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Remodeling of afferent arterioles from mice with oxidative stress does not account for increased contractility but does limit excessive wall stress

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Abstract

Since superoxide dismutase (SOD) knockout enhances arteriolar remodeling and contractility, we hypothesized that remodeling enhances contractility. In the isolated and perfused renal afferent arterioles from SOD wild type (+/+) and gene-deleted mice, contractility were assessed from reductions in luminal diameter with perfusion pressure from 40 to 80 mmHg (myogenic responses) or angiotensin II (ANG II; 10^{-6} mol·l^{-1}), remodeling from media:lumen area ratio, superoxide ($O_2^{\cdot-}$) and hydrogen peroxide (H_2O_2) from fluorescence microscopy and wall stress from wall tension/wall thickness. Compared to +/+ strains, arterioles from SOD1 −/−, SOD2 +/− and SOD 3−/− mice developed significantly (P<0.05) more $O_2^{\cdot-}$ with perfusion pressure and ANG II and significantly increased myogenic responses (SOD1 −/−: −20.7±2.2 vs 12.7±1.6%; SOD2 +/−: −7.4 ±1.3 vs 12.6 ±1.4% and SOD3 −/−: −9.1 ±1.9 vs −15.8 ±2.2%) and ANG II contractions and ~2-fold increased media:lumen ratios. media:lumen ratios correlated with myogenic responses (r^2 =0.23, P<0.01), ANG II contractions (r^2=0.57, P<0.0001), and active wall tension (r^2 =0.19, P<0.01) but not with active wall stress (r^2=0.08; NS). Differences in myogenic responses among SOD3 mice were abolished by bath addition of SOD and were increased 3 days after inducing SOD3 knockout (26.9 ± 1.7% vs −20.1 ± 0.7%; P<0.05), despite unchanged M:L ratios (2.01 ± 0.09 vs 2.02 ± 0.03, NS). We conclude that cytosolic, mitochondrial or extracellular $O_2^{\cdot-}$ enhance afferent arteriolar contractility and remodeling. Although remodeling does not enhance contractility, it does prevent the potentially damaging effects of increased wall stress.

Keywords

Reactive oxygen species; oxidative stress; hypertension; renal autoregulation; vascular remodeling; myogenic response

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Disclosures section

NONE

Introduction

Blood vessels in hypertensive humans [1–3] or animal models [4, 5] characteristically have evidence of remodeling, endothelial dysfunction [2, 6] and increased reactive oxygen species (ROS) [7]. Although these features predict subsequent cardiovascular disease (CVD) [8–10], the effects of the remodeling on microvascular function are unclear [4, 11, 12]. Folkow and colleagues proposed that repeated episodes of blood pressure elevation elicited vascular remodeling that enhanced vasoconstriction and sustained hypertension [11, 13]. Later studies identified a specific role for structural remodeling of the renal afferent arteriole in human and experimental hypertension [14, 15, 16]. Thus, an autopsy study of kidneys from 1,377 subjects reported that renal afferent arteriopathy, which entailed medial thickening and luminal narrowing, occurred in 97% of subjects known to be hypertensive yet in less than 12% of those known to be normotensive whereas remodeling was not prominent in arterioles from other sites [17]. Moreover, Mulvany and colleagues reported that young spontaneously hypertensive rats whose renal afferent arterioles from nephrectomy specimens had a lesser diameter developed a higher blood pressure when adult [18]. Indeed, a reduction in luminal diameter of renal afferent arterioles should increase renal vascular resistance (RVR) and limit the glomerular filtration rate (GFR), thereby contributing to hypertension.

To gain further insight into the consequences of remodeling of renal afferent arterioles, arteriolar media:lumen area ratios from mice with gene deletions for superoxide dismutase (SOD) isoforms were related to the generation of ROS and to contractile responses to perfusion pressure (myogenic response) or to angiotensin II (ANG II). The SOD −/− mouse model provides prolonged increases in afferent arteriolar ROS, contractility and remodeling without renal damage [7, 19, 20].

