

Tolerance to Acute Ischemia in Adult Male and Female Spontaneously Hypertensive Rats

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Summary

Clinical and experimental studies have repeatedly indicated that overloaded hearts have a higher vulnerability to ischemia/reperfusion injury. The aim of the present study was to answer the question whether the degree of tolerance to oxygen deprivation in hearts of spontaneously hypertensive rats (SHR) may be sex-dependent. For this purpose, adult SHR and their normotensive control Wistar Kyoto (WKY) rats were used. The isolated hearts were perfused according to Langendorff at constant pressure (proportionally adjusted to the blood pressure *in vivo*). Recovery of contractile parameters (left ventricular systolic, diastolic and developed pressure as well as the peak rate of developed pressure) was measured during reperfusion after 20 min of global no-flow ischemia in 5 min intervals. Mean arterial blood pressure was measured by direct puncture of carotid artery under light ether anesthesia in a separate group of animals. The degree of hypertension was comparable in both sexes of SHR. The recovery of contractile functions in SHR males and females was significantly lower than in WKY rats during the whole investigated period. There was no sex difference in the recovery of WKY animals; on the other hand, the recovery was significantly better in SHR females than in SHR males. It may be concluded that the hearts of female SHR are more resistant to ischemia/reperfusion injury as compared with male SHR. This fact could have important clinical implications for the treatment of cardiovascular disease in women.

Key words

Cardiac tolerance • Ischemia injury • Reperfusion injury • Spontaneously hypertensive rats • Gender differences

Introduction

Cardiac hypertrophy is an adaptive response that compensates for an increased workload by normalizing wall stress and preserving cardiac contractile function. In

advanced stages, however, when the high workload is maintained, hypertrophy progresses to ventricular dilatation, contractile dysfunction and finally to heart failure (Katz 2001, Friehs and del Nido 2003). It has been recognized for more than 30 years that the hypertrophied

heart shows a decreased tolerance to ischemia/reperfusion injury, with the first description of so-called “stone heart”. Data from the Framingham Heart Study identify left ventricular hypertrophy as the single most important contributor to cardiovascular morbidity and mortality. This is particularly important in cardiac surgery, as left ventricular hypertrophy is frequently associated with postischemic contractile dysfunction. It has been found that cardiac tolerance to ischemic arrest during open-heart surgery depends on the degree of hypertrophy (Schaper *et al.* 1976) and duration of ischemia (Beyersdorf *et al.* 1980).

To analyze the tolerance of the hypertrophic heart to ischemia/reperfusion injury under experimental conditions, models such as isoproterenol treatment (Minor *et al.* 1994), renal hypertension (Harmsen *et al.* 1994), aortocaval shunt (Harmsen *et al.* 1994), thyroxine treatment (Yu *et al.* 1997), saline drinking (Saupe *et al.* 2000, Shi *et al.* 2005), aortic constriction (Peyton *et al.* 1982, Gaasch *et al.* 1990, Snoeckx *et al.* 1990, Zhang and Su 1995, Yamamoto *et al.* 2001, Friehs and del Nido 2003), as well as spontaneous hypertension (Belichard *et al.* 1988, Snoeckx *et al.* 1989, 1993, Mill *et al.* 1998, Itter *et al.* 2004) have been used. In spite of the fact that the above mentioned experiments used different animal species (rats, rabbits, dogs), different end-points of injury (e.g. arrhythmias, contractile dysfunction, infarct size, mortality rate), and different stage of hypertrophy, they have confirmed the clinical observations that the hypertrophic myocardium is more susceptible to ischemic damage than the normal one. On the other hand, Saupe *et al.* (2000) have surprisingly observed in Dahl rats that during the natural history of left ventricular hypertrophy secondary to hypertension, a period occurs during which the response to ischemia is improved, probably by minimizing the size of the region of severe acidosis. Furthermore, Mozaffari and Schaffer (2003) found greater impairment of cardiac contractile function but reduced infarct size in rats with renal hypertension. They speculated that these results might be due to different factors regulating contractile function and affecting infarct size. Unfortunately, all mentioned experimental studies have used exclusively male animals; possible sex-dependent changes have not been analyzed. However, sex hormones may play an important role in the development of ischemic heart disease. The results of numerous studies indicate that coronary heart disease morbidity and mortality occur about ten years later in women than in men (Vaccarino *et al.* 1995). Accordingly, experimental

studies have repeatedly indicated significant sex differences in cardiac tolerance to ischemia; non-hypertrophied hearts of adult males have a higher vulnerability to ischemia/reperfusion injury than the normal hearts of female rats (Imahashi *et al.* 2004, Shinohara *et al.* 2004, Netuka *et al.* 2006).

