Effects of hypercapnia on peripheral vascular reactivity in elderly patients with acute exacerbation of chronic obstructive pulmonary disease

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Abstract: Blood acid-base imbalance has important effects on vascular reactivity, which can be related to nitric oxide (NO) concentration and increased during hypercapnia. Release of NO seems to be linked to H⁺ and CO₂ concentration and to exacerbation of chronic obstructive pulmonary disease (COPD), a common medical condition in the elderly. Flow-mediated dilation (FMD), a valuable cardiovascular risk indicator, allows assessment of endothelial-dependent vasodilation by measurement of FMD in 96 elderly patients with acute exacerbation of COPD. Patients underwent complete arterial blood gas analysis and FMD measurement before (phase 1) and after (phase 2) standard therapy for acute exacerbation of COPD and recovery. Significant differences between phase 1 and phase 2 were observed in the mean values of pH (7.38±0.03 versus 7.40±0.02, P<0.001), pO₂ (59.6±4.9 mmHg versus 59.7±3.6 mmHg, P<0.001), pCO₂ (59.3±8.63 mmHg versus 46.7±5.82 mmHg, P<0.001), FMD (10.0±2.8% versus 8.28±2.01%, P<0.001) and blood flow rate (1.5±0.3 m/s versus 1.5±0.3 m/s, P=0.001). FMD values were positively correlated with pCO₂ values (r=0.294, P=0.004) at baseline. A significant correlation was also found between relative changes in FMD and pCO₂ levels, passing from phase 1 to phase 2 (r=0.23, P=0.023). Patients with higher baseline endothelium-dependent vasodilation as evaluated by FMD showed greater modification with regard to pCO₂ changes (2.6±1.39 versus 1.59±1.4, P=0.012). In conclusion, endothelium-dependent vasodilatation as evaluated by FMD was elevated during hypercapnia, and varied significantly according to pCO₂ changes in patients with higher baseline levels, suggesting that vascular reactivity in acute COPD exacerbations in the elderly depends on integrity of the vascular endothelium.

Keywords: hypercapnia, elderly, chronic obstructive pulmonary disease, vascular reactivity, flow-mediated dilation

Introduction

Hypercapnia and the accompanying acidosis are considered to induce strong vasodilating effects on the coronary and cerebral circulation in mammals, and previous data have implicated nitric oxide (NO) in the vasodilatory response of vascular endothelium to hypercapnia.¹-³ Although the role of NO in the response of the cerebral circulation to hypercapnia has been extensively investigated,⁴ few studies have addressed the role of NO in the peripheral circulation under conditions of elevated blood carbon dioxide (CO₂) tension in the elderly.⁵ This issue is important considering that the vasculature of the brain is more sensitive to changes in arterial pCO₂ when compared with the peripheral circulation and in particular with regard to the vasculature of the forearm.⁶
Endothelium-derived NO has been shown to play an important contributory role in the coronary vasodilatory response to a variety of physiological stimuli, including hypoxia, hypercapnia, and reactive hyperemia subsequent to transient occlusion. However, the effect of acid-base homeostasis and NO on vascular reactivity has been mainly studied in animal models.

Flow-mediated dilation (FMD) measurement at the level of the brachial artery is a broadly available method used to test endothelium-dependent vasodilation, as well as to measure indirectly endothelial NO production induced by increased local blood flow (shear stress). Flow-induced changes in arterial diameter by forearm compression evoke the endothelial response to reduced blood flow, which is characterized by initial narrowing of the blood vessel reflecting the vascular/endothelial response to resting levels of shear stress. Conversely, in response to a sudden increase in blood flow, arterial dilatation ensues. FMD renders the ability of the endothelium to adjust the biosynthesis and release of mediators to produce vasodilation, at least in part mediated by NO, as substantiated by the results of a recent meta-analysis. FMD is a valuable and reliable indicator of cardiovascular risk and is an important and useful tool in cardiovascular risk stratification in the elderly.