Myogenic responses were assessed from reductions in luminal diameter of mouse isolated and perfused afferent arterioles during increases in perfusion pressure. Active wall tension (AWT) was calculated from the difference between wall tension developed in physiological solution ($WT_{physiol}$) and passive tension in Ca^{2+}-free solution with ethylene glycol-bis (2-aminoethylether)-N,N,N′,N′-tetraacetic acid (EGTA) ($WT_{passive}$). Myogenic and ANG II responses were related to remodeling and to the generation of arteriolar $O_2^{\cdot-}$ but these were dissociated by incubation of arterioles with pegalated (PEG) SOD or PEG-catalase (to metabolize ROS without changing remodeling) or from short-term induction of SOD-3 knockout (to increase ROS without remodeling). Active wall stress (AWS = AWT/wall thickness) normally increases with contractility and has been proposed to contribute to microvascular damage [21, 22]. Therefore, we related contractility to active wall tension and active wall stress to determine their roles in the functional adaption to a prolonged increase in afferent arteriolar ROS.

Methods

Animal models

The first series used male littermate SOD1, SOD2 and SOD3 +/+, +/− and SOD1 and SOD3 −/− mice (SOD2 −/− is lethal). The second series used male mice three days after induction of SOD3 knockout with tamoxifen (3 mg·20 g^{-1} body weight, i.p) compared to littermates

given vehicle [23]. Mice were aged 3 to 4 months and weighed 25–30 g. All procedures conformed to the Guide for Care and Use of Laboratory Animals prepared by The Institute for Laboratory Animal Research. Studies were approved by the Georgetown University Animal Care and Use Committee.

Isolation and perfusion of mouse afferent arterioles and measurements of superoxide ($O_2^{\cdot-}$) and hydrogen peroxide (H_2O_2)

As described previously [7, 24–26] and in Supplemental Methods, $O_2^{\cdot-}$ generation was assessed by fluorescence microscopy from PEG-SOD inhibitable ethidium:dihydroethidium (E:DHE) fluorescence ratio (f/f_0) [27] and H_2O_2 from PEG-catalase inhibitable 6-carboxy-2′,7′-dichlorodihydrofluorescein diacetate (C-H_2DCFDA) fluorescence, as described [28].

Renal SOD protein expression

This was assessed by Western analysis of lysates of renal cortex as described [29] (see Supplemental Methods).

Determination of passive wall compliance

This was assessed from passive wall stress/strain relationships as described [30] (see Supplemental Methods).

Statistics

Data were obtained from 5 to 7 mice per group and analyzed by ANOVA (with repeated measures for ANG II) to assess individual effects of genotype, intervention (perfusion pressure or ANG II) and interaction (effects of genotype on the response to the intervention). Where appropriate, a *post-hoc* Bonferroni t test was used to test differences between groups. Results (mean ± SEM values) are considered significant at $P<0.05$.

Results

The SOD protein expression was studied in renal cortical lysates to determine whether genetic deletion of one SOD isoform caused adaptive changes in renal expression in other SOD isoforms. Compared to littermate +/+ mice, the expression of the corresponding SOD isoforms were almost absent in SOD1 or SOD3 −/− mice, and were approximately one half in +/− mice (Supplemental figures S1 and S2). There were no apparent compensations by one SOD isoform for the loss of another.

PEG-SOD (200 units·ml^{-1}) blocked > 80% of the E:DHE fluorescence and PEG-catalase (1,000 units·ml^{-1}) blocked > 80% of the C-H_2DCFDA fluorescence in SOD3 mice (Supplemental figure S3A and S3B). Compared to arterioles from littermate +/+ mice, the increases in afferent arteriolar $O_2^{\cdot-}$ with perfusion pressure from 40 to 80 mmHg or with 10^{-6} mol·l^{-1} ANG II were enhanced significantly in arterioles from SOD1 −/−, SOD2 +/− or SOD3 −/− mice (Figure 1A and 1B). The increases in $O_2^{\cdot-}$ in arterioles from SOD2 +/− mice were generally similar to those in SOD1 −/− and SOD3 −/− but there were no differences between SOD1 or SOD3 +/+ and +/− mice. An increase in perfusion pressure did not increase H_2O_2 significantly in afferent arterioles from SOD3 +/+ mice but did

increase it in SOD3 −/− mice (Figure 1C). A strictly similar increase in H_2O_2 with perfusion pressure was also seen in arterioles from SOD1 −/− mice compared to SOD3 −/− mice (7.8±1.5 versus 7.4±0.5%). Compared to arterioles from littermate +/+ mice, contractility was increased significantly in response to perfusion pressure (Figure 1D) or ANG II (Figure 1E) in arterioles from SOD1 −/−, SOD3 −/− and SOD2 +/− mice. Bath addition of PEG-SOD prevented the enhanced contractions of SOD3 −/− mouse arterioles to perfusion pressure (Figure 2A) (without changing remodeling), whereas PEG-catalase was ineffective (Figure 2B). Arteriolar $O_2^{\cdot-}$ generation was correlated with contractions to both perfusion pressure (r^2 =0.39, P<0.05) and ANG II (r^2 =0.85, P<0.0001) (Supplemental Fig S4A and S4B). This analysis used group mean data since ROS and myogenic responses could not be measured in the same arterioles.

