20-HETE induces remodeling of renal resistance arteries independent of blood pressure elevation in hypertension

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Ding Y, Wu C, Garcia V, Dimitrova I, Weidenhammer A, Joseph G, Zhang F, Manthati VL, Falck JR, Capdevila JH, Schwartzman ML. 20-HETE induces remodeling of renal resistance arteries independent of blood pressure elevation in hypertension. Am J Physiol Renal Physiol 305: F753–F763, 2013. First published July 3, 2013; doi:10.1152/ajprenal.00292.2013.—20-Hydroxyeicosatetraenoic acid (20-HETE) is a cytochrome P-450 (CYP)-derived arachidonic acid metabolite that has been shown to increase smooth muscle contractions and proliferation, stimulate endothelial dysfunction and activation, and promote hypertension. We examined if 20-HETE contributes to microvascular remodeling in hypertension. In Sprague-Dawley rats, administration of the 20-HETE biosynthesis inhibitor HET0016 or the 20-HETE antagonist prevented 5α-dihydrotestosterone (DHT)-induced increases in blood pressure as well as abrogated DHT-induced increases in the media-to-lumen ratio (M/L), media thickness, and collagen IV deposition in renal interlobar arteries. Reserpine prevented blood pressure elevation in DHT-treated rats but did not affect microvascular remodeling (M/L, media thickness, and collagen deposition); under these conditions, treatment with the 20-HETE antagonist attenuated microvascular remodeling, suggesting that 20-HETE contributes to DHT-induced vascular remodeling independent of blood pressure elevation. In Cyp4a14−/− mice, which display androgen-driven and 20-HETE-dependent hypertension, treatment with the 20-HETE antagonist abolished remodeling of renal resistance arteries measured as media thickness (24 ± 1 vs. 15 ± 1 μm) and M/L (0.29 ± 0.03 vs. 0.17 ± 0.01). Moreover, in Cyp4a12 transgenic mice in which the expression of Cyp4a12–20-HETE synthase is driven by a tetracycline-sensitive promoter, treatment with doxycycline resulted in blood pressure elevation (140 ± 4 vs. 92 ± 5 mmHg) and a significant increase in remodeling of renal resistance arteries (media thickness: 23 ± 1 vs. 16 ± 1 μm; M/L: 0.39 ± 0.04 vs. 0.23 ± 0.02); these increases were abrogated by cotreatment with 20-HETE. This study demonstrated that 20-HETE is a key regulator of microvascular remodeling in hypertension; its effect is independent of blood pressure elevation and androgen levels.

20-hydroxyeicosatetraenoic acid; cytochrome P-450 4A; blood pressure; androgen

VASCULAR REMODELING of large and small arteries contributes to the development and complications of hypertension (25). This process renders arteries stiffer and thicker, leading to detrimental effects on blood pressure regulation (14). Structural alterations of the microcirculation, of which the media-to-lumen ratio (M/L) is the most important predictor, are likely to occur in renal microvessels, as previously shown in experimental models of hypertension (7), including spontaneously hypertensive rats (SHRs), DOCA-salt rats, and one-kidney, one-clip Goldblatt hypertensive rats (12). The mechanisms that contribute to arterial remodeling in hypertension are numerous and include stimulation of growth and apoptosis and increased inflammation and fibrosis. Numerous autacoids have been implicated as mediators of arterial remodeling in hypertension. The most prominent is ANG II, which has been shown to exert the capacity of stimulating vasoconstriction, smooth muscle growth, production of inflammatory cytokines and chemokines, and activating extracellular matrix proteins (26), all of which contribute to structural changes and remodeling of the arterial wall in hypertension.

20-Hydroxyeicosatetraenoic acid (20-HETE), a cytochrome P-450 (CYP)-derived arachidonic acid metabolite and a primary eicosanoid in the renal microcirculation, shares much of ANG II’s characteristics. It sensitizes smooth muscle cells to constrictor stimuli and contributes to myogenic, mitogenic, and angiogenic responses (17, 38). Several experimental models of hypertension, such as the SHR, display high levels of 20-HETE in the vasculature, and inhibition of its synthesis reduces blood pressure in these models, suggesting that 20-HETE, through its constrictor activity, contributes to increased renal and peripheral vascular resistance and, consequently, hypertension (40). Other mechanisms by which 20-HETE may contribute to hypertension include stimulation of endothelial dysfunction as well as the induction of angiotensin-converting enzyme and activation of the renin-angiotensin system (2, 3, 29, 34). 20-HETE has also been characterized as a proinflammatory mediator; it activates NF-κB, stimulates the production of inflammatory cytokines, and induces NADPH oxidase and superoxide production (8, 13, 28). These characteristics, together with its ability to stimulate vascular smooth muscle migration and growth (19, 30) and cell apoptosis (22), suggest that 20-HETE may be an important mediator of vascular remodeling in hypertension. To this end, studies have suggested that 20-HETE mediates ANG II-induced neointimal thickening in the balloon-injured rat carotid artery (43) and cardiac hypertrophy in Ren-2 transgenic rats (1).

