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Sense of impending doom: Inhibitory activity in waiting blood donors who subsequently experience vasovagal symptoms

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ABSTRACT

This study examined autonomic and hemodynamic processes associated with the development of naturally occurring vasovagal responses. Data from a study assessing the physiological correlates of an intervention to reduce vasovagal responses in blood donors were examined (Ditto et al., 2009). Ninety-eight participants were assigned randomly to groups that either practiced applied tension or not. Dependent variables included ratings of vasovagal symptoms, heart rate, blood pressure, and other parameters derived from ambulatory impedance cardiography. Participants who subsequently experienced vasovagal symptoms had a lower ratio between low and high frequency components (LF/HF HRV) of heart rate variability (HRV) before blood donation, suggesting lower sympathetic nervous system activity. They also showed sharper decreases in total peripheral resistance and lower respiration rates. The results suggest that vasovagal reactions that begin during anticipation of a medical procedure may be characterized by an inhibitory process from the outset and do not support the belief that reactions follow a diphasic pattern.

1. Introduction

The vasovagal response is a common phenomenon, especially during invasive medical procedures (e.g., injections, blood draws, dental care, blood donation) and in people who are particularly fearful of blood, injury, and injections (e.g., blood–injury–injection (BII) phobias; Barlow, 2002; Ditto, France, Lavoie, Roussos, & Adler, 2003; Enkling, Marwinski, & Jöhren, 2006; France, France, Roussos, & Ditto, 2004; Marks, 1988). At the same time, given the importance of inhibitory activity in the pattern, it is an unusual stress response that continues to present theoretical and clinical challenges (Ditto, Gilchrist, & Holly, 2012; Ritz, Meuret, & Ayala, 2010; van Dijk et al., 2006).

The vasovagal response can be elicited by a variety of physical and psychological stressors including abrupt postural change, prolonged standing, a warm environment, hemorrhage, and psychological stress. Symptoms such as dizziness and weakness are produced by a decrease in blood flow to the brain that is the result of a "maladaptive" physiological response (i.e., the vasovagal response) to such stimuli. A discussion of its evolutionary origin is beyond the scope of the present paper though it may be useful to note that some researchers have suggested that it is related to the need to reduce blood loss following injury or other situations of "impending doom" such as facing an inescapable predator (Barlow, 1988; Diehl, 2005; Ditto, Balegh, Gilchrist, & Holly, 2012). Regardless, the vasovagal response involves a decrease in blood pressure and other aspects of cardiovascular activity at a time when increases are required, at least in terms of avoiding symptoms and risk of vasovagal syncope (fainting). This has been a particular puzzle for psychological theories of vasovagal responses given that these are usually fear-related. For example, reactions among volunteer blood donors, a convenient model given their prevalence in this well monitored environment, are often associated with higher state anxiety, higher scores on measures of medical fears, and less previous blood donation experience, even with equivalent blood loss (Ditto, Balegh, et al., 2012a; Graham, 1961; Holly, Balegh, & Ditto, 2011; Labus, France, & Taylor, 2000; Newman, Pichette, Pichette, & Dzaka, 2003). This has led many to assume that the pattern of physiological activity leading up to vasovagal symptoms includes an increase in sympathetic nervous system activity that is, at some point, reversed. A "diphasic" assumption has been incorporated into most theories of the vasovagal response such as Engel's (1978) notion of a conflict between fight-flight and conservation-withdrawal responses, Page's (2003) theory of the simultaneous experience of fear and disgust, and the

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more physiologically-oriented ventricular afferent theory where a stress-related reduction in venous return leads to inadvertent stimulation of cardiac mechanoreceptors and bradycardia (Converse et al., 1992).

It is generally assumed that the first phase of the diphasic response, consistent with the classic alarm reaction (e.g., Cannon, 1929), involves a rise in heart rate and blood pressure. The second phase involves an increase in parasympathetic nervous system activity and a drop in blood pressure leading to reduced cerebral perfusion (Lewis, 1932). Although widely accepted, the diphasic theory has been criticized for its limited empirical support (Ritz et al., 2010), though the second phase clearly involves a strong inhibitory response including sympathetic withdrawal and vasodilation (Béchir et al., 2003; Sarlo, Buodo, Munafò, Stegagno, & Palomba, 2008; Shen et al., 2000). While reduced cerebral perfusion and symptoms of dizziness and lightheadedness are quintessential markers of the vasovagal response (Zervou et al., 2005), its autonomic and hemodynamic correlates vary and continue to be debated.