We had shown previously that blockade of nitric oxide synthase (NOS) with L-NAME increased the sensitivity and responsiveness of afferent arterioles to ANG II in SOD1 +/+ but not SOD1 −/− mice and abolished differences between genotypes [7, 19]. Thus, ANG II responses were not repeated. Myogenic contractility also was enhanced by NOS inhibition in SOD1 +/+ but an enhanced myogenic contractility in vessels from SOD-1 −/− mice persisted during L-NAME (Supplemental figure S5).

Compared to arterioles from littermate +/+ mice, those from SOD2 +/− and SOD1 −/− and SOD3 −/− mice had an increased media wall area, and/or a reduced vessel lumen area that resulted in striking and uniform increases by >2-fold in media:lumen ratios (Figure 3A, 3B and 3C). These structural changes persisted in Ca^{2+}-free solution which abolished vascular tone. The basal arteriolar lumen diameters are shown in Supplemental Table S1.

Active wall tension (AWT; dynes·cm^{-1}) increased lineally with perfusion pressure as in prior studies [24–26]. Compared to littermate +/+ mice, the slope of the regression of AWT on perfusion pressure [26] (to quantitate myogenic responses) was increased significantly in arterioles from SOD1 −/−, SOD2 +/− and SOD3 −/− mice (SOD1: 3.49±0.30 vs 2.30±0.27; P< 0.05; SOD2: 3.00±0.19 vs 1.77±0.22; P<0.05; SOD3: 3.51±0.20 vs 2.43±0.15; P<0.01) (Figure 4A and Supplemental Table S2). Active wall stress (AWS; dynes·cm^{-2}) also increased with perfusion pressure but, unlike AWT, there were no differences between littermate and SOD gene-deleted mice (Figure 4B and Supplemental Table S3).

After pooling individual data points across genotypes, changes in arteriolar diameter with perfusion pressure or ANG II were positively correlated with afferent arteriolar media:lumen ratio (perfusion pressure, r^2 =0.23, P<0.001, Figure 5A; ANGII, r^2=0.57, P<0.0001, Figure 5D). During increased perfusion pressure, AWT depended significantly on media:lumen ratio (r^2 =0.19, P<0.01, Figure 5B) whereas active wall stress was independent (r^2 = 0.08, NS, Figure 5C).

Compared to arterioles from littermate mice with the same genotype give vehicle, the afferent arterioles three days after induction of SOD3 knockout with tamoxifen were not remodeled (Figure 6A) but developed a similarly enhanced generation of $O_2^{\cdot-}$ with perfusion pressure or ANG II (Figure 6B) and similarly increased contractions with

perfusion pressure (Figure 6C) or ANG II (Figure 6D) as arterioles from lifetime SOD3 −/− mice.

The passive arteriolar wall compliance, which was assessed from passive wall stress/strain relationships, was unaffected by SOD genotype (Supplemental figure S6).

Discussion

These studies confirm that SOD1 −/− mice have afferent arteriolar remodeling and increases in $O_2^{\cdot-}$ generation and contractile responses to ANG II [7]. The main new findings are that there were no compensatory upregulations in renal expression of other SOD isoforms in SOD1, SOD2 or SOD3 gene deleted mice. There were similar increases in afferent arteriolar remodeling, $O_2^{\cdot-}$ generation and contractile responses to perfusion pressure and ANG II among afferent arterioles from SOD1 −/−, SOD2 +/− and SOD3 −/− mice. The sharp increase in $O_2^{\cdot-}$ with perfusion pressure in arterioles from SOD3 −/− deleted mice accounted for their enhanced contractility since metabolism of $O_2^{\cdot-}$ by PEG-SOD normalized the myogenic responses (without a change in media:lumen ratio) whereas the increase in H_2O_2 was not sufficient to impact myogenic responses significantly since they were unaffected by metabolizing H_2O_2 with PEG-catalase. The myogenic responses of arterioles from SOD3 −/− mice remained stronger than SOD3 +/+ mice during NOS blockade. Myogenic responses increased with $O_2^{\cdot-}$ but active wall stress was maintained since increases in tension in gene deleted mice were balanced by equivalent increases in wall thickness.

