *50*(4), 402–417.
Tabachnick, B. G., & Fidell, L. S. (2007). *Using multivariate statistics*. Boston: Pearson/Allyn & Bacon.
The Task Force for the Diagnosis and Management of Syncope of the European Society of Cardiology (ESC) (2009). Guidelines for the diagnosis and management of syncope (version 2009): The Task Force for the Diagnosis and Management of Syncope of the European Society of Cardiology (ESC). *European Heart Journal*, *30*(21), 2631–2671. http://dx.doi.org/10.1093/eurheartj/ehp298.
Thyer, B. A., & Curtis, G. C. (1985). On the diphasic nature of vasovagal fainting associated with blood-injury-illness phobia. *The Pavlovian Journal of Biological Science: Official Journal of the Pavlovian*, *20*(2), 84–87. http://dx.doi.org/10.1007/BF03003257.
Vogele, C., Coles, J., Wardle, J., & Steptoe, A. (2003). Psychophysiologic effects of applied tension on the emotional fainting response to blood and injury. *Behaviour Research and Therapy*, *41*(2), 139–155 Retrieved from http://ac.els-cdn.com/S0005796701001334/1-s2.0-S0005796701001334-main.pdf?_tid=89cac640-4055-11e5-90b2-00000aacb35f&acdnat=1439317363_f9225ee439990bf3963c9e2d92fefe1f.
Weissler, A. M., Warren, J. V., Estes, E. H., Jr., McIntosh, H. D., & Leonard, J. J. (1957). Vasodepressor syncope; factors influencing cardiac output. *Circulation*, *15*(6), 875–882 Retrieved from http://circ.ahajournals.org/content/15/6/875.full.pdf.
Willie, C. K., Macleod, D. B., Shaw, A. D., Smith, K. J., Tzeng, Y. C., Eves, N. D., & Ainslie, P. N. (2012). Regional brain blood flow in man during acute changes in arterial blood gases. *Journal of Physiology*, *590*(14), 3261–3275. http://dx.doi.org/10.1113/jphysiol.2012.228551.