

# Impaired vasodilation in pregnant African Americans: Preliminary evidence of potential antecedents and consequences

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## Abstract

Significant health disparities exist between African Americans (AA) and European Americans (EA) in hypertension and hypertension-related disorders. Evidence suggests that this is due to impaired vasodilation in AAs. Pregnancy is a potent systemic vasodilatory state. However, differences in vasodilation between AAs and EAs have not been investigated in pregnancy. We sought to examine the effects of pregnancy on vasodilation in AA and EA women and how this might be related to discrimination and low birth weight in their offspring. Hemodynamics [blood pressure (MAP), cardiac output (CO), total peripheral resistance (TPR)] and heart rate variability (HF-HRV) were examined at baseline in 40 pregnant AAs ( $n = 20$ ) and EAs ( $n = 20$ ) and matched nonpregnant women ( $n = 40$ ). The Experiences of Discrimination scale and birth weight were also measured in the offspring of the pregnant participants. Whereas pregnancy was associated with decreased MAP independent of race, AAs showed impaired vasodilation independent of pregnancy status as indicated by greater TPR despite greater HF-HRV. In AAs, but not EAs, reports of fewer incidences of discrimination were associated with greater TPR. Finally, the HF-HRV of EA mothers was inversely related to the birth weight of their offspring but was uncorrelated in AAs. We report novel evidence of impaired vasodilation to an endogenous vasodilatory stimulus in AAs. Higher TPR was related to discrimination in AAs and higher HF-HRV was related to low birth weight in EAs. These findings have implications for understanding the intergenerational transmission of impaired vasodilation in AAs.

**Abbreviations:** AA, African Americans; BMI, body mass index; BP, blood pressure; CO, cardiac output; EA, European Americans; EOD, experiences of discrimination; HF-HRV, high-frequency heart rate variability; HR, heart rate; HRV, heart rate variability; LBW, low birth weight; MAP, mean arterial pressure; TPR, total peripheral resistance; TSST, Trier Social Stress Test.

**KEYWORDS**

birth weight, blood pressure, cardiovascular, discrimination, heart rate variability, pregnancy, racial disparities, women

## 1 | INTRODUCTION

Significant health disparities exist between African Americans (AA) and European Americans (EA) such that rates of hypertension and hypertension-related disorders are greatly elevated in AAs compared to EAs (Karlamangla et al., 2010). For example, AAs have an earlier age of onset, greater impairment, and worse prognosis due to hypertension compared to EAs (Mensah et al., 1993). Whereas hypertension is clearly a multifactorial disorder and the source of the hypertension-related health disparities complex, there is a growing consensus that AAs show signs of vascular dysfunction characterized by impaired vasodilation in response to vasodilatory agents (Tahezadeh et al., 2010). This leads to greater total peripheral resistance (TPR)-mediated blood pressure (BP) elevations. BP elevations due to greater TPR are known to be more deleterious, as indicated by such factors as end-organ damage, compared to BP elevations due to increased cardiac output (CO) (Fagard et al., 1996; Mensah et al., 1993).

However, most of the evidence in support of impaired vasodilation has come from responses to exogenous vasodilatory agents such as acetylcholine (Tahezadeh et al., 2010). For example, to produce the same degree of vasodilation, greater doses of acetylcholine are needed in AAs compared to EAs (Jones et al., 1999). Further evidence for impaired vasodilation in AAs comes from the recently identified evidence of greater vagally mediated heart rate variability (HRV), a mechanism that should be associated with reduced TPR via the baroreflex, in the presence of elevated BP (Brownlow et al., 2020; Dorr et al., 2007; Hill et al., 2015). That is, in response to a BP increase baroreceptors enhance the vagal activity and inhibit the sympathetic activity via concomitant nucleus tractus solitarius (NTS) projections to the nucleus ambiguus (NA: to increase vagal activity) and to the caudal ventrolateral medulla (CVLM: to inhibit sympathetic activity) (Hesse et al., 2007). Specifically, the combination of greater HRV and greater TPR in AAs indicates that the vasodilatory effect of vagal activity via the baroreflex is less efficient in AAs compared to EAs. We have termed this phenomenon in AAs the “cardiovascular conundrum” (Hill et al., 2015). That is, the response to increased vagal activity which is associated with both increased baroreflex activation and increased HRV, as well as increased sympathoinhibition (Hesse et al., 2007), and its associated neurotransmitter, acetylcholine, is blunted in AAs such that despite greater HRV, AAs still show elevated TPR and thus a reduced response to a vasodilatory stimulus. In support of this idea we have

recently reported that the vascular branch of the baroreflex is less effective in AAs than in EAs; that is, the proportion of reflex changes in TPR associated with changes in BP is less in AAs than in EAs (Williams et al., 2016).

Whereas the evidence for impaired vasodilation in AAs has come primarily from studies of responses to exogenous vasodilatory agents, a unique natural experiment exists. One of the defining features of pregnancy is that it is associated with primary systemic vasodilation (Tkachenko et al., 2014). Thus, pregnancy is associated with a decrease in mean arterial pressure (MAP) due to early reductions in TPR that are not completely compensated by increases in CO (Tkachenko et al., 2014). Importantly, to the best of our knowledge, no studies have examined racial/ethnic differences in long-term vasodilation due to pregnancy in vivo. Because exogenous agents introduce complexities of interpretation due to the lack of long-term adaptive and compensatory mechanisms, pregnancy provides a unique opportunity to investigate racial differences in long-term vasodilation.

