

Psychophysiology of the Vasovagal Response

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General Abstract

Vasovagal responses (VVR) produce symptoms such as faintness, dizziness, weakness, lightheadedness, and possible syncope. VVR are a unique type of stress response, complicating and deterring people from various medical procedures such as blood donation, vaccinations, dental exams, etc. The specific psychological processes involved in VVR have puzzled theorists for decades, given the distinctive stress-related decreases in physiological activity. The psychophysiological processes of VVR continue to be debated. Three studies were conducted to examine the psychophysiology of VVR in both clinical and controlled laboratory settings, including factors related to primary appraisal, secondary appraisal, autonomic, and hemodynamic processes. The first laboratory-based study examined the importance of blood and injection stimuli in provoking VVR. A video of a blood draw led to greater VVR than one of an injection. Sympathetic nervous system activity decreased during both videos but significantly more during the blood-draw video. This decrease in sympathetic activity was reversed by the Applied Tension technique. In Study Two, participants were assigned to have high or low perceived control during exposure to a stimulus video of a mitral valve surgery, known to trigger VVR. Perceived control was manipulated by allowing some participants to choose a break time, though all received equivalent breaks. Low perceived control led to more vasovagal symptoms, higher anxiety, and lower stroke volume, cardiac output, and diastolic blood pressure. The third study examined autonomic and hemodynamic processes associated with the development of naturally occurring VVR. Participants who subsequently experienced vasovagal symptoms experienced lower low-frequency/high-frequency heart rate variability ratios throughout the blood donation process, suggesting lower sympathetic nervous system activity, consistent with Study One. These individuals also showed a greater decrease in total peripheral resistance. In

sum, these findings indicate the importance of perceived blood loss (primary appraisal) and perceived control (secondary appraisal) in VVR. The findings from Study Three contribute to knowledge of physiological processes of VVR, providing autonomic and hemodynamic data from clinical blood donation settings. Future research is recommended to examine the salience of blood stimuli and the effectiveness of the manipulation of perceived control on VVR in clinical settings.

Résumé

Les réactions vasovagale (VVR) comprennent des symptômes tels que la faiblesse, des étourdissements, et la possibilité de syncope. VVR démontre un type unique de la réponse au stress qui complique diverses procédures médicales telles que le don de sang, les vaccins, les examens dentaires, etc. Les processus psychophysiologiques spécifiques impliqués dans VVR ont intrigué les théoriciens depuis des décennies, compte tenu des particularités des baisses d'activité physiologique. Les processus psychophysiologiques de VVR continuent d'être débattues. Trois études ont été menées pour fournir un examen de la psychophysiologie de VVR dans les milieux cliniques et de laboratoire, y compris les facteurs liés à l'évaluation primaire, l'évaluation secondaire, et les processus autonomiques et hémodynamiques. La première étude a examiné l'importance des stimuli du sang et d'injection qui provoque VVR. Un vidéo d'un prélèvement de sang a stimuler une plus grande réponse VVR que celle d'une injection. L'activité du système nerveux sympathique a diminué au cours des deux vidéos, mais beaucoup plus au cours du vidéo du prélèvement de sang. Cette diminution de l'activité sympathique a été renversée par la technique de la tension appliquée. Dans l'étude numéro deux, les participants ont été désignés à une perception de contrôle haute ou basse lors de l'exposition à un vidéo d'une chirurgie cardiaque, connu pour déclencher VVR. La perception de contrôle a été manipulée en permettant à certains participants de choisir un temps de pause, mais tous ont reçu des pauses équivalentes. Le faible contrôle perçu a contribuer à des symptômes augmentés de VVR et d'anxiété, le volume de course cardiaque inférieure, le débit cardiaque diminué, et la pression artérielle diastolique plus faible. La troisième étude a examiné les processus autonomiques et hémodynamiques associées à l'élaboration de VVR naturelle dans un clinique de don de sang. Les participants qui ont rapporter des symptômes vasovagale ont montré des ratios plus faibles

du basse-fréquence/haute-fréquence de la variabilité cardiaque, qui suggère la baisse d'activité du système nerveux sympathique, cohérente avec l'étude numéro un. Les participants ont également montré une diminution générale de la résistance périphérique totale. En somme, ces résultats montrent l'importance de la perception d'une perte de sang (d'évaluation primaire) et le contrôle perçu (d'évaluation secondaire) sur VVR. Les résultats de l'étude numéro trois ont élucidé quelques processus physiologiques de VVR, fournissant des données autonomiques et hémodynamiques. Des recherches futures sont recommandées pour examiner l'efficacité de la manipulation de contrôle perçu et de la prégnance des stimuli de sang sur VVR en milieu clinique.

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Preface and Contribution of Authors

As the first author on the three manuscripts, I took the lead role in the research design, testing of participants, analyses, data interpretations, and writing. The second manuscript is co-authored by Gillian McGovern and Nadine Bekkouche, research assistants who helped test participants and process much of the raw physiological data. Also, Dr. Simon Bacon provided assistance in the procedures for analysis and interpretation of some of the physiological data as well as manuscript revision. My supervisor, Dr. Blaine Ditto, the final author on all three manuscripts, provided substantial contribution to the design, analyses, interpretation of data, and editing of the manuscripts. The findings of these three manuscripts are original scholarship and distinct contributions to scientific knowledge in Psychology.

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General Introduction

The Vasovagal Response: a Psychophysiological Perspective

Manifestations of associations between emotion and cardiovascular activity are a part of daily human experience. These responses originate in the cerebral cortex, pass through the corticohypothalamic pathways, and reach medullary cardiovascular centers where subsequent cardiovascular responses are controlled (Mohrman & Heller, 1997). Blushing, a clear and simple example of cardiovascular response to emotion, is caused by a loss of sympathetic vasoconstrictor activity to cutaneous vessels, thus engorging venous sinuses. A more complex example is the classic alarm ('fight-or-flight') reaction, a psychophysiological response to perceived harm or threat. This response includes a general increase in sympathetic and decrease in parasympathetic nervous system activity, preparing the body for action (Cannon, 1929; Selye, 1976). However, recent advances in evolutionary psychology have provided a more detailed description of the fight-or-flight response, now sometimes described as a 'freeze, flight, fight, fright, faint' response (Bracha, 2004; Bracha, Ralston, Matsukawa, Williams, & Bracha, 2004). Indeed, consistent with the trend in emotional neuroscience emphasizing differences in the peripheral physiological correlates of emotion linked to the nature of adaptive behaviour (e.g., Rolls, 2013), there is increasing interest in both similarities and differences in stress responses produced by different kinds of environmental challenges.

Fainting, or syncope, is the transient loss of consciousness caused by insufficient supply of oxygen or glucose to the reticular activating system of both hemispheres of the brain, from which recovery is spontaneous (Folino, 2007). This can be accompanied by the stereotyped loss of muscle tone and subsequent falling. The general causes of syncope include: neurally mediated (e.g., vasovagal) responses, orthostatic, cardiac, structural cardiopulmonary disease,

cerebrovascular disease, and neurological/psychiatric disease (Arthur & Kaye, 2000; Benditt & Blanc, 2003). Syncope accounts for 3% of emergency department visits, 1-6% of hospital admissions, and many unpleasant events outside the hospital. Its assessment remains a challenging task in hospital and community settings (Diehl, 2005; Kapoor, 1992; Sheldon et al., 2011).

Vasovagal syncope, a subtype of neurally mediated reflex syncope, is usually triggered by an emotional or painful event, but it can also be triggered by various medical procedures, heat, prolonged standing and other postural challenge (Benditt & Blanc, 2003). This type of syncope occurs in both healthy individuals as well as those with existing health problems. Vasovagal syncope, often described as ‘emotional fainting’ due to its most typical causes (Graham, Kabler, & Lunsford, 1961), is the most common form of syncope (Manolis, Linzer, Salem, & Estes, 1990). The ‘vaso’ part of the term ‘vasovagal’ refers to the involvement of vasodilation, contributing to a significant decrease in blood pressure. The ‘vagal’ part refers to the involvement of the vagus nerve which, among other functions, can slow the pulse (bradycardia), cause gastrointestinal changes, and affect a number of parasympathetic responses (Lewis, 1932). However, this is a bit of a loose, historically based definition. For example, building on earlier research showing that atropine is ineffective in reducing vasovagal responses (Lewis, 1932; Weissler, Warren, Estes, McIntosh, & Leonard, 1957), the role of vagal activity in the ‘vasovagal response’ has been seriously questioned (Gerlach et al., 2006). As well, recent research points to the importance of blood vessel constriction in the brain as well as peripheral vasodilation (Folino, 2006). Nevertheless, vasovagal responses (VVR) are generally associated with vasodilation of arterial and venous beds and bradycardia (Arthur & Kaye, 2000), though other nuances include the observation that vasodilation may be produced by withdrawal of

sympathetic vasoconstrictor activity and sympathetically mediated *active* vasodilation (Halliwill, Dietz, & Joyner, 1996). Based on such considerations, the term “vasovagal” has been challenged. An alternative term has been suggested –*vasodepressor* syncope. However, since the term ‘vasovagal’ is most often employed in the literature, it will be used here for sake of conventional terminology.

Vasovagal syncope was first described by Gowers in the 19th century (Nahm & Freeman, 2001), though Lewis (1932) presented the prototype of this fascinating psychophysiological phenomenon:

The patient was sitting, and a few cubic centimeters of blood had been withdrawn from a vein in the arm and the needle removed. He was watching the operation and began to feel queer, “as though his stomach had turned upside down”; he complained of dizziness, facial pallor was noticed, and his head fell forward to his knees The pulse was imperceptible; the heart sounds distant, its rate of beating being 50 per minute.... From time to time there were retching movements. The patient was limp, mentally confused, or actually unconscious, for several minutes; a heavy sweat broke.... Respiration was slow and sighing.... The systolic blood pressure was registered at 60mm; a little later the pressure fell to 55, then to 50.... Half an hour later he was able to leave the chair and walk unsupported across the room (Lewis, 1932, p. 876).

It is clear from this example that syncope is not necessarily the most distressing or only clinically significant symptom of VVR. Pre-syncopal responses, with or without syncope, include a number of identifiable and distressing experiences for the patient. The classic set of pre-syncopal symptoms includes: dizziness, lightheadedness, epigastric discomfort, nausea, pallor, diaphoresis, and blurred vision (Manolis, et al., 1990; Zervou, et al., 2005) and can be

considered to be on a continuum of severity with full-blown vasovagal syncope at one extreme (Ditto & Holly, 2009).

Clinical Relevance of the Vasovagal Response

VVR have an enormous impact on society with medical, psychological, social, and economic implications (Zurak & Bilic, 2004). Serious medical consequences (e.g., seizures or sudden death) are rare but have been observed even in children undergoing routine vaccinations (Braun, Patriarca, & Ellenberg, 1997). Various injuries from falling are more frequent. As noted earlier, even without complications, individuals who have experienced vasovagal syncope are common visitors to emergency rooms. VVR can trigger extensive medical testing to rule out other problems such as epilepsy and cancer. In addition to social and economic costs produced by “over-utilization” of the medical system, the ability of VVR to produce “under-utilization” may be even more serious.

As suggested by the previous quote from Lewis (1932), symptoms of VVR can be very unpleasant even if they do not include fainting. As these symptoms can be produced by a number of medical procedures especially those, as will be discussed in detail later, involving exposure to needles and blood, people who have experienced mild-severe VVR or who are even concerned about VVR are significantly more likely to avoid dental care (Enkling, Marwinski, & Jhren, 2006), vaccination (Nir et al., 2003), and especially “voluntary” activities like blood donation. VVR are among the most important predictors of reduced blood donor return (France, France, Roussos, & Ditto, 2004; Ogata, Linuma, Nagashima, & Akabane, 1980). Defined conservatively, they occur in about 2-5% of donors (Popovsky, 2002; Taylor, 1942; Zervou et al., 2005), though when examining self-report questionnaires, 47-69% of donors report at least a

mild experience of VVR (Ditto, France, Lavoie, Roussos, & Adler, 2003). Even mild symptoms of VVR predict reduced donor return (Sauer & France, 1999).

Even in non-clinical populations, the prevalence of VVR is surprisingly high. In the Framingham study, 822 of the 7814 (10.5%) participants reported they had experienced at least one episode of syncope over a 17 year period (Soteriades, et al., 2002). The most frequently identified cause was a vasovagal reaction (21.2%). In another study, 49 of 378 university students (13%) reported having fainted or almost fainted at the sight of Blood-Injury-Injection (BII) stimuli (Kleinknecht, 1987). Kleinknecht and Lenz (1989) studied a different pool of 204 students and found 19.3% of the participants reported having had one or more fainting or near fainting episode in response to BII stimuli. It has therefore been argued that BII fears and associated VVR are exaggerations of responses that are prevalent in the general population supporting the notion that it may be an evolutionarily adaptive response (Thyer, Himle, & Curtis, 1985). Indeed, many of us avoid blood or injury stimuli where the most feared element seems to be distressing vasovagal symptoms (Rachman, 1990, p. 82).

Given their familiarity with medical procedures and needles, it can be easy for medical personnel to minimize symptoms of VVR such as dizziness and even brief fainting. However, the loss of control and consciousness involved in fainting among blood donors, dental patients, etc. can be a terrifying and an almost “near death” experience. As a result, it is not surprising that a tendency to experience even mild symptoms in such settings can discourage a variety of health care behavior.

