Increased Susceptibility to Atrial Tachyarrhythmia in Spontaneously Hypertensive Rat Hearts

Stéphanie C.M. Choisy, Lesley A. Arberry, Jules C. Hancox, Andrew F. James

Abstract—Although hypertension is the most prevalent risk factor for atrial fibrillation, there is currently no information available from animal models of hypertension regarding the development of atrial remodeling or increased susceptibility to atrial tachyarrhythmia. Therefore, we examined the susceptibility to atrial tachyarrhythmia and the development of atrial remodeling in excised perfused hearts from male spontaneously hypertensive rats in comparison with age-matched male Wistar–Kyoto normotensive controls at age 3 and 11 months, corresponding with early hypertension and pre-heart failure stages, respectively. The incidence and duration of left atrial tachyarrhythmia induced by burst pacing was greater in hearts from 11-month–old hypertensive animals than either in age-matched controls or in 3-month–old hypertensive rats, although there was no difference between hypertensive and normotensive hearts at 3 months. Thus, hypertension was associated with the development of an arrhythmic substrate. Atrial effective refractory period and the duration of monophasic action potentials recorded from the left atrium were not altered with either hypertension or age, although there were changes in the whole-cell Ca$^{2+}$ current density of isolated left atrial myocytes. On the other hand, Masson’s trichrome staining of wax-embedded sections of left atrium revealed markedly greater interstitial fibrosis in 11-month–old hypertensive rats compared with controls. These data constitute the first experimental evidence that hypertension is associated with the development of a substrate for atrial tachyarrhythmia involving left atrial fibrosis without changes in the atrial effective refractory period and demonstrate that the spontaneously hypertensive rat represents a suitable model for investigating hypertension-associated atrial remodeling. (Hypertension. 2007;49:1-8)

Key Words: arrhythmias ■ fibrosis ■ hypertension, essential ■ ion channels ■ remodeling, atrial ■ rats, inbred SHR

Atrial fibrillation (AF) is the most common arrhythmia and can have potentially serious clinical consequences, most notably heart failure and stroke.1,2 AF derives from a complex continuum of predisposing factors, and there is often some underlying cardiac disease; but the most prevalent risk factor is hypertension.1–3 However, possibly because of the complex etiology, it is not yet clear whether the existence of atrial remodeling, contribute to the stabilization of the substrate for AF.

It has long been recognized that various mechanisms can underlie AF, including rapid local ectopic activity and reentrant mechanisms, and it is well established that structural and electrical changes to the atrial myocardium, termed “atrial remodeling,” contribute to the stabilization of the arrhythmia.3,4 The atrial effective refractory period (AERP) and action potential duration (APD) become shortened and their adaptation to faster rates reduced in patients with chronic AF.3–7 This electrical remodeling has been associated with changes in various ion current densities, including a reduction in the L-type Ca$^{2+}$ current ($I_{Ca}$) and transient outward current ($I_{to}$).5,7–10 However, reduction in $I_{Ca}$ and $I_{to}$ cannot account for the change in AERP, and it has been suggested that increased outward current through inward rectifier K$^+$ channels plays a key role in the shortening of AERP in human AF.7,11–13 Studies in animal models involving chronic rapid pacing of the atria have demonstrated that atrial tachyarrhythmia (AT) itself produces electrical remodeling reminiscent of that seen in chronic AF patients, accounting for the progressive nature of AF.14–19

On the other hand, comparatively little is known regarding the substrate for arrhythmia in which AF originates. Structural changes to the left atrium are considered to indicate risk of AF, and it is thought that hemodynamic overload may result in structural remodeling of the left atrial wall.3,20 Canine models of congestive heart failure and mitral valve regurgitation, risk factors for AF associated with hemodynamic overload of the left atrium, show an increased susceptibility to AT through a distinct form of atrial remodeling in which AERP is not shortened.21,22 The development of the arrhythmic substrate in these models was associated with interstitial fibrosis and enlargement of the left atrium.21,22 Although APD was prolonged at faster rates, $I_{Ca}$ density was reduced in...
congestive heart failure, consistent with the suggestion that remodeling of I_{Ca} does not necessarily result in shortening of AERP.\(^23\)