A classic study often cited as support for the diphasic pattern found that blood donors showed anticipatory increases in heart rate and blood pressure followed by decreases during insertion and/or removal of the needle (Graham, Kabler, & Lunsford, 1961). However, Ritz et al. (2010) note that diastolic blood pressure was characterized as diphasic even though it did not fall below initial baseline levels. Indeed, in many studies of diphasic patterns, increases in blood pressure and heart rate often lack a comparison condition, drops below baseline are not always evident, and the validity of the baseline is questionable (Ritz et al., 2010). Lastly, diphasic patterns have not been seen in more recent laboratory studies of patients diagnosed with BII phobia (Lumley & Melamed, 1992; Ritz, Wilhelm, Gerlach, Kullowatz, & Roth, 2005; Sarlo et al., 2008).

The physiological process of the vasovagal response is likely more complex and not limited to a diphasic response (Sarlo et al., 2008). For example, there is increasing emphasis in the emotion literature on physiological patterning of different emotions, and different subtypes of a particular emotion, in relation to the nature of adaptive behavior (Rolls, 2013). Thus, BII-related fear may not necessarily elicit classic alarm-like changes. Relatedly, while a number of studies have examined blood pressure and heart rate response patterns in the vasovagal response, the relative contribution of other cardiovascular measures such as cardiac output and total peripheral resistance lack investigation (Sarlo et al., 2008), especially in the context of naturally-occurring vasovagal reactions.

Using data from a previous study of the physiological correlates of an intervention (Applied Tension) aimed at reducing vasovagal symptoms in blood donors (Ditto, Byrne, & Holly, 2009), the present study examined physiological activity during the most anxiety-provoking part of the procedure, that is, the minutes immediately before arrival at the donation chair and insertion of the needle (Adler, Ditto, France, & France, 1994; Ditto, France, Albert, & Byrne, 2007; Sledge, 1978). Autonomic and cardiovascular measures derived from impedance cardiography in donors who subsequently experienced and did not experience vasovagal symptoms were studied. It was reasoned that if such symptoms are caused by a diphasic response, participants who experienced symptoms should display increased arousal during this period. On the other hand, given our skepticism about the diphasic response, it was predicted that, if anything, participants who subsequently experienced symptoms would display lower physiological activity. It was expected that those who experience symptoms would have lower sympathetic activity and end-organ functioning associated with vasodilation.

2. Methods

2.1. Participants and experimental conditions

As noted above, the data were obtained in a study of the physiological correlates of Applied Tension (AT; Ditto et al., 2009), a muscle-tensing strategy that has been found to reduce vasovagal symptoms in many blood donors and BII phobics (Ditto et al., 2003; Öst & Sterner, 1987). However, the previous study did not examine physiological activity during the pre-donation period when AT was not practiced. Recruitment and testing occurred at mobile blood clinics held in Montreal-area universities and colleges. Ninety-eight young adults (55% female) aged 18–30 years ($M = 20.9$, $SD = 2.4$ years) participated in the study. As would be expected in this environment, participants were relatively inexperienced blood donors ($M = 1.9$, $SD = 2.2$ previous donations). They were assigned randomly either to a control condition of donation-as-usual ($N = 31$) or to an experimental condition including AT ($N = 67$).

2.2. Materials

2.2.1. Blood donation reactions inventory (BDRI)

Subjective vasovagal symptoms were assessed after donation with the BDRI, a well-validated indicator of the vasovagal response in the blood donation context. This is a 4-item survey consisting of ratings of faintness, dizziness, lightheadedness, and weakness (France, Ditto, France, & Himawan, 2008; Meade, France & Peterson, 1996). Participants indicated on a six-point scale the degree to which they experienced these symptoms from "not at all" to "an extreme degree." Scores on the items show high internal consistency and correspond with phlebotomist ratings of donor reactions (France et al., 2008; Meade et al., 1996). Also, high scores on the BDRI predict decreased future donation (France et al., 2004). Inter-item correlation coefficients range from 0.61 to 0.87. Internal consistency is also high (Cronbach's α ranging from 0.93 to 0.96; France et al., 2008).

