Genetic analysis of salt-sensitive hypertension in Dahl rats reveals a link between cardiac fibrosis and high cholesterol

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Aims Previously we confirmed an important role of rat chromosome 19 (RNO19) for salt-sensitive hypertension and target organ damage in male Dahl salt-sensitive rats (SS rats). The aim of this study was to further analyse the basis of left ventricular (LV) fibrosis development in both male and female rats in this model. To this end we utilized a consomic SS-19SHR rat strain in which RNO19 was transferred from spontaneously hypertensive rats (SHR) into the susceptible background of SS.

Methods and results We compared the effects of low- (0.2% NaCl) and high-salt (4% NaCl) diet on the development of hypertension, blood lipids and LV fibrosis in male and female SS, SHR, and SS-19SHR rats. Systolic blood pressure was significantly lower in male and female SS-19SHR compared with SS under both diets (P < 0.001). Relative LV weight was similarly reduced in SS-19SHR compared with SS in either sex. Plasma cholesterol concentrations were significantly elevated in high-salt fed male and female SS (141 ± 6 and 110 ± 7 mg/dL) compared with SHR (47 ± 2 and 62 ± 8 mg/dL, P < 0.001) and were significantly lowered in male and female consomic rats (100 ± 7 and 87 ± 3 mg/dL). Both LV interstitial fibrosis (LVIF) and perivascular fibrosis (LVPF) were significantly reduced in high-salt male and female SS-19SHR. A significant correlation between cholesterol concentrations and LVPF (r = 0.464) and LVIF (r = 0.401, P < 0.0001, respectively) was detected. Fibrosis parameters demonstrated no correlation with blood pressure, LV weight or plasma triglycerides concentrations. LV immunohistochemistry analysis showed a significant higher number of ED-1 positive cells in SS compared with SS-19SHR. Depositions of collagen I and fibronectin were also greater in LV tissue of SS compared with SS-19SHR.

Conclusion Our findings point to a link between hypercholesterolemia and LV fibrosis in salt-sensitive hypertension of SS rats which is genetically modulated by RNO19.

1. Introduction

Hypertensive heart disease plays a key role in determining the clinical outcome in patients with arterial hypertension. Indeed it has been shown that the presence of left ventricular (LV) hypertrophy (LVH) is a major independent risk factor that profoundly results in morbidity and mortality from cardiovascular diseases. In particular, LVH represents an important predictor for both systolic and diastolic heart failure. In this regard, an increased LV collagen deposition and the development of LV fibrosis is a crucial deleterious process that impairs LV function in arterial hypertension. The development of hypertensive organ damage including cardiac damage is particularly pronounced in salt-sensitive hypertension and both high-sodium intake and salt-sensitive hypertension are significant factors contributing to LVH and LV fibrosis. In addition, the clinical importance of salt-sensitive hypertension results from the observation that the prevalence is high and increases with age. Thus, salt sensitivity is an important factor contributing to cardiac dysfunction in the ageing heart. The Dahl salt-sensitive rat (SS rat) represents a polygenic animal model which develops LVH and LV fibrosis in response to high-salt diet. The influence of cardiac fibrosis on the transition from compensatory hypertrophy to LV dysfunction has been previously studied in this model. The SS strain develops severe hypertension when fed a high-salt diet but it also exhibits spontaneous hypertension under low-salt conditions.
conditions.13 Accordingly SS rats develop target organ damage that is worsened by high salt intake.14,15 In addition to salt sensitivity, phenotypes related to the metabolic syndrome such as hyperlipidaemia have been demonstrated in the SS rat.16 Both blood pressure and plasma concentrations of lipids are influenced by multiple quantitative trait loci (QTL) in this strain.15,17 In previous linkage studies we identified several QTL for SS hypertension and organ damage in the SS rat.12,14 In these studies we used a strain of spontaneously hypertensive rats (SHR) as a model resembling spontaneous hypertension that is resistant to a 4% high-salt diet.18 More recently we confirmed that QTL on rat chromosome 19 (RNO19) exhibit indeed a significant effect on both salt-sensitive hypertension and organ damage in male rats.19 These data were obtained in a consomic rat strain SS-19\textsuperscript{SHR} in which RNO19 from SHR was transferred by selective breeding into the isogenic background of the SS strain.19 Male rats of the consomic strain showed significantly reduced systolic blood pressures (SBP) and organ damage. Interestingly this occurred not only in rats under a high-salt diet but already under low-salt conditions. Moreover a significant reduction in cardiac fibrosis could be detected in high-salt male SS-19\textsuperscript{SHR}.19 In this study we set out to further analyse the mechanisms associated with the reduction in LV fibrosis and salt-sensitive hypertension by replacement of RNO19 in the SS rat. We investigated particularly the role of increased cholesterol plasma concentrations observed in SS, since a high cholesterol diet has been shown to aggravate cardiac fibrosis and dysfunction in a rat model of ischaemic heart disease.20 In addition, we accounted for potential influences of sex by including both female and male rats in our analysis.