It is striking that, although elevated arterial pressure is associated with structural changes to the left atrium and represents a major risk factor for AF,\(^3,20,24\) there is to date no information concerning atrial electrical remodeling in any animal model of hypertension; therefore, very little is known concerning the development of the electrical substrate for AT in hypertension.\(^25\) The spontaneously hypertensive rat (SHR) is a genetic model of systemic hypertension\(^26\) that, in combination with the normotensive Wistar–Kyoto (WKY) control strain, has been extensively used to examine cardiac adaptations to elevated afterload (e.g., References 27–35). Indeed, it has been shown that left atrial pressure in the SHR is \(\approx 2\)-fold greater than normotensive controls,\(^33\) presumably arising from the reduced left ventricular compliance and increased end-diastolic pressure associated with hypertrophy.\(^34,35\)

Moreover, the SHR shows changes in the P wave of the body surface ECG consistent with those seen in hypertensive patients that provide evidence of significant atrial enlargement in this model.\(^36\) Accordingly, we have examined the electrical substrate for AT of excised perfused hearts from SHRs in comparison with WKY controls by electrophysiological recording from the left atrium.

**Methods**

All of the procedures were performed in accordance with United Kingdom legislation under the Animals (Scientific Procedures) Act, 1986, and Home Office guidelines. Systolic blood pressure was measured in conscious animals 1 week before experimentation by tail-cuff plethysmography (Harvard Apparatus Ltd). On the day of experimentation, hearts from both SHR and WKY animals were excised under terminal anesthesia (IP injection of 1 to 1.5 mL/kg of pentobarbital sodium solution, “Euthatal,” Merial Animal Health, Harlow). The intraperitoneal injection of sodium pentobarbital has been shown previously to affect the contractile function of rat hearts after excision and perfusion (e.g., see References 36, 37). However, because in the present study all of the groups of animals were treated in the same way, it is considered unlikely that the use of anesthetic can account for the differences between SHR and WKY hearts.

**Perfused Heart Studies**

Hearts were mounted on a whole heart perfusion apparatus and perfused retrogradely via the aorta with a Krebs’ Henseleit solution composed of (in mmol/L) 118.5 NaCl, 25.0 NaHCO\(_3\), 3.0 KCl, 1.2 MgSO\(_4\), 7 H\(_2\)O, 1.2 KH\(_2\)PO\(_4\), 2.5 CaCl\(_2\), and 11.1 d-glucose at 37°C and gassed with 95% O\(_2\)/5% CO\(_2\). After \(\leq 30\) minutes of Langendorff perfusion, the so-called “working heart” was established in which the left atrium was cannulated, the preload and afterload set to, respectively, 13 mm Hg and 62 mm Hg, and the heart perfused in the orthograde direction.\(^38\) Data were recorded to the hard disk of a PC using the PowerLab 8/SP data acquisition system and Chart software version 5 (AD Instruments Ltd). The aortic pressure was recorded using a pressure transducer and the developed pressure calculated as the difference between diastolic and systolic aortic pressures. The ECG was recorded via a bioamplifier from platinum electrodes placed on the epicardial surface of the heart near the apex of the left ventricle and on the cannula to the left atrium. Heart rate during sinus rhythm was calculated as the reciprocal of the R–R interval of the ECG in seconds, multiplied by 60. For the measurement of atrial electrophysiological parameters from excised perfused hearts,\(^39\) hearts were paced via bipolar platinum pacing electrodes placed on the right atrium using a Master-8 programmable stimulator with ISO-flex stimulus isolators (Intracel Ltd). The threshold stimulus intensity was found, the stimulus intensity set at double this value, and hearts paced at cycle lengths (CLs) of 75 to 200 ms. The atrial monophasic action potential (monophasic AP) was recorded using a Franz-like suction electrode made in our laboratory, based on a design described previously.\(^40,41\) Monophasic AP duration was measured at 70% repolarization (APD\(_{70}\)) for each CL to establish the monophasic APD\(_{70}\)–CL dependence. AERP was measured using an S\(_1\)–S\(_2\) protocol in which the interval between the last of a train of 8 S\(_1\) stimuli (CL = 200 ms) and the S\(_2\) stimulus was gradually reduced in 5-ms decrements until the S\(_2\) stimulus failed to elicit further excitation.\(^39\) Susceptibility to AT, defined as periods of atrial tachycardia deviating from sinus rhythm for \(>0.1\) s was investigated by applying bursts of very rapid pacing (CL = 10 ms) for \(\leq 3\) seconds and the duration of the subsequent tachycardia measured from the end of burst pacing.\(^39\)