The present study was undertaken to investigate the role of 20-HETE in remodeling of renal resistance arteries in hypertension using experimental models in which hypertension is dependent on increased 20-HETE biosynthesis. These models were 1) androgen-induced hypertension in rats and mice, 2) Cyp4a14 knockout (Cyp4a14−/−) mice, and 3) Cyp4a12 transgenic (Cyp4a12tg) mice. The hypertension in these models was abrogated by treatment with either an inhibitor of 20-HETE biosynthesis or an antagonist of 20-HETE bioactions (41). Here, we show that 20-HETE mediates remodeling of
renal resistance vessels in hypertension independent of blood pressure elevation or androgen levels.

MATERIALS AND METHODS

Animal experiments. All experimental protocols were performed following an Institutional Animal Care and Use Committee-approved protocol in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Sprague-Dawley male rats (6–7 wk old, Charles Rivers, Wilmington, MA) were treated with 5α-dihydrotestosterone (DHT; 56 mg·kg⁻¹·day⁻¹ ip) or its vehicle (20% benzyl alcohol in corn oil ip) for 21 days. The indicated dose of DHT has been previously shown to induce hypertension in normotensive rats (21, 28). In some experiments, rats were given the CYP4A-selective inhibitor 20-HEDE (10 mg·kg⁻¹·day⁻¹ in 5% ethanol in saline ip) (18) or the 20-HETE antagonist HET0016 (10 mg·kg⁻¹·day⁻¹ in 5% ethanol in saline ip) for 12 days. Male and female Cyp4a12tg mice (8–14 wk old) were administered doxycycline (DOX; 1 mg/ml in drinking water) for 42 days. In some experiments, 20-HEDE or 20-HEDGE (10 mg·kg⁻¹·day⁻¹ in 5% ethanol in saline ip) were administered for the indicated time period. For blood pressure measurement, animals were acclimated 7 days before the start of experiments. Systolic blood pressure was determined by the tail-cuff method (Kent Scientific, Torrington, CT). Animals were placed on a far infrared heating pad for 7–10 min. Systolic blood pressure measurements were recorded after five cycles of acclimatization. At the end of experiments, animals were anesthetized with xylazine-ketamine (25/50 mg/kg ip), and a laparotomy was performed. The kidneys were removed, and renal interlobar arteries from rats and preglomerular microvessels (PGMVs) from mice were microdissected for biochemical and functional experiments.

Measurements of 20-HETE. Rat renal interlobar arteries and mouse PGMVs were incubated in oxygenated Krebs bicarbonate buffer (pH 7.4) with 1 mM NADPH for 1 h at 37°C with gentle shaking. 20-HETE was extracted and quantified by liquid chromatography-tandem mass spectroscopy (Applied Biosystems, Foster City, CA) as previously described (11).

![Figure 1](http://ajprenal.physiology.org/) Androgen-driven 20-hydroxyeicosatetraenoic acid (20-HETE)-dependent hypertension and vascular remodeling in Sprague-Dawley rats. Rats were treated with vehicle, 5α-dihydrotestosterone (DHT), DHT + N-20-hydroxyeicos-6(Z),15(Z)-dieneoic acid (20-HEDE), and DHT + HET0016 for 21 days. A: systolic blood pressure (BP) on day 21. The media thickness (B), media-to-lumen ratio (MLR; C), and medial cross-sectional area (mCSA; D) of renal interlobar arteries were measured using a pressurized myograph. n = 4–6. *P < 0.05 vs. the vehicle-treated group.
Measurements of media thickness, M/L, and medial cross-sectional area. The same segments of renal resistance arteries, renal interlobar arteries from rats and PGMVs from mice, were dissected to minimize the difference along the arteries. Arteries were mounted on a pressurized myograph and equilibrated for 1 h in oxygenated Krebs buffer at 37°C. The operator was blinded to treatments except for the blood pressure range of the animal. Lumen diameters from normotensive animals were determined at 100 mmHg and hypertensive animals at 140 mmHg. Measurements of outer diameter (OD) and inner diameter (ID) under passive conditions were used to calculate media thickness \([\text{M/L} = \frac{(\text{OD} - \text{ID})}{2}]\), and medial cross-sectional area \([\text{mCSA} = \frac{\pi}{4} \times (\text{OD}^2 - \text{ID}^2)]\).