2.2.2. Spielberger State-Trait Anxiety Inventory (STAI)

State anxiety was assessed using an abbreviated version of the STAI both before and after donation. Participants reported how they currently felt on five four-point scales with anchors of "not at all" and "very much" (Spielberger, Gorsuch, & Lushene, 1970; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983). The STAI shows high internal consistency (Cronbach's α ranging from 0.86 to 0.95), high construct validity, and scores increase in response to stress and decrease following relaxation (Spielberger et al., 1983).

2.3. Apparatus

2.3.1. Blood pressure

Ambulatory measurements of systolic and diastolic blood pressure (converted to mean arterial pressure; MAP) were obtained in the final 30–60 s of five-minute intervals using a Suntech Instruments (SunTech Medical®, Morrisville, NC, USA; www.suntechmed.com) Accutracker DX ambulatory auscultatory blood pressure monitor. For example, the blood pressure measurements were taken just before the five-minute mark prior to sitting in the donation chair and the second blood pressure measurement was taken just after arrival at the chair.

2.3.2. Impedance cardiography and electrocardiogram

A number of physiological measures were obtained using a Bio-Impedance Technology (Microtronics Corp., Chapel Hill, NC, USA; www.microtronics-bit.com) Ambulatory Impedance Monitor model 8F. To limit the number of statistical analyses, the present study focused on the key variables of heart rate (HR), cardiac output (CO), systemic vascular (total peripheral) resistance (TPR), and pre-ejection period (PEP). To derive the impedance signal, a tetrapolar configuration of spot and band electrodes was used: one spot current electrode behind the right ear over the base of the mastoid process and the other over the lower right rib cage below the lower recording band electrode that encircled the thorax at the xiphoid process (Allen, Fahrenberg, Kelsey, Lovallo, & Doornen, 2007). The second recording band electrode encircled the base of the neck. To obtain the electrocardiogram signal and heart rate, a third spot electrode was placed over the lower left rib cage, used in concert with the two other spot electrodes.

2.4. Procedure

After providing written consent, the participant completed a brief demographic questionnaire and the STAI. They were then randomly assigned to Applied Tension or donation-as-usual. Following a short training video for AT (if applicable), the physiological recording equipment was attached and they proceeded through the normal blood donation procedure. Physiological measures were obtained throughout the procedure. All participants were sitting quietly somewhere in the 10-to-5 min period before arriving at the donation chair – either with the screening nurse or in the waiting room, following screening. The only movement in the 5-to-0 min pre-donation period was a short walk to the chair. AT was practiced only in the donation chair. When the donors arrived at the chair, they were asked by a research assistant for a verbal rating (0–100 scale) of how relaxed they were at the moment, to provide a more in vivo assessment of anxiety. They were asked for another rating

just before they left the chair. After blood donation, participants completed a longer questionnaire packet including the BDRI and STAI.

2.5. Data reduction and analysis

The main independent variable in the study was the severity of vasovagal symptoms indicated on the BDRI. The four symptom ratings were summed and log-transformed to improve the distribution. The primary dependent variables were eight physiological measures: MAP, HR, CO, TPR, PEP, respiration rate, high frequency heart rate variability, and the ratio of low/high frequency heart rate variability.

The impedance cardiography-based measures were averaged over 55-s intervals and post hoc editing was done using the Copworks program (Bio-Impedance Technology, Inc., Chapel Hill, NC, USA). These values were subsequently averaged within five-minute windows using sitting on the donation chair as the index event. MAP recorded during each window was used as the measure of blood pressure. TPR for the period was calculated using the standard formula: MAP/CO * 80.

