Differences in angiotensin (1–7) between men and women

Jennifer C. Sullivan, Paula Rodriguez-Miguelez, Margaret A. Zimmerman, and Ryan A. Harris

1Department of Physiology, Georgia Regents University, Augusta, Georgia; 2Division of Clinical Translational Science, Georgia Prevention Institute, Department of Pediatrics, Georgia Regents University, Augusta, Georgia; and 3Sport and Exercise Science Research Institute, University of Ulster, Jordanstown, Northern Ireland, United Kingdom

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Sullivan JC, Rodriguez-Miguelez P, Zimmerman MA, Harris RA. Differences in angiotensin (1–7) between men and women. Am J Physiol Heart Circ Physiol 308: H1171–H1176, 2015. First published February 6, 2015; doi:10.1152/ajpheart.00897.2014.—In experimental animal models of hypertension, angiotensin (1–7) [ANG-(1–7)] is higher in females compared with males; however, it is less clear whether the same applies to humans. Therefore, this study sought to compare circulating concentrations of ANG-(1–7) in apparently healthy men and women under normal physiological conditions. With the use of a cross-sectional experimental design, blood was collected in EDTA anticoagulant from 42 volunteers (21 men and 21 women; and age range, 19–48 yr) for analysis of plasma concentrations of ANG-(1–7) and ANG II. Blood pressure was measured and vascular endothelial function was determined (n = 25) using the brachial artery flow-mediated dilation (FMD) test. As a result, women exhibited a higher circulating concentration of ANG-(1–7) (P = 0.04) compared with men, whereas values of ANG II were similar between groups. Baseline arterial diameter, peak diameter, and shear rate were significantly greater (P < 0.02) in men compared with women. No significant differences in FMD, FMD normalized for shear, or time to peak dilation were observed between men and women. In addition, a positive correlation between ANG-(1–7) and FMD (P = 0.04) and negative association between ANG-(1–7) with ANG II (P = 0.01) were only identified in men, whereas a positive relationship between ANG-(1–7) and diastolic blood pressure (P = 0.03) was observed in women. In conclusion, women exhibit significantly higher plasma concentrations of ANG-(1–7) compared with men. In addition, this study describes a relationship between ANG-(1–7), vascular function, and diastolic blood pressure that appears to be sex dependent.

ANG-(1–7), sex; blood pressure; renin-angiotensin system

PREVALENCE AND TREATMENT of hypertension differs by sex and age (16). Women are more likely to receive treatment for their hypertension than men; however, they are less likely to have their blood pressure (BP) controlled. Only ∼50% of women and ∼55% of men achieve adequate BP control with current therapeutic options, which includes modulation of the renin-angiotensin system (RAS) (5). More studies are needed in both men and women to allow for a better understanding of the molecular pathways by which BP is controlled.

Overactivation of the “classical RAS pathway” [ANG II type-1 receptor (AT1), ANG II, and angiotensin-converting enzyme (ACE)] has a critical role in the development and maintenance of hypertension (25). Accordingly, ACE inhibitors and angiotensin receptor blockers (ARBs) are among the first line treatments for hypertension and they target the classical RAS cascade (26). The RAS also possesses a counter-regulatory axis, the “nonclassical RAS pathway,” comprised of ACE2, ANG II type-2 receptor (AT2), angiotensin (1–7) [ANG-(1–7)], and the Mas receptor (23). ANG-(1–7) exerts cardiovascular and renal effects that typically oppose the effects of ANG II (31).

The relevance of the RAS in cardiovascular health has been extensively studied in animal models (1, 40). Numerous differences between male and female experimental animals have been reported in the expression of the RAS pathway; males exhibit greater expression of classical RAS components, whereas females have greater expression of the nonclassical RAS pathway (4, 33, 39, 41). Higher concentrations of ANG-(1–7) in female spontaneously hypertensive rats (SHRs) attenuate ANG II-induced increases in BP relative to males. In addition, ANG-(1–7) contributes more to the BP-lowering effects of the ARB candesartan in females compared with males (33, 34, 40, 41).