Further, such avoidance is a defining feature of people who have very strong fears of blood, injury, and injections. That is, BII-phobia is associated with VVR rather than the typical increased arousal when confronting the feared stimulus –i.e., decreases in blood pressure and

heart rate rather than the common *increases* in other phobias and anxiety disorders (Barlow, 2002; Beck & Emery, 1985, p. 50; Graham, et al., 1961; Rachman, 1990; Thyer et al., 1985). BII-phobia is relatively common with a population lifetime prevalence of 3-3.5% (Bienvenu & Eaton, 1998; Fredrikson, Annas, Fischer, & Wik, 1996). This specific phobia involves the fear of stimuli associated with blood (hemophobia), injury, and/or injections (needles). 70% of blood phobics have experienced syncope at least once when exposed to relevant stimuli (Öst, 1992) whereas the prevalence of fainting in people with other specific phobias is no greater than the prevalence of fainting in the non-phobic population (Barlow, 2002; Ventura et al., 2001). VVR associated with BII-phobia also very commonly lead to significant psychosocial dysfunction such as the avoidance of important medical procedures including blood draws, vaccinations, and dental exams (Enkling et al., 2006; Kleinknecht & Lenz, 1989; Marks, 1988; Nir et al., 2003; Page, 1994; Page, 1996). Nonetheless, the psychophysiological mechanisms of VVR in BII phobics and others are poorly understood and requires further research (Ayala, Meuret, & Ritz, 2009; Rachman, 1990).

Physiological Mechanisms

Other than some variance explained by genetic markers, pathophysiological explanations of VVR continue to be debated (Zurak, & Bilic, 2004). Psychophysiological mechanisms are even more poorly understood (Popovsky, 2002). Fundamentally, VVR are due to decreased cerebral perfusion. Any physiological changes leading to impairment in blood flow to the cerebral vasculature will increase symptoms of VVR. Pre-syncopal symptoms of VVR are reported in about two-thirds of syncope patients (Wieling, van Dijk, van Lieshout, & Benditt, 2003). Symptoms, as previously mentioned, may include an inability to think clearly and diminished vision due to disturbances in retinal and cortical perfusion. Other possible symptoms

result from autonomic activity such as tachycardia, sweating, pallor, and later bradycardia and nausea. These symptoms may occur minutes or seconds before syncope.

Although the clearest physiological sign, and possible key mechanism, of a VVR is a decrease in blood pressure, it is useful to note that this is an active, stress-related response. For example, as discussed previously, not only are the situations that elicit VVR typically unpleasant but some aspects of sympathetic nervous system activity increase during a VVR such as sympathetic stimulation of sweat glands (Edwards, Benoit, & Schondorf, 2004) and, probably, sympathetic stimulation of arterial β -receptors that contribute to vasodilation (Halliwill, Dietz, & Joyner, 1996). However, other aspects of sympathetic activity decrease during a VVR, most notably sympathetic vasoconstriction. In fact, as noted by Halliwill et al. (1996), this has been viewed as the predominant mechanism of the decrease in blood pressure and cerebral perfusion since 1932 when Lewis found that atropine did not prevent fainting even though it blocked heart rate deceleration. The role of vasodilation and venous pooling is supported by a number of observations such as the everyday yet well-documented effectiveness of compensatory postural maneuvers (e.g., laying down, putting the head between the knees, squatting) in alleviating symptoms (Krediet, van Dijk, Linzer, van Lieshout, & Wieling, 2002; van Lieshout, Wieling, Karemaker, & Eckberg, 1991), the fact that postural stress (e.g., standing, passive head-up tilt) contributes to and can elicit VVR in and of itself (van Lieshout et al., 1991), and even the value of caffeine to reduce reactions (Sauer & France, 1999).

The contribution of vagally-mediated heart rate deceleration to blood pressure decrease is more controversial. For example, in addition to the results related to atropine (Lewis, 1932; Weissler et al., 1957), a number of researchers have found that high frequency heart rate variability, reflecting vagally-mediated respiratory sinus arrhythmia, was unchanged during the

vasovagal process (Gerlach et al., 2006; Sarlo, Buodo, Munafò, Stegagno, & Palomba, 2008). Nevertheless, heart rate deceleration is common and indeed often used in the diagnosis of VVR (Benditt & Blanc, 2003; Fenton, Hammill, Rea, Low, & Shen, 2000) so the issue may be one of heterogeneity. That is, the relative contributions of vasodilation and bradycardia may differ between individuals somewhat.

What causes this pattern of response? van Lieshout et al. (1991) contrast two possible pathways – essentially, a “bottom-up” and a “top-down” pathway. The classic “bottom-up” theory, also referred to as the ventricular afferent theory, was developed primarily by Thorén and was the predominant view for many years (Mosqueda-Garcia, Furlan, Tank, & Fernandez-Violante, 2000; Öberg, & Thorén, 1972; Sharpey-Schafer, 1956). This theory sought to explain the “maladaptive” vasodilatory response to situations that “should” elicit vasoconstriction and an increase in blood pressure as the result of what is essentially a biological accident. It was proposed that a strong contraction around a “nearly empty” heart chamber (due to a drop in venous return following postural change, hemorrhage, or psychological stress) could produce a paradoxical stimulation of cardiac stretch receptors. This would lead, in turn, to abrupt sympathetic withdrawal and parasympathetic stimulation. While there were a number of positive features of this theory including its ability to explain the effects of a number of stimuli known to elicit VVR, it also suffered from a number of weaknesses. Perhaps most important was the fact that VVR can be observed in denervated heart transplant patients who have no means of conveying information about cardiac stretching to the brain (Fitzpatrick, Banner, Cheng, Yacoub, & Sutton, 1993; Montebugnoli, & Montanari, 1999; Mosqueda-Garcia et al., 2000). The theory also incorporated the assumption that VVR are “diphasic”, that is, the inhibitory phase is preceded by an excitatory phase. While this may occur for some individuals, the

generality of the diphasic model has been questioned in recent years (Lumley & Melamed, 1992; Ritz, Meuret, & Ayala, 2010; Ritz, Wilhelm, Gerlach, Kullowatz, & Roth, 2005; Sarlo et al., 2008). The value of the diphasic model will be discussed in somewhat more detail below as well as in Study 3.

As a result, although the details remain unclear, the “top-down” view is most common today. That is, the pattern of autonomic activity involved in a VVR originates in the brain. This general perspective also incorporates more recent explanations for reduced cerebral perfusion that do not rely on a systemic decrease in blood pressure. For example, many investigators have wondered about the role of relatively specific cerebral vasoconstriction in VVR (Grubb et al., 1991; Immink, Pott, Secher, & Van Lieshout, 2014; Lagi, Cencetti, Corsoni, Georgiadis, & Bacalli, 2001). This may be related to recent observations of an association between susceptibility to VVR and migraine headaches (Daas, Mimouni-Bloch, Rosenthal, & Shuper; Piovesan et al., 2008). Related questions include the nature of psychological states that produce this pattern of physiological activity, and the origin of this unusual response. These will be discussed in the following sections on psychological mechanisms.

As suggested above, the physiological process of VVR has long been described as diphasic (Graham et al., 1961). This is more an assumption about the physiological process than an explanatory theory. For example, the assumption of a diphasic response is built into a number of theories of VVR such as Graham’s belief that VVR were due to the experience of strong relief following a period of elevated stress. According to the classic description, the first phase of this response, consistent with the alarm (‘fight-or-flight’) reaction, includes an initial rise in blood pressure. The second phase includes a relative increase in parasympathetic activity and a drop in blood pressure (Page & Tan, 2009). For example, blood donors who faint have shown initial

increases in heart rate and blood pressure followed by decreases during or following the removal of the needle (Graham et al., 1961; Ruetz, Johnson, Callahan, Meade, & Smith, 1967). However, Ritz et al. (2010) noted that the observed blood pressure did not fall below initial baseline levels and therefore call into question the ‘diphasic’ pattern. The diphasic theory has been criticized for its lack of comparison conditions, poor baseline validity, and general limited empirical support. Lastly, diphasic patterns have not been seen in patients diagnosed with BII phobia (Lumley & Malamed, 1992; Ritz et al., 2010; Sarlo et al., 2008). Indeed, many questions remain about the mechanisms of VVR.

Psychological Mechanisms: Fear and Anxiety

Graham et al. (1961) argued that the first phase of the diphasic response begins with anxiety and associated heart rate acceleration and vasoconstriction. But, if these anxiety-related cardiovascular responses are suddenly opposed by removal of the stimulus and anxiety relief, this leads to parasympathetic activation, sharp decreases in heart rate, and vasodilation in the second phase (Graham et al., 1961). This explanation has had appeal in the literature due to its parsimony. However, if this explanation were true, you would expect students, for example, to be fainting following presentations and exams (Ditto & Holly, 2009). This is clearly not the case and highlights some of the limits of this theory. Nonetheless, anxiety appears to play an important role whether or not the process is diphasic.

In addition to the high prevalence of vasovagal syncope, BII phobics often have high scores on measures reflecting fear of physical symptoms such as the Anxiety Sensitivity Index (ASI; Barlow, 2002; Lumley & Malamed, 1992; Öst, 1992; Öst, Lindalh, Sterner, & Jerremalm, 1984; Rachman, 1990). The ASI assesses the belief that unexplained somatic sensations are dangerous, a fundamental notion in cognitive models of panic which leads to hyper vigilance

towards these sensations and further anxiety (Clark, 1986; Rapee, Brown, Antony, & Barlow, 1992). Similar to Lewis' (1932) idea, it has been argued that the beginning moments of VVR in BII-phobics start with a state of anxious arousal, perhaps not physiologically dissimilar to the early stages of panic (Page & Tan, 2009). Clark's (1986) cognitive model of panic disorder proposes that catastrophic misinterpretations of physiological arousal lead to hyper vigilance, thus exacerbating the arousal. Interestingly, a common fear in panic disorder is the fear of fainting; however this is a rare occurrence during states of anxiety and panic due to the *rise* in blood pressure and heart rate. Conversely, VVR typically involves sharp *decreases* in blood pressure and heart rate (Barlow, 2002; Beck & Emery, 1985, p. 50; Graham et al., 1961; Rachman, 1990; Thyer et al, 1985). Thus, the majority of BII-phobic patients *do* faint when exposed to phobic stimuli (Öst et al., 1984). Some have therefore argued that fear of fainting in BII-phobia is 'realistic' (Rachman, 1990), suggesting that the problem would be best addressed by behavioural interventions focused on managing VVR and fainting rather than anxiety per se. Indeed, the first phase of BII-phobic fainting often includes significant anxiety about the impending response including real and uncomfortable feelings of faintness and disgust (Cisler, Olatunji, & Lohr, 2009; Lumley & Melamed, 1992).

In contrast to the arguments that fear of fainting in BII phobia is 'realistic', it can be observed in clinical settings that this fear can be real but still to some degree *exaggerated* –hence the diagnosis of phobia. Recent studies indicate that the effectiveness of behaviourally and physiologically focused techniques to manage VVR in BII phobia (i.e., Applied Tension) may also be moderated by a sense of perceived control and anxiety reduction (Rtiz et al., 2010). It is well established that higher ratings of fear and anxiety increase the risk for VVR (Ditto &

France, 2006; Meade, France, Peterson, 1996). Interventions to address such fear and anxiety therefore seem appropriate in order to manage VVR.

In addition to the concern about physical symptoms, another interesting similarity between panic disorder and BII phobia concerns respiration. Though this should not be overstated since they do not usually faint, panic patients often experience some symptoms of VVR such as dizziness and lightheadedness, which stem from their tendency to hyperventilate. As discussed above, some recent research suggests an important role of localized cerebral vasoconstriction in VVR, as opposed to systemic blood pressure decrease. Hyperventilation significantly reduces blood CO₂ levels which can contribute to cerebral vasoconstriction. People in medical settings (e.g., blood donors) and BII phobics do not generally breathe quickly yet recent research suggests that they may occasionally hyperventilate by regular slow, deep breathing or irregular ‘sighing.’ For example, Ritz et al. (2005) found that vasovagal symptoms were associated with deep breathing in BII phobics who watched a surgery video. It is possible that these individuals were engaged in maladaptive coping, taking the traditional advice to “take a deep breath” when confronted with stress too literally. In another study using a surgery film, Steptoe and Wardle (1988) found that people who fainted or almost fainted said that they took deep breaths to cope with the film. While hyperventilation cannot explain VVR entirely since, for example, panic patients do not usually faint, there is strong current interest in relationships among anxiety, hyperventilation, cerebral perfusion, and syncope (Immink et al., 2014).

Psychological Mechanisms: The Possible Role of Disgust

Related to the notion of blood loss discussed in more detail later, there seems to be an especially strong relationship between VVR and blood fears (Thyer et al., 1985). VVR are common among those who are fearful of blood, even moreso than those with specific fears of

needles (Öst, 1992; Page, Bennett, Carter, & Woodmore, 1997). This is consistent with the idea that VVR are triggered by concerns about body envelope violations that include feelings of disgust (Page et al., 1997). Indeed, phlebotomy patients have a tendency to report both disgust and fear (Deacon & Abramowitz, 2006).

Rachman (1990) has argued that blood phobias should be reconstrued as an adverse psychophysiological reaction including disgust and no longer regarded as a phobia for three reasons. First, those who are affected by the sight of blood do not usually describe their reaction as one of 'fear.' Second, blood phobics show a physiological reaction unlike any other fear reaction (i.e., vasovagal response). Third, the response to the sight of blood can be reduced by simply adopting a recumbent position. Rachman (1990) further argued the subjective reaction in BII phobia may better be understood as disgust rather than fear. If any fear is involved, he argues, it may be the fear of one's own reaction and not the stimulus itself; 'it becomes possible to reconstrue blood phobias as a fear of fainting' (Rachman, 1990, p. 81). Related to this argument, a number of other investigations have linked BII fear and associated VVR with greater disgust and disgust sensitivity (De Jongh, et al., 1998; Exeter-Kent & Page, 2006; Olatunji, Sawchuk, de Jong, & Lohr, 2006; Page, 1994; Tolin, Lohr, Sawchuk, & Lee, 1997). Page (2003) examined disgust in BII fear and VVR, as measured by symptom report and blood pressure, during exposure to BII stimuli. Participants with high disgust sensitivity reported more symptoms of VVR and more pronounced decreases in blood pressure. Conversely, others have found that although disgust sensitivity was related to BII fears, it was *not* related to fainting (Gerlach et al., 2006; Kleinknecht, Kleinknecht, & Thorndike, 1997). That is, the disgust-faint relationship might be mediated by disgust's covariation with fear. Separating these constructs, although intuitively distinct, has been a challenge.