2. Methods

2.1 Animals

Male SS and SHR rats were obtained from our colonies (laboratory code Rkb, http://dels.nas.edu/ilar/) at the Charité, Campus Benjamin Franklin, Germany. Rats were grouped under a 12:12 h light/dark cycle using an automated light switching device and climate-controlled conditions at 22°C. The consomic strain was generated as previously reported.19 All experiments were approved by the local ethics review board for the use of laboratory animals and conform to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996).

2.2 Phenotyping

Rats were phenotyped as reported.12 In brief, at 6 weeks of age male and female SHR, SS-19\textsuperscript{SHR}, and SS rats (n = 12–30, each) were fed for 8 weeks with a low- (0.2% w/w) or a high-salt (4% w/w) diet obtained from Ssniff (Soest, Germany). Both diets were primarily of corn and contained no animal oil. They consisted of 9–10% of fat in total with a similar composition of fatty acids.

SBP was measured in awake rats as reported.21 At 14 weeks of age, rats were weighed and sacrificed under a ketamine (Ketanest S, Pfizer, Karlsruhe, Germany)/xylazine (Rompun, Beyer, Leverkusen, Germany) anaesthesia (87 mg/kg and 13 mg/kg body weight, respectively). Blood was drawn from the vena cava, clotting factors were inactivated with ethylene diaminetetraacetic acid for the extraction of plasma. Triglycerides, total cholesterol concentrations, and high-density lipoproteins (HDL) were determined with an enzymatic reaction on a MODULAR\textsuperscript{®} ANALYTICS system from Roche Diagnostics (Mannheim, Germany) following standard operating procedures. The assay was validated by comparison with measurements performed by lipoprotein electrophoresis data. Beta [LDL (low-density lipoprotein)], pre-beta (very low-density lipoprotein), and alpha (HDL) lipoproteins were determined by agarose gel electrophoresis with subsequent specific enzymatic staining for cholesterol22 (with the use of the rapid electrophoresis system; Rolf Greiner Biochemical, Flacht, Germany). This analysis indicated that only total cholesterol and HDL-cholesterol concentrations were measured accurately by the enzymatic reaction, whereas LDL cholesterol as determined by lipid electrophoresis did not correlate with values calculated by the Friedewald formula (data not shown).

LV interstitial fibrosis (LVI) and LV perivascular fibrosis (LVPF) were quantified by morphometry as reported.12

2.3 Immunohistochemistry

Immunohistochemistry was performed in a shock-frozen transverse tissue section of the LV. Ice-cold acetone-fixed cryosections (6 μm) were stained with immunofluorescence. The sections were incubated with the following primary antibodies: monoclonal anti-ED-1 (1: 500, Serotec), polyclonal anti-collagen I (1:300, Southern Biotech.) and polyclonal anti-fibronectin (1:5000, Abcam) as described earlier.23 Cy3-conjugated secondary antibodies (1:500, Dianova) were used for colocalization of stainings.