Based on the potential of ANG-(1–7) to modulate BP in experimental animals, there is growing interest in defining how sex differences impact circulating concentrations of ANG-(1–7) in humans. To our knowledge, this has only been examined in one study (29), which reported higher concentrations of ANG-(1–7) in men compared with women. However, this finding is in contrast to the known cardiovascular roles of ANG-(1–7) and findings in experimental animals. Nonetheless, no studies have combined assessments of ANG-(1–7) with indexes of cardiovascular risk. The current study tested the hypotheses that 1) circulating concentrations of ANG-(1–7) are greater in women compared with men and 2) concentrations of ANG-(1–7) are positively associated with vascular endothelial function and inversely associated with BP.

METHODS

Participants. Forty-two participants comprised of both men (n = 21; ages, 19–48 yr; 38% black) and premenopausal women (n = 21; ages, 18–37 yr; 52% black) participated in the study. The inclusion criteria required all participants to be free of any evidence of cardiovascular, pulmonary, renal, hepatic, cerebral, or metabolic disease, as well as not having been prescribed or using any medication known to affect BP or vascular tone. Participants who reported to be smokers or taking oral contraceptives were excluded from the study. Following the informed consent process, a medical screening that included a comprehensive individual medical health history questionnaire and an anthropometric analysis was performed on all the participants. The study followed the principles of the Declaration of Helsinki and was approved by the Institutional Review Board at Georgia Regents University.

Anthropometrics and BP. Anthropometry testing included standard assessments of height, weight, waist-to-hip ratio, and calculation of body mass index. Systolic BP (SBP) and diastolic BP (DBP) were evaluated in all the participants using established protocols recommended by the American Heart Association (27).

Blood collection and processing. Venus blood samples (20 ml) were collected from the antecubital vein into EDTA anticoagulant
Table 1. Characteristics and blood chemistry of the men and women

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th>Women</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>21</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>26 ± 1</td>
<td>26 ± 1</td>
<td>0.70</td>
</tr>
<tr>
<td>Height, cm</td>
<td>180 ± 2</td>
<td>168 ± 2</td>
<td>&lt;0.01*</td>
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<tr>
<td>Weight, kg</td>
<td>86 ± 5</td>
<td>78 ± 9</td>
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</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.3 ± 1.2</td>
<td>27.8 ± 1.8</td>
<td>0.51</td>
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<tr>
<td>WHR, %</td>
<td>0.89 ± 0.02</td>
<td>0.76 ± 0.06</td>
<td>0.55</td>
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<tr>
<td>SBP, mmHg</td>
<td>124 ± 4</td>
<td>112 ± 5</td>
<td>0.04*</td>
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<tr>
<td>DBP, mmHg</td>
<td>73 ± 4</td>
<td>69 ± 4</td>
<td>0.53</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>61 ± 4</td>
<td>63 ± 6</td>
<td>0.34</td>
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<tr>
<td>TC, mg/dl</td>
<td>150 ± 8</td>
<td>161 ± 22</td>
<td>0.62</td>
</tr>
<tr>
<td>HDL, mg/dl</td>
<td>37 ± 2</td>
<td>71 ± 7</td>
<td>0.05*</td>
</tr>
<tr>
<td>LDL, mg/dl</td>
<td>99 ± 8</td>
<td>53 ± 4</td>
<td>0.27</td>
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<tr>
<td>TG, mg/dl</td>
<td>72 ± 8</td>
<td>53 ± 5</td>
<td>0.75</td>
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<tr>
<td>Glucose, mg/dl</td>
<td>87 ± 5</td>
<td>84 ± 2</td>
<td>0.54</td>
</tr>
<tr>
<td>Hemoglobin, g/dl</td>
<td>16.4 ± 0.4</td>
<td>12.4 ± 0.8</td>
<td>0.02*</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>47 ± 1</td>
<td>41 ± 2</td>
<td>0.06</td>
</tr>
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</table>

Data are means ± SE. BMI, body mass index; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; TC, total cholesterol; HDL, high-density lipoproteins; LDL, low-density lipoproteins; TG, triglycerides. *P < 0.05, significant differences between men and women.