A recent review of the characteristics of disgust emphasized its association with parasympathetic nervous system activation implicated in VVR such as changes in heart rate, blood pressure, respiration, salivation, and gastrointestinal mobility (Olatunji & Sawchuk, 2005). In one of the more influential studies discussed in this review, disgust was associated with heart rate deceleration (Levenson, 1992). However, a more recent study by Gerlach and colleagues (2006) found no evidence of parasympathetic activation as indicated by respiratory sinus arrhythmia during exposure to venipuncture. Further, no association was found between disgust and parasympathetic activation. Page and Tan (2009) argued that this may have been due to the fact that, although the all participants experienced venipuncture, none actually *viewed* the event (i.e., they looked away) and were therefore not exposed to the disgust-related stimulus (i.e., blood). Indeed, it was questionable to what extent the participants experienced VVR because symptoms were not assessed and physiological changes were only found in respiration and heart rate.

These unclear findings of disgust's role in VVR may be due to several reasons: the psychophysiology of disgust has largely been ignored until recently; the fact that the concept of disgust is not unitary (Olatunji & Sawchuk, 2005); the original *Disgust Questionnaire (DQ)* has limited utility as it solely focuses on *food*-related disgust (Arrindell, Mulken, Kok, & Vollenbroek, 1999); the nature of the disgust stimuli are variable between studies; and disgust questionnaires seem to more accurately represent disgust sensitivity rather than disgust *intensity*. A better way to tap into disgust would be domain-specific (e.g., Olatunji, Haidt, & David, 2008), clarifying sensitivity from intensity, and using recently improved disgust scales and other measures, such as facial markers, of disgust.

The James-Lange theory provides yet another possible explanation of the relation of disgust with fainting. The experience and label of disgust may come about as a *result* of the physiological activity of VVR. For example, implantable vagal stimulators are now fairly common for the treatment of epilepsy and certain cases of depression (Hatton et al., 2006). Interestingly, common side effects of this treatment include nausea, vomiting, and symptoms similar to those during VVR.

Psychological Mechanisms: Fear of Blood Loss

As noted above, one limitation of much of the research about disgust is the general nature of the construct. VVR and disgust have been linked to various blood, injury, and injection stimuli (Marks, 1988). The relative importance of various BII stimuli in contributing to VVR has been difficult to evaluate. However, when considering situational triggers of VVR, one common denominator of psychological stimuli seems to be the rupturing of the body and the sight of blood.

Although hemorrhage-related fainting is sometimes classified differently than typical VVR, major blood loss evokes a pattern of response that is similar and perhaps identical. Across species, blood loss related syncope is almost guaranteed when loss exceeds about 30% of total volume (Diehl, 2005). This is due to an active response to blood loss as opposed to simple volume depletion in most cases. The initial response to blood loss tends to be a baroreflex-mediated increase in cardiovascular activity, presumably as an attempt to keep blood pressure from decreasing (Ludbrook, Potocnik, & Woods, 1988). However, once the blood loss reaches a certain point, there is an active inhibitory response involving sympathetic withdrawal. This response might seem odd because it contributes to further decreases in blood pressure, symptoms, and possibly syncope. The ventricular afferent theory suggests that this is essentially

an accident caused by random contractions around a nearly empty heart chamber (Mosqueda-Garcia et al., 2000; Öberg, & Thorén, 1972; Sharpey-Schafer, 1956). On the other hand, it seems unlikely that such a dramatic response would have been an accident and *not* evolutionarily adaptive. Indeed, a mechanism to reduce bleeding and facilitate blood clotting through lowered blood pressure (i.e., VVR) would have been adaptive when resuscitation strategies were not available. Although controversial, a review of several randomized-controlled trials suggested that normalizing a patient's blood pressure following hemorrhage may be harmful in some cases (Roberts, Evans, Bunn, Kwan, & Crowhurst, 2001).

In support of this notion, Diehl (2005) has proposed that the vasovagal response can be triggered by the anticipation and preparation for blood loss, as well as by actual hemorrhage, and this may be the origin of the link between BII stimuli and risk for VVR. As discussed earlier, among phobic individuals, blood phobics are most likely to experience vasovagal syncope. This trend appears to extend to people with non-phobic levels of fear and less severe symptoms of VVR. In two large samples of blood donors, people with mild-moderate blood fear were found to report more symptoms of VVR and be more likely to require treatment for VVR than individuals with other types of fears, even needle fears (Ditto, Gilchrist, & Holly, 2012). Relatedly, the first study of this dissertation attempted to disentangle the effects of different stimuli that may trigger symptoms of VVR. The image (idea) of blood loss appeared to be more important than other stimuli (needles) in provoking VVR (Gilchrist & Ditto, 2012).

Several other findings from the blood donation environment suggest the importance of worry about blood loss, including the simple fact that VVR are especially common in this environment. However, the issue is not blood loss per se. For example, experienced blood donors, who are more accustomed and at ease with the procedure and sensations, hardly ever

react (Meade et al., 1996; Ogata et al., 1980; Trouern-Trend, Cable, Badon, Newman, & Popovsky, 1999). Similarly, another study asked donors to rate how much blood they felt they had lost (even though all had given an identical amount) and found that vasovagal symptoms were positively associated with degree of perceived blood loss (Ditto, Balegh, Gilchrist, & Holly, 2012). Another interesting fact is that although most reactions occur at the end of the blood collection procedure or a few minutes after, it is not at all unusual for them to occur much later, e.g., in the refreshment area and to be associated with activities such as discussion about the procedure or final blood pressure measurement (Newman & Graves, 2001). Ditto and Holly (2009) suggest that inadvertent reminders of blood loss may trigger such reactions. This is consistent with other findings such as the fact that distraction appears to reduce donation-related VVR (Hanson & France, 2009), and seeing other blood donors being treated for symptoms can increase donation-related VVR (Ditto, Byrne, Holly, & Balegh, 2014; Ferguson & Bibby, 2002).

The notion of blood loss is tied to theories of VVR as well as its physiological assessment. For example, techniques such as lower body negative pressure (LBNP) and head-up tilt ('tilt table testing') have been used for decades in physiological laboratories and hospitals to study the effects of orthostatic stress and to simulate blood loss in humans (Goswami, Loeppky, & Hinghofer-Szalkay, 2008; Kaufman, 1994; Kenny, Bayliss, Ingram, & Sutton, 1986). The procedure of LBNP is simple: negative pressure surrounding the participants' lower body is produced by a vacuum in an airtight box, sealed around the participant's waistline. Head-up tilt is achieved by moving a patient from a horizontal to a vertical position on a table. These tests are used in the diagnosis of syncope and VVR and have been described as producing states of 'simulated hemorrhage' – though there is some debate as to whether this is a separate type of reaction. It therefore may not be surprising, due to the intricate relations between symptoms of

VVR and physiological processes of blood loss, that the perception or feelings related to blood loss may have become strongly associated with VVR.

Techniques to Manage Vasovagal Responses

Biology and medical students are often exposed to BII stimuli gradually through their programs; those who are squeamish are told that their feelings will eventually subside. Usually this does, in fact, occur. Embedded in these curricula, and perhaps with an implicit understanding by their designers, is a process of graded exposure and an habituation process akin to those understood in behavioural approaches to the effective treatment of these types of fears (M. Spevack, personal communication, 2007). Indeed, exposure-based treatments have received empirical support in the treatment of BII phobia (Ayala, Meuret, & Ritz, 2009). The treatments have become more complex since the 1980s, however, and deviate from standard behaviourally-based treatments for specific phobia largely due to VVR seen when confronting BII stimuli. That is, VVR impaired exposure treatments –people can hardly be exposed to stimuli when unconscious! As a result, techniques such as Applied Tension (AT) were added to the behavioural protocols in order to directly address VVR. AT is a simple technique of repeatedly tensing major muscles in order to reduce VVR. The exact mechanisms of AT are not well understood, though it is traditionally believed to help maintain blood pressure and has found to be effective in reducing VVR in both phobic and non-phobic samples (Ditto, Byrne, & Holly, 2009; Ditto et al., 2003; Ditto, Wilkins, France, Lavoie, & Adler, 2003; Öst, 1991; Öst, Fellenius, & Sterner, 1991).

A recent review of controlled clinical trials for BII phobia revealed that only a small number of studies are available, published mostly by the same team (Ayala et al., 2009). Öst and colleagues (1991) studied BII phobia treatments in depth, though independent replications are

lacking. Recently, Ayala and colleagues (2009) summarized a complex pattern of responses to such treatment techniques. Improvement has been highly variable between AT, in vivo Exposure, and Tension-only techniques. Nonetheless, AT has been recommended as the treatment of choice for BII phobia (e.g., Barlow, 2002). In the context of treatment for BII phobia, the AT technique involves: (1) learning to recognize signs of dropping blood pressure and to subsequently apply the tension technique, and (2) exposure to phobic situations while practicing this skill.

There are likely to be common effective elements yet to be considered within these different treatments. Exposure treatments fare best when outcome measures include the degree of fear (Ayala et al., 2009). On the other hand, AT, as compared to exposure and tension-only, tends to produce the most improvement on in-session measures of fainting, anxiety and physiological measures associated with fainting (Öst et al, 1991). Not surprisingly, therefore, the success of the treatment depends on how you measure the success. Interestingly, *both* fainters and non-fainters with BII phobia appear to benefit from the AT technique. This is odd since the AT technique was designed specifically to address the fainting response.

In their review, Ayala and colleagues (2009) argue that the tension component of AT may provide a safety-behaviour, a type of *short-term* anxiety alleviation. In some respects, this might seem unproductive in this type of treatment. That is, it has been empirically demonstrated that safety-behaviours can interfere with the habituation process during exposure-based treatments for anxiety disorders (Salkovskis, 1991; Salkovskis, Clark, Hackmann, Wells, & Gelder, 1999), and this observation is consistent with dominant cognitive theories for anxiety (e.g., Clark, 1986). AT may, however, play an important role in behavioural treatments for reasons unintended. A recent review has shown that some safety-behaviours can facilitate

exposure therapy, especially when used in the *early* stages of treatment (Rachman, Radomsky, & Shafran, 2008). In this adaptive form, perhaps as is the case with AT, safety-behaviours (maybe more aptly named “coping” strategies in this situation) reduce excess anxiety *without* preventing the exposure, habituation, and disconfirmation of catastrophic fears to the feared stimulus.

Conversely, in their maladaptive form, safety-behaviours can prevent facing a feared stimulus and disconfirmation of catastrophic fears (Thwaites & Freeston, 2005). Thus, in the treatment of a BII phobia, patients may benefit from using but then weaning off the AT technique as exposure exercises progress (Ayala et al., 2009). On the other hand, when an individual does not meet criteria for BII phobia and simply experiences unpleasant VVR in response to rare and brief stimuli, not requiring exposure-based treatment (e.g., yearly vaccinations or blood donation clinics), a ‘safety-behaviour’ may be sufficient and practical.

Aside from anxiety disorders, managing and preventing VVR in blood donor clinics continues to be a challenge for researchers and practitioners. The majority of complications at blood donation clinics are related to VVR. Depending on the population, syncope ranges from 2-5% of donors (Popovsky, 2002; Taylor, 1942), and many other donors experience milder symptoms such as dizziness and weakness. Beyond in-clinic problems, VVR are important due to the fact that blood supply barely meets demand, and most of the supply comes from *repeat* donors. VVR is the best documented predictor reduced donor return (Ditto & France, 2006; France et al., 2004; Olatunji, Etzel, & Ciesielski, 2010); even simply witnessing these distressing reactions in other patients can predict lower donor return (Ditto et al., 2014; Ferguson & Bibby, 2002). AT has demonstrated usefulness in reducing VVR at blood donation clinics, improving donor return (Ditto et al., 2003; Ditto & France, 2006).

AT is not the only technique that may alleviate VVR during blood donation or other medical procedures. Social support during donation (Hanson & France, 2009), distraction from the needle (Bonk, France, & Taylor, 2001), drinking water (Ando, et al., 2009; Newman et al., 2007), combined hydration with AT (France et al., 2010), ingesting caffeine (Sauer & France, 1999), social skills of the phlebotomist (Stewart, France, Rader, & Stewart, 2006), and adopting a recumbent position (Godin, Conner, Sheeran, Belanger-Gravel, & Germain, 2007; Rapp, Pavlin, Nessly, & Keyes, 1993) all reduce VVR. The psychological and physiological mechanisms of these treatments remain unclear. Indeed, AT, for example, may work for several reasons, including both physiological and psychological factors (Ditto et al., 2009; Ditto, France, Albert, & Byrne, 2007).

This section was intended as a brief introduction to the psychophysiology of VVR rather than an exhaustive review. Many of the issues raised here such as the role of blood fears in VVR, the physiological correlates and pattern (e.g., diphasic or not) of the response and even, though to a lesser degree, the ability of AT to dampen this response will be discussed in the following chapters. However, this background leads to some general thoughts and predictions.

Though still controversial, it has been argued that the vasovagal response may have developed from an earlier adaptive hemodynamic response to hemorrhage. A similar reaction may have developed to the anticipation of, or exposure to, stimuli associated with blood loss. This is consistent with the increased risk for VVR observed among blood phobics (Öst, 1992), the significant association between perceived blood loss and vasovagal symptoms in blood donors (Ditto et al., 2011), and the importance of blood fears in predicting VVR (Ditto, Gilchrist, & Holly, 2011). Conversely, VVR have been linked to various blood and injury stimuli and their relative importance remain unclear (Hepburn & Page, 2000; Marks, 1988). Study One aimed to

disentangle these differences and to compare the psychophysiological correlates of blood versus needle stimuli. The primary hypothesis was that the image of a blood draw would elicit greater vasovagal symptoms than an image of injection.