**Histology**

Hearts rapidly excised under terminal anesthesia were mounted on a modified Langendorff apparatus and retrogradely perfused via the aorta with a physiological solution at 37°C of the composition used for cell isolation (see below) and containing 0.75 mmol/L of Ca\(^2+\). After 5 minutes, the solution was switched to a Ca\(^2+\)-free PBS containing (in mmol/L) 110.0 NaCl, 2.1 KCl, 5.1 Na\(_2\)HPO\(_4\), 0.7 KH\(_2\)PO\(_4\), 0.9 CaCl\(_2\), and 0.9 MgCl\(_2\) (pH 7.3) for a further 5 minutes. While still cannulated, the heart was removed from this apparatus and perfusion fixed with neutral buffered formalin containing 4% wt/vol formalin, 33.3 mmol/L NaH\(_2\)PO\(_4\) and 45.8 mmol/L Na\(_2\)HPO\(_4\) (pH 7). Atrial tissue was dissected from the hearts and stored in neutral buffered formalin for 5 days. Hearts were subjected to ethanol dehydration, embedded in wax, and 10-μm slices obtained using a microtome. Sections were stained with Masson’s trichrome.

**Isolation of Left Atrial Myocytes**

Hearts were rapidly excised under terminal anesthesia, mounted on a modified Langendorff perfusion apparatus, and perfused retrogradely via the aorta with a series of solutions at 37°C, based on an isolation solution composed of (in mmol/L) 130 NaCl, 5.4 KCl, 1.4 MgCl\(_2\), 0.4 NaHPO\(_4\), 4.2 HEPES, 10 d-glucose, 20 taurine, and 10 creatine (pH 7.3).\(^32\) Hearts were initially perfused for \(\approx 4\) minutes with a solution containing 0.75 mmol/L of CaCl\(_2\). The heart was then perfused for 4 minutes with a Ca\(^2+\)-free isolation solution containing 0.1 mmol/L of EGTA; this was followed by perfusion with low Ca\(^2+\) isolation solution (Ca\(^2+\) = 5 to 10 mmol/L containing 0.4 mg/mL of Worthington type I collagenase (“Lorne Laboratories”). After 12 to 20 minutes, the heart was removed from the apparatus, and the left atrium was dissected from the heart, finely chopped, and gently triturated using a glass Pasteur pipette at room temperature in Krafbruhe (KB) medium of composition (in mmol/L) 70 l-glutamic acid, 30 KCl, 10 HEPES, 5 MgCl\(_2\), 5 Na-pyruvate, 20 taurine, 10 d-glucose, 5 succinic acid, 5 creatine, 2 Na\(_2\)ATP, and 5 β-hydroxybutyric acid (pH 7.2).\(^43\) Cells were stored in KB medium in a refrigerator (\(\approx 4°C\)) and used within 9 hours of isolation.