Vacutainer systems (Becton Dickinson, Franklin Lakes, NJ), following an overnight fast. Whole blood was centrifuged at 3,000 rpm for 10 min at 4°C to obtain plasma. Strata phenyl extraction columns (Phenomenex) were placed at the top of a vacuum manifold and washed with 1 ml of HPLC-grade water. Fresh plasma (2 × 1 ml) was applied to the column, and angiotensin peptides were subsequently eluted using 500 μl of HPLC methanol (Sigma-Aldrich) and placed in an evaporator centrifuge (Jouan RC1010) overnight to remove the methanol. The resultant peptide sample was stored at −80°C until later analyzed.

Assessment of biomarkers. Concentrations of ANG II were measured by enzyme immunoassay according to the manufacturer’s instructions (No. 589301; Cayman Chemicals, Ann Arbor, MI). According to the manufacturer’s kit, quality control testing revealed that there was 4% cross-reactivity with ANG I, 100% cross-reactivity with ANG II, 36% cross-reactivity with ANG III, 33% cross-reactivity with ANG-(3–8), and <0.01% cross-reactivity with ANG-(1–7). ANG-(1–7) concentrations were measured by enzyme immunoassay via manufacturer’s protocol III (Bachem, Torrance, CA). According to the manufacturer’s kit, cross-reactivity for this enzyme immunoassay is 100% for ANG I/II-(1–7) and 0% for ANG I, II, III, and A.

Flow-mediated dilation. The brachial artery flow-mediated dilation (FMD) test was performed in a subset of 25 participants (12 women and 13 men) in accordance with the current methodological recommendations (18). All women were tested during days 1–7 of their menstrual cycle. Briefly, simultaneous B-mode and blood velocity profiles (duplex mode) of the brachial artery were obtained (Logiq 7, GE Medical Systems, Milwaukee, WI). Shear was calculated from the simultaneous measurements of blood velocity and brachial artery diameter according to the following equation: shear rate = (8·V)/d where V is the mean velocity (in cm/s) and d is the brachial artery diameter (in cm). Shear rate (in s⁻¹) area under the curve to the point of peak vasodilatation has been proposed to represent the stimulus of the vasodilatory response (27). FMD is expressed as the percent increase in peak diameter from baseline diameter. In addition, because of individual differences in both the hyperemic shear response as well as sex differences in brachial artery diameter, FMD/shear area under the curve was calculated to normalize the vasodilator response for shear stimulus. In our laboratory, the intraobserver reliability for FMD analysis (coefficient of variations) for baseline diameter, FMD, and FMD/shear are 0.5, 12.8, and 12.2%, respectively.

Statistical analysis. All data are presented as means ± SE. Independent samples Student’s t-test were performed to compare differences between men and women for FMD parameters and concentrations of ANG II and ANG-(1–7). One-tailed Pearson’s correlations were performed to determine the relationship among FMD parameters, DBP, SBP, ANG II, and ANG-(1–7) concentration. Differences were considered significant when P < 0.05. All statistical analyses were performed using SPSS version 18 (SPSS, Chicago, IL).

RESULTS

Participant characteristics. Participant characteristics are displayed in Table 1. Differences in height (P < 0.01), SBP (P = 0.04), high-density lipoprotein (P = 0.05), and hemoglobin (P = 0.02) were observed between men and women.

Concentrations of ANG II and ANG-(1–7). Figure 1 illustrates the plasma concentrations of ANG-(1–7) and ANG II in men and women (in pg/ml). Women exhibited statistically higher (P = 0.04) plasma concentrations of ANG-(1–7) compared with men (Fig. 1A), whereas concentrations of ANG II were similar between men and women (Fig. 1B).

Vascular endothelial function. Men exhibited a larger brachial artery diameter and a greater peak diameter following cuff release compared with women (Table 2). In contrast, shear rate area under the curve (in s⁻¹) was greater (P < 0.02) in women compared with men. No significant differences in FMD (P < 0.66), FMD normalized for shear (FMD/shear) (P < 0.41), or time to peak vasodilatation (P < 0.65) were observed between men and women.