Immunofluorescence. Dissected arteries were washed twice with PBS, fixed in 4% paraformaldehyde at 4°C overnight, and embedded in OCT compound (Sakura Finetek, Torrence, CA). Cryostat sections were cut transversely into 5-µm sections. Immunofluorescence staining was performed using the following antibodies: anti-collagen IV antibody (ab6586, Abcam, Cambridge, MA) and anti-collagen I antibody (ab34710, Abcam). Briefly, frozen vessel sections were fixed in acetone at 4°C for 20 min and blocked in 5% goat serum in PBS for 45 min at room temperature. Sections were then incubated with primary antibody at 4°C overnight, washed, and further incubated with Cy3-conjugated secondary antibody (111-165-144, Jackson Immunoresearch, West Grove, PA) for 2 h at room temperature. To further verify cellular entity, sections were washed and counterstained for nuclei with 4,6-diamino-2-phenylindole for 15 min. Immunofluorescence was visualized using a Zeiss Axioplan-2 fluorescent microscope. Images were captured and analyzed using AxioVision 2 multichannel image processing software (Zeiss, Gottingum, Germany).

Statistics. Data are presented as means ± SE. Statistical significance \((P < 0.05)\) between the experimental groups was determined by the Fisher method of analysis for multiple comparisons. For comparison between treatment groups, the null hypothesis was tested by single-factor ANOVA (Dunnett’s multiple-comparison test) for multiple groups or an unpaired t-test for two groups.

RESULTS

20-HETE mediates vascular remodeling in DHT-treated Sprague-Dawley rats. Administration of DHT to normotensive rats significantly increased systolic blood pressure (153 ± 8 vs. 104 ± 4 mmHg) at the end of the 21-day treatment. Cotreatment with the 20-HETE biosynthesis inhibitor HET0016 or with the 20-HETE antagonist 20-HEDE prevented the increase in blood pressure (106 ± 9 and 113 ± 5 mmHg, respectively; Fig. 1A). Treatment with DHT increased media thickness, M/L, and mCSA in renal interlobar arteries by twofold compared with vehicle (Fig. 1, B–D). Cotreatment with either 20-HEDE or HET0016 abrogated the increase in media thickness, M/L, and mCSA to levels not different from renal interlobar arteries of vehicle-treated rats (Fig. 1, B and C). We (28, 39) have previously shown that 20-HETE levels in interlobar arteries from DHT-treated rats increase by twofold compared with HET0016 to DHT-treated rats resulted in a 90% decrease in renal interlobar 20-HETE levels,
whereas these levels remained unchanged in vessels from rats cotreated with 20-HEDE (28, 39). We (42) have also demonstrated that DHT-mediated increases in blood pressure and vascular 20-HETE production are inhibited by cotreatment with flutamide, suggesting that these effects of DHT are mediated through the androgen receptor.

Inhibition of 20-HETE biosynthesis or action attenuates collagen IV deposition in renal interlobar arteries. Collagen IV is primarily localized in the basal lamina of the vessels. A previous study (12) has shown that in vascular remodeling, collagen IV levels increase and contribute to the increased stiffness of the vessels. As shown in Fig. 2, treatment with DHT for 21 days increased collagen IV deposition in renal interlobar arteries by 3.1-fold. Administration of either 20-HEDE or HET0016 to rats treated with DHT negated the increase in collagen IV deposition (Fig. 2).

Reserpine abrogates DHT-induced high blood pressure without altering vascular remodeling of renal interlobar arteries. To determine whether vascular remodeling in DHT-treated rats occurs in the absence of hypertension, the antihypertensive drug reserpine was administered together with DHT. As shown in Fig. 3, administration of reserpine to DHT-treated rats prevented DHT-induced hypertension. At the end of the 21-day treatment, the blood pressure of rats co-treated with DHT and reserpine was significantly lower than those treated with DHT alone (104 ± 6 vs. 140 ± 6 mmHg). Reserpine alone had no significant hypotensive effect (Fig. 3).