**Whole-Cell Patch-Clamp Recording**

Cells were superfused with an external solution composed of (in mmol/L) 134 NaCl, 4 KCl, 1.2 MgCl\(_2\), 1 CaCl\(_2\), 10 HEPES, and 11 d-glucose (pH 7.35) at 35°C. Pipettes were pulled from borosilicate glass capillaries (Corning 9250; A-M Systems) to tip resistances of 1.5 to 3.0 mol/LI when filled with the pipette solution, which contained (in mmol/L) 130 HCHO\(_{3}\), 130 KOH, 10 KCl, 10 1.2-bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid, 2 MgCl\(_2\), 10 HEPES, 5 d-glucose, 4 MgATP, and 0.2 Na\(_2\)GTP (pH 7.2; KOH). Whole-cell currents were recorded by EPC-9 (HEKA GmbH) or Axopatch 200B (Axon Instruments Inc) patch-clamp amplifiers and recorded to the hard drive of a PC using Pulse software (version 8.11, HEKA GmbH). Although the EPC-9 amplifier had a built-in A/D converter, currents recorded using the Axopatch 200B were acquired using an ITC-16 A/D converter (InstruTECH Inc, Digitimer Ltd). The sampling rate was typically 2 kHz. Junction potentials and

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capacitance transients were compensated electronically. Currents were elicited by a series of pulses at 10-s intervals to voltages increasing from $-120$ mV to $+40$ mV in 20-mV increments from a holding potential of $-70$ mV. Currents were not corrected for leak and were normalized to capacitance as a measure of cell size.

**Statistics**

Data were analyzed using Prism version 4 (GraphPad Software, Inc). All of the data sets were subject to a Kolmogorov–Smirnov normality test before statistical test by Student's t test, 1-way ANOVA, or Kruskal–Wallis tests, as appropriate; details are provided in the text or figure legends. $P<0.05$ was considered statistically significant.

**Results**

Experiments were conducted on hearts from male SHRs in comparison with age- and sex-matched WKY controls at age 3 months and 11 months, corresponding with early hypertension and pre-heart failure stages, respectively.27,29,35 Background data from these experiments are summarized in Tables 1 and 2. As expected, systolic blood pressure was greater in conscious SHRs compared with WKY rats at both ages (Table 1),29,35 Note that there was also an age-related increase in systolic pressure in both WKY rats and SHRs (Table 1). Wet heart weight:body weight ratios demonstrated that hearts from SHRs were hypertrophied in comparison with WKY rats at both ages (Table 1), a finding that is also consistent with previous reports.29,35 Presumably, because cardiac remodeling in SHRs up to age 12 months has been shown not to involve changes in myocardial water content,29 the increased wet heart weight:body weight ratios in the present study reflect myocardial hypertrophy in response to elevated arterial pressure. In experiments with excised perfused hearts, the heart rate during sinus rhythm was $\approx 20\%$ higher in SHR hearts than in WKY hearts at both ages (Table 2), consistent with previous reports of elevated heart rates in vivo.32,35 On the other hand, there was no difference in the developed pressure between SHRs and WKY rats at either age, although developed pressure was increased in the hearts from the older animals (Table 2). Thus, consistent with previous reports,27,29,35 hypertrophied SHR hearts did not show evidence of heart failure at ages 3 and 11 months.

Paroxysms of AT could be induced in the excised, perfused hearts from SHRs and WKY rats of both ages by application of brief bursts ($\leq 3$ s) of rapid pacing ($CL\leq 10$ ms; Figure 1A). These spontaneously reverted to sinus rhythm after a period of time that ranged from 0.1 to 76.7 s. Both the incidence and the duration of AT were markedly increased in hearts from 11-month–old SHRs compared with those from 3-month–old SHRs and with 11-month–old WKY rats, although there was no difference in the susceptibility to AT between WKY and SHR hearts at age 3 months (Figure 1B), demonstrating the development of a substrate for arrhythmia with progressive hypertension. This arrhythmic substrate in hearts from hypertensive animals was not associated with any change in AERP (Figure 2A), nor was the monophasic AP duration at 70% repolarization ($APD_{70}$) altered in SHR hearts (Figure 2B).