Stress responses are related, at least to some degree, to a lack of perceived control over the environment (Lazarus & Folkman, 1984; Sanderson, Rapee, & Barlow, 1989). Similarly, as previously discussed, the importance of lack of control or submission to a threat has been especially important in models of VVR (e.g., Ritz et al., 2010; Sledge, 1978). It can also be observed that VVR are most common in settings in which people are required to passively endure distressing procedures (Enkling, et al., 2006; France, et al., 2004; Nir, et al., 2003; Page, 1996). The aim of Study Two was to examine the role of perceived control in VVR and the effects of individual differences in blood and needle fears, and their interaction with perceived control. We predicted that perceived control would moderate VVR.

The ‘diphasic’ assumption that the pattern of physiological activity leading to VVR includes an initial increase in sympathetic nervous system activity that is later reversed has been incorporated into several theories of VVR (e.g., Converse et al., 1992; Engel, 1978; Page, 2003). The diphasic theory has been criticized for its limited supporting data (e.g., Ritz et al., 2010; Sarlo et al., 2008). Study Three aimed to examine this pattern in autonomic and cardiovascular activity in blood donors who subsequently experienced vasovagal symptoms.

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Study One:**The Effects of Blood-Draw and Injection Stimuli on the Vasovagal Response**

Gilchrist, P. T., & Ditto, B. (2012). The effects of blood-draw and injection stimuli on the vasovagal response. *Psychophysiology*, 49(6), 815-820.

Abstract

Vasovagal reactions (VVR) are common, complicating and deterring people from various medical procedures. A recent perspective (R. R. Diehl, 2005) suggests that VVR developed from the adaptive process of hemorrhagic fainting, perhaps as a means of preparing for anticipated blood loss. The primary goal of this study was to compare vasovagal symptoms during intravenous-injection and blood-draw videos. Sixty-two young adults watched the videos. Vasovagal symptoms were assessed with self-report, blood pressure, and heart rate variability. As predicted, participants reported more vasovagal symptoms and anxiety following the blood-draw video. Sympathetic nervous system activity (low-to-high frequency ratio) decreased during both videos but significantly more during the blood-draw video, although this could be reversed by the Applied Tension technique. Results are discussed in terms of the relevance of specific stimuli and emotions in VVR.

Vasovagal syncope is the most common cause of unconsciousness (Manolis, Linzer, Salem, & Estes, 1990). One million people are evaluated for syncope in the United States annually (Fenton, Hammill, Rea, Low, & Shen, 2000), accounting for 3% of emergency department visits (Kapoor, 1992). While unconsciousness is usually brief and self-limiting, injury from falling is not unusual (Newman & Graves, 2001). As suggested by the quantity of emergency room visits, the problem also involves significant economic cost. Finally, whether they involve fainting or not, vasovagal reactions complicate a variety of medical procedures and deter people from activities such as immunization, dental care, blood donation, and other medical activities (France, France, Roussos, & Ditto, 2004; Kleinknecht & Lenz, 1989; Öst, 1992; Page, 1996).

While there are exceptions (Sarlo, Buodo, Munafo, Stegagno, & Palomba, 2008), the vasovagal response has long been described as diphasic (Graham, Kabler, & Lunsford, 1961). The first phase of this response, consistent with the alarm (“fight-or-flight”) reaction, includes a rise in blood pressure. The second phase includes an increase in cardiac parasympathetic vagal activity, vasodilation, and a drop in blood pressure leading to reduced cerebral perfusion (Graham et al., 1961; Page & Tan, 2009; Ruetz, Johnson, Callahan, Meade, & Smith, 1967). Self-reports typically include distressing symptoms such as dizziness, lightheadedness, weakness, and faintness (France, Ditto, France, & Himawan, 2008). Although the classic diphasic perspective has been questioned in recent years (Ritz, Meuret, & Ayala, 2010), the latter phase clearly involves a strong inhibitory response.

The origins of this seemingly maladaptive response have puzzled researchers for years, since it can render the individual weak and even unconscious in a threatening situation. Pathophysiological explanations continue to be debated (e.g., Zurak & Bilic, 2004), although

others have argued strongly that vasovagal syncope is not a “disease” (Alboni, Brignole, & degli-Uberti, 2007). For example, they suggest that the neural mechanisms of the vasovagal reaction are universal in healthy humans. That said, the psychophysiological mechanisms of this response remain poorly understood (Popovsky, 2002).

A recent evolutionary perspective suggests that the vasovagal response developed from the earlier hemodynamic response to hemorrhage (Diehl, 2005). Fainting following a 30% or greater blood loss is observed across species. Diehl (2005) argues that this response improved an injured animal’s chances of survival by lowering blood pressure, facilitating clotting, and reducing blood loss. A similar reaction may have developed to the *anticipation of* blood loss. This is consistent with findings that those with blood, injection, and injury (BII) phobia are uniquely predisposed to fainting compared to people with other phobias (Barlow, 2002; Beck & Emery, 1985; Graham et al., 1961; Öst, 1992; Rachman, 1990; Thyer, Himle, & Curtis, 1985). We also recently observed a significant association between amount of *perceived* blood loss and vasovagal symptoms in blood donors (Ditto, Balegh, Gilchrist, & Holly, 2011).

On the other hand, fainting has been linked to various blood and injury stimuli including needles and knives as well as blood (Marks, 1988), and the relative importance of different BII stimuli have been difficult to disentangle. Interestingly, blood phobics are more likely to report fainting than injection phobics (Öst, 1992). Similarly, in a different study of blood donors, we recently found that fear of blood was the strongest fear-related predictor of vasovagal symptoms (Ditto, Gilchrist, & Holly, 2011). Another study found that participants experienced the diphasic effect in diastolic blood pressure when exposed to a bloody wound, but not to an injection (Page, 2003).

In a further attempt to disentangle the effects of needles and blood, the present study compared the psychophysiological correlates of two similar videos involving needles. In one case, an intravenous injection was administered. In the other case, blood was withdrawn using the same type of needle. The primary hypothesis was that the image of a blood draw would elicit greater vasovagal symptoms than an image of injection.

Applied Tension (AT) was originally developed to alleviate vasovagal symptoms during exposure-based treatments for BII phobics (Öst & Sterner, 1987). An abbreviated version of the technique was later successfully applied to the blood donation setting (Ditto, Wilkins, France, Lavoie, & Adler, 2003). The psychophysiological effects of this technique are only beginning to be understood (Ditto, Byrne, & Holly, 2009). Therefore, in addition to examining the effects of the two videos, another purpose of the experiment was to examine the effects of AT on reducing susceptibility to vasovagal symptoms.

Method

Participants and Experimental Conditions

Participants were 62 undergraduate and young adult community volunteers (22 male and 40 female) aged 18–27 years ($M = 21.3$, $SD = 2.4$). Potential participants who reported any neurological or cardiovascular illness were excluded. As it was expected that responses would be seen in nonphobic populations, and for purposes of generalizability, a phobic sample was not used in this study. Prior to watching the videos, 31 learned AT and 31 did not. Consistent with random assignment of participants, preliminary analyses revealed no associations between experimental condition and participant variables of sex, age, medical fear subscales, and state anxiety.

Materials and Apparatus

Blood-draw and intravenous-injection stimuli. Two similar 90-s videos were taped, one depicting an intravenous injection and one a blood draw. A 23-gauge butterfly needle was used, injecting or extracting 5 cc of saline or blood, respectively. The videos were filmed from a first-person perspective and were identical other than the nature and direction of flow through the needle. It was therefore assumed that any differences in valence, arousal, or other responses would be due to this difference in the nature and direction of flow (i.e., blood). Videos provided the additional advantage of standardizing participant experience. The videos were preceded by the instructions: “In a few moments, a video will begin involving a simple blood draw [intravenous injection] with a standard needle. While watching this video, we’d like you to imagine that it is you receiving the blood draw [intravenous injection]. We’d like you to imagine yourself fully into the scene as though it is actually happening.” Next, the video was played once and followed by the instructions: “In a few moments, the same video will repeat involving the same simple blood draw [intravenous injection] with a standard needle. While watching this video, we’d like you, again, to imagine that it is you receiving the blood draw [intravenous injection]. We’d like you to imagine yourself fully into the scene as though it is actually happening.” The video was played a second time. The instructions and video repetition totaled 5 min.

AT training video. This 2-min video instructed participants in the practice of AT (Ditto et al., 2003). Participants were asked to simply engage in repeated 5-s isometric contractions of their arms and legs simultaneously while breathing regularly. Movement during AT was such that it did not interfere significantly with electrocardiogram (ECG) readings.

Medical Fears Survey (MFS; Kleinknecht, 1991). Participants completed an abbreviated 30-item version of the MFS including the three subscales that have been shown to

have the greatest relevance to blood donation contexts: fear of needles, blood draws, and blood and mutilation (Kleinknecht, Thorndike, & Walls, 1996). Participants indicated on a 5-point Likert scale the extent to which they experienced the fear. The MFS correlates well with other BII-phobia measures, and it shows good internal consistency (Kleinknecht, Kleinknecht, Sawchuck, Lee, & Lohr, 1999).

Disgust Scale—Revised (DS-R; Haidt, McCauley, & Rozin, 1994, modified by Olatunji et al., 2007). This scale measured individual differences in sensitivity to disgust on a 5-point Likert scale from “*strongly disagree*” to “*strongly agree*” with statements such as: “It would bother me tremendously to touch a dead body.” The three subscales, core, animal reminder, and contamination, have distinct personality, behavioral, physiological, and clinical correlates (Olatunji, Haidt, McKay, & David, 2008).

Blood Donation Reactions Inventory (BDRI; France et al., 2008). Subjective vasovagal symptoms were assessed with the BDRI, a well-validated 11-item survey including ratings of symptoms such as dizziness, lightheadedness, and weakness. Participants indicated on a 6-point Likert scale the degree to which they experienced these sensations from “*not at all*” to “*an extreme degree*.”

State-Trait Anxiety Inventory (STAI-Y; Spielberger, Gorsuch, & Lushene, 1970). State anxiety was assessed using the STAI-Y. Participants responded according to how they currently felt on 20 4-point Likert items. State anxiety has been found to increase in response to psychological stress and physical danger and to decrease following relaxation (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983).

Blood pressure. Repeated measurements of systolic and diastolic blood pressure (SBP and DBP) were obtained at 5-min intervals using an automatic blood pressure monitor (Accutorr

Plus, Data Scope Corp., Mont Vale, NJ, USA) with the cuff attached to the upper nondominant arm.

Heart rate variability (HRV). HRV provides a noninvasive means of assessing short-term effects of the autonomic nervous system on the heart (Task Force, 1996). HRV reflects the variation in interbeat intervals produced by the interplay of the sympathetic (SNS) and parasympathetic activity (PNS). Low-frequency HRV (LF; 0.04–0.15 Hz), believed to reflect a mixture of sympathetic and parasympathetic influences, high-frequency HRV (HF; 0.15– 0.4 Hz), believed to reflect primarily vagal regulation of HR, and LF/HF, an index of sympathovagal balance or sympathetic activity, were calculated. A three-lead configuration was used to measure the ECG and to extract HRV data. Two spot electrodes were placed bilaterally on the rib cage, with a ground spot electrode on the right ankle.

Procedure

Participants were tested individually in a university psychophysiology laboratory. Following consent, they were connected to the physiological recording equipment and completed the demographic, STAI, MFS, and DS-R questionnaires. Baseline measures began 5 min after they started completing questionnaires. Half of the participants viewed the AT training video and were asked to use the technique during the subsequent blood and injection videos. All participants then viewed, in a counterbalanced order, the video of an intravenous injection and the blood draw. In order to confirm adherence to AT instructions, participants were observed unobtrusively through a one-way mirror. Following each video block, participants completed the STAI and BDRI. HRV measures were obtained once at baseline and during each video block; BP measurements were taken at the end of these periods.

Data Reduction and Analysis

To provide information on the effects of AT and blood/injection stimuli on autonomic activity, analyses of HRV were conducted. The ECG signal was evaluated by visual inspection and corrected for artifacts where possible, in accordance with current standards (Task Force, 1996). Within each 5-min baseline and video period, 2-min segments that were free of artifacts were selected for analyses. Sequential cardiac interbeat interval values were extracted from the ECG signal and analyzed by 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 the HF (0.15– 0.40 Hz) and LF (0.04–0.15 Hz) HRV frequency bands. HRV data were normalized by log transformation (i.e., $\log[1 + x]$). Estimates of respiration rate were obtained using the HF peak frequency band of the autoregressive model (Thayer, Sollers III, Ruiz-Padial, & Vila, 2002), and did not confound the HRV data. Baseline stress change scores in the physiological measures were analyzed using 2 Video (blood vs. injection) X 2 AT (AT or not) analysis of covariances (ANCOVA), with age, sex, and baseline values as covariates.

According to a recent factor analysis, the BDRI has four items that capture the main experience of VVR: dizziness, weakness, faintness, and lightheadedness (France et al., 2008). As such, ratings of these items were summed and log-transformed to normalize the data.

The DS-R subscales and 30 MFS questionnaire items were used in two separate stepwise regressions to predict BDRI symptoms, along with other known predictors such as age, sex, and previous blood donation experience, which were forced into the equation first (Trouern Trend, Cable, Badon, Newman, & Popovsky, 1999).