The primary aim of this study is to examine the evidence for impaired vasodilation in AAs. The emerging physiological profile of AAs is one of higher TPR and higher HRV relative to their EA counterparts. Thus we expect that in pregnant and nonpregnant women, higher TPR and higher HRV will be observed in AAs as compared to EAs. Second, we anticipate that in response to pregnancy, both AAs and EAs will exhibit lower MAP relative to nonpregnant women of the same race. These patterns together would provide evidence of impaired vasodilation to the potent vasodilatory stimulus of pregnancy in AAs; that is, higher TPR in pregnant AAs relative to EAs even though both pregnant AAs and EAs show lower MAP relative to their nonpregnant counterparts. This differential effect of pregnancy on EAs and AAs would be further illustrated by examination of the proportional differences in the physiological variables between the nonpregnant and the pregnant EAs and AAs, respectively. In addition, as pregnancy is known to be associated with a physiological profile of lower BP due to lower TPR as well as higher HR and lower HRV due to a relative shift toward sympathetic cardiovascular control, further evidence for impaired vasodilation in AAs would be found if the pregnant AAs did not show the expected lower TPR compared to their nonpregnant counterparts but did show the other expected pregnancy related cardiovascular adaptations.

As a secondary aim, in the context of this unique natural experiment it may be possible to examine potential antecedents and consequences of the elevated TPR in AAs. Whereas

it is well documented that AAs have higher BP than EAs, the source of this difference is not well understood. Several hypotheses have been put forward including genetic differences, differences in sodium retention, and the impact of racial discrimination. To date, none of these factors have been found to completely account for the observed health disparity in BP. Whereas some genes associated with BP and vasodilation in particular have been identified, the evidence for genetic differences in AAs is confounded in part due to genetic admixture (Cooper, 2003). Similarly, the role of sodium in hypertension has previously (Midgley et al., 1996) and more recently, come into question by the release of an Institute of Medicine report that notes that the level of sodium intake associated with health benefits is difficult to specify (Institute of Medicine, 2013). In addition, only about one-third of individuals are salt sensitive and thus it is unlikely that salt sensitivity accounts for the totality of the racial difference in BP. Finally, a recent meta-analysis suggests a modest effect of racial discrimination on BP, particularly night-time and ambulatory BP (Dolezsar et al., 2014).

However the effect of discrimination on BP has been extensively studied with less than clear cut results. In a landmark study, Krieger and Sidney (1996) found, somewhat paradoxically, that AAs reporting lower levels of discrimination had higher BP compared to those reporting more incidences of discrimination (Krieger & Sidney, 1996). They hypothesized that AAs that experienced discrimination but felt unable to challenge or respond to such discrimination might find it difficult to express their anger at such discrimination and, therefore, not report the discrimination (Krieger & Sidney, 1996, p. 1,375). Importantly, we have reported that AAs that had to inhibit their anger in response to an anger provocation showed elevated TPR during the subsequent post-provocation period (Dorr et al., 2007). Thus, the way in which AAs respond to unfair treatment and discrimination may be associated with elevated TPR such that those that report low levels of discrimination may evince higher levels of vasoconstriction. In the present study we utilized the same self-report measure of discrimination as used by Krieger and Sidney to examine racial discrimination as a potential antecedent or concomitant of elevated TPR in AAs. Given that pregnancy is associated with primary vasodilation it is important to investigate whether reports (or more precisely lack of reports) of discrimination are associated with TPR in pregnant AAs. This may give some clues as to how psychosocial factors may impact the vasodilatory response in AAs.

If the evidence for a genetic transmission of elevated BP from one generation to the next is lacking, a natural question arises as to how does elevated BP (and elevated TPR in particular) propagate across generations? Barker has written extensively about the effects of so called “fetal programming” on the health of future generations (Barker, 2000). Thus antenatal events may be one way in which deleterious factors in one generation may be transmitted to future generations via an epigenetic pathway (without recourse to genetic explanations).

Low birth weight (LBW) is a risk factor for future cardiometabolic disease and has been associated with mortality and future hypertension and diabetes (Srinivasan, 2011). In addition, AAs have markedly higher rates of LBW babies than EAs even after accounting for nutrition and socioeconomic factors (Giscombé & Lobel, 2005; Hobel et al., 2008; Srinivasan, 2011). Pre-eclampsia, or elevated BP during pregnancy, has been linked to LBW (Tkachenko et al., 2014). Importantly, LBW has been associated with coincident as well as future impaired vasodilation (Ligi et al., 2010; Leeson et al., 2001). It is possible that even without frank pre-eclampsia, elevated TPR during pregnancy may increase the risk for LBW. Thus, one consequence of elevated TPR during pregnancy may be infants with LBW, potentially imparting impaired vasodilation in the future leading to more mothers with elevated TPR. In this manner, a vicious cycle may begin by which the pathway from discrimination to elevated TPR to LBW and elevated TPR in the next generation is laid. In the present study we examined the factors associated with birth weight in AA and EA mothers. Relatedly, a small recent literature exists which finds that higher HRV (and lower HR) in mothers during pregnancy is associated with poor birth outcomes including lower birth weight offspring (Voss et al., 2006). We hypothesize that in EA mothers HRV would be inversely (and HR positively) related to birth weight in their offspring consistent with their lower TPR as HRV and TPR should be inversely related. However in AAs, due to the altered pattern of cardiovascular regulation, we suspect that these relationships may not hold.