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Whereas treatment with reserpine lowered blood pressure in DHT-treated rats, it did not alter vascular remodeling (Fig. 4). DHT treatment increased media thickness, M/L, and mCSA in renal interlobar arteries by twofold compared with the vehicle-treated group. Remodeling in arteries from rats treated with reserpine and DHT remained unchanged compared with arteries from rats treated with only DHT (Fig. 4). Importantly, administration of 20-HEDGE to rats treated with DHT and reserpine inhibited vascular remodeling, bringing media thickness, M/L, and mCSA to levels not different from those in arteries of vehicle- or reserpine-treated rats (Fig. 4).

Similar results were obtained with regard to collagen I and IV deposition in renal interlobar arteries. DHT treatment increased collagen I (Fig. 5) and collagen IV (Fig. 6) deposition by 2.5- and 5-fold, respectively. Administration of reserpine had no significant effect on DHT-induced collagen I and IV deposition, demonstrating 2- and 4.5-fold increases, respectively, compared with the vehicle-treated group. Reserpine alone had no effect on collagen deposition (Figs. 5 and 6). Importantly, basal and DHT-stimulated 20-HETE production in renal interlobar arteries were not affected by reserpine (Fig. 7).

Vascular remodeling in androgen-driven hypertension in mice is mediated by 20-HETE. Administration of DHT pellets to C57BL/6 mice significantly increased systolic blood pressure (134 ± 8 vs. 100 ± 5 mmHg) at the end of 21-day treatment. Cotreatment with the 20-HETE antagonist 20-HEDGE prevented the increase in blood pressure (94 ± 6 mmHg; Fig. 8A). Treatment with DHT increased media thickness and M/L of preglomerular arteries by twofold compared with the placebo-treated group. Cotreatment with 20-HEDGE attenuated the increase in media thickness and M/L of PGMVs (Fig. 8, B and C). Similar to what was observed in DHT-treated rats, preglomerular arteries from DHT-treated mice also displayed 20-HETE-dependent increases in mCSA (7.5 ± 1.9,

**Fig. 5.** Reserpine does not affect collagen I deposition in renal interlobar arteries from DHT-treated rats. Rats were treated with vehicle, DHT, DHT + reserpine, and reserpine for 21 days. A: representative immunofluorescence images of collagen IV (red) in renal interlobar arteries with DAPI staining (blue). B: fold changes of immunofluorescence intensity relative to the vehicle-treated group. n = 4–6. *P < 0.05 vs. the vehicle-treated group.
14.7 ± 1.0, and 9.7 ± 0.9 × 10^3 μm^2 in placebo-, DHT-, and DHT + 20-HEDGE-treated groups, respectively, n = 5–6, P < 0.05), suggesting hypertrophic remodeling.

Cyp4a14−/− mice display male-specific hypertension that is associated with androgen-driven induction of Cyp4a12 expression and 20-HETE biosynthesis (10). Male Cyp4a14−/− mice are hypertensive compared with their counterpart wild-type mice (153 ± 4 vs. 120 ± 1 mmHg) without any pharmacological intervention (Fig. 9A). Administration of 20-HEDGE resulted in a gradual decrease in blood pressure, reaching that of wild-type mice after 12 days of treatment (122 ± 3 vs. 120 ± 1 mmHg). Renal preglomerular arteries from male Cyp4a14−/− mice displayed a 60% and 40% increase in media thickness (Fig. 9B) and M/L (Fig. 9C), respectively, compared with wild-type mice. The increases in media thickness and M/L were abrogated by the administration of 20-HEDGE. Similarly, treatment with 20-HEDGE reduced mCSA to levels observed in wild-type mice (7.7 ± 0.3, 14.5 ± 1.8, and 8.6 ± 0.5 × 10^3 μm^2 in wild-type, Cyp4a14−/−, and 20-HEDGE-treated Cyp4a14−/− mice, respectively, n = 4, P < 0.05).

20-HETE mediates vascular remodeling in the absence of androgen. To examine whether 20-HETE contributes to vascular remodeling in hypertension in the absence of androgen, we used Cyp4a12tg mice. These mice were developed to overexpress Cyp4a12 under the control of a tetracycline-sensitive promoter (Tet-on). A recent study from our laboratory showed that renal preglomerular arteries from Cyp4a12tg mice treated with DOX demonstrated increased Cyp4a12 protein and 20-HETE levels compared with Cyp4a12tg mice placed on water alone. The blood pressure elevation as well as the increased 20-HETE production in DOX-treated Cyp4a12tg mice were negated by the administration of 20-HEDGE (41).