Several measures were derived from analysis of beat-to-beat heart rate variability (HRV), also obtained from the impedance monitor. Sequential cardiac interval data from five-minute blocks were analyzed using the HRV Analysis program (Biomedical Signal Analysis Group, Department of Applied Physics, University of Kuopio, Finland). This program uses Fast Fourier Transformation to calculate power within conventional high frequency (0.15–0.40 Hz) and low frequency (0.04–0.15 Hz) bands. HRV provides a non-invasive means of assessing the short-term effects of the autonomic nervous system on the heart (Task Force, 1996). In particular, high-frequency heart rate variability (HF HRV), reflecting vagally-mediated respiratory sinus arrhythmia, is often used as an index of vagal regulation of heart rate. Low frequency variability reflects greater a mixture of sympathetic and parasympathetic activity hence the ratio of low and high frequency heart rate variability (LF/HF HRV) is often used as an index of sympathetic activity though this is more controversial than HF HRV (Reyes del Paso, Langewitz, Mulder, Roon, & Duschek, 2013; Task Force, 1996). The central frequency in the high frequency band of the autoregressive spectrum was used to estimate respiration rate (RR; Thayer, Sollers III, Ruiz-Padial, & Vila 2002).

Based on practical and theoretical considerations, statistical analyses focused on the two five-minute windows prior to the participant arriving at the donation chair. On the practical side, while waiting time varied, it required at least ten minutes between attachment recording equipment and arrival at the chair, allowing for the medical screen. Further, while activities during waiting can vary depending on clinic flow (e.g., donors may watch television or talk with others during a longer wait), the last ten minutes before arrival at the chair are fairly standardized. On the theoretical side, the minutes just before arrival at the chair are highly interesting as needle insertion is imminent and the ascending phase of the diphasic response, if one exists, should be evident.

Preliminary regression and ANOVA analyses were conducted to examine possible associations between age, sex, blood donation experience, anxiety, and BDRI symptom reports. Pre-to-post-donation anxiety and relaxation ratings were compared by *t*-tests. Linear regressions were used to predict BDRI symptom reports from anxiety and relaxation. Logistic regressions were used to predict nurse initiated treatment and fainting from BDRI symptom reports. To determine the physiological correlates of vasovagal symptoms, the primary analyses were Symptoms (treated as a continuous variable) × 2 Applied Tension (yes, no) × 2 Time (10–5 min before sitting on chair, 5–0 min before sitting on chair) general linear models (GLMs). While AT did not actually influence BDRI scores in this study (Ditto et al., 2009) and the analyses focused on the pre-donation period before anyone practiced the technique, AT had other effects on blood donation outcome (discussed in the previous paper) hence it was included as a factor in the analyses as a precaution. As well, those assigned to the AT condition may have felt better able to cope with the upcoming procedure, possibly influencing the physiological measures.

3. Results

There was no association between vasovagal symptoms (i.e., BDRI score) and age, sex, or previous blood donation experience. As noted above, this was a fairly homogenous sample of inexperienced donors. Consistent with the idea that pre-donation period is particularly stressful, pre-donation STAI scores were significantly higher than post-donation STAI scores ($t(95) = 6.04$, $p < .001$) and in-chair pre-donation ratings of relaxation were lower than in-chair post-donation ratings of relaxation ($t(96) = 2.00$, $p = .048$). Both pre-donation STAI and the in-chair pre-donation rating of relaxation were strong predictors of BDRI score (standardized $B = .35$ and $-.34$, respectively, both $p < .001$). For example, of the 11 participants who rated their pre-donation relaxation 95 or greater, none reported symptoms on the BDRI (results were similar for the pre-donation STAI). Despite the loss of approximately 450 ml of blood, at least some anxiety seems to have been necessary for a vasovagal response.

Table 1
Physiological response to the anticipation of blood donation.