Fig. 1. Plasma concentrations of angiotensin 1–7 [ANG-(1–7)] peptide (A) and ANG II peptide (B) in men (n = 21) and women (n = 21). Data are presented in pg/ml and expressed as means ± SE. *Significant differences between men and women. ANG-(1–7) concentrations for women and men are 49.5 ± 4.4 and 35.9 ± 3.1 fmol/ml, respectively. ANG II concentrations for women and men are 81.6 ± 19.1 fmol/ml and 80.2 ± 20.7 fmol/ml, respectively.
classical RAS components in a sex difference-specific manner. Science studies have identified a differential expression of factors of BP and fluid balance (42). Several clinical and basic primary effectors ANG II and ANG-(1–7) as essential regulation, and BP regulation in humans. The multienzymatic RAS system acts through its women.

Accounting for sex when investigating ANG-(1–7); however, findings in the current study underscore the importance of cardiovascular risk outcomes in humans remains insufficient. Our examining circulating ANG-(1–7) and the relationship to car-

Fig. 2. Pearson’s correlations between ANG-(1–7) and flow-mediated dilatation (A). ANG-(1–7) and ANG II (B), and ANG-(1–7) and diastolic blood pressure (C). Data are expressed as individual values. Black dots, data for men; white dots, data for women.

Table 2. Parameters of vascular endothelial function testing

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th>Women</th>
<th>P</th>
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<tbody>
<tr>
<td>Baseline diameter, cm</td>
<td>0.396 ± 0.021</td>
<td>0.285 ± 0.008</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Peak diameter, cm</td>
<td>0.412 ± 0.019</td>
<td>0.311 ± 0.008</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>FMD absolute change, cm</td>
<td>0.02 ± 0.03</td>
<td>0.02 ± 0.02</td>
<td>0.21</td>
</tr>
<tr>
<td>FMD, %</td>
<td>7.1 ± 0.9</td>
<td>7.7 ± 0.9</td>
<td>0.66</td>
</tr>
<tr>
<td>Shear rate, s&lt;sup&gt;−1&lt;/sup&gt;, AUC</td>
<td>41.019 ± 3.360</td>
<td>64.412 ± 7.738</td>
<td>0.02*</td>
</tr>
<tr>
<td>FMD/shear, %/s&lt;sup&gt;−1&lt;/sup&gt;, AUC</td>
<td>0.17 ± 0.02</td>
<td>0.15 ± 0.02</td>
<td>0.41</td>
</tr>
<tr>
<td>TTP, s</td>
<td>45 ± 3</td>
<td>48 ± 5</td>
<td>0.65</td>
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Data are means ± SE. FMD, flow-mediated dilatation; AUC, area under the curve; TTP, time to peak vasodilatation. *Significant differences between men and women.

Relationships among BP, ANG-(1–7), and endothelial function. Figure 2A illustrates a significant positive correlation between ANG-(1–7) and FMD in men (r = 0.478, P = 0.04) and a modest relationship in women that did not reach significance (r = 0.392, P = 0.08). Figure 2B illustrates a significant inverse association between ANG-(1–7) and ANG II in men (r = −0.551, P = 0.01), whereas no relationship was observed in women (r = 0.116, P = 0.29). Figure 2C further illustrates a significant positive correlation between ANG-(1–7) and DBP in women (r = 0.493, P = 0.03), whereas no relationship was observed in men (r = 0.307, P = 0.15). Of additional interest, there were significant positive associations between ANG-(1–7) and FMD absolute change (r = 0.562, P = 0.02) and ANG-(1–7) and FMD/shear rate (r = 0.561, P = 0.02) and negative associations between ANG II and FMD absolute change (r = −0.671, P = 0.05) and between ANG II and time to peak vasodilatation (r = −0.766, P = 0.02); however, these associations were only found in men.

To offer further insight into the overall impact of ANG-(1–7) on cardiovascular function, several additional relationships were observed independent of sex. A significant positive relationship between ANG-(1–7) and FMD (r = 0.419, P = 0.01) was observed. There were also significant positive associations between ANG-(1–7) and FMD absolute change (r = 0.387, P = 0.02), FMD/shear rate (r = 0.396, P = 0.02), DBP (r = 0.406, P = 0.01), and SBP (r = 0.329, P = 0.04).