To examine whether vascular remodeling takes place in this 20-HETE-mediated hypertensive model, mice were treated with vehicle, DOX, and DOX + 20-HEDGE for 42 days. After 42 days of treatment, systolic blood pressure in the DOX-
treated group rose to 140/110 mmHg, whereas the blood pressure in mice cotreated with DOX and 20-HEDGE remained unchanged (89/110 mmHg; Fig. 10A). Treatment of Cyp4a12tg mice with DOX for 6 wk resulted in a 73% increase in M/L (0.39 ± 0.04 vs. 0.23 ± 0.02). There was also a 50% increase in media thickness (23 ± 1 vs. 16 ± 1 μm). In the DOX + 20-HEDGE-treated group, both media thickness and M/L were attenuated (18 ± 2 μm and 0.28 ± 0.03, respectively; Fig. 10, B and C). Similar results were obtained with regard to mCSA (5.2 ± 1.0, 9.3 ± 1.3, and 6.2 ± 1.2 × 10³ μm² in vehicle-, DOX-, and DOX + 20-HEDGE-treated Cyp4a12tg mice, respectively, n = 6–8, P < 0.05).

**DISCUSSION**

This study identifies 20-HETE as a key mediator of vascular remodeling of renal resistance arteries in hypertension independent of blood pressure elevation. Remodeling of microvessels occurs in hypertension and involves structural, functional, and mechanical changes that result in decreased lumen size, increased M/L, and increased thickness. These vascular changes are believed to be important contributors of cardiovascular complications associated with hypertension, including end-organ damage. Numerous autacoids, including bioactive peptides and lipids, have been implicated in the process of vascular remodeling. 20-HETE is a CYP-derived eicosanoid whose synthesis and actions have been linked to the pathogenesis of hypertension in experimental models and humans (38, 42). Numerous reports have demonstrated that the vascular synthesis of 20-HETE increases in experimental models of hypertension; vascular overexpression of CYP4A2–20-HETE synthase leads to hypertension, and inhibition of 20-HETE synthesis results in lower blood pressure (11, 28, 29, 34). 20-HETE exerts powerful biological activities in the vasculature; it constricts smooth muscles, stimulates smooth muscle...
proliferation and migration, inhibits endothelial nitric oxide synthase, and activates the NF-κB-mediated inflammatory program in the vascular endothelium (3, 13, 17). However, its contribution to vascular remodeling in the microcirculation is unknown.

Here, we demonstrated a significant remodeling of renal resistance arteries in experimental models in which blood pressure elevation is largely dependent on an increase in 20-HETE synthesis and action. These animal models include androgen-treated rats and mice, Cyp4a14−/− mice, and Cyp4a12tg mice (41). Treatment with a 20-HETE synthesis inhibitor or an antagonist of 20-HETE action prevented the rise in blood pressure in response to androgen, normalized blood pressure in androgen-driven hypertensive CYP4A14−/− mice, and abrogated the rise in blood pressure in response to DOX in Cyp4a12tg mice. These results clearly indicated that hypertension in these models is largely dependent on increases in 20-HETE biosynthesis and actions (41). The present study also showed that hypertension in these models is associated with marked remodeling of renal resistance arteries, i.e., renal interlobar arteries, as exemplified by structural and biochemical changes that are indicative of this process. Thus, structural changes, including media thickness, M/L, and mCSA, significantly increased in all three models, and, in DHT-treated rats, remodeling was also evidenced by marked increases in collagen I and V deposition. Importantly, remodeling in all of these hypertensive models was fully abrogated by either inhibition of 20-HETE biosynthesis or blockade of 20-HETE actions. These findings clearly implicate 20-HETE as an important mediator of vascular remodeling in hypertension.