Variable	Units	10-to-5 min before donation chair Mean (SD)	5-to-0 min before donation chair Mean (SD)
MAP	mmHg	92.0 (8.2)	92.3 (9.3)
HR	beats per minute	78.5 (11.1)	80.6 (11.1)*
CO	l/min	9.4 (3.3)	9.7 (2.8)
TPR	dynes * s/cm^5	841.9 (243.5)	795.3 (224.3)
PEP	ms	121.6 (14.8)	121.6 (14.7)
RR	Hz	.2481 (.062)	.2470 (.057)
HF HRV	ms^2	432.5 (464.3)	396.6 (519.0)
LF/HF HRV	units	2.20 (1.4)	2.87 (2.1)*

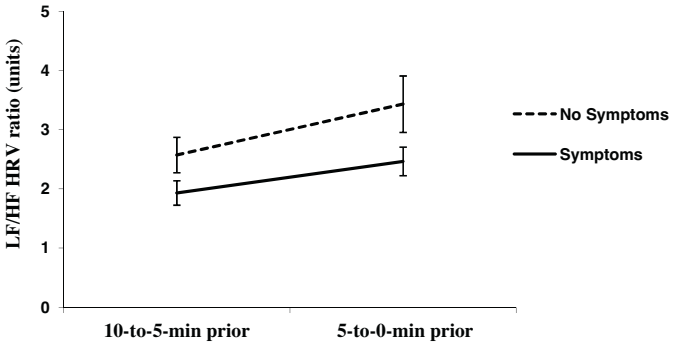

Fig. 1. LF/HF HRV ratio mean data. Standard errors are represented by error bars.

Consistent with previous research (France et al., 2008; Meade et al., 1996), the validity of BDRI score as an index of vasovagal symptoms was supported by strong relationships with the need for nurse-initiated treatment (OR = 56.20, 95% CI = 7.35–429.79, $p < .001$; 11 participants required some form of treatment) and fainting (OR > 100, $p = .038$; 4 participants fainted).

3.1. Physiological response to the anticipation of blood donation

There were no significant effects in the analyses of mean arterial pressure, cardiac output, and high frequency heart rate variability. In general, MAP, CO, and HF HRV remained stable during the pre-donation period and did not distinguish people who subsequently experienced and did not experience vasovagal symptoms.

In contrast, the GLM of heart rate produced a significant main effect of Time ($F(1,68) = 4.55$, $p = .037$, $\eta^2_p = .063$; Table 1). HR increased in the five minutes immediately before arrival at the chair. The GLM of LF/HF HRV also produced a significant main effect of Time ($F(1,60) = 6.26$, $p = .015$, $\eta^2_p = .094$) due to increasing values. Combined with the absence of an effect of time on HF HRV, this suggests that the pre-donation increase in HR may have been due to greater sympathetic nervous system activity.[1] More important in the present context, the main effect of Symptoms was also significant ($F(1,60) = 6.31$, $p = .015$, $\eta^2_p = .095$). Participants who subsequently experienced vasovagal symptoms had significantly *lower* LF/HF HRV during the pre-donation period (Fig. 1). Given the potential impact of respiration rate on HRV and an effect of Symptoms on RR (discussed below), a Mixed Model of LF/HF HRV was conducted with RR included as a within-subjects covariate.

[1] Relatedly, LF/HF HRV dropped significantly during the first five minutes of the blood donation procedure even among those who did not subsequently experience symptoms, $t(27) = 2.09$, $p = .046$.

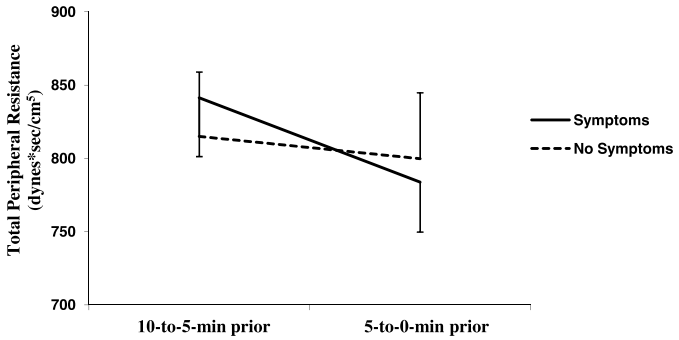

Fig. 2. Total peripheral resistance mean data. Standard errors are represented by error bars.