In sum, the above factors lead us to make two primary hypotheses (i) that, compared to EAs, pregnant and nonpregnant AAs would show impaired vasodilation as indicated by higher TPR despite higher HRV (the cardiovascular conundrum pattern) and (ii) that whereas pregnancy would be associated with lower MAP in both AAs and EAs, AAs would show impaired vasodilation to this potent primary systemic vasodilatory stimulus as indicated by higher TPR in pregnant AAs as well as a lack of compensatory increase in CO compared to pregnant EAs and relative to nonpregnant AAs. We also had two secondary, exploratory hypotheses (i) that reports of discrimination (or the lack thereof) would be associated with elevated TPR in the AAs and (ii) that HRV and HR would be related to birth weight in EAs but not AAs based on the still small literature on HRV and birth weight. Thus a potential intergenerational pathway from discrimination to future health outcomes may be identified.

## 2 | MATERIALS AND METHOD

### 2.1 | Participants

Participants included 40 pregnant women (20 African American; 20 White) who were assessed during the second

trimester of pregnancy (21–24 weeks gestation) and 40 non-pregnant control participants matched for age, race, parity, and income that had been recruited for a larger study on stress reactivity and inflammation (31). Two women (one pregnant AA and one nonpregnant AA) were excluded from analyses due to incomplete data (due to incomplete blood sampling in the larger study (Christian et al., 2013, p. 659), resulting in final sample of 78 women.

Study visits were conducted between August 2009 and November 2011. The study was approved by the Ohio State University Biomedical Sciences Institutional Review Board. Women were recruited from the Ohio State University Wexner Medical Center General Prenatal Clinic, which serves a racially diverse group of primarily socioeconomically disadvantaged women. In addition, women were recruited from the general community of Columbus, Ohio.

In terms of the trimester of assessment, we focused on the second trimester rather than the first trimester because a primary goal of the larger study from which the current data were derived was to examine differences in stress reactivity due to pregnancy status; more significant adaptations in cardiovascular, neuroendocrine and immune function are evidenced by the second trimester than in the first trimester. We chose to focus on the second rather than the third trimester for two reasons. First, increasing evidence suggests that stressors which occur earlier in pregnancy are more likely to have detrimental effects (Glynn et al., 2001). However, research to date has focused almost exclusively on stress reactivity during the third trimester. Second, assessment in the second trimester avoids systematic exclusion of women who may go on to deliver preterm during the third trimester.

Women were ineligible if they reported current tobacco use or chronic health problems which affect immune, endocrine, or cardiovascular function including cancer, diabetes, chronic hypertension, gestational hypertension, preeclampsia, or anemia at the time of screening. In addition, women were excluded if they were taking anti-depressants, anti-anxiety medications, or mood stabilizers. If a woman reported antibiotic use, she was scheduled at least 2 weeks following usage.

Women were excluded if they reported consuming more than 300mg of caffeine per day. Women reporting use of any recreational drugs (e.g., marijuana, cocaine, methamphetamines) in the previous 6 months were excluded. Women were excluded if they were obese, defined as a prepregnancy (if pregnant) or current (if nonpregnant) body mass index (BMI)  $\geq 30$  (kg/m<sup>2</sup>). Because the racial disparity in preterm birth most clearly affects US-born African American women, women who were not US-born were ineligible (Giscombé & Lobel, 2005).

Women were not eligible as nonpregnant control participants if they had given birth within the past 6 months or were currently breastfeeding. Among the pregnant participants, women were excluded if they had multifetal gestation or known fetal anomaly. Because previous pregnancy has been associated with more significant physiological changes

in subsequent pregnancy, pregnant participants with at least one previous live birth were targeted. Pregnancy timing in terms of maternal age varies considerably with sociodemographic factors such as income and marital status. Thus, to provide ideal demographic matching, nonpregnant women with a prior live birth were also targeted.

## 2.2 | Study visit overview

All study sessions were conducted in the afternoon, beginning at 12:00 p.m. Upon arrival to the Ohio State University Clinical Research Center, participants provided informed consent and were given a standardized lunch to ensure a euglycemic state. Next, baseline questionnaires were completed assessing mood. Following a 20-min acclimation/rest period, ten minute baseline cardiovascular measures were obtained. Next, the Trier Social Stress Test (TSST) was initiated (Kirschbaum et al., 1993). Physiological variables were calculated during the following epochs of equal recording length (10 min each): baseline, speech preparation (stress) and recovery. The original study design included a mental arithmetic task (5 min), following the speech preparation that was not included in the present analysis due to its unequal recording length. The baseline data were the primary data for the present report.

## 2.3 | Physiological measures

BP was measured every 2 min during the 10-min baseline with a GE Carescape V100 blood pressure monitor. Mean arterial pressure (MAP) was calculated as (diastolic BP plus 1/3 of the pulse pressure). We recorded electrocardiographic activity and impedance cardiography via a standard 6-electrode setup. The ECG and impedance signals, which were sampled at 1,000 Hz (Task Force of the European Society of Cardiology the North American Society of Pacing, 1996), passed through Mindware Technology's BioNex 50-3711-02 two-slot mainframe to an Optiplex GX620 personal computer (Pentium D, 2.80 GHz, 2.00 GB RAM) running Mindware Technology's BioLab 1.11 software. The ECG and impedance signals were inspected offline using Mindware Technology's HRV 2.51 software with which the ECG trace (plotted in mV against time) was carefully reexamined. Successive R spikes (identified by an automatic beat detection algorithm) were visually inspected and any irregularities (such as an occasional ectopic beat) were edited using standard procedures (Task Force of the European Society of Cardiology the North American Society of Pacing, 1996). Cardiac output was calculated from the impedance derived stroke volume and TPR was calculated using CO and MAP (Sherwood et al., 1990; Thayer et al., 2010). High-frequency HRV (HF-HRV) was calculated using an FFT algorithm by averaging the power in milliseconds squared over the range of 0.15–0.40 hertz. All



physiological variables (heart rate (HR), HF-HRV, MAP, CO, and TPR) were calculated using Mindware software and averaged over the entire 10-min baseline.