It is well known that low pH values induce vascular smooth muscle relaxation and that blood vessels have high sensitivity to changes in pCO₂. Moreover, pCO₂ is considered to be an important regulator of the cerebral circulation in mammals. An essential and intrinsic property of the cerebral vasculature with the aim to maintain metabolic constancy is autoregulation of local blood flow. This physiological process, also known as chemoregulation, is frequently challenged by the CO₂ concentration. The CO₂-NOS axis is a cardinal pathway in the chemoregulation of cerebral blood flow in humans, and impairment of endothelial function associated with decrease of CO₂ cerebrovascular reactivity has been demonstrated in patients affected by cardiovascular disease.

Endothelial dysfunction, defined as a functional and reversible alteration of endothelial cells, leading to a shift of the actions of the endothelium toward reduced vasodilation, proinflammatory state and proliferative and prothrombotic properties, results from functional changes characterized by vasoconstriction, coagulation abnormalities, and increased vascular proliferation, and has been reported to be the initial step in atherosclerosis. Peripheral endothelial function can be noninvasively evaluated by measurement of FMD at the level of the brachial artery by using high-resolution ultrasound methods.

As stated above, an important mediator of FMD is endothelium-derived NO, and in the present study we investigated the role of NO in the peripheral circulation during hypercapnia in patients with exacerbation of chronic obstructive pulmonary disease (COPD) by means of FMD measurement. We assessed the relationship between endothelium-dependent vasodilation and pCO₂ changes in the clinical setting of acute exacerbation of COPD after treatment with standard therapy (β₂-agonists, anticholinergic drugs, and corticosteroids, as well as oxygen and antibiotic therapy in cases of respiratory failure) as indicated by the international guidelines. We demonstrated a significant increase in pH values and a decrease in pCO₂ and FMD values, and higher baseline endothelium-dependent vasodilation corresponding to higher pCO₂ reactivity. Our findings suggest that endothelium-dependent vasodilation, as evaluated by FMD measurement, increases during hypercapnia and depends on the integrity of the vascular endothelium in elderly patients with acute COPD exacerbation.

Materials and methods

Standard protocols and patient consent

This was a cross-sectional cohort study fulfilling the requirements of the Declaration of Helsinki and the guidelines for Good Clinical Practice, the Strengthening the Reporting of Observational Studies in Epidemiology, and the National Institute for Health and Clinical Excellence guidelines. Approval to conduct experiments using human subjects was obtained from the local ethics committee on human experimentation. Written informed consent for this research was obtained from each patient or from relatives/legal guardians in the case of critically disabled patients.

Patient recruitment

From January to December 2010, 220 consecutive elderly patients with a clinical diagnosis of acute exacerbation of COPD were evaluated for enrollment in the study. The recruitment process was conducted on consecutive subjects hospitalized in the Department of Medical Sciences, specifically in the Division of Internal Medicine and in the Geriatrics Unit. The diagnosis of COPD was made according to Global Initiative for Chronic Obstructive Lung Disease criteria for the diagnosis, classification, and severity of COPD.
second <80% of predicted), and were evaluated by spirometry, arterial blood gas analysis (ABGA), and chest radiography. Exclusion criteria included other coexisting pulmonary diseases, body mass index <20 or >30 kg/m², metabolic syndrome, diabetes mellitus, arterial hypertension (blood pressure values >130/80 mmHg), arterial hypotension (blood pressure values <90/60 mmHg), blood pressure values in the left and right arm differing by more than 15 mmHg, a history of Raynaud’s phenomenon, a congenital abnormality of the arm or hand, known cardiovascular comorbidities, neoplastic diseases or a radical mastectomy on either side, acute and chronic renal failure, carotid stenosis, normal pCO₂ levels, and no recovery after standard therapy for COPD exacerbations (inhaled β₂-agonists, anticholinergic drugs, and oxygen and antibiotic therapy when respiratory failure was present).

Only those patients affected by acute exacerbation of COPD, who reported pCO₂ >45 mmHg as evaluated by ABGA before treatment (phase 1) and who responded to 5 days of standard therapy with at least a 5% reduction of their respective baseline pCO₂ after treatment (phase 2) were considered for the study. Patients taking medications that could influence endothelial function (eg, nitrates) were excluded.