Afferent arterioles from mice 3 days after inducing SOD3 knockout had similar increases in $O_2^{\cdot-}$ and contractions with PP and ANG II as those from lifelong SOD3 −/− mice but lacked any change in arteriolar media:lumen ratio. This, and the finding of similar myogenic responses in SOD3 +/+ and −/− mice during metabolism of $O_2^{\cdot-}$ despite a maintained enhanced media:lumen ratio in the knockout mice, dissociates the increases in contractile responses in SOD3 −/− mice from vessel remodeling. Finally, passive vessel wall compliance was preserved in SOD1 −/−, SOD2 +/− and SOD3 −/− mice. Thus, both short and long term gene deletions of SODs increase afferent arteriolar $O_2^{\cdot-}$ generation which is implicated in an increased contractility to perfusion pressure or ANG II. The remodeling of the vessel wall that develops in the long term does not account for the increased contractility but does permit an increase in contractility without an increase in active wall stress. An increase in vascular wall stress is a stimulus for cell growth and can be provoked by an increase in myogenic tone[31]. However, the medial hypertrophy does not appear to cause the enhanced myogenic tone and apparently does not make a dominant contribution to hypertension either since SOD1, SOD2 and SOD3 gene deleted mice all had prominent vascular remodeling yet have generally been reported to be normotensive [19].

A strong afferent arteriolar contraction is a key component of renal autoregulation [7, 32, 33] which maintains a constant renal blood flow, GFR and glomerular capillary pressure during changes in blood pressure [34]. These adjustments of preglomerular vascular tone prevent transmission of the hypertension into the glomeruli [34] thereby damaging podocytes [35] and the renal parenchyma [16, 36].

The SOD3 −/− mouse has increased excretion of 8-isoprostane $F_{2\alpha}$ and increased RVR [29], consistent with the increased $O_2^{\cdot-}$ and tone in isolated afferent arterioles in this study. ANG II generates both arteriolar NO that blunts the contraction [37] and $O_2^{\cdot-}$ that bioinactivates NO [38–40]. The enhanced ANG II contractions in afferent arterioles from SOD1 −/− mice were ascribed to the enhanced NO bioinactivation since they were normalized during NOS inhibition [7]. In contrast, a stronger myogenic response persisted in arterioles from SOD1 −/− mice during NOS blockade. Thus, all of the enhanced ANG II contractility, but only about one half of the enhanced myogenic responses, in arterioles from SOD1 −/− mice can be ascribed to NO bioinactivation. This is consistent with strong modulation of afferent arteriolar contractions to ANG II [38], thromboxane [41] or endothelin-1 [39] by NO but a minor role of endothelial NOS in modulation of myogenic responses [42] and no effect of eNOS deletion [25].

Although arterioles from SOD3−/− mice generated more H_2O_2 with perfusion pressure, the enhanced contractility likely relates primarily to the enhanced generation of $O_2^{\cdot-}$ since deletion of $p47^{phox}$, which is a prominent source of $O_2^{\cdot-}$, prevents myogenic responses [24] and PEG-SOD, but not PEG-catalase, prevented the exaggerated myogenic responses in arterioles from SOD3−/− mice. The enhanced generation of H_2O_2 in arterioles from SOD3 −/− mice may reflect metabolism of increased $O_2^{\cdot-}$ by other SOD isoforms. On the other hand, aortic vascular remodeling is reduced in NOX2 gene deleted mice [43] and is prevented in vascular smooth muscle cell catalase transgenic mice [44]. Thus, enhanced vascular contractility during oxidative stress is dependent on $O_2^{\cdot-}$ whereas remodeling can be dependent on H_2O_2, thereby further dissociating contractility from remodeling.

In conclusion, afferent arterioles from SOD gene deleted mice generate more $O_2^{\cdot-}$ with increased perfusion pressure and ANG II which accounts for enhanced contractions. Their vessels are prominently remodeled but the enhanced contractions can be ascribed to $O_2^{\cdot-}$ whereas the remodeling permits an enhanced active wall tension during increased perfusion pressure without the potentially damaging effects of increased wall stress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Perspectives