## 2.4 | Racial discrimination

The Experiences of Discrimination (EOD) scale is an 11-item measure assessing the instances of perceived discrimination and responses to such occurrences. Specifically, participants indicate whether they have experienced discrimination over their lifetime (Yes or No) in the following settings: 1) at school, 2) getting hired or getting a job, 3) at work, 4) getting housing, 5) getting medical care, 6) getting service in a store or restaurant, 7) getting credit, bank loans or a mortgage, 8) on the street or in a public setting, and 9) from the police or in the courts. For items endorsed, participants rate the frequency of this occurrence: once, 2–3 times, or 4+ times. In addition two questions ask about their response to unfair treatment with lower scores indicating passive responding and higher scores indicating more active responding (e.g., try to do something/talk to others). This scale has high test-retest reliability and predictive validity for health outcomes in Black adults (Krieger, 1990; Krieger et al., 2005; Krieger & Sidney, 1996). Moreover, validation studies indicate that scores are not related to social desirability (Krieger et al., 2005).

## 2.5 | Birth weight

Birth weight (in grams) of the infants of the pregnant women was measured immediately post-delivery and collected from the medical chart.

## 2.6 | Statistical analyses

This study was powered for the inflammatory markers used in the previous publication (Christian et al., 2013, p. 661). Separate race (AA vs. EA) by pregnancy status (nonpregnant vs. pregnant) two-way ANOVA's were calculated for each continuous dependent variable.  $\chi^2$  were used for categorical data. Preplanned contrasts using directional *t* tests were used to examine our hypotheses. Effect sizes (Cohen's *d*) were derived from between subjects *t*-test values and the degrees of freedom ( $d = 2t/\sqrt{df}$ ). These effect sizes will be used to aid interpretation of the results. To examine the differential effect of pregnancy on EA and AA women, percentage change scores were calculated by subtracting the group mean of the pregnant group from the group mean of the nonpregnant group for EAs and AAs separately and expressing that difference as a percentage of the nonpregnant group mean for each physiological variable. These percentage differences between EA and AA women were then tested using a nondirectional chi-square test for

differences in proportions (Campbell, 2007). To explore the differences between groups on stress reactivity, change scores between the baseline and stress, as well as the baseline and recovery condition were computed. Pearson correlation coefficients (non-directional) were used to examine relationships between the dependent variables.

## 3 | RESULTS

### 3.1 | Demographic and descriptive characteristics

As previously reported women did not significantly differ by race or pregnancy status in age, education, income, nulliparity, or BMI (based on prepregnancy weight for pregnant women; see (31)). In addition, the pregnant women did not differ on maternal weight gain in pounds during pregnancy [AA = 34.35 (17.24), EA = 38.24 (15.86);  $t(27) = 0.63, p = .53$ ] and their infants did not differ on gestational age in days [AA = 271.1 (9.88), EA = 274.8 (8.75);  $t(35) = 1.21, p = .23$ ]. Nonpregnant women were less likely to be married than pregnant women ( $\chi^2(1) = 8.67, p = .003$ ). This effect was driven by nonpregnant AA who were less likely to be married than pregnant White ( $\chi^2(1) = 11.3, p = .001$ ) or pregnant African American women ( $\chi^2(1) = 5.7, p = .017$ ). AA women gave birth to infants with lower birth weights (in grams) compared to their matched EA counterparts [AA = 3,035 (477), EA = 3,438 (625);  $t(32) = 2.11, p = .04, d = 0.746$ ] despite having similar gestational age and maternal weight gain.

### 3.2 | Baseline differences on physiological variables

Means and standard deviations for the physiological variables by race and pregnancy status are presented in Table 1. Importantly, there were no significant race by pregnancy interactions for any physiological variable ([TPR:  $F(1,63) = 0.55, p = .46$ ; MAP:  $F(1,68) = 0.22, p = .64$ ; CO:  $F(1,65) = 1.0, p = .32$ ; HR:  $F(1,65) = 0.32, p = .57$ ; RSA:  $F(1,66) = 1.56, p = .22$ ]). Therefore, to test our hypotheses we examined the effects of race and pregnancy separately using preplanned directional *t* tests.<sup>1</sup>

<sup>1</sup>This pattern of results was identical at recovery as indicated by non-significant differences between the baseline and recovery values for all variables (all  $p > .05$ , data not shown). Similarly, whereas all variables, except for TPR and CO (both  $p > .05$ ), indicated that the stressor was effective (differences between baseline and speech preparation condition, all  $p < .05$ , data not shown), the only significant difference between the groups found in response to the stressor was a greater decrease in HF-HRV for the pregnant AAs ( $F(1,70) = 11.392, p = .001$ ). These stressor and recovery effects will not be discussed further as they are essentially the same as the baseline effects.

TABLE 1 Physiological baseline data by race, and pregnancy status

	Nonpregnant EAs			Nonpregnant AAs			Pregnant EAs			Pregnant AAs		
	<i>n</i>	Mean	<i>SD</i>	<i>n</i>	Mean	<i>SD</i>	<i>n</i>	Mean	<i>SD</i>	<i>n</i>	Mean	<i>SD</i>
MAP (mmHg)	20	79.77*	6.79	18	78.23*	8.22	19	74.36*	3.91	19	73.89*	3.74
HR (bpm)	17	81.00*	8.75	19	78.41*	8.80	20	86.60*	8.30	17	86.13*	9.03
CO (L/min)	16	16.30*	4.77	19	13.04*	5.59	20	20.05	12.62	17	15.12	13.75
TPR (dyne <sub>sec</sub> /cm <sup>5</sup> )	16	436.22*	144.96	18	627.18*	396.68	19	383.81*	215.51	17	653.85*	493.79
HF-HRV (ln ms <sup>2</sup> )	17	6.04*	0.71	19	6.69*	0.93	20	6.04	1.10	18	6.14	1.23

Note: All values are means and standard deviations (*SD*).