The inclusion criteria for the initial study sample were used for the screening stage of 220 subjects with acute exacerbation of COPD; 96 patients satisfied the inclusion criteria and were enrolled. All patients enrolled in the study underwent ABGA and FMD measurement in both phase 1 and phase 2 (Figure 1). In order to avoid the possible influence of hypoxemia on endothelial function, we titrated oxygen administration when necessary to maintain arterial oxyhemoglobin saturation at ≥94%.

Assessment of vascular function
Noninvasive evaluation by ultrasonography of the endothelial-dependent vasodilatation was done by measurement of FMD in the brachial artery of the nondominant arm according to international standards. The diameter of the brachial artery was measured by an expert sonographer (AdM) on ultrasound images obtained in B-mode with a high resolution 5–10 mHz multifrequency linear probe connected to a Technos MPX (Esaote, Genova, Italy). All the subjects were fasting and had not been smoking, drinking alcohol or coffee, or taking antioxidant agents for at least 16 hours (last meal at 6 pm on the day before evaluation). During phase 1 and phase 2 of the study, the subjects were examined between 10 am and 11 am and after 15 minutes of rest in the supine position in a quiet, temperature-controlled room (20°C–22°C). We explored the brachial artery at the level of the antecubital fossa on a longitudinal plane, optimizing the depth and the acoustic window pre-sets and keeping them in the same position during the study, using a mechanical probe-holder arm. An automated sphygmomanometer was used to monitor blood pressure and pulse throughout the examination. A standard blood pressure cuff was positioned around the nondominant arm 5 cm below the

![Flow diagram](https://www.dovepress.com/)

**Figure 1** Flow diagram for identification of eligible patients.

**Abbreviations:** ABGA, arterial blood gas analysis; FMD, flow-mediated dilation; COPD, chronic obstructive pulmonary disease.
factor on the effect of standard therapy a multivariate hierarchical linear model for repeated measurements was performed using FMD values as continuous outcome, and baseline patient characteristics, clinical variables, and pharmacological treatment as covariates. This method borrows strength from correlated measures within each subject over time. Specifically, two separate models were built. The first model (the so-called “fully adjusted” model) included the time variable (ie, an indicator variable which takes the value 1 if referred to phase 2 FMD measurements) and the following baseline covariates: age, sex, smoking habit, pCO₂, hyperemic blood flow rate, inhalation therapy (bronchodilators), and treatment with antibiotics, oxygen, calcium channel blockers, aspirin, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and β-blockers. The second one (so-called “selected model”) included a parsimonious set of the mentioned covariates, other than the time variable, using the classical stepwise selection method (retention threshold, *P*<0.10). A two-sided *P*-value <0.05 was considered to be statistically significant. Statistical analyses were performed using SAS Release version 9.1 (SAS Institute, Cary, NC, USA).

**Results**

**Sample size and power analysis**

A sample size of 96 patients had 90% power to detect a mean of paired differences for FMD values (phase 2 – phase 1) of 0.05 using an estimated standard deviation of differences of 1.44 and with a significance level (type I error) of 0.05 using a two-sided paired *t*-test.

The study sample included 96 patients, ie, 74 men (77%) and 22 women (33%) with a mean age of 72.4±5.4 (range 65–96) years. Both baseline patient characteristics and the list of medications being taken are reported in Table 1. No statistically significant sex differences were observed.