Results

Self-Report Measures

Two planned comparisons were conducted, revealing that participants reported significantly more vasovagal symptoms, $t(61) = 3.150, p = .003$, and anxiety, $t(61) = 3.107, p = .003$, following the blood draw than the injection video. One exploratory stepwise multiple regression was conducted for each video. The primary MFS fear predictor of BDRI score following the blood draw video was “seeing a large bottle of your own blood” ($partial\ r = .396, p = .002$). Interestingly, the primary fear predictor of BDRI scores following the injection video was also blood related, “seeing a large bottle of your own blood” ($partial\ r = .462, p < .001$). The DS-R whole scale and subscale scores were not associated with BDRI scores following either video.

Physiological Measures

Baseline-stress change scores in physiological measures are summarized in Table 1. Although BP and HR decreased from baseline to video condition, there were no significant effects of Video on SBP, $F(1,53) = 1.409, p = .241$; DBP, $F(1,53) = .100, p = .753$; or HR, $F(1,53) = 2.449, p = .124$, change. There were also no effects of AT on SBP, $F(1,53) = 2.982, p = .090$; DBP, $F(1,53) = .083, p = .774$; or HR, $F(1,53) = 3.850, p = .055$, although each displayed a trend suggesting higher levels during AT. Similarly, there were no significant effects of Video, $F(1,51) = 1.170, p = .284$, or AT, $F(1,51) = .286, p = .595$, in the ANCOVA of HF HRV, although high frequency and thus presumably vagal activity increased during the videos (Figure 1). However, the analysis of LF HRV produced a significant main effect of Video, $F(1,51) = 8.98, p = .004$. Participants had smaller increases in LF HRV during the blood-draw video than the intravenous-injection video (Figure 2). Given the absence of an effect of Video on HF HRV, this was probably due to a difference in sympathetic activity during the videos, since low frequency activity reflects both cardiac sympathetic and parasympathetic activity. This belief

is supported by the results of the ANCOVA of the LF/HF ratio. This also produced a significant main effect of Video, $F(1,51) = 4.36, p = .042$, as well as an effect of AT, $F(1,51) = 5.42, p = .024$. As can be seen in Figure 3, the ratio and thus presumably sympathetic activity decreased during the videos when AT was not practiced and increased among participants asked to practice the technique. However, participants experienced larger decreases (or in the case of those asked to practice AT, smaller increases) in LF/HF when they watched the blood draw video compared to the injection video.

Discussion

Consistent with the finding that feelings of faint are more common in those more concerned about blood than injections (Öst, 1992; Page, Bennett, Carter, Smith, & Woodmore, 1997), viewing an intravenous blood draw was more likely to elicit self-reported vasovagal symptoms and anxiety than viewing an intravenous injection. Both videos produced an increase in HF HRV and thus presumably PNS activity. Both videos also produced an increase in LF HRV, reflecting both PNS and SNS activity. The effect of video for the LF HRV, but not the HF HRV, implies that there was lesser SNS activity during the blood-draw video. As suggested by the changes in LF/HF HRV, SNS activity was dampened during both videos. This effect was stronger during the blood-draw video, which could suggest changes in autonomic cardiac control consistent with an inhibitory response in VVR. At the same time, AT increased LF/HF HRV suggesting that it may function in part by increasing SNS activity. However, one potential confound in this regard is the frequency overlap of repetitive muscle tension and LF HRV. AT at 0.1 Hz may yield increases in the LF band due to effects on cardiovascular resonance and the baroreflex (Lehrer, Vaschillo, Trost, & France, 2009). Thus the impact of AT on SNS activity is unclear.

These findings of an inhibitory response to blood-related stimuli within this nonphobic population are also consistent with the suggestion that VVR may have developed from the adaptive process of hemorrhagic fainting, perhaps as a means of preparing for anticipated blood loss (Diehl, 2005). Also consistent with the hypothesis and previous research in the blood donation setting (Ditto, Gilchrist, & Holly, 2011), blood fears, not needle fears, were significant predictors of self-reported vasovagal symptoms in the presence of both blood-draw and injection stimuli.

That said, one possible criticism of the study is that the blood draw video involved two “fear-inducing” images—insertion of a needle into the vein and withdrawal of blood—whereas the injection video included only one—insertion of a needle into the vein. As a result, it might be argued that the differences in terms of self-reported vasovagal symptoms and physiological activity are better explained by quantitative rather than qualitative differences in the videos. However, the injection video also involved the injection of saline, which was visible and equal in volume to the amount of blood withdrawn. While people are generally more accustomed to injections than blood draws, there is no reason in principle that an injection would not be more fear provoking. Indeed, the idea of bodily “invasion” is a classic theme in literary and film horror and commonly studied in relation to strong emotions of disgust (Page, 1994). Thus, an interesting idea for future research would be to inject a colored substance (e.g., green) to control the dimension of color more closely (colorless saline was used in the present experiment for safety).

Inconsistent with previous studies, we did not find a decrease in vagal activity during AT (Freyschuss, 1970; Martin et al., 1974; Taylor, Hayano, & Seals, 1995). However, possibly due

to the mild nature of the videos, many participants occasionally stopped and had to be reminded. Thus, there were periods during the videos when AT was not being practiced.

As well, in contrast to some previous research (Page, 2003; Page & Tan, 2009), disgust sensitivity did not predict VVR to either video and was not related to trait anxiety, blood draw, or injection fears. Indeed, some researchers have found that disgust sensitivity was *not* related to fainting, although it may be associated indirectly via BII fears (Gerlach et al., 2006; Kleinknecht, Kleinknecht, & Thorndike, 1997). At the same time, the video stimuli in this study were mild and consequently evoked modest physiological responses; identifiable relations with disgust may have therefore been difficult to identify. A phobic sample might have shown stronger responses. It would be interesting to see similar investigations with more evocative stimuli, in larger samples, and in clinical populations. A better understanding of the mechanisms underlying VVR will help inform clinical interventions, and will aid in the notoriously difficult clinical assessment of this elusive phenomenon.

Table 1. Mean Baseline-Stress Change Scores (SE) in Physiological Measures.

Physiological measure	Blood-draw video No AT	Blood-draw video AT	Injection video No AT	Injection video AT
HR (bpm)	-7.8 (1.8)*	-1.0 (1.5)	-6.8 (1.6)*	-2.1 (1.5)
SBP (mmHg)	-12.2 (3.9)*	-1.6 (1.9)	-10.1 (2.3)*	-3.1 (2.6)
DBP (mmHg)	-1.5 (1.8)	-1.8 (1.5)	-3.2 (1.7)	-2.3 (1.3)
LF HRV (units)	0.4 (0.1)*	0.5 (0.1)*	0.5 (0.1)*	0.5 (0.1)*
HF HRV (units)	0.4 (0.1)*	0.4 (0.1)*	0.5 (0.1)*	0.4 (0.1)*

* $p < .01$.

Figure 1. Change values in HF HRV, representing PNS activity, from baseline. Standard errors are represented in the figure by the error bars attached to each column.

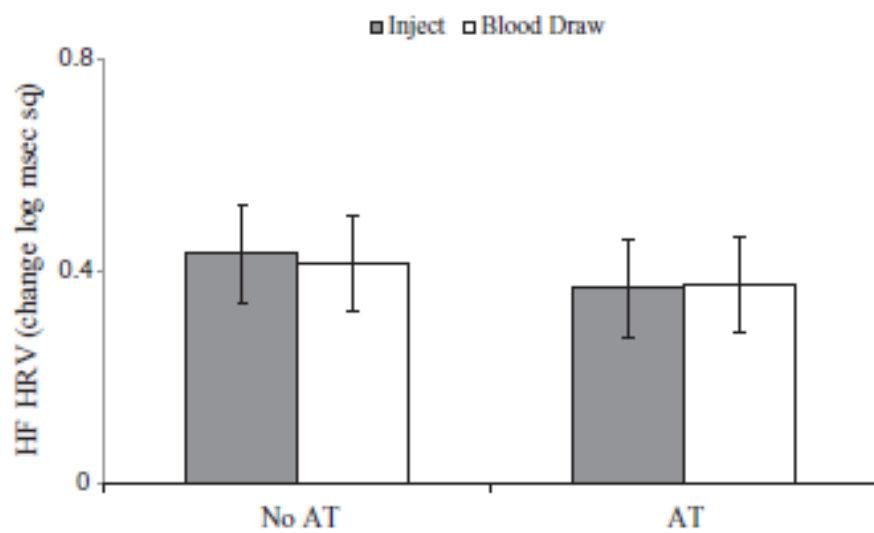


Figure 2. Change values in LF HRV, representing both PNS and SNS activity, from baseline. The blood draw video showed significantly less of an increase in LF HRV than the intravenous-injection video. Standard errors are represented in the figure by the error bars attached to each column.

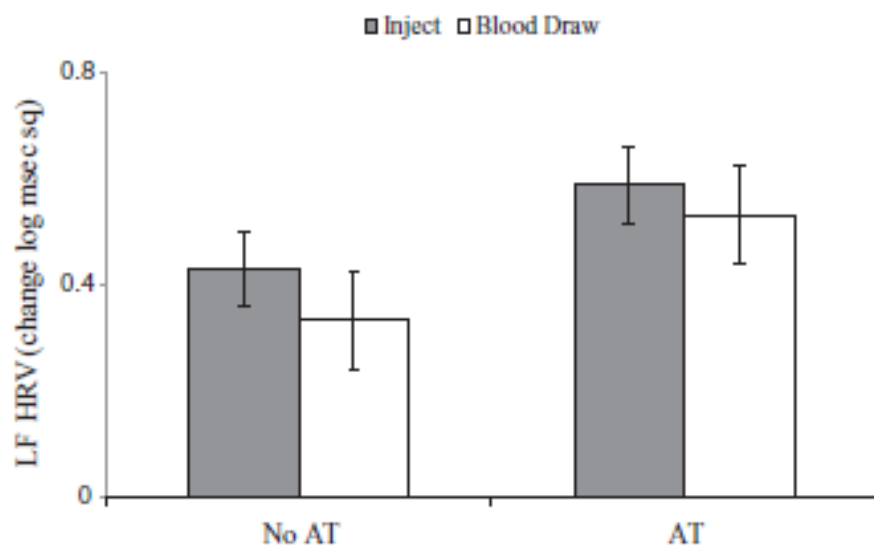
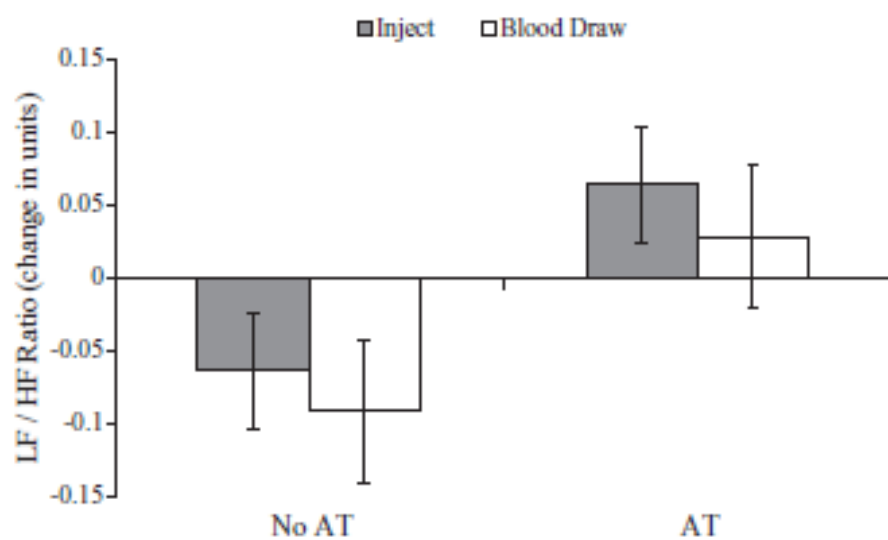


Figure 3. Change values in LF/HF HRV ratios representing change in SNS activity from baseline. SNS activity was generally dampened during the blood-draw video while AT generally increased the ratio, regardless of video. Standard errors are represented in the figure by the error bars attached to each column.



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Transition from Study 1 to Study 2

VVR have been linked to various stimuli whose relative importance have been difficult to disentangle (Marks, 1988). Study One attempted to elucidate some of these differences. Participants reported more vasovagal symptoms and anxiety following a blood-draw rather than an injection stimulus, underlining the importance of blood stimuli in evoking VVR. Sympathetic nervous system activity decreased during both videos but significantly more during the blood draw video. This could be reversed by the Applied Tension technique suggesting that it may function, in part, by increasing sympathetic nervous system activity.

An inhibitory response during confrontation with blood-related stimuli is consistent with the recent perspective that VVR may have developed from the adaptive process of hemorrhagic fainting, perhaps as a means of preparing for anticipated blood loss (Diehl, 2005). These results are consistent with previous studies indicating an association between perceived blood loss predicted vasovagal symptoms in blood donors (Ditto, Balegh, Gilchrist, & Holly, 2011), a higher prevalence of fainting in blood than injection phobics (Öst, 1992), and that fear of blood was the strongest predictor of vasovagal symptoms, more so than needle fears (Ditto, Gilchrist, & Holly, 2012).

One limitation of this study was the lack of additional comparison videos. While the two videos were tightly matched, it could be argued that the blood draw video contained two “stressors”, seeing the insertion of a needle and the withdrawal of blood. However, seeing the injection of a “foreign” substance could also be, in principle, stressful yet it was the withdrawal of blood that seemed to bother participants. An interesting future study might inject different colored substances to see if that influenced results.

Another limitation was the level of intensity of the stimulus videos. The videos were mild and consequently evoked fairly modest responses. Relatedly, while this study demonstrated the significance of perceived blood-stimuli in evoking VVR (a form of primary appraisal), the role of any further cognitive processes in VVR remain unknown. In our second study, we used a much more evocative video stimulus (of an open-heart surgery) and examined the effects of secondary appraisal (i.e., perceived control) on resultant VVR.