The model of DHT-induced hypertension has been identified as a model of 20-HETE-dependent hypertension in which the contribution of 20-HETE to blood pressure elevation consists of promoting vasoconstriction while interfering with vasodilation and, consequently, increases in vascular tone and peripheral vascular resistance (42). An important finding in the present study is that reserpine, a general blood pressure-lowering drug, prevented DHT-induced blood pressure but did not inhibit DHT-induced remodeling of renal resistance arteries. The remodeling that occurred in the presence of reserpine, however, was inhibited by the administration of 20-HEDE, indicating that the 20-HETE-mediated increase in blood pressure is independent of its effect on vascular remodeling. This key finding suggests that 20-HETE exerts effects on the vascular wall other than simply affecting its contractile behavior. Additionally, these effects appear to be independent of androgen since 20-HETE-dependent remodeling of renal microvessels was also observed in DOX-treated Cyp4a12tg mice in which overexpression of Cyp4a12, the major 20-HETE synthase in mice, was driven by a tetracycline-sensitive promoter.

The biochemical changes preceding the structural changes that characterize remodeling include increased extracellular matrix deposition along with enhanced expression of adhesion molecule and growth factors, which, in turn, contribute to the onset of vascular inflammation and smooth muscle migration, hypertrophy, hyperplasia, and apoptosis (12). The findings that the 20-HETE-mediated increase in M/L was also accompanied with an increase in mCSA suggests that 20-HETE-mediated hypertrophic remodeling of these small resistance arteries occurs in all models (25). The mechanisms by which 20-HETE contributes to vascular remodeling are unclear; however, 20-HETE has been implicated in many of the biochemical changes preceding remodeling of the arterial wall. 20-HETE has been shown to contribute to collagen accumulation in kidneys from hypertensive rats overexpressing CYP4A2 protein (11). It has also been shown to exert proinflammatory actions. In vascular endothelial cells, 20-HETE increases ROS, including superoxide (3, 8, 16), and stimulates NF-κB activity (4, 13), resulting in endothelial activation with increased expression of ICAM-1 and IL-8 levels (13). 20-HETE-dependent increases in NADPH oxidase, ROS, and NF-κB activity are also seen in the renal microvasculature of androgen-treated rats (28, 39). Moreover, inhibition of NF-κB activation attenuates androgen-induced 20-HETE-dependent increases in blood pressure (39). In smooth muscle cells, 20-HETE has been shown to act as a mitogen. In cultured vascular smooth muscle cells from adult rabbits (19) and rats (33) as well as in isolated renal arterioles (31), 20-HETE induces the phosphorylation of ERK1/2, a
MAPK that plays a pivotal role in the proliferation induced by the activation of receptor tyrosine kinases and G protein-coupled receptors (9). Blockade of the formation of 20-HETE attenuated norepinephrine-induced and ANG II-induced ERK1/2 phosphorylation, suggesting that 20-HETE may serve as a second messenger of these growth factors (20, 24). The same investigators also showed that 20-HETE contributed to ANG II-induced neointimal thickening in the injured carotid artery (43). Stec et al. (30) demonstrated that 20-HETE promotes platelet-derived growth factor-stimulated vascular smooth muscle cell migration via pathways that involve MEK and phosphatidylinositol 3-kinase activation. 20-HETE has also been shown to inhibit apoptosis of pulmonary artery smooth muscle cells (35). Collectively, these actions may underlie, at least in part, the ability of 20-HETE to stimulate remodeling of resistance arteries.

The findings in this study have implications to vascular remodeling in other forms of hypertension. This stems from observations that 20-HETE is a microcirculatory eicosanoid that is often produced in response to stimuli that are highly relevant to the pathogenesis of hypertension, including ANG II and endothelin (5, 23, 32). Increases in vascular 20-HETE are also observed in SHRs (6), a common model for essential hypertension and vascular remodeling, and in models of salt-sensitive hypertension, such as Dahl salt-sensitive rats (15). Several clinical studies (36, 37) have shown increased 20-HETE levels in hypertensive individuals. A recent study by Schuck et al. (27) demonstrated that enhanced plasma levels of 20-HETE are associated with more advanced endothelial dysfunction and vascular inflammation in patients with established atherosclerotic cardiovascular disease. The proinflammatory and progrowth bioactions of 20-HETE in vascular cells together with its increased occurrence in hypertensive patients suggest that it may play a role in microvascular remodeling and contributes to the development and cardiovascular complications of hypertension.

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DISCLOSURES

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

AUTHOR CONTRIBUTIONS

Author contributions: Y.D., C.-C.W., V.G., I.D., A.W., G.J., F.Z., and J.H.C. analyzed data; Y.D., C.-C.W., V.G., I.D., and J.H.C. wrote the manuscript; Y.D., V.G., I.D., and J.H.C. edited and revised the manuscript; F.Z., and J.H.C. interpreted results of experiments.

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