Results from this study do not support the hypothesis that remodeling of resistance vessels sustains hypertension [11, 13]. Indeed, careful studies in SOD gene deleted mice generally report consistent remodeling [7] yet normal basal levels of BP [19] although the early increase in blood pressure with ANG II is usually enhanced, consistent with the increased ANG II contractions of their afferent arterioles in this study [7, 19]. Sustained hypertension requires renal Na^+ and fluid retention to prevent the corrective effects of a pressure natriuresis [45, 46]. Whereas ROS enhance Na^+ reabsorption in the loop of Henle [47], they impair reabsorption in the proximal tubule [48]. Thus, the absence of hypertension in SOD gene deleted mice, despite enhanced arteriolar contractility, may relate to a preserved pressure natriuresis (not yet tested), or perhaps to confounding effects of renal H_2O_2. On the other hand, an increase in afferent arteriolar wall thickness in SOD gene-deleted mice permits an increase in active wall tension with PP during generation of $O_2^{\cdot -}$, as required for enhanced myogenic responses, without an increase in active wall stress. The renal, cerebral, and epicardial resistance arterioles are exposed directly to high levels of pressure and are designated “strain vessels” [21, 22]. The finding that afferent arteriolar wall tension can be dissociated from active wall stress suggests that microvascular remodeling may be an adaptive response to prevent the potentially damaging vascular effects of wall stress while permitting the beneficial effects of enhanced wall tension that are required for strong myogenic responses to maintain autoregulation and prevent the damaging effects of hypertension on the renal parenchyma. This scenario postulates that hypertensive remodeling may convey some cryptic adaptive advantage and could account for its remarkably close association with human hypertension [17].

Novelty and significance

What Is New?

Our studies of the afferent arteriolar myogenic and angiotensin responses in SOD gene deleted mice have dissociated the enhanced contractility from the remodeling and shown rather that the enhanced contractility was due to the enhanced superoxide.

What Is Relevant?

Since the remodeling of resistance arterioles in this study did not enhance contractility, microvascular remodeling cannot be essential for increased vascular resistance in hypertension. However, remodeling did prevent the enhanced contractility from enhancing wall stress and thereby may exert a cryptic adaptive advantage in limiting vascular damage during oxidative stress.

Summary

This provider a novel view of microvascular remodeling as an adaptation to hypertension or oxidative stress that permits enhanced contractility without the potentially damaging effects of prolonged increases in microvascular active wall stress.

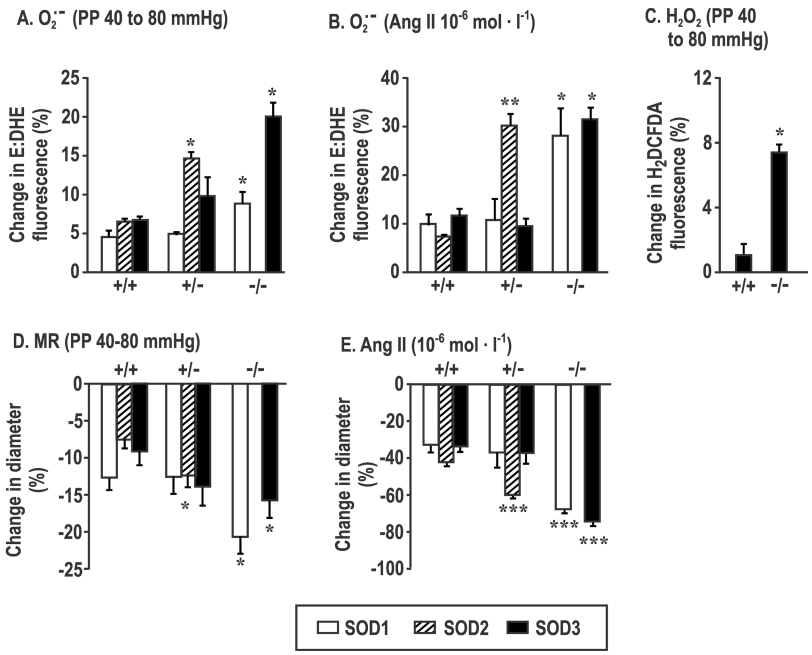

Figure 1.

Deletion of SOD genes enhances afferent arteriolar generation of reactive oxygen species and contractility. Changes in superoxide with perfusion pressure (Panel A) or angiotensin II (Panel B) or hydrogen peroxide with perfusion pressure (Panel C) or contraction with perfusion pressure (Panel D) or angiotensin II (Panel E) in arterioles from SOD-1 (open boxes), SOD-2 (cross-hatched boxes) or SOD-3 (solid boxes) gene manipulated mice (mean ± SEM; n = 5–7 per group). Compared to corresponding +/+ mouse vessels; *****, P<0.05; ******, P<0.01; *******, P<0.005.