The aim of the present study was, therefore, to answer the question whether the degree of cardiac tolerance to oxygen deprivation may be sex-dependent also in the hypertrophied heart since significant sex differences have been described in the left ventricular adaptation to pressure overload (Jain *et al.* 2002). For this purpose, adult male and female spontaneously hypertensive rats (SHR) and their appropriate controls, Wistar-Kyoto rats (WKY), have been used. Prominent myocardial hypertrophy is generally present in the SHR and is believed to be a consequence of sustained systemic hypertension, although it cannot be excluded that the development of cardiac hypertrophy in this rat strain is also caused by genetic factors. The blood pressure of SHR was usually found to be significantly higher compared with WKY already in newborns, characteristic acceleration mainly occurs between the 3rd and 10th week of age, when their blood pressure rapidly increases by 30 % above that of WKY (Zicha and Kuneš 1999).

Methods

Adult (3-month-old) male and female SHR and their age-matched normotensive controls WKY were used. Rats were kept under standard conditions and had free access to water and a standard laboratory diet. The study was conducted in accordance with 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).

Adult male and female SHR and their WKY controls were divided into two groups: the first group was used for blood pressure measurement, the second group for the isolated heart procedure. Mean arterial blood pressure was measured by a direct puncture of carotid artery under light ether anesthesia; after cessation, the animals were killed by decapitation. Data were used for setting of constant perfusion pressures in the *in vitro* experiments.

For the isolated heart procedure the rats were anesthetized with sodium pentobarbital (60 mg/kg i.p., Sanofi, France). Hearts were rapidly excised and perfused according to Langendorff under constant pressure

Table 1. Mean arterial blood pressure in the WKY and SHR male and female rats.

	Male WKY	Male SHR	Female WKY	Female SHR
<i>n</i>	6	6	6	6
MAP (mm Hg)	108 ± 4.7	160 ± 5.9*	114 ± 3.2	151 ± 3.4*

n - number of animals; MAP - mean arterial blood pressure. Values are means ± S.E.M.; **P*<0.05 SHR vs. WKY.

Table 2. Weight parameters in the WKY and SHR male and female rats groups.

	Male WKY	Male SHR	Female WKY	Female SHR
<i>n</i>	8	9	8	10
BW (g)	319 ± 10	312 ± 8	209 ± 3 [×]	189 ± 2 ^{**×}
HW (g)	0.93 ± 0.04	1.22 ± 0.03*	0.76 ± 0.06 [×]	0.79 ± 0.02 [×]
HW/BW	2.9 ± 0.1	3.9 ± 0.1*	3.6 ± 0.3 [×]	4.2 ± 0.1*

BW - body weight; HW - heart weight; HW/BW, relative weight of the heart; *n* - number of animals. Values are means ± S.E.M.; **P*<0.05 SHR vs. WKY, [×]*P*<0.05 female vs. male.

(perfusion pressure was proportionally adjusted to the blood pressure *in vivo*; for WKY male and female hearts 108 cm H₂O and 114 cm H₂O, respectively, and for SHR male and female hearts 160 cm H₂O and 151 cm H₂O, respectively, Table. 1) with non-recirculating Krebs-Henseleit solutions containing (mmol/l): NaCl 118.0, KCl 4.7, CaCl₂ 1.25, MgSO₄ 1.2, NaHCO₃ 25.0, KH₂PO₄ 1.2 and glucose 7.0. The medium was saturated with 95 % O₂ and 5 % CO₂ (pH 7.4) and maintained at 37 °C. The left ventricle was vented at the apex and stimulated at 300 beats/min with platinum electrodes placed on the base of the right ventricle. The contractile function was measured with a non-elastic balloon inserted into the left ventricle via incision in the left atrium and connected to the pressure transducer (Hewlett-Packard 1280, USA). The balloon was gradually filled with water to give diastolic pressure of 7 to 10 mm Hg. The amplified pressure signal was monitored and immediately analyzed on a computer using our software. The left ventricular systolic (LVSP), diastolic (LVDP), developed pressure (LVDevP), and the peak rate of developed pressure [(+dP/dt)_{max}] were expressed as the means of ten cardiac cycles during a 2-s sampling period at selected time intervals. Coronary flow was measured by timed collection of coronary effluent and subsequently normalized to heart weight.

After 25 min, during which the contractile parameters were allowed to stabilize, hearts were subjected to 20-min global no-flow ischemia followed by

40 min of reperfusion. Global ischemia was induced by clamping the perfusate inflow line while the hearts were placed in a bath of Krebs-Henseleit solution saturated with 95 % N₂ and 5 % CO₂ (pH 7.4) and maintained at 37 °C. After restoration of flow, the functional parameters were recorded at 5-min intervals and their recovery was expressed as percentage of initial preischemic values. The hearts were weighed at the end of experiments.

Statistics

The results are expressed as means ± S.E.M. Differences in the recovery of (+dP/dt)_{max} and between the groups were compared by the Mann-Whitney U test. One-way ANOVA or ANOVA for repeated measures and subsequent Student-Newman-Keuls test were used for comparison of differences in parametric variables within the group. Differences were assumed as statistically significant when *P*<0.05.

Results

Weight parameters and blood pressure

The mean arterial blood pressure (MAP) of male and female SHR was significantly higher than that of WKY rats; there were no significant differences of MAP between male and female rats in either groups (Table 1).

The body weight (BW) and absolute heart

Table 3. Baseline contractile parameters and coronary flow of the isolated perfused hearts of SHR and WKY male and female rats.

	Male WKY	Male SHR	Female WKY	Female SHR
<i>n</i>	8	9	8	10
<i>LVSP</i> (mm Hg)	129.7 ± 2.0	163.5 ± 4.3*	127.9 ± 3.3	153.2 ± 4.0*
<i>LVD_{DevP}</i> (mm Hg)	121.6 ± 2.0	154.7 ± 4.5*	119.2 ± 3.3	144.4 ± 4.1*
<i>(+dP/dt)_{max}</i> (mm Hg/s)	3946 ± 133	5144 ± 252*	3804 ± 155	4544 ± 157*
<i>CF</i> (ml/min/g)	14.0 ± 1.0	15.8 ± 0.7	14.9 ± 0.7	15.9 ± 0.5

LVSP - left ventricular systolic pressure; LVD_{DevP} - developed pressure; *(+dP/dt)_{max}*, peak rate of pressure development; CF, coronary flow; *n* - number of animals. Values are means ± S.E.M. **P*<0.05 SHR vs. WKY.

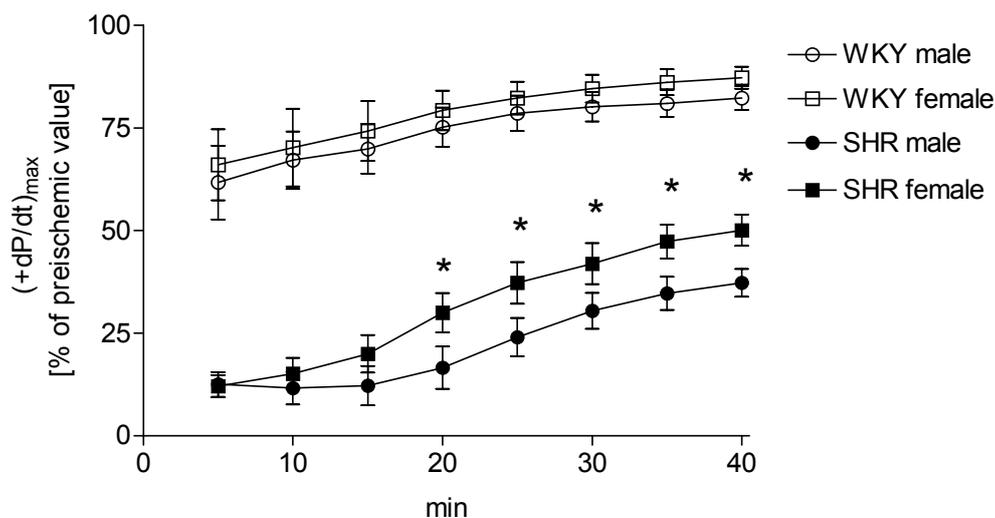


Fig. 1. Time course of recovery of peak rate of pressure development $[(+dP/dt)_{max}]$ during reperfusion after 20 min of global ischemia, expressed as percentage of preischemic values, in the SHR and WKY male and female animals. Values are means ± S.E.M. **P*<0.05 SHR female vs. SHR male.

weight (HW) of WKY and SHR male rats was significantly higher as compared with age-matched female animals (Table 2). HW and HW/BW ratios were significantly increased in the male SHR group as compared with the corresponding male WKY rats; BW was comparable in both groups. BW of SHR female rats was markedly reduced in comparison with the corresponding WKY group, the difference in absolute HW did not reach statistical significance, but HW/BW ratio of the SHR females was significantly higher in comparison with WKY rats and comparable with SHR males.

Postischemic contractile dysfunction

Baseline preischemic values of contractile parameters and coronary flow did not differ either between WKY male and female group, or between SHR male and female animals (Table 3). Contractile parameters of the SHR male and female hearts were

significantly increased as compared with corresponding WKY controls.

The time course of the postischemic recovery of contractile function is shown in Figure 1. Recovery of the peak rate of pressure development $(+dP/dt)_{max}$ in SHR male and female rats was significantly lower during the whole investigated period when compared to WKY controls. There was no sex difference in the time course of recovery in WKY animals; on the other hand, the recovery in female SHR was significantly better as compared to male SHR.

Maximum recovery of $(+dP/dt)_{max}$ reached 82.8 ± 3.1 % of the preischemic value in the WKY male group and it did not differ from that in female WKY hearts (88.1 ± 2.8 %) (Fig. 2). Hearts of the SHR of either sex were more sensitive to acute ischemia as compared with WKY: recovery of contractile function was markedly decreased in SHR of both sexes (37.3 ± 3.4 % in the male group; 50.2 ± 3.8 % in the female group).

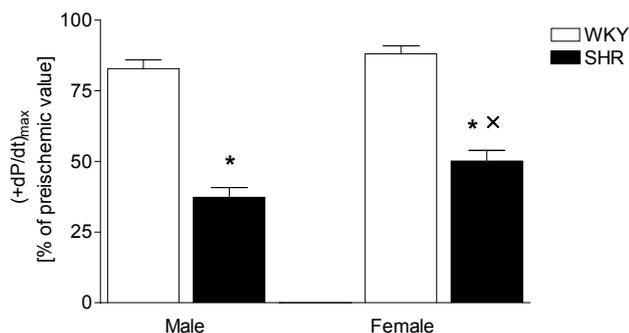


Fig. 2. Maximum recovery of peak rate of pressure development $[(+dP/dt)_{\max}]$ during reperfusion after 20 min of global ischemia, expressed as percentage of preischemic values, in the SHR and WKY male and female animals. Values are means \pm S.E.M. * $P < 0.05$ SHR vs. WKY, $\times P < 0.05$ female vs. male.

However, hypertrophied hearts of adult SHR females were more tolerant to acute ischemia than hypertrophied hearts of adult SHR males.

Discussion

Our results demonstrate that cardiac tolerance to ischemia-reperfusion injury, as judged from the degree of postischemic contractile dysfunction, was significantly lower in SHR male and female hearts as compared with corresponding WKY controls. Moreover, cardiac tolerance in SHR was sex-dependent: recovery of female SHR hearts was significantly better than in SHR males despite the fact that the degree of hypertension was comparable.

The fact that the hypertrophied heart of SHR is significantly less tolerant to ischemia than that of normotensive controls is in good agreement with the previously published data (Belichard *et al.* 1988, Snoeckx *et al.* 1989, 1993, Itter *et al.* 2004). The mechanism responsible for the decreased tolerance of hypertrophied hearts to ischemia is likely to be a complex array of interactive events. During myocardial ischemia, hypertrophied hearts exhibit an accelerated loss of high-energy nucleotides, greater accumulation of tissue lactate and hydrogen ions, earlier onset of ischemic contracture, accelerated calcium overload during early reperfusion (Friehs and del Nido 2003), impaired sodium handling (Golden *et al.* 1994) and decreased NO availability. Moreover, during development of myocardial hypertrophy, myocytes enlarge and there may not be concomitant microvascular growth: when the area of myocardial tissue supplied by one capillary increases, delivery of oxygen as well as other nutrients is potentially

impaired (Turek and Rakušan 1981, Batra and Rakušan 1992, Ashruf *et al.* 1999). The diminished microvascular supply in the hypertrophied heart was according to Friehs and del Nido (2003) temporally associated with the decline in contractility and with increased vulnerability to ischemia-reperfusion injury. These results indicate that the impaired glucose uptake and, potentially, impairment of all substrates available to the hypertrophied myocardium is due, at least in part, to decreased microvascular density.

To the best of our knowledge, this is the first study demonstrating that the hearts of adult female SHR are more tolerant to the ischemia-reperfusion injury as compared with the male myocardium, despite the fact that the degree of hypertension was comparable. On the other hand, in WKY controls the cardiac vulnerability to ischemia/reperfusion was comparable in both sexes, probably because of high recovery of contractility after 40 min of ischemia. We cannot exclude that more severe degree of ischemic injury might be more discriminative.

For the explanation of the gender differences in the cardiac tolerance to ischemia-reperfusion injury, a different response to hemodynamic overload has to be taken into consideration. Clinical studies have documented gender differences in the pattern of adaptive left ventricular hypertrophy in response to increased afterload, such as occurs in aortic stenosis and hypertension. Cardiac performance is more frequently preserved in female compared to male patients with a similar degree of aortic stenosis (Buttrick and Scheuer 1992). Douglas *et al.* (1998) and Weinberg *et al.* (1999) have observed a similar degree of left ventricular hypertrophy in the rat model of ascending aortic stenosis but earlier transition to failure manifested as left ventricular dilation and depressed systolic performance in male compared to female rats; analogous gender differences were also described in SHR (Pfeffer *et al.* 1982) and in Dahl salt-sensitive rats (Jain *et al.* 2002). Tamura *et al.* (1999) have demonstrated that the cardiac myocyte volume is significantly larger in male than in female SHR, suggesting a reduced adaptive hypertrophic reserve in males, which is likely to contribute to the higher morbidity and mortality of males with chronic heart failure. In this connection the question arises whether these gender-related differences in cardiac adaptation to a pressure overload are solely related to differences in geometric remodeling or may be, at least in part, related to differences in cardiac gene expression that precede the development of heart failure. Pressure-

overload left ventricular hypertrophy in multiple animal models and human heart failure is associated with the up-regulation of cardiac genes and isoforms that are normally expressed in fetal life and down-regulated during postnatal development (Matsui *et al.* 1995). Weinberg *et al.* (1999) found that messenger ribonucleic acid (mRNA) levels of both β -myosin heavy chain and atrial natriuretic factor were higher in male compared with female hearts in animals with aortic stenosis, despite a similar magnitude of left ventricular hypertrophy as well as the systolic load. Furthermore, mRNA levels of SERCA-2 were markedly depressed in male but not in female hypertrophied hearts. All these observations may contribute to the explanation of the depressed contractile reserve and increased ischemic vulnerability of the male overloaded heart.

Gender differences have frequently been attributed to female hormones; however, the underlying mechanisms responsible for the cardioprotective effect are still poorly understood. Brower *et al.* (2003) found that the extent of myocardial remodeling and the decrease in left ventricular function in ovariectomized females was comparable to changes reported for males. Lee *et al.* (2000) have found that acute administration of 17 β -estradiol resulted in a significant, dose-dependent

limitation of infarct size in both males and females. The infarct size-limiting effect of estrogen was abolished by 5-hydroxydecanoate, suggesting that the cardioprotective effect of this hormone may result from activation of myocardial mitochondrial K_{ATP} channels. Molecular mechanisms probably also involve estrogen-induced production of NO (Node *et al.* 1997), an inhibitory effect on Na^+/Ca^{2+} exchanger during myocardial infarction (Sugishita *et al.* 2001) and decreased Na^+ influx by an NO-dependent mechanism (Imahashi *et al.* 2004).

In conclusion, we have shown that hearts of female SHR are more tolerant to ischemia/reperfusion injury as compared with males, despite a comparable degree of hypertension. The results support the hypothesis that the mechanisms of cardiac adaptation to a pressure overload differ in male and female rats, suggesting an important role of the hormonal milieu in this process. This fact would have important clinical implications for the treatment of cardiovascular disease in women.

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