



## Exhaled nitric oxide and vascular endothelial growth factor as predictors of cold symptoms after stress

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### ABSTRACT

**Objective:** Prior research has demonstrated that psychosocial stress is associated with respiratory infections. Immunologic, endocrine, and cardiovascular predictors of such infections have been explored with varying success. We therefore sought to study the unexplored role of airway mucosal immunity factors, nitric oxide (NO) and vascular endothelial growth factor (VEGF). NO is secreted by airway epithelial cells as part of the first line of defense against bacteria, viruses, and fungi. VEGF is expressed by mast cells in respiratory infections and recruits immune cells to infected sites, but in excess lead to vulnerability of the airway epithelium.

**Methods:** In this proof-of-concept study we measured exhaled NO, exhaled breath condensate (EBC) VEGF, salivary VEGF, and salivary cortisol in 36 students undergoing final academic examinations at three occasions: a low-stress baseline during the term, an early phase of finals, and a late phase of finals. Participants also reported on cold symptoms at these time points and approximately 5 and 10 days after their last academic examination.

**Results:** Higher baseline NO was associated with fewer cold symptoms after stress, whereas higher baseline VEGF in EBC and saliva were associated with more cold symptoms after stress. Perceived stress at baseline as well as salivary VEGF and cortisol late in the finals also contributed to the prediction of later cold symptoms.

**Conclusion:** Basal levels of NO and VEGF may inform about mucosal immunocompetence and add to preventative treatments against airway infections from periods of stress in daily life.

### 1. Introduction

The common cold is a substantial burden to health care worldwide and particularly problematic for patients with existing respiratory disease such as asthma, chronic obstructive pulmonary disease, and cystic fibrosis (Busse et al., 2010; George et al., 2014; Elborn, 2016). Previous research has demonstrated a link between psychosocial stress and cold symptoms or upper respiratory tract infections using observational designs (e.g., Evans & Edgerton, 1991; Cobb & Steptoe, 1996; Smith & Nicholson, 2001; Smolderen, Vingerhoets, Croon, & Denollet, 2007; Turner-Cobb & Steptoe, 1998) or experimental respiratory infection paradigms (e.g., Cohen, Tyrrell, & Smith, 1991; Stone, Bovbjerg, Neale, & Napoli, 1992). Moderators and mediators underlying this association have also been explored, with some studies suggesting a role for various psychological factors including perceived stress or daily hassles, negative affect, perceived health, and social support (Cohen, 2005; Falagas, Karamanidou, Kastoris, Karlis, & Rafailidis, 2010; Pedersen, Zachariae,

& Bovbjerg, 2010), as well as biological pathways, such as systemic proinflammatory cytokine production (Cohen, Doyle, & Skoner, 1999), natural killer cell cytotoxicity (Cohen et al., 2002), catecholamine levels (Cohen, Doyle, Skoner, Rabin, & Gwaltney, 1997), and cortisol levels or cortisol stress reactivity (Cohen et al., 2002; Janicki-Deverts, Cohen, Turner, & Doyle, 2016). Comparably fewer studies have explored local airway processes, in particular airway mucosal immunity responses, to stress (Trueba & Ritz, 2013). A number of studies have examined immunoglobulin A (IgA; Deinzer & Schüller, 1998; for review see Bosch et al., 2004) and other molecules relevant to innate immunity extracted from saliva (Bosch, de Geus, Veerman, Hoogstraten, & Nieuw Amerongen, 2003), but a clear relationship with cold symptoms has not been established and factors more directly linked to airway mucosal immunity have not been studied. Two of these factors, nitric oxide (NO) and vascular endothelial growth factor (VEGF), are intimately involved in the airways' response to pathogen exposure (Proud, 2005; Vareille, Kieninger, Edwards, & Regamey, 2011; Xu, Zheng, Dweik, & Erzurum,

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2006), yet little is known about their roles in stress-induced cold symptoms.

NO serves as a signaling molecule involved in multiple organismic processes, including impulse transmission in the nervous system, dilation of blood vessels, and inflammation (Förstermann & Sessa, 2012). In asthma, exhaled NO has been used as an indicator of airway inflammatory processes, because large amounts of it are produced by immune cells involved in allergic inflammation, including macrophages, eosinophils, and mast cells (Dweik et al., 2011; Forsythe, Gilchrist, Kulka, & Befus, 2001; Ricciardolo, Sterk, Gaston, & Folkerts, 2004; Silkoff et al., 2006). However, NO is also produced in well-controlled asthma and healthy airways by epithelial cells (Lane et al., 2004) as part of the innate immunity, where it is secreted in response to pathogen contact and unfolds cytostatic and cytotoxic properties (Xu et al., 2006). NO levels are substantially increased in airway infection (Kharitonov, Yates, & Barnes, 1995) and higher NO levels in experimental human rhinovirus infection have been linked to more effective viral clearance and fewer symptoms (Sanders, Proud, & Siekeierski, 2004). Whereas processes of adaptive immunity have been linked to clearance of pathogens from the airways and the resolution of infections, NO also serves an immediate, early line of defense against pathogens (Proud, 2005). Recent research has shown that the fraction of exhaled NO ( $FE_{NO}$ ) also varies with psychosocial factors (for review, see Ritz & Trueba, 2014). In particular, academic stress that is sustained over days reduces  $FE_{NO}$  levels (Höglund et al., 2006; Trueba, Bassi Smith, Auchus, & Ritz, 2013a; Ritz, Trueba, Liu, Auchus, & Rosenfield, 2015).

VEGF is a cytokine that stimulates the growth of new blood vessels (angiogenesis) by proliferation of vascular endothelial cells in arteries, veins and lymphatics (Ferrara & Davis-Smyth, 1997). Multiple cells are known to secrete VEGF, including endothelial cells, mast cells, peripheral blood mononuclear cells, and tumor cells (Shweiki, Itin, Soffer, & Keshet, 1992). VEGF is intimately involved in mucosal immunity. It is expressed by mast cells in respiratory infections and is involved in the recruitment of immune cells (Zhang et al., 2010). In contrast to these beneficial effects, VEGF also stimulates vascular permeability facilitating the passage of proteins and water in and out of the blood vessels (Papaioannou, Kostikas, Kollia, & Gourgoulialis, 2006). There have been suggestions that it may be 50,000 times more powerful than histamine in increasing vascular permeability. VEGF expressed in excess can also increase the likelihood of infections by increasing the permeability of the airway epithelium, with the consequence of increased bacterial adhesion, translocation, and penetration of mucosal cells (Söderholm et al., 2002). Emerging evidence shows a susceptibility of VEGF to psychosocial factors, including higher levels of serum VEGF in stress and affective disorders (Åsberg et al., 2009; Nowacka & Obuchowicz, 2013), higher VEGF levels in tumor tissue in cancer patients who report being lonelier (Nausheen et al., 2010), lower serum VEGF levels in cancer patients with stronger social support (Lutgendorf et al., 2002) and higher postoperative serum VEGF levels in anxious and depressed cancer patients (Sharma, Greenman, Sharp, Walker, & Monson, 2008). We have recently shown that VEGF increases during final exam stress in exhaled breath condensate, and also to a smaller extent, in saliva (Trueba, Rosenfield, Oberdorster, Vogel, & Ritz, 2013b).

Thus, airway NO and VEGF are major factors in mucosal immunity relevant in multiple stages of respiratory infections and might thus serve as powerful predictors of cold symptomatology. We therefore sought to examine their role in predicting cold symptom development following a period of sustained psychological stress, as operationalized through an academic final exam period. To generate proof-of-concept for this relationship, we analyzed a subset of participants from our recent studies which explored psychobiological responses to an academic final exam period (Trueba et al., 2013b; Ritz et al., 2015). Students were assessed twice during the final exam period and once during a low-stress period of the same or the following semester

(counterbalanced). In line with the beneficial effects of  $FE_{NO}$  in pathogen defense, we hypothesized that low  $FE_{NO}$  would predict greater susceptibility to cold symptoms at approximately 5–10 days after the finals. We expected that cold symptoms in response to a period of sustained stress would be more likely to develop after rather than during that period, due to the cumulative burden of the stress experience. We planned to examine both basal levels of  $FE_{NO}$  and  $FE_{NO}$  change during the final exam period. For VEGF the prediction was less straightforward given that both beneficial (revascularization in wound healing, chemotactic) and detrimental (vulnerability of mucosa due to enhanced permeability) effects might result from its action. However, we expected that stress-induced elevations of VEGF would constitute exaggerated levels with more detrimental consequences, given its potency in increasing permeability (Papaioannou et al., 2006). Because VEGF was collected in both exhaled breath condensate and saliva in our study, we were also able to explore the relations of VEGF from different airway compartments with cold symptoms. We elected to study respiratory infection on the symptom level, because symptoms are a relevant clinical end-point of infection, the identification of individual pathogens is extremely challenging, and a meta-analysis of respiratory infection and stress studies found no differences in effect sizes between self-reported and biologically verified respiratory infection (Pedersen et al., 2010).

## 2. Method

### 2.1. Study overview

Participants were assessed at five time points, a non-stress baseline period, two stress assessments during the final exam stress period, and two follow-up cold symptoms severity assessments after the finals period. The non-stress assessment was scheduled around the middle of a 15-week semester during a low stress period of the same term or the subsequent term, when no exams or demanding projects were scheduled. During the final exam period, the early and late exam assessments were separated by 5–7 days across participants. A follow-up survey of cold symptoms was administered online twice approximately 5 and 10 days after the individual's last examination. The present study included all participants who responded to that follow-up survey of cold symptoms.

### 2.2. Participants

Participants were recruited from psychology undergraduate classes through flyers, course announcements, and research participant pool participation. Criteria for inclusion were having a minimum of three written examinations or large final projects (end-of-term papers) during the final exam period. Exclusion criteria were current smoking, intake of antibiotics or oral or injected corticosteroids within the past 6 weeks, and history of any of the following physical conditions: angina, myocardial infarction, congestive heart failure, transient ischemic attacks, or cerebrovascular accidents. The study was approved by the Southern Methodist University Institutional Review Board and participants gave written informed consent.

### 2.3. Physiological assessments

$FE_{NO}$  (in ppb) was measured with an electrochemical analyzer (NIOX MINO; Aerocrine, Solna, Sweden) in adherence to current guidelines (American Thoracic Society and European Respiratory Society, 2005; Silkoff et al., 2006). For general sample characterization, we also obtained forced expiratory volume in the first second (the best of three valid forced expiratory efforts) expressed as percent of predicted ( $\%FEV_1$ ) from spirometry. This measurement was not scheduled until the end of the session to avoid interference of the forced expiratory maneuvers with  $FE_{NO}$  assessments (American Thoracic Society

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