The effect of Symptoms remained ($F(1,65) = 4.10$, $p = .047$). In contrast to these results, however, the GLM of PEP did not produce a significant main effect of Time ($F(1,68) = .038$, $p = .846$, $\eta^2_p = .001$) or Symptoms ($F(1,68) = .508$, $p = .478$, $\eta^2_p = .007$); though not statistically significant, participants who experienced Symptoms had somewhat higher PEP values (lower sympathetic activity).

Similar to LF/HF HRV, the analysis of total peripheral resistance suggests sympathetic withdrawal in donors who subsequently experienced symptoms. The interaction between Symptoms and Time was significant ($F(1,60) = 6.80$, $p = .012$, $\eta^2_p = .102$). Analyses of simple main effects revealed that this was due to the fact that TPR was stable among participants without symptoms whereas it decreased significantly ($F(1,33) = 4.44$, $p = .043$, $\eta^2_p = .119$) among those who subsequently developed vasovagal symptoms (Fig. 2).[2]

The only variable that was influenced by assignment to AT (which participants had not yet begun to practice) was respiration rate. The Symptoms × AT interaction was significant in the GLM of RR ($F(1,65) = 4.32$, $p = .041$, $\eta^2_p = .062$). This was due to the fact that assignment to AT seemed to buffer the impact of the upcoming procedure on RR. A significant effect of Symptoms was observed only in participants who were not assigned to AT ($F(1,22) = 12.40$, $p = .002$, $\eta^2_p = .360$). Participants assigned to AT were intermediate and the difference between those who developed symptoms and those who did not was not significant. Somewhat surprisingly, the difference in non-AT participants reflected *lower* RR in those who subsequently developed symptoms.

3.2. Anxiety and respiration rate

The negative association between respiration rate and vasovagal symptoms was somewhat unexpected despite the indirect measurement of RR via HRV and absence of information about other parameters such as respiratory depth. To examine this interesting finding a bit more, two additional GLMs were conducted: a Pre-Donation STAI (treated as a continuous variable) × 2 Time GLM and a Pre-Donation Relaxation Rating (treated as a continuous variable) × 2 Time GLM of RR. While the first analysis did not produce any significant effects, the second yielded a significant main effect of Relaxation Rating ($F(1,67) = 4.01$, $p = .049$, $\eta^2_p = .117$). Participants who felt less relaxed at arrival at the donation chair were breathing slower.

[2] Although the present analyses stopped at the moment the participant arrived at the donation chair, it may be useful to note that this trend continued during the blood draw. The results of a Symptoms × AT × 4 Time (10–5 min before sitting on chair, 5–0 min before sitting on chair, 0–5 min after sitting on the chair, 5–10 min after sitting on the chair) produced a similar Symptoms × Time interaction ($F(3,55) = 2.89$, $p = .044$, Wilks' lambda = .864, $\eta^2_p = .136$).

Table 2
Physiological variables for participants who fainted ($N = 4$).

Variable	Units	10-to-5 min before donation chair Mean (SD)	5-to-0 min before donation chair Mean (SD)
MAP	mmHg	102.7 (7.1)	98.2 (3.5)
HR	beats per minute	75.2 (20.4)	75.3 (17.1)
CO	l/min	8.4 (2.3)	11.3 (4.8)
TPR	dynes * s/cm^5	1125.4 (177.7)	670.8 (327.7)
PEP	ms	115.4 (13.3)	116.8 (18.7)
RR	Hz	.1738 (.015)	.2202 (.068)
HF HRV	ms^2	623.5 (629.8)	840.5 (1237.2)
LF/HF HRV	units	1.40 (.53)	1.61 (.83)

3.3. Fainters vs. non-fainters

As noted above, due to the prompt and effective efforts of nursing staff, relatively few donors fainted ($N = 4$). Despite the small number of fainters, an examination of the pre-donation physiological activity in these more severe cases reveal similar patterns to others who reported symptoms: relatively low RR, sharp decreases in TPR, and lower LF/HF HRV ratios (Table 2).

4. Discussion

Although there were a number of limitations, one advantage of this study was the ability to examine physiological correlates of real and in some cases clinically significant vasovagal reactions, as opposed to mild symptoms produced by analog stimuli. While only a minority of participants required treatment for a vasovagal reaction (as judged by nursing staff) and fewer fainted, the fact that this real-life situation led to such events in some supports the value of the research approach.