The increased susceptibility to AT in animal models of congestive heart failure and mitral valve regurgitation, in which AERP was not shortened, was associated with fibrosis and enlargement of the left atrium.21,22 Therefore, we examined whether the increased susceptibility to AT in hypertensive hearts was associated with structural remodeling. The degree of fibrosis in Masson’s trichrome-stained slides was markedly greater in sections from SHR hearts compared with WKY controls at age 11 months (Figure 3). The mean percentage of fibrosis in sections from SHR hearts at age 3 months was also greater than age-matched controls (Figure 3C). In addition, the left atrial weights were increased in hearts from SHRs at age 11 months compared with age-matched WKY hearts (SHR: $98.4\pm 7.1$ mg, n = 21; WKY: $54.3\pm 2.1$ mg, n = 14; $P<0.0001$). As a result, the left atrial:
whole heart weight ratios were increased in 11-month–old SHR hearts compared with age-matched WKY hearts (SHR: 45.0 ± 3.3 mg/g; WKY: 29.8 ± 1.2 mg/g; P < 0.001). Taken together, these data provide evidence for atrial enlargement and fibrosis in hypertensive hearts.

To examine the existence of cellular electrical remodeling, whole-cell patch-clamp recordings were made from myocytes isolated from the left atrium of SHR and WKY hearts at both age 3 and 11 months from a holding potential of −70 mV. As reported by Heaton et al for whole-cell recordings from pacemaker cells isolated from SHRs,32 we found that cell isolation, particularly from the older animals, produced only a low yield of cells that was often fragile and difficult to patch. Nevertheless, the mean holding current densities (WKY 3 months: 0.19 ± 0.07 pA/pF, n = 14; SHR 3 months: 0.28 ± 0.18 pA/pF, n = 11; WKY 11 months: 0.09 ± 0.30 pA/pF, n = 9; SHR 11 months: 0.64 ± 0.41 pA/pF, n = 10) were not significantly different, indicating that leak did not contribute to differences between the groups of cells. Inwardly rectifying currents were activated by hyperpolarizing pulses, whereas depolarizing pulses elicited either inward or outward currents (depending on the test potential) that activated rapidly to a peak before inactivating to a quasi–steady state level at the end of the pulse (Figure 4A). The mean current density–voltage relations for the quasi–steady state current (I<sub>ss</sub>) and the peak current of myocytes from SHR and WKY hearts at ages 3 and 11 months are shown in Figures 4B and 4C, respectively. Although there were no differences in inwardly rectifying currents at negative potentials (−120 to −80 mV; Figure 4B), peak current at positive potentials (−20 to +60 mV) was significantly greater in myocytes from 11-month–old SHRs compared with age-matched WKY controls and with 3-month–old SHRs (Figure 4C). In addition, outward I<sub>ss</sub> in myocytes from 11-month–old SHR were slightly, but significantly, greater than those from age-matched WKY rats at very positive potentials (+60 mV; Figure 4B). Transient inward currents were activated by pulses to voltages between −20 and +20 mV (Figure 5A). These currents were completely blocked by the L-type Ca<sup>2+</sup> channel blocker, nifedipine (3 μmol/L), and, therefore, rep-
resent I_{Ca}. The mean I_{Ca} density at 0 mV was significantly smaller in left atrial myocytes from SHR hearts compared with WKY controls at age 3 months (Figure 5B). I_{Ca} density in myocytes from both SHRs and WKY rats was decreased further at age 11 months, although the difference between SHR and WKY myocytes did not achieve statistical significance in the older age group ($P=0.095$; Figure 5B). The increased outward peak current at positive potentials in myocytes from 11-month–old SHRs compared with age-matched WKY rats and with 3-month–old SHRs is consistent with an increase in the I_{to} (Figure 4C). This is further supported by the observation that the difference in I_{to} at +60 mV (WKY: 6.12±2.36 pA/pF; SHR: 11.15±1.27 pA/pF) between left atrial myocytes from 11-month–old SHRs (n=3) compared with age-matched WKY hearts (n=3) was not eliminated by 3 μmol/L of nifedipine ($P<0.05$, 2-way ANOVA with Bonferroni’s posthoc test). On the other hand, in the presence of the L-type channel blocker, there was no difference in I_{to} density at 0 mV (WKY: 2.53±0.51 pA/pF; SHR: 2.20±1.40 pA/pF), indicating that the differences in I_{to} did not contribute to differences in I_{Ca} in the present study. Of note, the whole-cell capacitance of isolated left atrial myocytes (see legend, Figure 4), which is directly related to the total surface area of the cell membrane, was not different between SHR and WKY hearts, indicating that enlargement of the left atria was not associated with cardiac myocyte hypertrophy.