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Study Two:**The Vasovagal Response During Confrontation with Blood-Injury-Injection Stimuli: the Role of Perceived Control**

Gilchrist, P. T., McGovern, G., Bekkouche, N., Bacon, S., & Ditto, B. The vasovagal response during confrontation with blood-injury-injection stimuli: the role of perceived control. (under review).

Abstract

The vasovagal response (VVR) is a common medical problem, complicating and deterring people from various procedures. It is an unusual stress response given the widespread decreases in physiological activity. Nevertheless, VVR involves processes similar to those observed during episodes of strong emotions and pain. We hypothesized that heightened perceived control would reduce symptoms of VVR. Eighty-two young adults were randomly assigned to have high or low perceived control during exposure to a stimulus video of a mitral valve surgery, known to trigger VVR in non-medical personnel. Perceived control was manipulated by allowing some participants to specify a break time, though all received equivalent breaks. Outcomes included subjective symptoms of VVR, anxiety, blood pressure, heart rate, and other measures derived from impedance cardiography. Compared to participants with higher perceived control, participants with lower perceived control reported significantly more vasovagal symptoms and anxiety, and experienced lower stroke volume, cardiac output, and diastolic blood pressure. Participants who were more fearful of blood were more likely to benefit from higher perceived control in several measures. Perceived control appears to moderate vasovagal symptoms. Results are discussed in terms of cognition and emotion in VVR.

Keywords: Blood-Injury-Injection Fears; Vasovagal; Perceived Control; Syncope; Appraisal; Anxiety

The vasovagal response during confrontation with blood-injury-injection stimuli: the role of perceived control

Over one million people are evaluated for syncope in the United States annually (Fenton, Hammill, Rea, Low, & Shen, 2000) accounting for 1% of emergency department visits (Blanc et al., 2002; Brignole et al., 2003) and 3.6% of hospital admissions (Morichetti & Astorino, 1998). Many more cases do not come to the attention of medical personnel. Of the various possible causes of syncope, the vasovagal response (VVR) is the most common (Manolis, Linzer, Salem, & Estes 3rd, 1990). VVR, with or without syncope, also cause significant distress and can deter people from routine medical activities such as immunization, dental care, and blood donation (Enkling, Marwinski, & Jöhren, 2006; France, France, Roussos, & Ditto, 2004; Marks, 1988; Nir, Paz, Sabo, & Potasman, 2003; Page, 1996).

The vasovagal process is complex and can be triggered by different physical and psychological stimuli such as a hot environment, prolonged standing, hemorrhage, and psychological stress. For many years, theorists have emphasized low control or submission to a threat as key determinants of the likelihood of a stress-related VVR (Engel, 1962, 1978; Sledge, 1978). While all stress responses are related to at least some lack of perceived control over the environment – life problems with easy and available solutions are unlikely to cause a stress response (Lazarus & Folkman, 1984; Sanderson, Rapee, & Barlow, 1989) – the emphasis has been especially strong in models of VVR.

Graham and colleagues (Graham, Kabler, & Lunsford, 1961) argued that vasovagal syncope is the result of parasympathetic rebound related to a state of relief that follows a period of strong uncontrollable stress. Although his ideas changed with time, Engel consistently emphasized the idea of an adaptive surrender to uncontrollable stress (Engel, 1978; Engel &

Romano, 1947). Page (1994) suggested that vasovagal syncope results from a dual process in which fear is accompanied by a sense of disgust perhaps due to the possibility of unavoidable body envelope violation. More recent models have suggested that stress-related vasovagal syncope develops as a physiological preparation for unavoidable injury, perhaps as a means of deterring aggression (Bracha, 2004) or stemming blood loss (Barlow, 1988; Diehl, 2005; Ditto, Balegh, Gilchrist, & Holly, 2012). Relatedly, it is interesting to note that VVR are most common in medical settings in which people are required to passively endure unpleasant procedures (Enkling, et al., 2006; France, et al., 2004; Nir, et al., 2003; Page, 1996) and are especially common among individuals with pre-existing fears of blood, injury, and injections (Marks, 1988).

Given this focus on lack of control, it is reasonable to predict that enhancing an individual's sense of control over stress would reduce VVR. Indeed, it has been argued that the fear of losing control may be central to the progression of VVR (Ritz, Meuret, & Ayala, 2010). Fainting and related vasovagal symptoms are often a primary complaint and a central treatment focus in cognitive-behavioural therapies for Blood-Injury-Injection Phobia (Hellström & Fellenius, 1996; Öst, Fellenius, & Sterner, 1991). In a recent review, Ritz and colleagues (Ritz, et al., 2010) discussed successful treatment studies of Blood-Injury-Injection-Phobia which did not focus on treatment of fainting. Patients who had improved at follow-up also reported no longer using a technique designed to manage fainting or other symptoms of VVR, (i.e., Applied Tension). The authors point to perceived control as a possible explanation (Ritz, et al., 2010).

The primary goal of this study was to examine the effects of an experimental manipulation believed to enhance participants' sense of perceived control on their responses to a "prototypical" VVR-inducing stimulus, i.e., passively watching a video of a surgical procedure.

It was predicted that an increased sense of perceived control would reduce physiological correlates of VVR and vasovagal symptoms. A secondary aim of the study was to examine the relative effects of individual differences in fear of blood and fear of needles on VVR, and their interaction with perceived control. In a previous study (Gilchrist & Ditto, 2012), we found that a video of blood withdrawal elicited stronger VVR than a virtually identical video of an intravenous injection. Thus, in the present study, it was predicted that participants who were especially fearful of blood loss would be most likely to display VVR and to benefit from enhanced perceived control.

Method

Participants and Experimental Conditions

Eighty-two undergraduate and young adult community volunteers (51 female) aged 18-30 years ($M = 22.3$, $SD = 3.1$) participated in the study. Participants were unobtrusively (i.e., without their knowledge and randomly) assigned to either the high perceived control ($N = 41$) or low perceived control ($N = 41$) condition. Potential participants who reported any neurological or cardiovascular illness, hearing problems, or English not as a first or second language were excluded. Three participants were excluded due to technical issues with the physiological recordings and computer. As it was expected that responses would be seen in non-phobic populations and for purposes of generalizability, a phobic sample was not used in this study. Participants were asked to refrain from vigorous physical activity on the day of the study, to avoid caffeine for four hours and smoking for two hours prior to the experiment.

Materials and Apparatus

Medical Fears Survey (Kleinknecht, 1991). Participants completed an abbreviated 30-item version of the Medical Fears Survey that included two subscales especially relevant to

medical contexts: blood-related fears and needle-related fears (Kleinknecht, Thorndike, & Walls, 1996). Participants rated their fearfulness of a number of events on a 5-point Likert-like scale anchored at 0, “no fear at all”, and 4, “terror.” The Medical Fears Survey correlates well with other Blood-Injury-Injection-Phobia measures and shows good internal consistency (Kleinknecht, Kleinknecht, Sawchuk, Lee, & Lohr, 1999).

Blood Donation Reactions Inventory (BDRI; France, Ditto, France, & Himawan, 2008; Meade, France, & Peterson, 1996). Subjective vasovagal symptoms were assessed with the Blood Donation Reactions Inventory, a well-validated 11-item survey including ratings of symptoms such as dizziness, lightheadedness, and weakness. Participants indicated on a six-point Likert-like scale the degree to which they experienced these sensations from “not at all” to “an extreme degree.”

State-Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, & Lushene, 1970). State anxiety was assessed using the State-Trait Anxiety Inventory, a 20-item questionnaire scored on a four-point Likert-type scale from “not at all” to “very much.” State anxiety scores have been found to increase in response to psychological stress and physical danger and to decrease following relaxation (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983).

Blood Pressure. Measurements of systolic and diastolic blood pressure were obtained at baseline and four minutes into the stimulus video, before participants took their breaks. Measurements were obtained using an oscillometric monitor (Accutorr Plus™, Data Scope Corp., Mont Vale, NJ, USA) with the cuff attached to the upper non-dominant arm.

Heart Rate and Heart Rate Variability (HRV). A three-lead electrocardiogram (ECG) was used to extract heart rate and HRV data. Two spot electrodes were placed bilaterally on the rib cage, with a ground spot electrode on the right ankle. A Biopac MP150 (Biopac Systems

Canada Inc.) system was used to obtain ECG and impedance cardiography data (sampling rate: 1000Hz). HRV provides a non-invasive means of assessing short-term effects of the autonomic nervous system on the heart (Task Force, 1996). HRV reflects the variation in inter-beat intervals produced by the interplay of the sympathetic and parasympathetic activity.

Impedance Cardiography. Several physiological measures were obtained through impedance cardiography analyses: stroke volume, cardiac output, and pre-ejection period (total peripheral resistance was not analyzed due to too much missing data). A tetrapolar configuration of spot electrodes was used: one recording- and one current-electrode (3 cm apart) on the dorsal surface around the base of the neck, and the same arrangement around the thorax at the level of the xiphoid process (Allen, Fahrenberg, Kelsey, Lovallo, & Doornen, 2007). Pre-ejection period is the time interval during ventricle contraction and closure of aortic and mitral valves and is a good noninvasive measure of cardiac sympathetic activity (Burgess, Penev, Schneider, & Van Cauter, 2004; Newlin & Levenson, 2007).

Stimulus Video. This five-minute video includes clips from surgical education videos on an open heart mitral valve surgery, including scenes of initial blood-taking with spilling, the opening of a patient's chest with a saw, and cardiac surgery. The video was constructed to stimulate VVR (Ritz, Wilhelm, Gerlach, Kullowatz, & Roth, 2005). Since the video is relatively brief (5 min), it was repeated once in order to increase the intensity of the experience for participants.

Procedure

Following a telephone screening to determine eligibility, participants were tested individually in a university laboratory. After providing consent, participants were connected to the physiological recording equipment and completed the demographic, Medical Fears Survey

and State-Trait Anxiety Inventory questionnaires in counterbalanced orders. Baseline physiological measures began five minutes after they started completing questionnaires.

Participants were then randomly assigned to one of two groups manipulating perceived control: they were told either that they could take a two-minute break during the video whenever they requested by signaling the experimenter (i.e., high perceived control), or they were told that the experimenter would assign them a two-minute break and pause the video at some point (i.e., low perceived control). The timing of the break was pair-matched between the two groups. Following these instructions, the experimenter left to the adjoining room to observe through a one-way mirror. Participants were seated in front of a computer to hear subsequent recorded instructions and view the stimulus video.

After watching the video twice, participants completed the Blood Donation Reactions Inventory, State-Trait Anxiety Inventory, and a manipulation check asking participants to what extent they felt a sense of control over watching the video and whether they felt free to take a break. These items were rated on a ten-point Likert-type scale from “not at all” to “completely.”

Data Reduction and Analysis

To provide information on the effects of perceived control on autonomic and cardiovascular activity, analyses of HRV and impedance cardiography variables were conducted. A two-minute segment was selected during the baseline period and another during the video, ending at 30 seconds before the end of the first presentation. This point was selected because all participants in the high control condition took their breaks soon after this time. The ECG signal was evaluated in accordance with current standards (Task Force, 1996). Sequential cardiac inter-beat interval values were extracted from the ECG signal and analyzed by 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 the high-frequency HRV (HF; 0.15-0.40 Hz) frequency band, an index of parasympathetic vagal activity. Impedance cardiography variables were calculated using BIOPAC software (www.biopac.com) according to current standards (Allen, et al., 2007). Impedance cardiography and HF HRV data were normalized by log transformation (i.e., $\log[1 + x]$).

According to a recent factor analysis, the Blood Donation Reactions Inventory has four items that capture the main experience of VVR: dizziness, weakness, faintness, and light-headedness (France, et al., 2008). As such, ratings of these items were summed and log-transformed to normalize the data.

In the first set of analyses, the effects of perceived control condition on Blood Donation Reactions Inventory, State-Trait Anxiety Inventory, and physiological baseline-stress change scores were analyzed by one-way analyses of covariance (ANCOVAs) with sex and baseline physiological score, if applicable, entered as covariates. In the second set of analyses, general linear models (GLMs) of the dependent measures were conducted including the same covariates and perceived control as well as the participant's scores on the Medical Fears Survey blood and injection subscales and the interactions with perceived control.

Results

Consistent with random assignment of participants, preliminary analyses revealed no association between experimental condition and sex, age, medical fear subscales, state anxiety, and baseline physiological measures.

The manipulation check revealed that those in the high perceived control condition reported a greater sense of freedom to take a break ($F(1,78) = 30.473, p < .001; \eta^2_p = .281$) and a significantly greater sense of control ($F(1,80) = 6.794, p = .011; \eta^2_p = .078$). Irrespective of

condition, 70% of participants reported vasovagal symptoms on the BDRI following the video. As indicated by paired baseline-video t-tests, the stimulus video evoked a significant decrease in heart rate ($t(77) = 7.930, p < .001$). It also produced significant increases in HF HRV ($t(64) = -3.498, p < .01$) and pre-ejection period ($t(48) = -2.714, p < .01$), suggesting an increase in parasympathetic activity and decrease in sympathetic activity, respectively. Combined with the fact that testing had to be discontinued for two participants due to strong vasovagal reactions (reported symptoms of nausea, lightheadedness, and feelings of faintness), the previous analyses suggest that the stimulus video was sufficient to elicit at least a mild vasovagal reaction, consistent with previous findings (Ritz et al., 2005).

The Effects of the Perceived Control Manipulation on Self-Report Measures

The high perceived control condition resulted in lower BDRI (vasovagal) scores ($F(1, 79) = 4.215, p = .043; \eta^2_p = .051$) and significantly less anxiety as measured by the STAI ($F(1, 78) = 5.384, p = .023; \eta^2_p = .065$), with medium effect sizes.