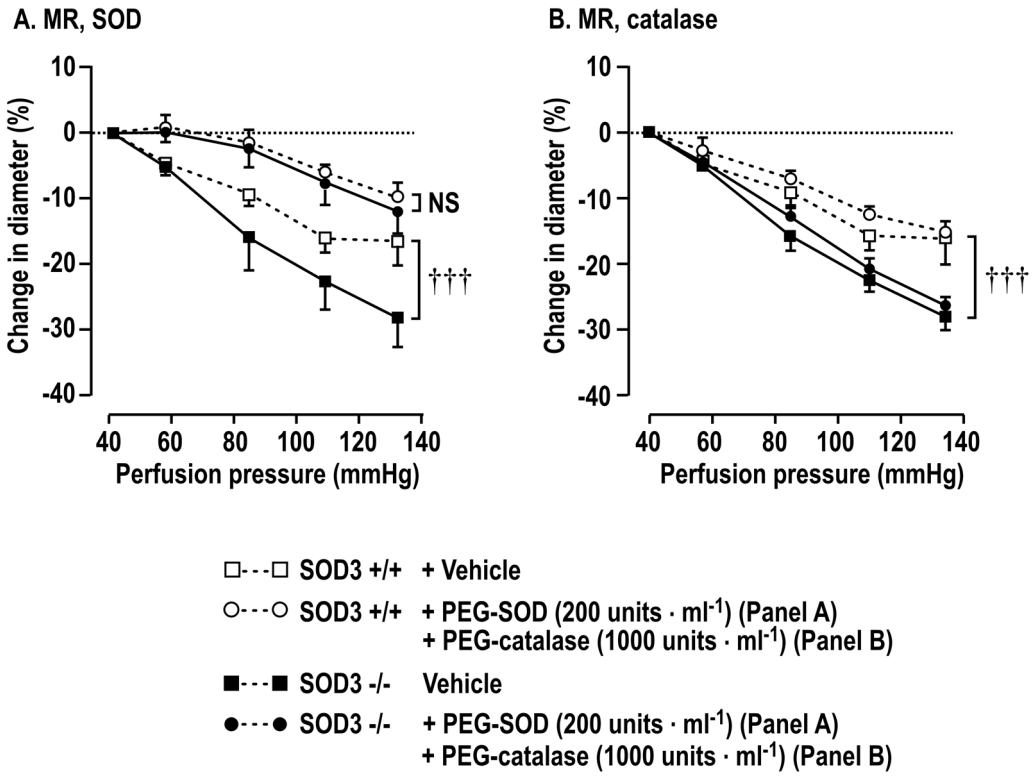

Figure 2.

Changes in diameter of afferent arterioles with perfusion pressure in the presence of pegalated agents. Comparing vessels from SOD3 +/+ (open symbols) with SOD3 −/− (solid symbols) mice incubated with vehicle (square symbols) or pegalated agents (circular symbols). Compared to SOD3 +/+, †††, P<0.005.

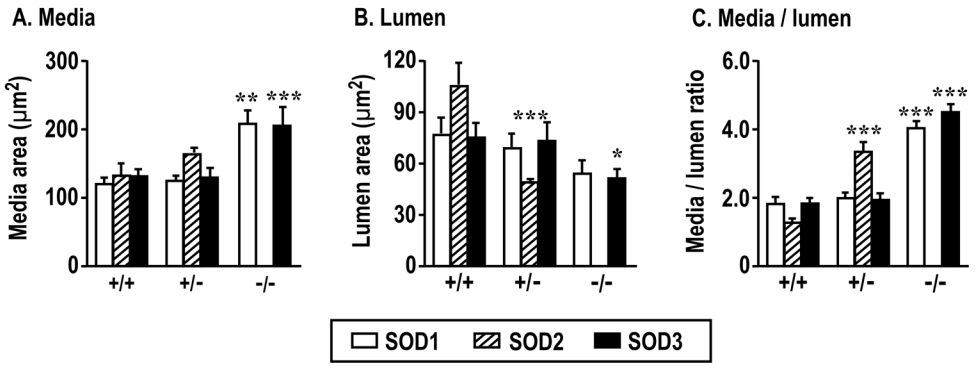

Figure 3.

Deletion of SOD genes enhances afferent arteriolar remodeling in SOD-1 (open boxes), SOD-2 (cross hatched boxes) or SOD-3 (solid boxes) gene manipulated mice. Compared to corresponding +/+ mouse vessels: *****, P<0.05; ******, P<0.01; *******, P<0.005.