2.4 Statistical analysis

Data were summarized as means ± SEM. Differences in means between experimental groups were tested using a three-way analysis of variance (ANOVA) for strain, gender, and diet with post hoc Bonferroni adjustments. Mann–Whitney U test was performed when necessary. Correlation analyses were done with the Pearson’s test. A probability of P < 0.05 was considered to be statistically significant (SPSS 13.0, SPSS Inc., USA).

3. Results

Overall body weights were higher in males than in females and lower in SHR compared with the two other strains (P < 0.01, respectively, Table 1). The high-salt diet had no effect on body weights.

In comparison with low-salt diet groups SBP values were significantly higher in response to high-salt diet in both male and female SS rats, while SBP in SS males were overall higher than in SS females under both diets (Figure 1A). The SHR strain showed neither a response to high-salt diet nor differences between male and female rats. Introgression of RNO19 led to a significant blood pressure decrease in both male and female consomic rats compared with the SS parental strain under high-salt conditions (P < 0.001). Similarly, transfer of RNO19 resulted already in lower SBP values in SS-19\textsuperscript{SHR} males and females under low-salt diet conditions (P = 0.010 and 0.057, respectively).

The data obtained for relative ventricular weight as an index for LVH paralleled the SBP findings (Figure 1B). Thus, both male and female SS rats showed a significant increase in relative LV weight in response to high-salt diet compared with low-salt diet (P < 0.001, respectively). In contrast, in the SHR strain no differences between diet groups were detected. In agreement with the SBP, data transfer of RNO19 from the SHR strain led to significantly lower relative LV weights in male and female consomic rats compared with the SS strain under high-salt diet (P < 0.001, respectively). Overall, relative LV weights were higher in females compared with males due to the lower body weights observed.
in female rats (Table 1). We previously demonstrated by quantitative analysis of Sirius-red stained LV sections a similar and marked increase in LVIF and LVPF in response to high-salt diet in male SS rats, while this increase was completely abolished in male consomic rats. Similar results were obtained for female SS and SS-19SHR rats in the current study (Figure 1C).

Unlike the SBP and relative LV weight phenotypes, ANOVA demonstrated that total plasma cholesterol concentrations and HDL-cholesterol concentrations (data not shown) were overall not significantly affected by dietary sodium content (Figure 2A). Independent of salt-diet, cholesterol concentrations were about two- to three-fold higher in female and male SS compared with SHR rats (Figure 2A, \( P < 0.001 \), respectively). Male and female SS-19SHR rats demonstrated significantly lower cholesterol levels compared with the SS-strain (\( P < 0.05 \), respectively, Figure 2A). However, in comparison with SHR, cholesterol levels were still elevated in consomic rats (\( P < 0.05 \), Figure 2A). In both SS and SS-19SHR rats cholesterol concentrations were somewhat higher in males than in females. These differences were significant in the SS parental strain under high-salt (\( P = 0.005 \)) and in consomic rats under low-salt diet conditions (\( P < 0.001 \)). When the previously discussed group comparisons were made between strains and both genders for total plasma cholesterol concentrations, and for HDL-cholesterol concentrations in separate analysis, similar differences were obtained (data not shown).

Triglyceride concentrations were also unaffected by diet in all three strains (Figure 2B). Figure 2B clearly demonstrates the marked strain-dependent sexual dimorphism in plasma triglyceride concentrations. No strain differences were obtained in female rats while male SS rats demonstrated more than two-fold elevated triglyceride concentrations compared with female rats or to male SHR rats (\( P < 0.001 \), respectively). Transfer of RNO19 had no significant influence on triglyceride concentrations, as both male and female SS-19SHR were indistinguishable from the SS strain (Figure 2B).