The Effects of the Perceived Control Manipulation on Physiological Measures

There were significant effects of condition on stroke volume ($F(1,45) = 8.264, p = .006; \eta^2_p = .155$) and cardiac output ($F(1,45) = 6.529, p = .014; \eta^2_p = .127$; Figure 1) responses, with large effect sizes. High perceived control led to relative increases in stroke volume and cardiac output, while decreases were present in the low perceived control group. There was no significant effect of condition on heart rate ($F(1,45) = 3.588, p > .05; \eta^2_p = .074$). Lower heart rate did not appear to contribute significantly to the increased cardiac output (standardized $\beta = -.147, p > .05$). Changes in cardiac output therefore appeared to be mostly due to higher stroke volume resulting from increased perceived control.

Similar to these measures related to cardiac activity, there was a significant effect of perceived control on diastolic blood pressure response with low control participants showing a relative decrease ($F(1,76) = 4.800, p = .032; \eta^2_p = .059$; Figure 2). Similarly, there was a statistical trend for a larger decrease in systolic blood pressure in the low perceived control group ($F(1,72) = 3.040, p = .086; \eta^2_p = .041$). There were no significant effects of condition in the ANCOVAs of pre-ejection period or HF HRV.

The Effects of Different Kinds of Fear

The second set of analyses were perceived control x blood fear score x needle fear score GLMs, including baseline value (if applicable) as a covariate. As predicted, individual differences in blood fears ($F(1,74) = 4.438, p = .039; \eta^2_p = .057$) but not needle fears were related to vasovagal symptoms, though the relationship between blood fear and BDRI score was not moderated by perceived control. That is, the interaction effect was not significant. Also, blood fears predicted higher anxiety ($F(1,73) = 5.527, p = .021; \eta^2_p = .070$). There was a statistical trend for an interaction between blood fear and perceived control ($F(1,73) = 3.335, p = .072; \eta^2_p = .044$). That is, blood fears and low perceived control were related with higher anxiety.

The GLM of stroke volume change revealed, as before, a significant perceived control main effect ($F(1,40) = 6.889, p = .012; \eta^2_p = .147$) as well as a blood fear by perceived control interaction ($F(1,40) = 7.684, p = .008; \eta^2_p = .161$). Similarly, there was a significant main effect of perceived control ($F(1,40) = 5.249, p = .027; \eta^2_p = .116$) and a significant blood fear by perceived control interaction ($F(1,40) = 4.604, p = .038; \eta^2_p = .103$) for cardiac output (Figure 3). High blood fear participants benefitted more from enhanced perceived control in terms of greater increases in stroke volume and cardiac output. The ANCOVA of pre-ejection period also produced a blood fear by perceived control interaction that approached significance ($F(1,40) =$

3.567, $p = .066$; $\eta^2_p = .082$). This was due to the elimination of the video-related increase in pre-ejection period in high blood fear participants assigned to the high perceived control condition (in other words, the high control condition appeared to prevent the decrease in cardiac sympathetic activity in high blood fear participants).

There was a main effect of blood fear on HF HRV ($F(1,55) = 6.280$, $p = .015$; $\eta^2_p = .102$). Participants who were less fearful of blood displayed greater increases in HF HRV compared to those who were more fearful of blood.

Interestingly, the needle fear by perceived control interaction was also significant in the GLM of stroke volume change ($F(1,40) = 5.210$, $p = .028$; $\eta^2_p = .115$) and there was a similar trend for cardiac output change ($F(1,40) = 3.791$, $p = .059$; $\eta^2_p = .087$). There were no effects of fear scores on blood pressure or heart rate.

Discussion

High perceived control resulted in lower anxiety and fewer vasovagal symptoms. These behavioural results were corroborated by the stroke volume and blood pressure data. Perceived control prevented reductions in key variables mediating vasovagal reactions such as diastolic blood pressure, stroke volume, and cardiac output. Consistent with previous studies, blood fears predicted vasovagal symptoms better than needle fears, though both types of fears resulted in similar effects on stroke volume and cardiac output (Diehl, 2005; Ditto et al., 2012; Ditto, Gilchrist, & Holly, 2012; Gilchrist & Ditto, 2012). There was also some evidence that increasing a sense of control reduced the chance of a VVR for high fear participants, at least in terms of their physiological profile.

A strength of this study includes the number of significant psychophysiological effects evoked by a very subtle manipulation of perceived control. It is noteworthy that this study

comprised volunteers who were well aware they were going to watch a film of a heart surgery and therefore had low enough levels of fear such that they were non-avoidant –avoidance is a criterion in diagnosing phobic individuals who were, by definition, not present in the study. Medical Fear Survey scores were within the range expected in this healthy young adult population. Moreover, the vasovagal responses were seen despite the sole use of a short video stimulus, as opposed to actual experience. Further studies might use real-life medical procedures conducted directly with the participants (e.g., blood draws). The effects of perceived control on clinical populations (e.g., Blood-Injury-Injection-Phobia) also remain to be seen.

One possible criticism of the observed effects of perceived control could be that those who chose their break may have done so at a time in the video that was idiosyncratically distressing to them, at the beginning of a potentially escalating physiological response. As a result, it might be argued that the effect of perceived control was really an effect of *actual* control. However, this seems not to have been the case given that all participants in the high control condition opted to take their break during the transition between the repetitions of the video at about the 4.5-minute mark. Indeed, during debriefing, some participants mentioned that the choice of their break time was associated with this transition period. Relatedly, measures in this study were obtained prior to the break/pause since this was judged to better represent *perceived* control (i.e., having the idea of being able to take a break) than *actual* control (i.e., having the break or pause).

Although the behavioural and physiological results are consistent with current views of VVR, they are not especially revealing in terms of the physiological mechanisms of VVR. For example, while participants in the high and low control conditions differed significantly in diastolic blood pressure response, the decrease in low perceived control participants was modest.

Interestingly, participants who were less fearful of blood showed greater increases in HF HRV despite reporting fewer vasovagal symptoms. This is consistent with previous investigations that failed to find evidence of higher HF HRV during the supposed ‘vasovagal’ response (Vossbeck-Elsebusch, Steinigeweg, Vögele, & Gerlach, 2012; Gerlach et al., 2006; Sarlo, Buodo, Munafò, Stegagno, & Palomba, 2008). Instead, recent evidence points more to the importance of reduced sympathetic activity in VVR. This view is supported somewhat by the absence of a decrease in cardiac sympathetic activity (as measured by pre ejection period) in high fear participants in the high perceived control condition. The increase in HF HRV in low fear participants may reflect a typical response to movie viewing, perhaps including a decrease in respiration rate.

The impact of perceived control and self-efficacy on various stress reactions has been studied intensively for almost 50 years (Averill, 1973; Miller, 1979). However, experimental tests of the effects of perceived control have used “high arousal” situations such as pain (Bowers, 1968; Salomons, Johnstone, Backonja, & Davidson, 2004) and doing mental arithmetic (Gerin, Litt, Deich, & Pickering, 1995) almost exclusively. The present results indicate that perceived control can prevent stress-related *decreases* in blood pressure that may lead to symptoms of dizziness and weakness, providing further evidence of the generalizability of the construct.

The results from this study have implications for clinical practice. The ease with which perceived control can be manipulated makes it suitable for various clinical settings. For example, simply offering a patient the *option* to take a break during a medical procedure may reduce undesirable vasovagal responses, anxiety, and possibly reduce the likelihood of syncope. Admittedly, it is not always practical or easy to allow a patient to take a break during a medical procedure, but other means have been employed in, for example, the area of pain (Johnston, Gilbert, Partridge, & Collins, 2011). Future studies are needed to examine such processes in

phobic populations and during real medical procedures. Continued investigation of cognitive and emotional factors in VVR may help shed light on the mechanisms and management of this phenomenon.

Figure 1. Mean cardiac output data. Standard errors are represented by error bars.

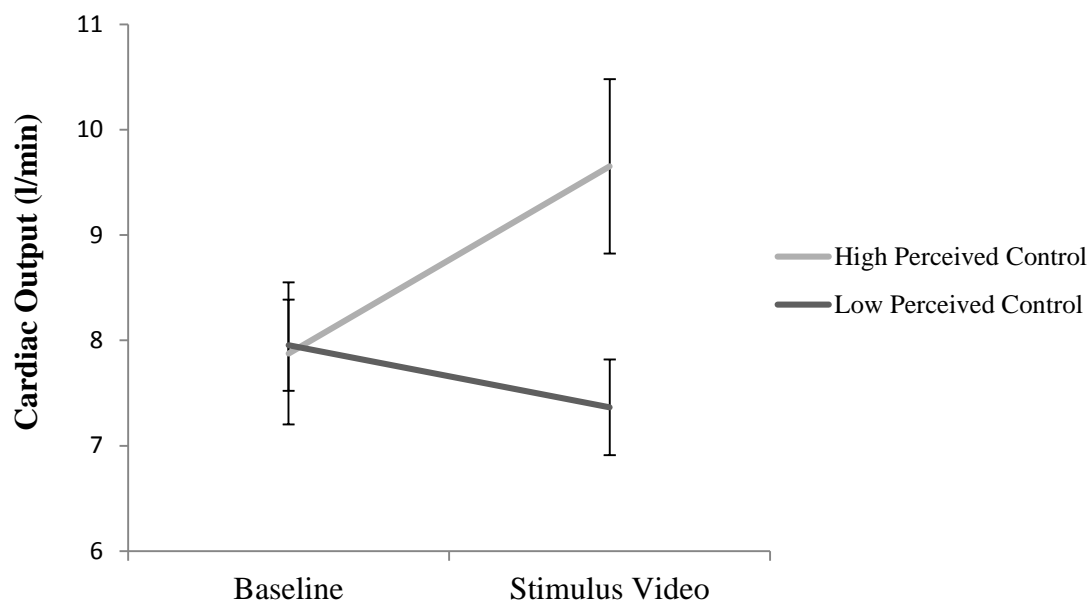


Figure 2. Mean diastolic blood pressure data. Standard errors are represented by error bars.

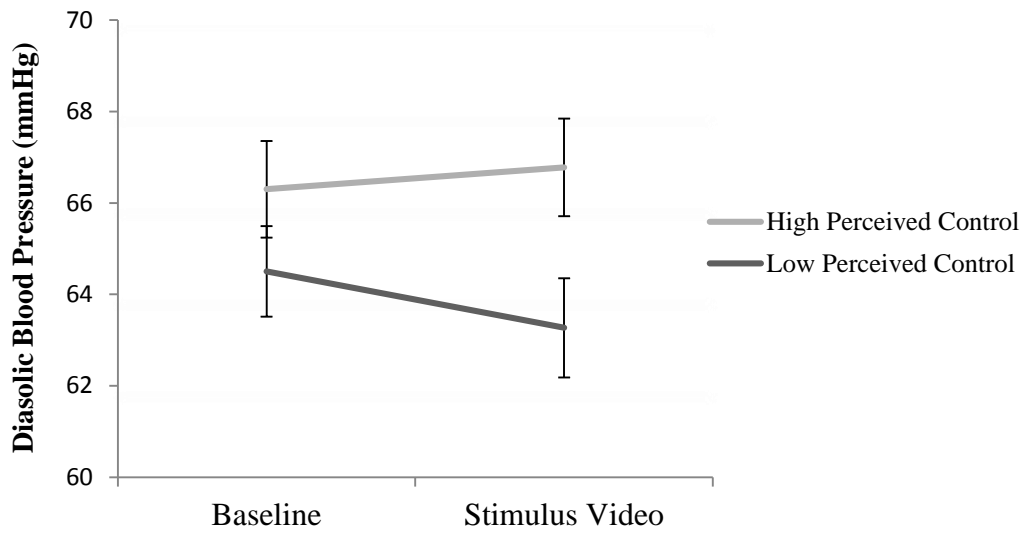
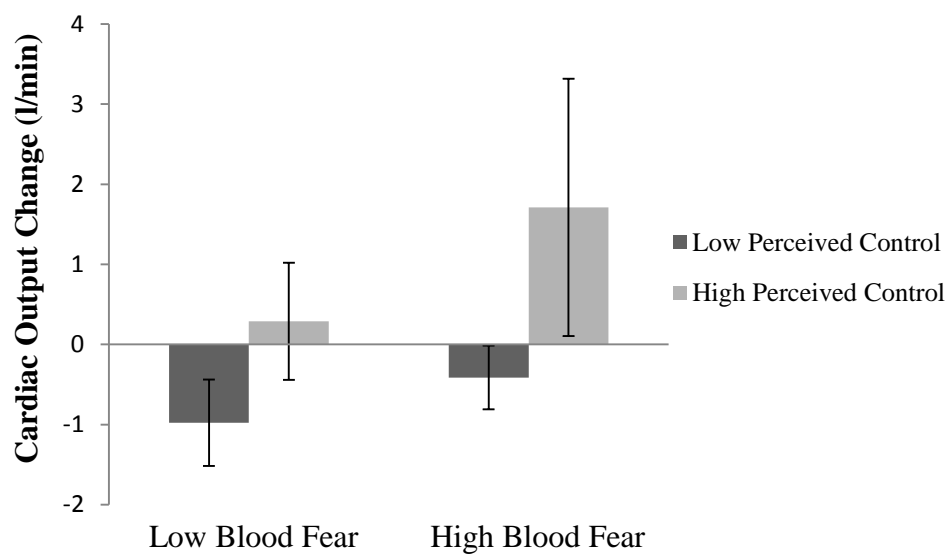


Figure 3. Mean cardiac output change data. Standard errors are represented by error bars.