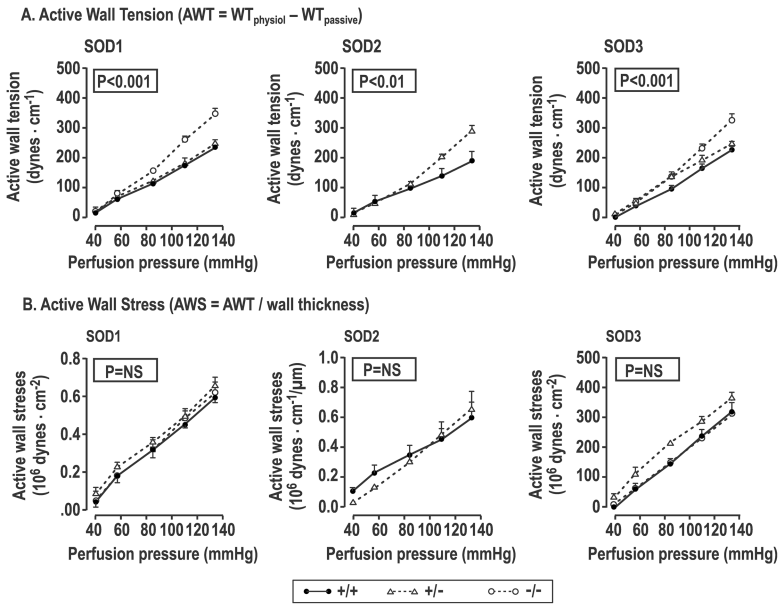

Figure 4.

Active wall tension and active wall stress increase with perfusion pressure in SOD +/+ (solid circles and continuous lines), +/− (open triangles and dashed lines) or −/− (open squares and dotted lines) mice. P values refer to ANOVA with repeated measures for differences between genotypes.