Further analysis including all rats revealed a significant correlation between LVIF (\( P = 0.0006 \), \( r = 0.4 \)) and LVPF (\( P = 0.00019 \), \( r = 0.44 \)) and total plasma cholesterol levels (Figure 3A and B, respectively). In contrast, both LV fibrosis parameters showed no appreciable correlation with SBP (\( P = 0.414 \), \( r = 0.099 \) and \( P = 0.025 \), \( r = 0.266 \), respectively) or with relative LV weight (\( P = 0.114 \), \( r = 0.189 \) and \( P = 0.316 \), \( r = 0.121 \), respectively). We further analysed the association between cholesterol and LV fibrosis in a multivariate regression analysis accounting for SBP and LV weight as potentially important covariates. This analysis revealed that the correlations between cholesterol plasma concentration and LVPF and LVIF remained highly significant, respectively. In the multivariate analysis SBP exhibited only a minor effect on perivascular (\( P = 0.037 \)) and LV weight on interstitial (\( P = 0.044 \)) fibrosis as effect modifiers. In the adjusted analysis cholesterol plasma concentrations accounted for 25% (\( P = 0.0001 \)) and 20% (\( P = 0.0006 \)) of the variability of LVPF and LVIF, respectively. Thus, both SBP and LV mass could be excluded as confounders affecting the correlation between cholesterol and LV fibrosis.

Qualitative histology analysis by immunostaining of LV sections obtained from high-salt fed male SS and consomic SS-19SHR demonstrated a stronger staining pattern in SS for collagen I in both the interstitial and perivascular compartment of the LV in agreement with the data obtained by Sirius red staining (Figure 4). This qualitative strain difference in collagen I staining was more pronounced in the perivascular tissue surrounding coronary arteries as shown in Figure 5. A stronger qualitative expression of interstitial fibronectin was found throughout the LV tissue of SS compared with consomic rats (Figure 5). In addition, macrophage infiltration as estimated by immunohistological detection of ED-1 positive cells showed differences between both strains (Figure 5). ED-1 positive cells were evenly distributed in the interstitial compartment of LV sections, while only negligible numbers of these cells were detected in the perivascular areas. ED-1 positive cells were evenly distributed throughout LV sections of the heart and salt-fed male SS exhibited a significantly higher number of ED-1 positive cells compared with consomic SS-19SHR (99 \( \pm \) 21 vs. 22 \( \pm \) 4 cells/field of vision, \( P < 0.001 \)).

Further analysis demonstrated a significant correlation between ED-1 positive cells and total cholesterol concentrations (\( r = 0.731 \), \( P = 0.039 \)). LVIF (\( r = 0.75 \), \( P = 0.031 \)) and although not significantly LVPF (\( r = 0.71 \), \( P = 0.07 \)) demonstrated also a positive correlation with the number of ED-1 positive cells.

### 4. Discussion

In addition to our previous analysis in male rats we show here that transfer of RNO19 into the SS background also induces blood pressure lowering effect in female consomic SS-19SHR rats under both a low- and a high-salt diet. Interestingly both the SS and SS-19SHR strain showed a strong sexual dimorphism regarding blood pressure. This is in agreement with Gong et al. who showed a sexual dimorphism for the Dahl strain with an age of onset at 10 weeks. In agreement with the blood pressure findings introgression of RNO19 lowered LV weight in both male and female consomic rats. SBP and relative LV weight showed a significant

| Table 1 Body weights (g) under low-salt and high-salt diet in male and female rats |
|---------------------------------|-----------------|-----------------|
| Low-salt diet                   | High-salt diet  |
| Males                           | Females         | Males           | Females         |
| SHR                             | 304.5 ± 3.4*    | 185.3 ± 1.9*    | 304.0 ± 4.9*    | 185.7 ± 2.4*    |
| SS-19SHR                        | 354.7 ± 8.0     | 242.0 ± 7.2     | 355.0 ± 9.4     | 236.6 ± 2.4     |
| SS                              | 371.0 ± 4.8     | 239.6 ± 10.3    | 342.3 ± 6.6     | 225.9 ± 2.3     |

* \( P < 0.01 \) vs. other strains, respectively.
Figure 1  Systolic blood pressure (SBP), relative left ventricular weight (LVW) and left ventricular perivascular fibrosis (LVPF) are presented in (A)-(C), respectively. White bars represent low-salt diet and black bars represent high-salt diet. *P < 0.05 high-salt vs. low-salt diet compared with same strain; #P < 0.05 vs. SS-19SHR, compared with same dietary group; § values previously reported.19
correlation ($r = 0.4$, $P < 0.001$). On the other hand, this finding indicates in agreement with studies in humans,\(^2\) that the variance of LV mass is only in part attributable to variations in SBP, while a significant portion is influenced by genetic factors such as the QTL on RNO19.