Abbreviations: CO, cardiac output (L/min); HF-HRV, high-frequency heart rate variability (ln ms<sup>2</sup>); HR, mean heart rate (beats per minute); MAP, mean arterial pressure (mmHg); TPR, total peripheral resistance (dyne<sub>sec</sub>/cm<sup>5</sup>).

\*indicates a significant mean difference (see Figures 1 and 2 for illustration of group comparisons).

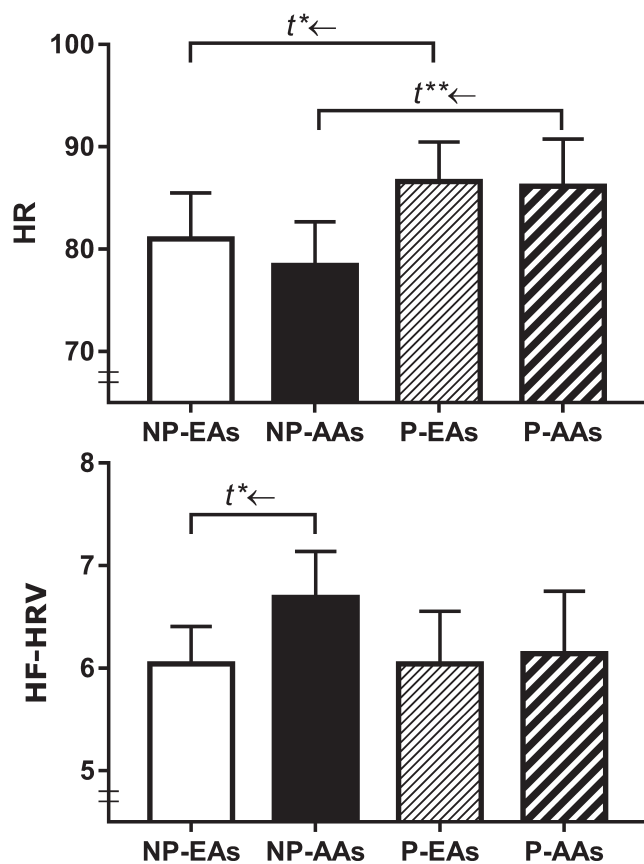


FIGURE 1 Heart rate (HR) and high-frequency heart rate variability (HF-HRV) by race and pregnancy status indicating differences between groups. AA = African American; EA = European American; NP = nonpregnant; P = pregnant. Error bars indicate 95% confidence intervals. HF-HRV, high-frequency heart rate variability (ln ms<sup>2</sup>); HR, mean heart rate (beats per minute)

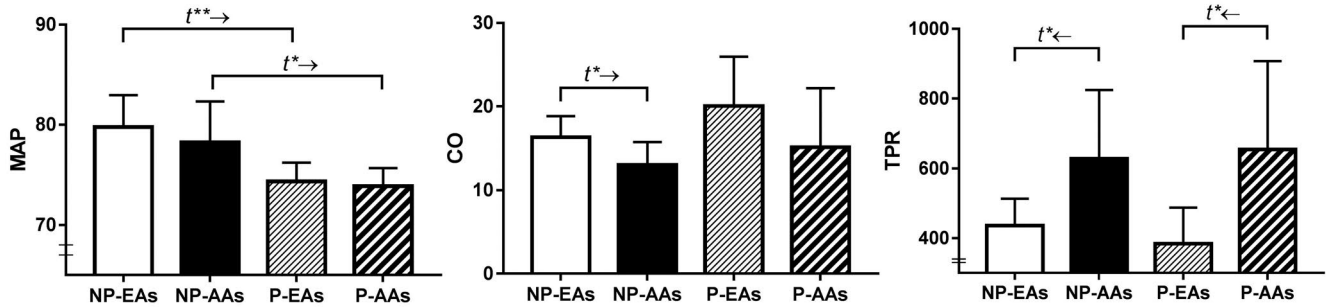
AAs, regardless of pregnancy status (simple effect tests for race), had significantly greater TPR [ $t(63) = 3.06, p = .001$ , Cohen's  $d = 0.771$ ], significantly lower CO [ $t(65) = -3.10, p = .001, d = 0.769$ ] compared to EAs. AAs showed a trend toward greater HF-HRV compared to EAs [ $t(66) = 1.52, p = .066, d = 0.374$ ], approaching significance. When examined

by pregnancy status using simple effects tests, nonpregnant AAs had significantly greater TPR [ $t(32) = 1.82, p = .039, d = 0.643$ ], significantly lower CO [ $t(33) = -1.83, p = .038, d = 0.637$ ], and significantly greater HF-HRV [ $t(34) = 2.33, p = .013, d = 0.799$ ] compared to nonpregnant EAs. Pregnant AAs had significantly greater TPR [ $t(34) = 2.17, p = .02, d = 0.744$ ] compared to pregnant EAs. Consistent with the pattern observed in the nonpregnant participants, pregnant AAs also had lower CO [ $t(32) = -2.49, p = .018, d = 0.879$ ] and greater HF-HRV [ $t(33) = 0.016, p = .871, d = 0.057$ ] compared to pregnant EAs, however this later difference was not statistically reliable. Taken together these results are consistent with the cardiovascular conundrum pattern and suggest that AAs have impaired vasodilation (see Figures 1 and 2).