**Table 1** Baseline patient characteristics and pharmacological treatments according to sex

<table>
<thead>
<tr>
<th></th>
<th>All (100%)</th>
<th>Men (77%)</th>
<th>Women (33%)</th>
<th><em>P</em>-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>96 (100%)</td>
<td>74 (77%)</td>
<td>22 (33%)</td>
<td>–</td>
</tr>
<tr>
<td>Age (years)</td>
<td>72.4±5.4</td>
<td>72.2±5.7</td>
<td>72.9±4.0</td>
<td>0.757</td>
</tr>
<tr>
<td>Smokers</td>
<td>48 (50%)</td>
<td>37 (50%)</td>
<td>11 (50%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Inhalation therapy</td>
<td>43 (44.8%)</td>
<td>36 (48.6%)</td>
<td>7 (31.8%)</td>
<td>0.166</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>24 (25%)</td>
<td>19 (25.7%)</td>
<td>5 (22.7%)</td>
<td>0.780</td>
</tr>
<tr>
<td>ACE-I</td>
<td>42 (43.8%)</td>
<td>32 (43.2%)</td>
<td>10 (45.5%)</td>
<td>0.855</td>
</tr>
<tr>
<td>ARBs</td>
<td>21 (21.9%)</td>
<td>16 (21.6%)</td>
<td>5 (22.7%)</td>
<td>0.913</td>
</tr>
<tr>
<td>β-blockers</td>
<td>18 (18.8%)</td>
<td>14 (18.9%)</td>
<td>4 (18.2%)</td>
<td>0.938</td>
</tr>
<tr>
<td>Oxygen</td>
<td>64 (66.7%)</td>
<td>48 (64.9%)</td>
<td>16 (72.7%)</td>
<td>0.494</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>27 (28.1%)</td>
<td>21 (28.4%)</td>
<td>6 (27.3%)</td>
<td>0.920</td>
</tr>
<tr>
<td>Aspirin</td>
<td>30 (31.3%)</td>
<td>20 (27%)</td>
<td>10 (45.5%)</td>
<td>0.103</td>
</tr>
</tbody>
</table>

**Notes:** Data are expressed as means ± standard deviations or frequencies and percentages for continuous and categorical variables, respectively. The *P*-value was estimated by the chi-square test and the two-sample *t*-test for categorical and continuous variables, respectively. The *P*-value was estimated by the chi-square test and the two-sample *t*-test for categorical and continuous variables, respectively. **Abbreviations:** ACE-I, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers.
Baseline clinical variables for the patients in phase 1 and phase 2 are reported in Table 2. Statistically significant differences between phase 1 and phase 2 were observed for all the considered variables (Table 2, all \( P = 0.001 \)). FMD values were positively correlated with pCO\(_2\) values \((r=0.294, P=0.004)\) at baseline. A scatter plot of FMD values against pCO\(_2\) values (both measured at phase 1) is reported on Figure 2. Besides, a significant positive correlation was found between relative changes in FMD and pCO\(_2\) levels, passing from phase 1 to phase 2 \((r=0.23, P=0.023)\). Patients with higher baseline endothelium-dependent vasodilation during hypercapnia showed greater modification with regard to pCO\(_2\) changes \((2.6\pm1.39 \text{ mmHg} \text{ change})\) compared to patients with lower baseline endothelium-dependent vasodilation \((1.59\pm1.4 \text{ mmHg} \text{ change})\) \((r=0.294\) \((P=0.012)\).

FMD and pCO\(_2\) were also measured in 76 independent elderly subjects (mean age 69.8±7.3 years, 32.9% males). No significant difference in mean FMD values was found between COPD patients at baseline and controls \((10.0\pm2.8 \%\) versus \(9.6\pm2.7 \%)\), respectively, \(P=0.344\)), whereas a marked difference was found between mean pCO\(_2\) values \((59.3\pm8.6 \text{ mmHg} \text{ versus} 39.6\pm1.8 \text{ mmHg}, P<0.001)\). No correlation was found between FMD and pCO\(_2\) values in the control group \((r=0.03, P=0.812)\).

Regression coefficients with the standard error from a multivariate hierarchical linear model for repeated measurements are reported in Table 3. As shown, after standard therapy, mean FMD values decreased significantly by \(1.8\pm0.15 \%\) \((P<0.001)\) controlled for baseline characteristics of patients, clinical variables, and pharmacological treatments. Only hyperemic blood flow rate \((P=0.001)\) and aspirin therapy \((P=0.010)\) were associated with basal FMD values.

**Discussion**

The present study found an improvement in endothelial-dependent vasodilation during hypercapnia in patients with acute exacerbation of COPD. Higher vasodilation during hypercapnia is a common finding in the acute phase of COPD, and is reversed after recovery. Our data highlight an enhanced endothelium-dependent vasodilation that might be explained by increased NO production during hypercapnia. Our results are consistent with reports that alterations in NO production or activity may have a major role in endothelium-dependent vasodilation, and are corroborated by recent data implicating NO in the vasodilatory responses to hypercapnia.