DISCUSSION

The primary novel finding of this study is that normotensive, apparently healthy women exhibit higher circulating concentrations of ANG-(1–7) compared with men. Despite the growing support for a role of ANG-(1–7) in the regulation of BP and cardiovascular health in experimental animals, the literature examining circulating ANG-(1–7) and the relationship to cardiovascular risk outcomes in humans remains insufficient. Our findings in the current study underscore the importance of accounting for sex when investigating ANG-(1–7); however, more studies are certainly needed to fully understand the complex relationships among ANG-(1–7), endothelial function, and BP regulation in humans.

Circulating concentrations of ANG-(1–7) in men and women. The multi-enzymatic RAS system acts through its primary effectors ANG II and ANG-(1–7) as essential regulators of BP and fluid balance (42). Several clinical and basic science studies have identified a differential expression of classical RAS components in a sex difference-specific manner including plasma renin (20), AT<sub>1</sub> receptors (35), AT<sub>2</sub> receptors (32), neprilysin (7), and ANG-(1–7) (34, 40). However, despite a vast amount of data describing the different phenotypic profiles that men and women exhibit in BP values (30), the potential impact of a sex difference on ANG-(1–7) remains unclear because of predominately male cohorts investigated in clinical studies of ANG-(1–7) (22).

Our results indicate that women have significantly higher circulating concentrations of ANG-(1–7) compared with men, whereas values of ANG II remain similar between men and women. Our findings in humans are in agreement with previous investigations from our group and others who documented greater concentrations of ANG-(1–7) in female mice, SHRs, Wistar-Kyoto rats, and Sprague-Dawley rats compared with...
male counterparts, albeit similar concentrations of ANG II between both sexes (4, 17, 34). In contrast to our results, Reyes-Engel and colleagues (29) reported higher concentrations of ANG-(1–7) in men compared with women. The disparity in findings could be explained by the methodology of blood collection. Reyes-Engel and colleagues collected and processed plasma samples in the presence of protease inhibitors. Based on the large number of physiological and pharmacological differences between the sexes, we cannot rule out the possibility that the inclusion of protease inhibitors stabilized ANG-(1–7) to a greater extent in plasma from men in the other study. As a result, the lack of protease inhibitors in our study would be more evident in men, and therefore women would appear to have higher circulating levels of ANG-(1–7). Alternatively, the geographical location of the participants could be a contributing factor (Spain vs. Georgia, USA). The cohort in our study was comprised of whites and blacks. Although the racial demographic of the previous study was not reported (29), ethnic differences, the environment, and lifestyle factors could also explain disparity in results. Regardless, larger population studies are needed to further investigate sex differences in ANG-(1–7) and determine its impact on cardiovascular health in humans.

Potential role of sex-steroid hormones on ANG-(1–7). It is likely that the higher concentration of ANG-(1–7) in women is mediated, in part, by female sex hormones. Chronic estrogen exposure decreases nonclassical RAS components including mRNA and protein expression of ACE, a carboxyl-directed dipeptidase, which primarily converts ANG I to ANG II (15) and AT1 (28) and stimulates the nonclassical RAS pathway, including increases in ACE2 and nephrilysin activity, AT2 and Mas receptor activation, and ANG-(1–7) formation (7, 8). ACE2 is a monocarboxypeptidase homologue of ACE, and a primary substrate for ACE2 is ANG II, resulting in ANG-(1–7) formation. Nephrilysin is a zinc metalloendopeptidase that directly metabolizes ANG I to ANG-(1–7). Consistent with reports of sex differences in the nonclassical RAS, in both male rodents (9) and ovariectomized female rats (17), low concentrations of estrogens have been associated with higher circulating levels of ANG II, an increase in ACE activity, and a marked decline in plasma concentrations of ANG-(1–7). In support, data from the present study in humans document a significant negative correlation between ANG II and ANG-(1–7) only in men (Fig. 2B). Although female sex hormones have been linked to increases in ACE2 which could promote ANG-(1–7) formation from ANG II, there was not less ANG II in women relative to men. This raises the possibility that ANG II may not be the primary substrate for the formation of circulating ANG-(1–7) in humans. Consistent with this, we recently published that higher levels of renal ANG-(1–7) in female Wistar-Kyoto rats is associated with an increase in ACE activity (4) and ACE can catalyze the formation of ANG-(1–7) via ANG-(1–9) (14). Interestingly, recent evidence appears to suggest that human ACE2 prefers to process ANG I to ANG-(1–9) rather than ANG II to ANG-(1–7) (38). Nonetheless, additional studies, including larger cohorts of men and women, are needed to better understand the mechanisms responsible for greater ANG-(1–7) levels in women.