Pregnant women, regardless of race (simple effect tests for pregnancy), had significantly lower MAP [ $t(68) = -3.72, p < .001, d = 0.902$ ], and significantly greater HR [ $t(65) = 3.16, p = .001, d = 0.784$ ] compared to nonpregnant women. When examined by race using simple effects tests, pregnant AAs had significantly lower MAP [ $t(35) = -2.09, p = .022, d = 0.707$ ], and significantly higher HR [ $t(34) = 2.59, p = .007, d = 0.888$ ], compared to nonpregnant AAs. Pregnant EAs had significantly lower MAP [ $t(37) = -3.03, p = .002, d = 0.996$ ], and significantly higher HR [ $t(35) = 1.99, p = .027, d = 0.673$ ], compared to nonpregnant EAs. Taken together these results are consistent with the literature and show that pregnancy is associated with lower MAP and higher HR regardless of race compared to their nonpregnant counterparts (see Figure 1).

### 3.3 | Differential effects of pregnancy on EA and AA women

Both pregnant EAs and AAs showed a similar expected lower MAP compared to their nonpregnant counterparts (approximately 7% in EAs and 6% in AAs:  $\chi^2(1) = 0.014, p = .90, d = 0.038$  for difference in proportions). However,



**FIGURE 2** Mean arterial pressure (MAP), cardiac output (CO), and total peripheral resistance (TPR) by race and pregnancy status indicating differences between groups. AA = African American; EA = European American; NP = nonpregnant; P = pregnant. Error bars indicate 95% confidence intervals. CO, cardiac output (L/min); MAP, mean arterial pressure (mmHg); TPR, total peripheral resistance (dyne<sub>sec</sub>/cm<sup>5</sup>)

while pregnant EAs showed expected lower TPR than nonpregnant EAs (approximately 12%), pregnant AAs actually showed *higher* TPR than nonpregnant AAs (approximately 4%:  $\chi^2(1) = -4.8, p = .028, d = 0.784$  for difference in proportions).

Both EAs and AAs showed the expected higher HR during pregnancy (EA 7% higher and AA 10% higher in the pregnant groups,  $\chi^2(1) = 0.2, p = .65, d = 0.146$  for differences in proportions) and the expected higher CO (EA 23% higher and AA 10% higher,  $\chi^2(1) = 2.24, p = .13, d = 0.507$  for differences in proportions). However, whereas the AAs showed the expected lower HF-HRV in the pregnant group (8% lower), the EAs showed no difference between the pregnant and nonpregnant groups (0% difference:  $\chi^2(1) = 3.04, p = .08, d = 0.590$  for the difference between EAs and AAs). Thus, these results add to the literature indicating that AAs show signs of vascular dysfunction that is characterized by impaired vasodilation in response to a vasodilatory stimulus (Taherzadeh et al., 2010).

### 3.4 | Relationships among discrimination, physiological variables, and birth weight by race

As previously reported (see Christian et al., 2013, for detailed results) AA women reported greater racial discrimination both in terms of the number of situations and total frequency. For the AAs, regardless of pregnancy status, the EOD number of situations and frequency of discrimination were inversely correlated with TPR [For AAs:  $EOD_{sit} r = -0.35, p = .04$ ;  $EOD_{freq} r = -0.32, p = .06$ ; For EAs:  $EOD_{sit} r = -0.16, p = .37$ ;  $EOD_{freq} r = -0.18, p = .30$ ]. Examination separately by pregnancy status demonstrated that these relationships were statistically significant among the pregnant AAs [ $EOD_{sit} r = -0.52, p = .03$ ;  $EOD_{freq} r = -0.57, p = .02$ ], but not the nonpregnant AAs [ $EOD_{sit} r = -0.16, p = .52$ ;  $EOD_{freq} r = -0.12, p = .63$ ]. Furthermore, among the pregnant AAs, those who endorsed more actively responding to discrimination delivered babies with higher birth weights [ $EOD_{resp} r = 0.52,$

$p = .03$ ]. These relationships were absent in the EAs [For EAs:  $EOD_{resp} r = 0.17, p = .50$ ].

The relationships between birth weight and the physiological variables for the pregnant group as a whole and for each race separately are shown in Table 2. In the total group, a trend was observed for a negative association between TPR and birth weight ( $r_{(31)} = -0.13, p = .24$ , one-tailed). However, whereas EAs showed the expected inverse relationship between HF-HRV and birth weight ( $r = -0.76, p = .002$ ) no such inverse relationship was found in the AAs ( $r = 0.18, p = .51$ ) and this difference was statistically significant ( $p < .05$ ). Similarly, a positive association, approaching significance, between HR and birth weight was observed in the EAs ( $p = .08$ ) and no such relationship observed among the AAs.

## 4 | DISCUSSION

Impaired vasodilation may be both a cause and a consequence of hypertension-related health disparities between AAs and EAs. Importantly, we provide novel evidence of impaired vasodilation in pregnant AAs relative to pregnant EAs as indicated by higher HRV and higher TPR in AAs despite the potent vasodilatory stimulus of pregnancy, as indicated by lower MAP in both pregnant AAs and EAs relative to their nonpregnant counterparts. Furthermore, we found higher TPR in association with lower reports of discrimination in AAs, consistent with the results of Krieger and Sidney (Krieger & Sidney, 1996) as well as Dorr et al. (2007). Finally, we report that, whereas in EAs, mother's HRV was significantly negatively associated with birth weight, consistent with the few studies that have examined mother's HRV and their offspring's birth weight (Voss et al., 2000, 2006). However, this association was not observed among AAs.

In the present study, consistent with two recent meta-analyses, we found evidence for main effects of race on TPR and HF-HRV. Specifically, AAs, independent of pregnancy status, showed elevated TPR and elevated HF-HRV compared to EAs. We have previously identified this pattern as the

**TABLE 2** Correlation matrix of birth weight and physiological variables

	Total ( <i>n</i> = 29)	AA ( <i>n</i> = 15)	EA ( <i>n</i> = 14)
MAP	0.103	-0.039	0.225
HR	0.295	0.093	0.476 <sup>#</sup>
CO	0.009	0.094	-0.210
HF-HRV	-0.264	0.185	<b>-0.757**</b>
TPR	-0.116	-0.066	0.023

Note: All values represent zero-order correlation coefficients (*r*); <sup>#</sup> indicates *p* = .08; \* and bold: indicates a significant correlation on the *p* < .01 level.

Correlations (non-directional) presented for the total pregnant sample and for the African American (AA) and European American (EA) groups separately. The difference in correlation between birth weight and HF-HRV between AA and EA groups was statistically significantly different (*p* < .05).

“cardiovascular conundrum;” higher HF-HRV should be cardioprotective and associated with lower TPR. This is due to the baroreflex-mediated vasodilatory effect of vagal activity and associated release of acetylcholine and sympathoinhibition via NTS projections to the NA and CVLM (Benarroch, 2008, p. 1,734; Fadel, 2008; Hill et al., 2015). Impaired vasodilation in response to vasodilatory agents has been identified as a likely factor in the elevated BP and associated disparity in hypertension-related disorders found in AAs (Taherzadeh et al., 2010). Whereas the evidence for this impaired vasodilation has come primarily from studies using exogenous vasodilatory agents we provide novel evidence of impaired vasodilatory responses in AAs in vivo to the potent endogenous vasodilatory stimulus of pregnancy.

Whereas the prevailing model of long-term BP regulation implicates sodium retention-based fluid volume as the major determinant of long-term BP, there is increasing evidence for the role of the baroreflex, in long-term BP regulation independent of fluid volume (Lohmeier et al., 2007; Thrasher, 2006). In fact, baroreflex stimulation is being suggested as a therapeutic intervention for treatment resistant hypertension (Victor, 2015). Consistent with this idea, as well as the current notion of the cardiovascular conundrum in AAs, we have recently reported that the effectiveness of the peripheral resistance arm of the baroreflex is lower in AAs compared to EAs (Williams et al., 2016). That is, there are fewer baroreflex-mediated adjustments in peripheral resistance related to vagally mediated HR decreases in AAs compared to EAs. Thus, the effectiveness of the baroreflex to decrease peripheral resistance via vagally mediated HR changes is impaired in AAs compared to EAs. As such, the elevated HF-HRV in AAs compared to EAs may represent an attempt to compensate for this less effective compensatory response, thus leading to both elevated HF-HRV and elevated TPR simultaneously. Consistent with this notion, in our previous study we found HF-HRV and TPR to be positively

related in AAs but not in EAs (Williams et al., 2016). In the present study, we found this cardiovascular conundrum pattern of higher HF-HRV and higher TPR among AAs versus EAs even in the context of the potent vasodilatory stimulus of pregnancy.

Consistent with prior research, both pregnant AAs and pregnant EAs showed lower MAP compared to their nonpregnant counterparts (Tkachenko et al., 2014). Pregnancy is associated with primary systemic vasodilation that is reflected in lower MAP and TPR and a partially compensatory increase in CO. This pattern was clearly evident in the pregnant EAs. However, despite a significantly lower MAP in pregnant versus nonpregnant AAs that was not different than that of pregnant EAs, the pregnant AAs showed impaired vasodilation as indicated by higher TPR compared to the EAs and a lack of lower TPR compared to nonpregnant AAs as well as a failure to show the associated partially compensatory increase in CO. To put this in perspective, both EAs and AAs showed lower MAP during pregnancy compared to nonpregnant women of the same race (approximately 7% lower in EAs and 6% in AAs). However, while pregnant EAs showed ~ 12% lower TPR than nonpregnant EAs, as would be expected, pregnant AAs actually showed ~ 4% higher TPR compared to nonpregnant AAs. Moreover, the compensatory increase in CO due to pregnancy was less than half as large in AAs (approximately 10%) compared EAs (approximately 23%). Thus, these results add to the literature indicating that AAs show signs of vascular dysfunction that is characterized by impaired vasodilation (Taherzadeh et al., 2010). The specificity of these differences to the vasculature is supported by the expected higher HR and CO in both pregnant groups and the expected lower HF-HRV in the EA group.

Interestingly, the primary vasodilation associated with pregnancy differs importantly from other states associated with primary systemic vasodilation such as cirrhosis, high output heart failure, and sepsis, in that in pregnancy renal vasodilation also occurs (Tkachenko et al., 2014). This is critical in understanding the health disparity in hypertension, as increased renal vasodilation is associated with increased glomerular filtration rate (GFR) and decreased sodium retention (Tkachenko et al., 2014). Thus the elevated TPR in the pregnant AAs is unlikely to be due to sodium retention, as has been suggested by some to be the source of the racial difference in BP and hypertension (Jackson, 1991; Wilson & Grim, 1991) but may be associated with decreased baroreflex effectiveness as we have recently reported (Williams et al., 2016).

One factor that has been thought to be associated with the greater BP in AAs, including pregnant AAs (Giscombé & Lobel, 2005), is racial discrimination (Christian, 2019). In the present study, largely independent of pregnancy status, reports of little or no discrimination were correlated with greater TPR. Consistent with previous research, low reports



of discrimination and inhibition of anger expression have been associated with elevated BP and TPR in AAs (Dorr et al., 2007; Krieger & Sidney, 1996). The current and previous findings suggest that the association between discrimination, reports of discrimination, and BP may not be simple or straightforward. Individuals differ greatly in their responses to anger provocation. Hokanson and colleagues in an elegant series of studies showed that the vascular response to anger provocation differed between individuals largely as a function of social learning theory such that the response that was most likely to decrease future aggression toward an individual was the one most likely to lead to more rapid recovery of BP responses to anger provocation (Hokanson, 1970; Hokanson & Burgess, 1962; Hokanson & Edelman, 1966; Hokanson & Shetler, 1961; Hokanson et al., 1963, 1968). We previously built on those pioneering studies and showed that in AAs inhibition of anger was associated with elevated TPR during the recovery period (Dorr et al., 2007). AAs who expressed their anger had elevated BP in the recovery period that was supported by increased CO and decreased HF-HRV. Thus, AAs showed poor BP recovery, albeit by different mechanisms, regardless of their response (expression or inhibition) to anger provocation. Taken together, the prior results and our present findings suggest that the association between racial discrimination, the response to and reporting of such discrimination, and vascular responses is complex and that careful dissection is necessary to understand the sometimes apparently contradictory findings in the literature. Important to note, the employed EOD measure assesses lifetime prevalence of racial discrimination. Thus, we cannot rule out potential recall bias in the assessment of discrimination.

In the present study, we also found preliminary evidence for a potential pathway for the intergenerational transmission of the vascular dysfunction and impaired vasodilation in AAs. Despite being closely matched on sociodemographic variables, the AAs in the present study gave birth to infants with lower birth weights than similar EAs. Whereas we found no significant correlation between birth weight and TPR in either group (for the pregnant group as a whole the correlation was in the predicted direction;  $r_{(31)} = -0.13$ ,  $p = .24$ , one-tailed), on average pregnant AAs had greater TPR than pregnant EAs. However, we did find the expected inverse relationship between birth weight and HF-HRV in the EAs and this relationship was not present in the AAs. Higher HF-HRV during pregnancy is associated with poor birth outcomes including lower birth weight (Christian et al., 2013; Voss et al., 2000). This is thought to be due in part to altered uterine perfusion that leads to endothelial dysfunction via inhibition of normal pregnancy-induced adaptations of vascular resistance (Voss et al., 2000, 2006). Thus both the higher TPR and the higher HF-HRV in pregnant AAs may predispose their offspring to lower

birth weight and to the risk of impaired vasodilation and greater TPR. In addition, we found that in pregnant AAs, reports of more active responses to discrimination were associated with higher birth weights. Relatedly, Krieger and Sidney (1996) found that such active responses to discrimination were associated with lower BP. Indeed, numerous studies have reported the effects of discrimination on birth outcomes including birth weight (Collins et al., 2004; Dailey, 2009; Dominguez, 2008; Giscombé & Lobel, 2005; Hilmert et al., 2014). LBW is a known risk factor for future health problems (Baker, 2001; Ligi et al., 2010; Srinivasan, 2011). The mechanisms via which LBW affects health have been extensively investigated. Whereas these pathways are multi-factorial and complex, one factor that has emerged is endothelial dysfunction, particularly impaired vasodilation (Elvan-Taşpinar et al., 2005; Ligi et al., 2010). LBW has been associated with impaired vasodilation at birth, in childhood, and in adulthood (Leeson et al., 2001; Ligi et al., 2010). Thus impaired vasodilation in mothers can lead to impaired vasodilation in their offspring via LBW, which then leads to impaired vasodilation over their lifespan including through the childbearing years of females, which sets the stage for future offspring with impaired vasodilation. That responses to racial discrimination are related to TPR and birth weight in the AAs, suggests that discrimination may play a role in the intergenerational transmission of impaired vasodilation and subsequent health problems.

The present study is not capable of definitively establishing all of these links but clearly additional research is needed to explicate this potential pathway. Importantly, the present study does not have measures of vascular function in the offspring. However, previous literature has shown that LBW is associated with impaired vasodilation across the lifespan in LBW individuals and, therefore, it is likely that the offspring with LBW in the current study would have impaired vasodilation. Therefore, if this pathway turns out to be true, the implications could be far reaching. Interventions designed to impact maternal health and fetal health as well as exposure and responses to discrimination may be viable points at which this negative spiral could be affected.

In summary, we provide new evidence of impaired vasodilation in AAs in response to the *in vivo* challenge of pregnancy, as indicated by higher TPR despite lower MAP in pregnant versus nonpregnant AAs. This impaired vasodilation in response to a potent long-term systemic vasodilatory stimulus suggests, consistent with growing evidence, that impaired vasodilation is a potential factor in the hypertension-related health disparities between AAs and EAs. In addition, we found that lower reports of exposures to discrimination were associated with higher TPR in pregnant AAs with potential impact on the birth weight of their offspring

provides new evidence for the role of discrimination in the health of AA.

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## CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

## AUTHOR CONTRIBUTION

**Lisa Christian:** Conceptualization; Data curation; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Writing-review & editing. **Julian Koenig:** Conceptualization; Formal analysis; Writing-original draft. **DeWayne Williams:** Formal analysis; Writing-original draft; Writing-review & editing. **Gaston Kapuku:** Formal analysis; Writing-original draft; Writing-review & editing. **Julian F Thayer:** Conceptualization; Formal analysis; Methodology; Supervision; Writing-original draft; Writing-review & editing.

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