We observed that higher mean FMD basal values were associated with greater changes between phase 1 and phase 2 FMD mean values, indicating higher endothelium-dependent vasodilation. This evidence suggests that endothelium-dependent vasodilation in response to altered metabolic determinants, such as hypercapnia, requires normal endothelial function, and vascular reactivity in acute COPD exacerbations depends on vascular endothelium integrity in the elderly.

The role of NO in hypercapnia-induced vasodilation is not confined to the central nervous system. Several studies have shown increased coronary blood flow during hypercapnia, and
Table 3 Results of multivariable longitudinal linear models for variation in FMD

<table>
<thead>
<tr>
<th>Variables</th>
<th>Multivariable (fully adjusted)</th>
<th>Multivariable (stepwise selection method)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regression coefficients (SE)</td>
<td>P-value</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>10.04 (0.26)</td>
<td>0.058</td>
</tr>
<tr>
<td>Effect of standard therapy</td>
<td>–1.75 (0.15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patient characteristics at baseline (phase 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>–0.01 (0.03)</td>
<td>0.761</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>–0.45 (0.42)</td>
<td>0.293</td>
</tr>
<tr>
<td>Smoking (yes)</td>
<td>0.04 (0.35)</td>
<td>0.914</td>
</tr>
<tr>
<td>Patients’ clinical variables at baseline (phase 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pCO2 (mmHg)</td>
<td>0.03 (0.03)</td>
<td>0.330</td>
</tr>
<tr>
<td>pH (−log[H2O2])</td>
<td>–13.14 (7.29)</td>
<td>0.075</td>
</tr>
<tr>
<td>pO2 (mmHg)</td>
<td>0.02 (0.05)</td>
<td>0.705</td>
</tr>
<tr>
<td>Hyperemic blood flow rate (m/sec)</td>
<td>2.01 (0.60)</td>
<td>0.001</td>
</tr>
<tr>
<td>Pharmacological treatments at baseline (phase 1)</td>
<td></td>
<td>2.13 (0.59)</td>
</tr>
<tr>
<td>Inhalation therapy (yes)</td>
<td>–0.31 (0.44)</td>
<td>0.481</td>
</tr>
<tr>
<td>Antibiotics (yes)</td>
<td>–0.46 (0.55)</td>
<td>0.400</td>
</tr>
<tr>
<td>ACE-I (yes)</td>
<td>–0.17 (0.40)</td>
<td>0.664</td>
</tr>
<tr>
<td>ARBs (yes)</td>
<td>0.00 (0.04)</td>
<td></td>
</tr>
<tr>
<td>β-blockers (yes)</td>
<td>–0.12 (0.49)</td>
<td>0.108</td>
</tr>
<tr>
<td>Oxygen (yes)</td>
<td>–0.08 (0.04)</td>
<td>0.056</td>
</tr>
<tr>
<td>Calcium channel blocker (yes)</td>
<td>–0.03 (0.49)</td>
<td>0.045</td>
</tr>
<tr>
<td>Aspirin (yes)</td>
<td>–0.04 (0.38)</td>
<td>0.090</td>
</tr>
<tr>
<td></td>
<td>–1.01 (0.38)</td>
<td></td>
</tr>
</tbody>
</table>

Notes: “Intercept” estimate corresponds to the overall mean value of FMD at phase 1 whereas “effect of standard therapy” was estimated as the changes in FMD mean values from phase 1 to phase 2 (ie, from 10.04% to 10.04%–1.75%) controlled for baseline patient characteristics, clinical variables and pharmacological treatments.

Abbreviations: FMD, flow-mediated dilation; SE, standard error; ACE-I, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers.

Our data are in contrast with a previous study reporting impaired endothelial function in patients affected by stable COPD and a negative correlation between the severity of illness and endothelium-dependent vasodilation.39 Importantly, we have to bear in mind that study considered normocapnic patients with COPD, whereas we focused on FMD changes related to hypercapnia during the acute phase of COPD exacerbation. Notably, acute stress may induce known (eg, hypercapnia) and unknown factors contributing