Discussion

This study demonstrates for the first time that remodeling of the left atrium results in a substrate for tachyarrhythmia in a widely used model of systemic hypertension. The increased susceptibility to AT of hypertensive hearts at age 11 months compared with age-matched normotensive animals and with hearts from 3-month–old hypertensive animals (Figure 1B) was associated with a significantly increased systolic tail-cuff pressure in the conscious animals (Table 1), consistent with hypertension being the primary cause of the atrial remodeling. The substrate for arrhythmia in the left atrium of hypertensive hearts was associated with markedly increased interstitial fibrosis (Figure 3C), but AERP was unchanged (Figure 2). Enlargement and dilatation of the left atrium is widely regarded to be an epidemiological risk indicator for AF, and has been suggested that atrial enlargement in hypertension contributes to the increased incidence of arrhythmia. However, although the left atria were enlarged in hypertensive hearts compared with controls in the present study, consistent with ECG changes reported previously in the SHR, there was no significant correlation between the left atrial:whole heart weight ratio and duration of AT, indicating that atrial enlargement itself was not the primary cause of the increased susceptibility to arrhythmia of hypertensive hearts. On the other hand, our findings support the notion of an association between AT and interstitial fibrosis in rodent hearts and are consistent with localized conduction abnormalities contributing to an arrhythmic substrate in structural heart disease. Our findings indicate that future measurements of atrial conduction in this model are warranted to examine this possibility.

Figure 3. Atrial structural remodeling in hypertensive hearts. A, Representative example of Masson’s trichrome–stained left atrial section from WKY rats at 11 months. B, Representative example of Masson’s trichrome–stained left atrial section from SHRs at 11 months. Scale bars represent 100 μm. C, Mean (±SEM) percentage fibrosis measured as the percentage of blue pixels using Adobe Photoshop CS2. WKY 3 months: n=7; SHR 3 months: n=9; WKY 11 months: n=23; SHR 11 months: n=19. ***$P<0.001$, 1-way ANOVA with Bonferroni’s posthoc test vs aged-match WKY. #$P=0.05$, Student’s t test vs age-matched WKY rats.
The development of the arrhythmic substrate in this study was not associated with heart failure. Nevertheless, similar to models of congestive heart failure, I_{Ca} density was reduced in left atrial myocytes from hypertensive hearts,23,47 consistent with remodeling of cellular electrophysiology in dilated atria.48 On the other hand, the increased I_{to} density in atrial myocytes from SHR hearts at 11 months is in contrast to previous studies of atrial myocytes from a canine model of heart failure,23 to patients with dilated atria48 or with chronic AF,5,7,10 and to a previous study of ventricular myocytes from the SHR28 in which I_{to} has been shown to be reduced. Outward I_{so} also showed a small but significant increase in SHR-11–month myocytes compared with age-matched WKY rats at positive potentials (Figure 4B). A preliminary analysis of differences in left atrial gene expression between 11-month–old SHRs and age-matched WKY rats using the