The current study demonstrates also in agreement with previous reports that the Dahl SS strain exhibits about two- to three-fold higher cholesterol levels compared with SHR rats.\(^{17,25}\) Introgression of chromosome 19 from SHR had beneficial effects on cholesterol plasma concentrations in both male and female consomic rats. RNO19 lowered the cholesterol levels in both sexes to an intermediate phenotype between SHR and SS. Although SHR showed no sexual dimorphism, female SS rats had significantly lower cholesterol levels compared with male rats. Previously, a genetic linkage study in recombinant inbred strains derived from SHR and normotensive Brown Norway rats\(^{26}\) indicated already that a QTL influencing plasma cholesterol fractions, i.e., HDL2 concentrations, maps to a region on RNO19, which carries also blood pressure regulating QTL.\(^{19,27–29}\) In this regard, our current study supports the co-localization of blood pressure and plasma cholesterol regulating QTL on RNO19 although the underlying genetic mechanisms have not been elucidated yet.

The elevated triglyceride levels of male SS rats are comparable with previous studies.\(^{25}\) Interestingly females of all three strains showed low similar triglyceride levels that were unaffected by salt diet. Unlike total cholesterol levels, replacement of RNO19 had no significant effect on the elevated triglycerides levels observed in male SS. Thus both SS and the SS-19\(^{19}\)SHR rats exhibited a profound sexual dimorphism with male triglyceride levels being two- to three-fold higher compared with females, respectively.

Our previous genome wide search for loci contributing to the development of cardiac fibrosis by linkage analysis did not reveal any significant QTL affecting the amount of

Figure 2 Data for cholesterol and triglyceride concentrations in plasma are presented in (A) and (B). White bars represent low-salt diet and black bars represent high-salt diet. \(* P < 0.05\) vs. SHR (spontaneously hypertensive rats); \# $P < 0.05\) vs. SHR and SS (Dahl salt-sensitive rats).
either LV PF or LV IF. Our analysis indicated that the quantity of LV fibrosis was not directly linked to genetic factors or blood pressure variation in the overall hypertensive background in response to high salt diet. We therefore assumed that secondary mechanisms such as either systemic or local activation of profibrotic mechanisms such as angiotensin II or other factors that are not primarily genetically determined are responsible for the quantitative modulation of LV fibrosis in salt-sensitive hypertension.

Particularly, the relevance of the renin–angiotensin system for fibrosis development in SS rats has been previously demonstrated.34–36 A recent report showed that the amount of interstitial fibrosis is increased in SS rats in both the LV and right ventricle (RV) in response to a high-salt diet compared with regular salt intake.36 In the latter study treatment with ACE (angiotensin-converting enzyme) inhibitors prevented 50% of the increase in blood pressure in response to high-salt diet, while the increase in fibrosis was fully prevented in both ventricles. The same investigators could show in another study, that AT1-receptor densities increased in the aorta and decreased in the kidney of SS rats in response to high-salt diet, while receptor densities in the RV and LV of the heart remained unchanged.35 Nevertheless, treatment with two different AT1-receptor blockers prevented high-salt-induced interstitial and perivascular fibrosis in the LV and RV ventricle as well as fibrosis in the aorta and kidney. A more previous study demonstrated that AT1-receptor blockade inhibits LV fibrosis already in a

Figure 3  Correlation analysis of left ventricular interstitial fibrosis (LVIF) in (A) \( P = 0.0006, r = 0.40 \) or left ventricular perivascular fibrosis (LVPF) in (B) \( P = 0.00019, r = 0.44 \) with plasma cholesterol levels performed in all rats including both genders and all three strains.
dose that does not significantly lower SBP in salt-loaded SS rats. Taken together, these data support an important role of the renin–angiotensin system for the development of cardiac fibrosis in this model. In addition, treatment with statins has been also shown in several studies to prevent target organ damage in salt-loaded SS rats due to pleitropic effects among which antioxidative mechanisms play an important role. More recently we could show, however, that the introgression of RNO19 led to a significant reduction in both LVIF and LPVF in male consomic rats, while SBP was lowered at the same time.