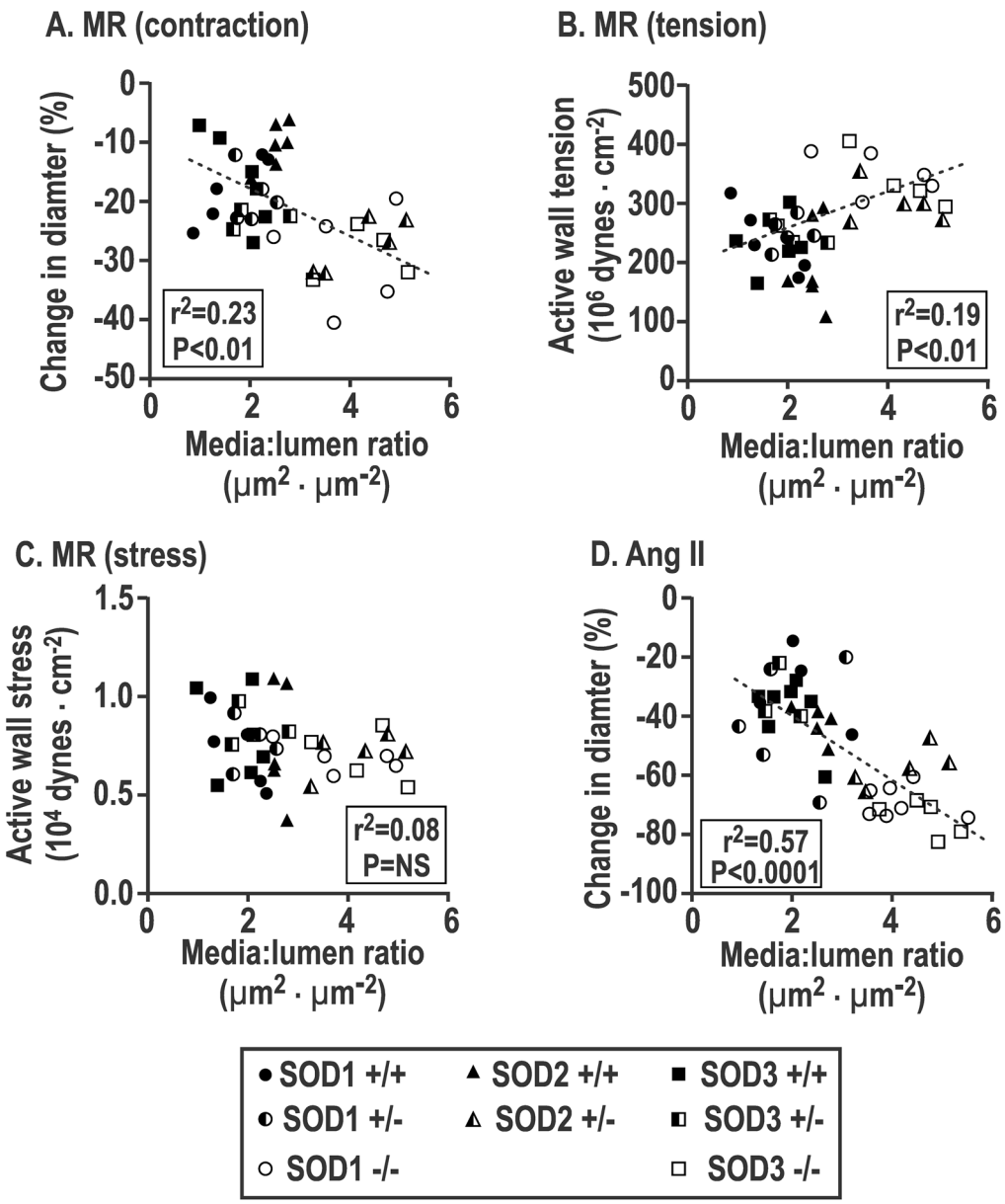

Figure 5.

Correlation of individual afferent arteriolar values for changes in diameter (Panel A), active wall tension (Panel B) or active wall stress (Panel C) with perfusion pressure or angiotensin II (Panel D) related to vessel media to lumen area ratio.

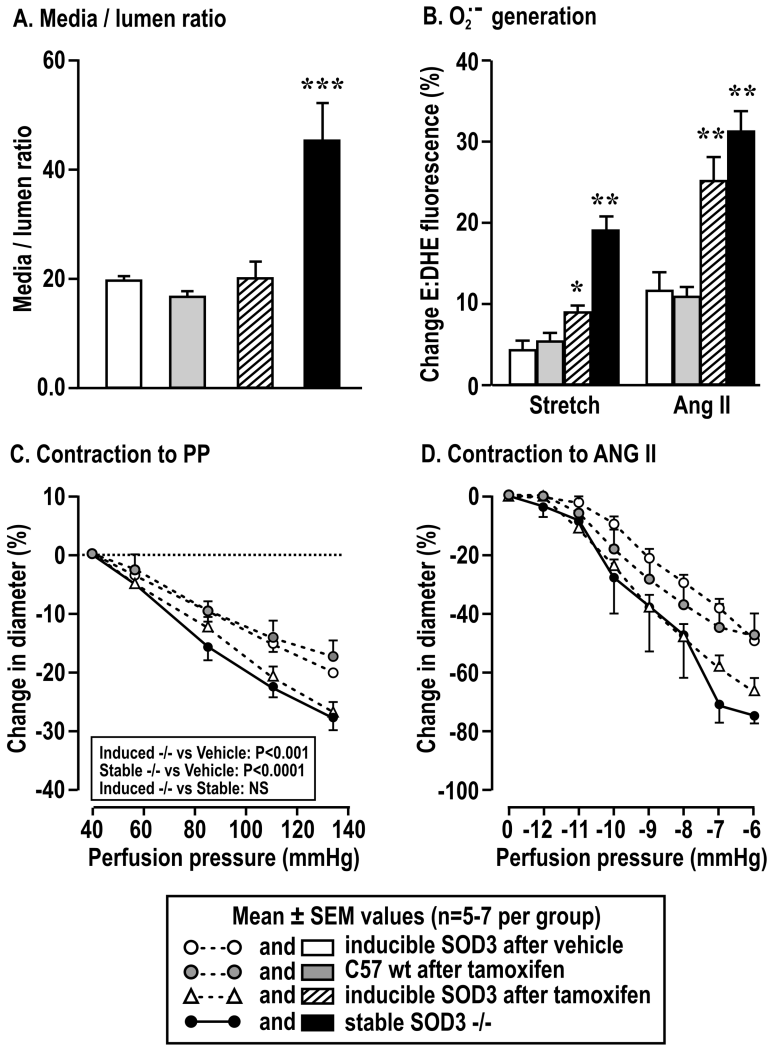

Figure 6.

Structural change, superoxide generation and contraction of afferent arterioles from mice with tamoxifen inducible SOD-3 −/− after vehicle (open boxes and open circles), inducible SOD-3 after tamoxifen (cross hatched boxes and open triangles) or stable SOD-3 −/− (solid boxes and solid circles). Compared to arterioles from inducible SOD-3 −/− after vehicle: *****, P<0.05; ******, P<0.01; *******, P<0.005.