Figure 4. Electrical remodeling of left atrial myocytes. A, Top, representative current traces. Bottom, voltage protocol. Cell from a 3-month–old WKY heart. B, Mean (±SEM) current density–voltage relations for steady-state current measured at the end of voltage pulses (P<0.0001 for strain, 2-way ANOVA). Open symbols, WKY; closed symbols, SHR; circles, 3-month–old; squares, 11-month–old. **P<0.01, Bonferroni’s posthoc test comparisons of SHR 11 months vs WKY 11 months. Mean whole-cell capacitances were: WKY 3 months, 52.0±1.1 pF (n=14); SHR 3 months, 50.7±3.2 pF (n=11); WKY 11 months, 64.2±8.7 pF (n=9); SHR 11 months, 71.3±13.2 pF (n=10). C, Mean (±SEM) current density–voltage relations for peak current measured at the start of voltage pulses (P<0.0001 for strain, 2-way ANOVA). Open symbols, WKY; closed symbols, SHR; inverted triangles, 3-month–old; upright triangles, 11-month–old. **P<0.01, ***P<0.001, Bonferroni’s posthoc test comparisons of SHR 11 months vs WKY 11 months. ##P<0.01, ###P<0.001, Bonferroni’s posthoc test comparisons of SHR 11 months vs SHR 3 months.

Figure 5. Evidence for remodeling of L-type Ca^{2+} current in myocytes from hypertensive rats. A, Example currents at 0 mV in the absence and presence of 3 μmol/L nifedipine. The nifedipine-insensitive current at the end of the pulse represents the steady-state current. B, Top shows representative current traces from a 3-month–old SHR left atrial myocyte and an age-matched WKY control. Bottom shows mean (±SEM) I_{Ca} density at 0 mV. *P<0.05, one-way ANOVA with Bonferroni’s posthoc test versus WKY at 3 months. Mean I_{Ca} density in 11-month SHR myocytes was significantly smaller than 3-month WKY rats (P<0.001) but not significantly different from age-matched WKY rats or 3-month SHRs. Sample sizes as indicated in Figure 4.
Affymetrix rat 230 microarray suggests that significantly increased expression of the transient outward K⁺ channel α-subunit, Kc.4.3, and the twin-pore domain K⁺ channel, TWIK-2,49 (data not shown) may contribute to the differences in \( I_{\text{to}} \) and \( I_{\text{iss}} \), respectively. The changes in the outward currents, \( I_{\text{to}} \) and \( I_{\text{iss}} \) observed in the present study were not associated with changes in AERP, and their significance to AT, per se, remains unclear. However, reduction in \( I_{\text{to}} \) and the consequent APD prolongation have been implicated in the hypertrophic response of left ventricular myocytes to hemodynamic overload.28,50 Notably, the cellular hypertrophy was abrogated by in vivo gene transfer of Kc.4.3.50 Thus, the increase in left atrial \( I_{\text{to}} \) in hypertension may explain the absence of atrial cellular hypertrophy in the present study. On the other hand, there were no differences in the inwardly rectifying current in the present study. It is well established that outward currents through inward rectifier channels play a major role in the final phase of repolarization,51 and it has been suggested that increased outward currents through inward rectifier channels are required to account for the shortening of AERP in patients with chronic AF.11 Thus, the absence of differences between myocytes from hypertensive and normotensive animals in the outward currents in the range of −80 to −40 mV may explain the lack of a difference in AERP in the present study. Concordant with our finding of atrial cellular electrical remodeling in the SHR, Guinanard et al.51 have recently reported increased atrial expression of mRNA for a nonselective cation channel in the SHR compared with the WKY rat, although the functional significance to atrial electrophysiology of this change remains unclear.

**Perspectives**

This study represents the first demonstration that hypertension induces remodeling of the left atrium that results in a substrate for tachyarrhythmia. The remodeling involved atrial enlargement, interstitial fibrosis, and cellular electrical remodeling, but AERP was unchanged. The mechanisms underlying hypertension-induced atrial remodeling are yet to be established. Although hypertension in the SHR is associated with pressure changes in the left atrium,51 it has been suggested that the structural remodeling is mediated by the effectors of the renin–angiotensin system rather than altered wall stress or hypertension, per se.52,53 The present work establishes the SHR as a model that can be used to determine the role of these and other factors in mediating the development of the substrate for AT in systemic hypertension.

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**Disclosures**

None.

**References**


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