In this study of real-life vasovagal reactions, there was no evidence of a diphasic pattern or, at least, the ascending phase of a diphasic pattern. If blood donation-related vasovagal reactions are diphasic, people who eventually develop symptoms should display greater arousal during the pre-donation period. In essence, the diphasic model states that the rollercoaster has to go up before it goes down. The anticipation period is the most stressful part of the procedure as reflected by both subjective and physiological measures (Adler et al., 1994; Sledge, 1978). In the present study, participant ratings of relaxation were significantly lower when they arrived at the chair compared to 10–15 min at the end of the blood draw and both HR and LF/HF HRV increased in the five minutes before arrival at the chair.

However, people who subsequently developed vasovagal symptoms displayed, if anything, lower rather than higher physiological activity at this time. For example, while HR and LF/HF HRV increased, donors who developed symptoms did not differ in HR from those who did not and had lower LF/HF HRV. The total peripheral resistance results are even more persuasive. TPR decreased significantly in this period in donors who developed symptoms. While it is possible that the ascending phase occurred earlier and these individuals "peaked" before the 10–5 min window, this seems unlikely given that stress appears to have peaked just before needle insertion (which usually occurs within a minute or two following arrival at the chair). Similarly, based on these analyses, the possibility that some measures may have reversed course after arrival at the chair and gone up and then down cannot be excluded (although theoretically justified, the decision to restrict analyses to the pre-donation period was related to the fact that some participants practiced the muscle-tension technique Applied Tension during the blood draw, complicating interpretation of the physiological measures). However, this is also unlikely since participants rated

themselves as more relaxed at the end of the blood draw. It seems more parsimonious to conclude that reactions were characterized by reduced activity in some physiological parameters from the start of this stressful procedure. In fact, despite widespread acceptance of the diphasic model dating to the 1960s, earlier descriptions of the vasovagal response emphasized low and decreasing arousal. For example, Lewis (1932, p. 873–874) argued that "nervous agitation and emotional stress . . . are commonly provocative . . .. From the start there is a progressive lowering of blood pressure. . ..".

In addition to the findings of LF/HF HRV and TPR, PEP was higher in participants who experienced symptoms (suggesting lower sympathetic activity), though this effect was not statistically significant. This might raise questions on the interpretation of the current results. PEP is a reliable indicator of cardiac sympathetic activity, while the validity of the LF/HF HRV ratio, though sometimes still used, has been strongly debated (Goedhart, Willemsen, Houtveen, Boomsma, & De Geus, 2008; Heathers, 2012; Task Force, 1996). On the other hand, the consistency of the effect of TPR with LF/HF HRV supports the possibility of some form of sympathetic withdrawal.

Due to the ambulatory nature of this study, one limitation was the inability to continuously record or control for all physical activities prior to the donor arriving at the chair. The contribution of any such physical activity to sympathetic activity remains unknown. Further research with continuous monitoring of physical activity could directly address this question. However, physical activity was significantly limited in all participants and any possible contribution to sympathetic activity is probably small. First, all participants had a number of electrodes attached to their chest, a blood pressure cuff on their arm, two pouches on a belt (one for the impedance monitor and one for the blood pressure monitor), and were guided by staff through a blood collection clinic. Therefore, even for an ambulatory setting, activity was restricted and all participants were moving cautiously and continuously guided. Second, the particular nature of this ambulatory setting meant that all participants were sitting quietly somewhere in the 10-to-5 min pre-donation period – either with the screening nurse or in the waiting room, following screening. The only movement in the 5-to-0 min pre-donation period was a short walk to the chair. Once on the chair, the only physical activity was (for some) Applied Tension, which was only practiced following the donation chair and is not relevant to this investigation. As a result, the results concerning individual differences in symptoms do not appear to be confounded by differences in physical activity.

The results are consistent with those of several other recent studies emphasizing the importance of sympathetic withdrawal and vasodilation in the vasovagal response (Béchir et al., 2003; Sarlo et al., 2008; Shen et al., 2000). For example, Sarlo and colleagues (2008) found that exposure to a surgery film increased total peripheral resistance in control participants but produced a significant decrease in BII phobics. The investigators suggest that this may be a key mechanism in the production of symptoms.