Our current results shed new light on the overall important mechanisms involved in the development of LV fibrosis in this model of salt-sensitive hypertension. Most importantly, multivariate correlation analysis in both male and female rats of all strains revealed that both SBP and LV weight parameters exhibited only a negligible effect on the amount of LV fibrosis. In contrast, the highly significant association between LV fibrosis parameters and plasma cholesterol concentrations was detected in univariate and multivariate analysis after adjusting for SBP and LV mass phenotypes. Furthermore the positive correlation between cholesterol concentrations, numbers of ED-1 positive cells and levels of interstitial and perivascular LV fibrosis supports the functional link between cholesterol, LV inflammation, and fibrosis. It has been shown that a high-cholesterol diet exhibits deleterious effects on LV function and fibrosis in rats with myocardial ischaemia due to coronary artery stenosis, while cholesterol diet in control rats induces no significant effect. In this model, although plasma concentrations were not elevated, the high cholesterol diet has been linked to LV infiltration by ED-1 positive inflammatory cells and subsequent development of fibrosis. These findings are in keeping with our observation obtained in the severely hypertensive Dahl SS rats with increased cardiac fibrosis after feeding a high salt diet. Accordingly we observed a significant increase in ED-1 positive cells in the LV of male SS rats in response to high salt diet as compared with male SS-19SHR consomic rats in which LV fibrosis, ED-1 positive cell infiltration, collagen I and fibronectin expression were reduced.

![Figure 4](image1.png)

Figure 4  Representative left ventricle tissue section with Sirius-red staining of male SS (Dahl salt-sensitive rats) and consomic SS-19SHR after a high-salt diet. SS rats exhibit increased fibrosis both in the interstitial and perivascular compartment.

![Figure 5](image2.png)

Figure 5  Representative left ventricle tissue section with immunohistological staining against collagen I (A), fibronectin (B) and ED-1 (C) staining of male SS (salt-sensitive) and SS-19SHR after high-salt diet. (C) ED-1 positive cells: red; DAPI counterstaining: blue.
The increased number of ED-1 positive cells in SS rats was only found in the LV interstitial tissue but not in the perivascular compartment of coronary arteries in which these cells were only very infrequently found in all strains. This finding supports a role of interstitial macrophage infiltration for the progression of interstitial reactive fibrosis in this model of pressure overload hypertrophy. \(^9\) Taken together our results suggest a link between the development of LV inflammation and fibrosis that is modulated by plasma cholesterol concentrations. As a limitation of our study we have not elucidated the potential molecular mechanism involved in this processes yet. However, in agreement with previous studies in SS rats the development of endothelial dysfunction \(^40\) and oxidative stress \(^41\) may provide an important pathophysiological basis for the development of LV infiltration, and LVFP and LVIF in salt-sensitive hypertension. In this regard we correlated the overall plasma concentration of non-HDL lipoproteins with LV fibrosis parameters and found an even somewhat stronger correlation as compared with total cholesterol concentrations of interstitial \((r = 0.464, P = 0.001)\) and perivascular \((r = 0.528, P = 0.0002)\) LV fibrosis. This supports the potential link between cardiac fibrosis and atherogenic non-HDL lipoproteins that may affect oxidative stress and endothelial dysfunction in this model. Based on the current findings future studies may now focus on the functional role of plasma cholesterol in the modulation of LV fibrosis. \(^40\) In addition, our analysis of the SS-19\(^{SHR}\) consomic strain has established that a gene or several genes on RNO19 have a significant impact on the development of LV fibrosis in this model. Further experimental dissection of the underlying genetic factors will subsequently allow targeted molecular analysis to unravel the mechanisms of LV injury in this important disease phenotype of salt-sensitive hypertension. \(^7\)

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