NO has been proposed as a mediator of in situ hypercapnia-induced coronary vasodilation in the dog heart.31,32 Coronary vasodilation during selective intracoronary hypercapnia was attenuated after in situ inhibition of NO synthase with Nω-nitro-L-arginine methyl ester or Nω-monomethyl-L-arginine in the canine heart. These data suggest that NO plays an important role in coronary vasodilation during hypercapnia. Moreover, studies in isolated aortic strips suggest that vasorelaxation in response to CO2 could be mediated, at least in part, by NO.33 Indeed, most of the studies performed in animal models report that NO synthase activity may be increased, with consequent stimulation of NO production in conditions of low pH.34–36 Overall, although the precise contribution of endothelial NO synthase during hypercapnia is still unclear, previous animal and human studies indicate that endothelial NO synthase is an important, but not exclusive, mediator of hypercapnia-induced vascular modifications.

Our results are in agreement with the involvement of NO in hypercapnia and post-hypercapnia-related vasodilation, and suggest that assessment of endothelium-dependent vasodilation by measurement of FMD is a useful method for evaluating the NO vasodilator system in the setting of aging and COPD in vivo.10,11,13 It has also been reported that endothelial-derived NO may be involved in CO2-dependent systemic blood flow regulation, which in turn depends on the integrity of the vascular endothelium.37,38 Our findings are in agreement with this. Further, we found a significant difference in post-hyperemic flow rate in the hypercapnia and normocapnia phases (Table 2). This suggests that good hypercapnia-induced endothelial-dependent vasodilation is related to efficient endothelial function, as well as increased NO production, the latter likely due to a direct effect of CO2 on the vascular endothelium rather than related to the shear stress induced by an increased peripheral flow rate. The significant positive correlation found between increased endothelium-dependent vasodilation as assessed by measurement of FMD and elevated pCO2 values suggests a functional role for NO in peripheral vascular reactivity to CO2.
to increased production of endothelial NO. In fact, previous studies have reported significantly increased expression of inducible NO synthase in the neutrophils and macrophages of COPD patients.\textsuperscript{40} Other studies have also shown higher NO levels in breath condensate and induced sputum in patients with mild or severe COPD, as compared with control subjects.\textsuperscript{41–43} Persistent stress may result in derangement and dampening of endothelial function, and consequently lower endothelial vasoreactivity. In fact, patients with COPD have an increased risk of cardiovascular disease, probably due to their endothelial dysfunction. COPD is linked to systemic inflammation, which has a propensity to augment in due course and become boosted during acute exacerbations. In turn, systemic inflammation promotes evolution of cardiovascular disease, and an association between systemic inflammation and increased risk of cardiovascular morbidity and mortality has been documented in patients with COPD.\textsuperscript{39} The link between COPD and cardiovascular disease may be represented by abnormalities in systemic vascular function, and FMD may depict vasomotor function, as well as predict cardiovascular morbidity and mortality during acute exacerbations.

The main limitations of our study are its cross-sectional design and the use of only one method to assess endothelial function, in particular the lack of evaluation of nitroglycerin-mediated dilation, which indicates endothelial-independent dilation. We must also stress that the pO\textsubscript{2} levels recorded in our COPD patients were very low, although severe hypoxemia is common in the context of the baseline hypercapnic states frequently seen in COPD patients and is related to the altered response of respiratory drive, especially in the clinical setting of acute functional worsening.\textsuperscript{44}

In conclusion, our data demonstrate that hypercapnia during acute exacerbations of COPD can influence endothelium-dependent vasodilation as assessed by measurement of FMD, and a larger decrease in FMD could point to greater reactivity to pCO\textsubscript{2} changes. The modifications in vascular reactivity induced by variations of CO\textsubscript{2} tension in peripheral blood could depend on the integrity of the vascular endothelium, could be mediated by the NO synthase/NO pathway, and could be related to cardiovascular risk in this clinical setting, particularly in elderly patients.

**Author contributions**

AdM performed the FMD measurements, conceived the original idea, and developed the protocol. AG conceived the original idea, developed the protocol, completed the analysis, and wrote the manuscript. MPD helped with data collection, participated in protocol development, and approved the manuscript. GM and MV helped with data collection, completed the analysis, and wrote the manuscript. GP, DS, and GV provided overall supervision and revised the manuscript for intellectual content. AF performed statistical analysis. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

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**Disclosure**

The authors report no conflicts of interest in this work.

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