The results are also consistent with those of other studies that have found limited evidence of vagal activity, operationalized by HF HRV, in the "vasovagal" response (Gerlach et al., 2006; Sarlo et al., 2008; Vossbeck-Elsebusch, Steinigeweg, Vögele, & Gerlach, 2012). That said, the observation of higher pre-donation HF HRV in fainters provides some solace for this traditional belief and is consistent with the other results indicating early inhibitory activity. While interpretation of the findings from the subsample of only four fainters should be made with caution, an examination of the pre-donation physiological activity in these severe cases show similar patterns to those who reported milder symptoms: relatively low respiration rates, sharp decreases in TPR, and lower LF/HF HRV.

The difference in respiration rate between participants who did and did not subsequently develop symptoms is intriguing and lends further strength to the idea that some prospective donors experienced a sense of "impending doom", especially given the relationship between RR and rating of relaxation at arrival at the donation chair. Yet these findings raise more questions than they answer. For example, when confronted with fear-relevant stimuli, BII phobics are more likely to increase rather than decrease respiration parameters such as tidal volume and sigh breaths, resulting in consequent drops in pCO_2 indicative of hyperventilation (Gerlach et al., 2006; Ritz, Wilhelm, Meuret, Gerlach, & Roth, 2009; Ritz, Meuret, & Simon, 2013). These findings are partially compatible with our results – i.e., hyperventilation by taking long breaths. Do anxious non-phobics (blood donation is a voluntary activity) react differently to "inescapable injury"? It is interesting to note that laboratory manipulations designed to produce sadness, typically by conveying a sense of hopelessness and loss, usually decrease RR (Kreibig, Wilhelm, Roth, & Gross, 2007). On the other hand, perhaps lower RR is a coping response rather than a manifestation of fear. Steptoe and Wardle (1988) found that people who experienced vasovagal symptoms while watching a surgery video reported breathing slowly and deeply to cope with the film. Relatedly, was low RR associated with greater respiratory depth? "Sighing" is a common clinical observation in blood clinics and stressful situations in general (Vlemincx et al., 2009). It will be important to examine this issue given the current interest in relations among hyperventilation, CO_2 expiration, cerebral vasoconstriction, and risk for syncope (Immink, Pott, Secher, & Van Lieshout, 2014).

Another limitation is use of the HRV signal to estimate respiration rate. This indirect estimation does not include tidal volume, which can be of particular importance when respiration rate and tidal volume dissociate during states of over breathing, for example. Direct and more sophisticated measures of respiration are recommended in future studies.

Despite interesting findings, there were quite a few limitations to the study. In addition to those mentioned above such as the lack of a true baseline period and direct measures of respiration is the fact that data were averaged within five-minute windows and blood pressure was only taken at the end of these periods. Thus, it is possible that faster-moving changes more consistent with a diphasic response were not detected.

As well, the results do not provide a complete explanation of the presumed cerebral hypoperfusion which produced the symptoms. While participants may have experienced changes in autonomic activity and TPR fell, this did not produce a significant decrease in blood pressure at this time though this may have occurred later. Indeed, psychological and physical (e.g., prolonged standing) stressors that impair the return of blood to the heart are prototypical stimuli for a vasovagal response. Nevertheless, it seems likely that other mechanisms such as hyperventilation and/or specific changes in cerebral vasoconstriction are also involved (Immink et al., 2014). Finally, while the study focused on the relatively simple question of the presence or absence of the diphasic response, it is very possible that there are subtypes of reactors, some of whom display a diphasic pattern and some (perhaps most) who do not (Ritz et al., 2013). This question will require larger and more diverse samples to answer. That said, the results highlight the complexity of the vasovagal response and support the view that the traditional diphasic description focused on parasympathetic activity is not sufficient (Gerlach et al., 2006; Ritz et al., 2010; Sarlo et al., 2008). The vasovagal response is a common problem in psychiatric, medical, and community settings. A better understanding of this fascinating reaction has a number of theoretical and clinical implications.

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