BP and ANG-(1–7). Data in the literature support an antihypertensive role for ANG-(1–7) during treatment with RAS inhibitors in hypertensive experimental animal models (2, 3). Moreover, our group (40) recently reported that ANG-(1–7) has a larger contribution to the BP-lowering effects of the specific AT1 receptor antagonist candesartan in female SHRs compared with males. The present study demonstrates the existence of a significant positive association between ANG-(1–7) and DBP in women that is not observed in men. It should be noted that this result may be a consequence of the variability in the data set. All of the collected data points were included in the analyses; no data were identified as outliers following two statistical outlier tests (Mahalanobis D and Z-score formation). However, there is one female participant who had a very high ANG-(1–7) concentration and a high DBP, and this female is likely driving the results. Indeed, if this participant is not included in the analysis, the relationship between ANG-(1–7) and DBP tends to be reversed in women, such that ANG-(1–7) is negatively associated with DBP. Regardless, our data support a sex difference-specific relationship between ANG-(1–7) and DBP, consistent with other studies reporting sex differences in RAS perturbation on BP. Men exhibit greater decreases in SBP in response to the ACE inhibitor lisinopril compared with women (11) and the treatment with ARBs results in greater decreases in BP (6), greater blockade of ANG II-mediated increases in BP (24), and greater stroke prevention (36) in women compared with men. This limited clinical trial data in combination with our present findings allow us to speculate that reported sex differences in the efficiency of traditional RAS inhibitors in men and women are related to differential formation and activation of ANG-(1–7). Indeed, future investigations are needed to determine the effects of ANG-(1–7) on BP regulation in both men and women.

Endothelial function and ANG-(1–7). Accumulating evidence has described how hypertension is associated with the development of vascular endothelial dysfunction (10), an early manifestation of cardiovascular disease. Accordingly, antihypertensive therapy appears to be more effective at reducing cardiovascular disease risk if they concomitantly improve both BP and endothelial function (21). The present study used the brachial artery FMD test to represent a functional bioassay for endothelium-derived nitric oxide (NO) bioavailability and endothelial function in humans (18). Endothelial cells are capable of releasing NO through the stimulation of ANG-(1–7) receptors (19) and promoting subsequent improvements in endothelial function (12). In addition to NO, estrogens can mediate the production of both prostaglandins and endothelium-derived hyperpolarizing factor that contribute to the FMD response (37). ANG-(1–7) has also been shown to increase prostacyclin release in isolated arteries from SHRs (13), although we are unaware of any studies to date that have examined the effect of ANG-(1–7) on endothelium-derived hyperpolarizing factor production. For the first time in humans, we have documented a positive relationship between endothelial function and circulating concentrations of ANG-(1–7) that is independent of a sex difference (r = 0.419; P = 0.01) (Fig. 2A). Since the current experimental approach cannot infer causation between ANG-(1–7) and FMD, further investigations are needed to determine the relative contribution of ANG-(1–7) on vascular endothelial function in both sexes.

In summary, the present study documents that women exhibit significantly greater circulating concentrations of ANG-(1–7) compared with men, which is consistent to data previously published by our group in hypertensive and normoten-
sive experimental animal models. Additionally, for the first time in humans, we describe a complex relationship between ANG-(1–7), endothelial function, and BP that appear to be sex dependent. This sex disparity supports a key role for circulating ANG-(1–7) in BP regulation and endothelial function in humans. Although contributions of other factors in BP regulation cannot be ruled out, data obtained from the present investigation suggests that modulation of ANG-(1–7) could be used as a novel therapeutic target in the treatment of hypertension and endothelial dysfunction; however, efficacy of the treatment response is likely to be sex dependent.

ACKNOWLEDGMENTS

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GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES