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Transition from Study 2 to Study 3

Study Two provided further evidence that VVR may be construed as a type of stress response, involving similar processes to those observed in pain and anxiety. Results indicated that heightened perceived control reduced symptoms of VVR. Compared to participants with high perceived control, participants with low perceived control reported significantly more vasovagal symptoms, and experienced lower stroke volume, cardiac output, and diastolic blood pressure. Strengths of the study include the number of significant psychophysiological effects evoked by a very subtle manipulation of perceived control in a non-phobic population. Also, this study is the first to indicate that perceived control can prevent stress-related *decreases* in physiological activity, providing further evidence of the generalizability of the construct. The ease by which perceived control can be manipulated makes it very suitable for various clinical settings.

Similar to Study One, one of the limitations of Study Two was the virtual nature of the stimulus in a controlled laboratory setting. In order to address this limitation, the limited empirical research of the physiological *process* of VVR in naturalistic settings, and the limited support for the notion of the ‘diphasic’ pattern of VVR, we decided to examine VVR in a blood donation setting for Study Three. The aim of Study Three was therefore to examine the autonomic and hemodynamic processes associated with the development of naturally occurring VVR. Another goal of Study Three was to replicate and extend the finding from Study One that lower sympathetic nervous system activity, more than parasympathetic activity, is associated with VVR.

Study Three:**Sense of Impending Doom: Inhibitory Activity in Waiting Blood Donors who Subsequently Experience Vasovagal Symptoms**

Gilchrist, P. T., & Ditto, B. Sense of impending doom: inhibitory activity in waiting blood donors who subsequently experience vasovagal symptoms (under review).

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, Byrne, & Holly, 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 ratio) 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.

Keywords: Vasovagal; Syncope; Blood Donation; Diphasic Response

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 et al., 2012; 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 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). 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 et al., 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 behaviour (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 et al., 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.

Methods

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 to 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 ($N = 67$).

Materials

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 Likert 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). Chronbach's alpha for the current sample was 0.94.

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 Likert scales with anchors of "not at all" and "very much" (Spielberger, Gorsuch, & Lushene, 1970; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs 1983). The STAI is well-validated, with high internal consistency and discriminant validity. State anxiety has been shown to increase in response to stress and physical danger and to decrease following relaxation (Spielberger et al., 1983). Chronbach's alpha for the current sample was 0.81.

Apparatus

Blood Pressure. Ambulatory measurements of systolic and diastolic blood pressure (converted to mean arterial pressure; MAP) were obtained in the final 30-60 seconds of five-minute intervals using a Suntech Instruments (www.suntechmed.com) Accutacker 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.

Impedance Cardiography and Electrocardiogram. A number of physiological measures were obtained using a Bio-Impedance Technology (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.

Procedure

After providing 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 minute 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 minute pre-donation period was a short walk to the chair. AT was practiced only in the donation chair. When the donor 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.

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-second intervals and post hoc editing was done using the Copworks program. 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) frequency and low frequency (0.04 to 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) x 2 Applied Tension (yes, no) x 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.

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 450ml of blood, at least some anxiety seems to have been necessary for a vasovagal response.

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 ($p < .001$; 11 participants required some form of treatment) and fainting ($p = .038$; 4 participants fainted).

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 (Figure 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. 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 (Figure 2).²

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, $t(27) = 2.09, p = .046$.

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 x AT x 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 x Time interaction ($F(3,55) = 2.89, p = .044, \text{Wilks' lambda} = .864, \eta^2_p = .136$).

The only variable that was influenced by assignment to AT (which participants had not yet begun to practice) was respiration rate. The Symptoms x 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 ($F(1,22) = 12.399$, $p = .002$, $\eta^2_p = .360$). 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.

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) x 2 Time GLM and a Pre-Donation Relaxation Rating (treated as a continuous variable) x 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.

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).

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 analogue 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 minutes 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 minute 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 minutes pre-donation period – either with the screening nurse or in the waiting room, following screening. The only movement in the 5-to-0 minute 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 (Shen et al., 2000; Bechir et al., 2003; Sarlo et al., 2008). 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 (Vossbeck-Elsebusch et al., 2012; Gerlach et al., 2006; Sarlo et al., 2008). 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 pCO₂ indicative of hyperventilation (Gerlach et al., 2006; Ritz, Meuret, & Simon, 2013; Ritz, Wilhelm, Meuret, Gerlach, & Roth, 2009). 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, CO₂ 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 biphasic 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 (Ritz et al., 2010; Sarlo et al., 2008; Gerlach et al., 2006). 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.

Table 1. Physiological Response to the Anticipation of Blood Donation.

Variable	Units	10-to-5 minutes before donation chair Mean (SD)	5-to-0 minutes 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*sec/cm ⁵	841.9 (243.5)	795.3 (224.3)
PEP	msec	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)*

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

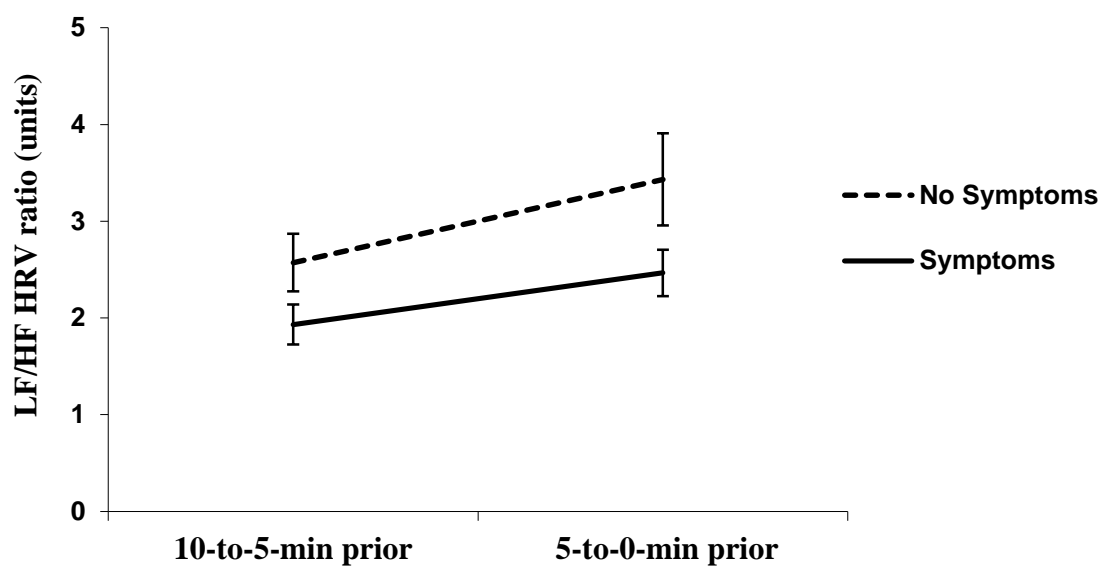


Figure 2. Total peripheral resistance mean data. Standard errors are represented by error bars.

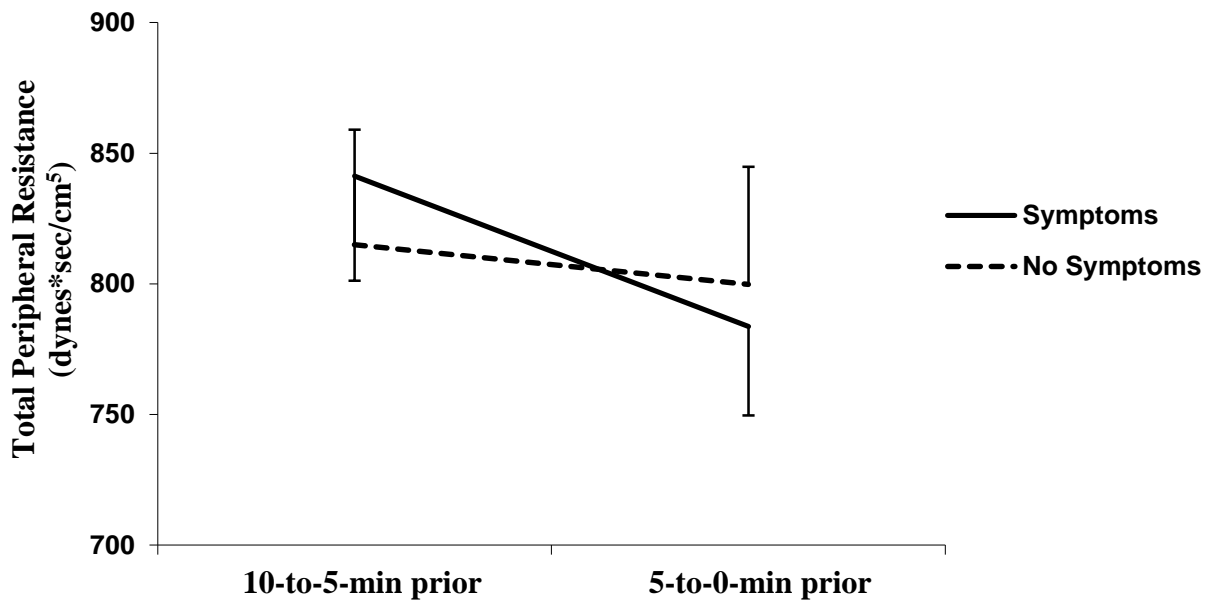


Table 2. Physiological variables for participants who fainted (N=4).

Variable	Units	10-to-5 minutes before donation chair Mean (SD)	5-to-0 minutes 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*sec/cm ⁵	1125.4 (177.7)	670.8 (327.7)
PEP	msec	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)

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General Discussion

VVR are a unique form of stress response involving widespread decreases in physiological activity rather than typical increases. This thesis aimed to examine this elusive phenomenon in both clinical and laboratory settings. Primary appraisal, secondary appraisal, autonomic, and hemodynamic processes were explored. Results suggest that VVR involve processes similar to those observed during episodes of other forms of stress and pain. Both forms of appraisal were important in evoking VVR: the perception of blood stimuli and low perceived control. Also in this research, VVR were associated with general decreases in total peripheral resistance and a process of sympathetic nervous system activity withdrawal, inconsistent with a diphasic pattern.

Study One's results are consistent with the speculative idea that VVR might be an adaptive stress response to perceived or anticipated blood loss (Diehl, 2005). This is also consistent with our other studies indicating that perceived blood loss (Ditto, Balegh, Gilchrist, & Holly, 2011) and blood fears (Ditto, Gilchrist, & Holly, 2012) predict VVR in blood donation settings. From an evolutionary perspective, blood loss is obviously a very threatening situation, whether its cause is accidental or, worse yet, resulting from a fight with an opponent or predator. The animal is in a state of vulnerability and 'fight or flight' may no longer be an adaptive response. A dramatic decrease in blood pressure, along with the other symptoms of VVR, in order to reduce blood loss and increase chances of coagulation might be a better strategy. In such circumstances, the sense of lack of control –both of the situation and one's bodily control – might be particularly acute. Indeed, the sense of loss of control may be intricately associated with VVR. These arguments are supported by the findings of Study Two: increased perceived control reduced symptoms of VVR.

Finally, the third study examined autonomic and hemodynamic processes associated with the development of VVR in a blood donation setting. Participants who subsequently experienced vasovagal symptoms had lower sympathetic nervous system activity, consistent with physiological results in study one, and inconsistent with the notion of a ‘diphasic’ pattern. Other mechanisms such as hyperventilation may be involved, but further studies are needed. These results highlight the complexity of VVR and demonstrate limitations to the traditional diphasic description focused on parasympathetic activity. Indeed, Study Three underlines the elusive physiological definition of VVR.

Limitations of Study Three include the five-minute windows of analysis. Diphasic patterns might have been obscured by this method of analysis. Perhaps most importantly, all three studies showed modest changes in measures of VVR. While this is not surprising given the mild and virtual nature of the stimuli (e.g., blood draw video or surgery video), and the fact that blood donation is a voluntary activity (fearful participants likely avoid such situations), future studies would benefit from more evocative stimuli, e.g., invasive medical procedures, tilt-table testing, etc.

Further research is recommended to examine the possible subtypes of VVR. For example, diphasic patterns may be observed in some individuals, and some people may experience greater drops in cardiac output versus peripheral resistance, etc. Such questions require larger and more diverse samples. Also, future studies should examine the effectiveness of the manipulation of perceived control and salience of blood stimuli on VVR in real clinical settings. Finally, the addition of more proximal measures of decreased cerebral perfusion could be used to corroborate current measures of VVR – for example, Doppler Ultrasound and other measures of central nervous system blood flow.

Some of the first studies to investigate the neural correlates of BII fear and related vasovagal responses were conducted only recently (e.g., Ceseras et al., 2010; Hermann et al., 2007). A functional neuroimaging study found that BII phobics had diminished activity in the dorso- and ventromedial prefrontal cortex compared to control participants when viewing either blood-type or disgust inducing-pictures (Hermann et al., 2007). Interestingly, the dorsomedial and dorsolateral prefrontal cortex are activated during reappraisal and efforts to modulate negative affect (see Ochsner & Gross, 2005) and are critically involved in cognitive regulation of emotions in general (Bishop, 2007; Ochsner & Gross, 2005, 2007; Phelps & LeDoux, 2005). Consistent with these findings, Hermann and colleagues (2007) partly explained their results as reflecting reduced cognitive control of emotions in BII phobics. Interestingly, activation of the medial prefrontal cortex is also associated with levels of perceived-control (Amat et al., 2005). Therefore, another possible extension of Study Two could include neuropsychological investigations of the association between medial prefrontal cortex activation, VVR, and appraisal processes. It would be interesting to see if appraisal strategies can attenuate any decreases in activation in the ventral tegmental area during confrontation with BII stimuli in phobic and non-phobic populations.

VVR are a dramatic and unique stress response common in medical settings, BII phobia, blood donation, and other procedures. It presents several theoretical challenges and illustrates a complex example of mind-body interaction (Ditto & Holly, 2009). Continued interest in VVR is highly probable as given its significant implications for health care and other contexts. Continued psychophysiological investigations of the cognitive and emotional factors in VVR may help shed light on the mechanisms and effective management of VVR.

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