# Genetically Determined Differences in the Resistance to Myocardial Infarction in Wistar and August Rats

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In intact August rats, the cardiac contractile function at rest was by 76% higher than in Wistar rats, while their hearts, both intact and after acute myocardial infarction, were more resistant to isometric load than the hearts of Wistar rats. Postinfarction mortality in August rats was 18% *vs.* 70% in Wistar rats. Adrenoreactivity of the myocardium in August rats was decreased compared to that in Wistar rats. These peculiarities can determine high resistance of August rats to myocardial infarction.

**Key Words:** *myocardial infarction; Wistar and August rats; adrenoreactivity; cardiac contractile function*

Myocardial ischemia is always accompanied by emotional and pain stress aggravating the damage to both ischemic and non-ischemic areas of the myocardium [4,10,11]. Heart resistance to ischemic damage is determined not only by myocardial resistance to ischemia, but also by its resistance to stress-induced damages. It is known that rats of different strains differ in their sensitivity to stress. For instance, experiments on isolated spontaneously contracting atria showed that the myocardium of August rats is more resistant to stress than that of Wistar rats [1]. Moreover, August rats are more resistant to stress-induced (*i.e.* adrenergic [9]) stomach ulcers [6], but less resistant to stress-related decrease in blood pressure [8] and heat shock [3]. The more pronounced decrease in blood pressure during stress in August rats is associated with higher degree of endothelium-dependent vascular relaxation and more intensive production of nitric oxide than in Wistar rats, and with low sensitivity to vasoconstrictor stimuli (in particular, adrenoreacti-vity) [3].

These genetically determined peculiarities suggest that August rats can be more resistant to acute heart ischemia than Wistar rats.

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The aim of the present study was to compare the resistance of Wistar and August rats to acute myocardial infarction (MI).

## MATERIALS AND METHODS

Experiments were carried out on male Wistar (350±14 g) and August (235±6 g) rats. Myocardial infarction was modeled by ligation of the descending branch of the left coronary artery according to H. Selye. Sham-operated rats (without ligation) served as the control. Acute experiments were conducted on open-chest jet-ventilated rats anesthetized with nembutal (50 mg/kg) 2 days after MI. The contractile function of the heart was assessed by changes in the left ventricular pressure measured using a Mingograf-34 device (Siemens-Elema) at rest, after epinephrine administration (5 mg/kg, intravenously), and during maximum isometric load (60-sec aortic occlusion). The following parameters were evaluated: heart rate (HR) before and after chest opening; systolic, diastolic, and developed pressure; the rates of pressure rise and decrease reflecting the rates of myocardium contraction and relaxation; Katz index (a product of HR by developed pressure); the intensity of myocardial function (IMF=Katz index/left ventricle weight); the maximum effort of the left ventricular myocardium (ME=developed pressure/left

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ventricle weight). The study included 6 groups of animals: groups 1 and 2 consisted of intact Wistar and August rats, respectively, groups 3 and 4 (controls) comprised sham-operated animals of the two strains, and groups 5 and 6 included Wistar and August rats with MI.

## RESULTS

Since the parameters of heart function in intact and sham-operated Wistar and August rats at rest or after load did not differ significantly, the data obtained on sham-operated rats were taken as the control. The control open-chest rats of both strains showed similar HR at rest (Table 1). However, intact (not operated) August rats demonstrated higher HR than intact Wistar rats (382±10 *vs.* 349±17 bpm, $p<0.05$, Mann—Whitney *U* test). The developed pressure, Katz index, and myocardium relaxation rate in August rats were higher than in Wistar rats by 31% ($p<0.05$), 34% ($p<0.05$), and 36% ($p<0.1$), respectively. The most pronounced difference between the groups was revealed when calculating IMF and ME: in August rats, these values were higher than in Wistar rats by 76% ($p<0.001$) and 50% ($p<0.01$), respectively. It should be noted that the weights of the heart and left ventricle in August rats are significantly lower than in Wistar rats (by 17 and 21%, $p<0.05$ and $p<0.001$, respectively), while their body weights differ by 34%. These data suggest that the efficiency of the heart contractile function in August rats is higher than in Wistar rats.

In rats of both strains, MI considerably impaired cardiac function at rest (Table 1), but in August rats this impairment (compared to control rats of the same strain) was more pronounced than in Wistar rats. In August and Wistar rats with MI, the developed pressure decreased by 34% ($p<0.05$) and 21% ($p<0.001$) from the control, Katz index by 29% ($p<0.05$) and 18% ($p<0.1$), and ME by 28% ($p<0.001$) and 17% ($p<0.01$), respectively. However, the absolute values of the IMF and ME in August rats surpassed the corresponding values in Wistar rats by 29% ($p<0.05$) and 28% ($p<0.001$), respectively. These findings suggest that the cardiac function in August rats after MI remains more efficient than in Wistar rats.

Dramatic difference between August and Wistar rats at rest and after MI was revealed in the test with maximum isometric load. The control August rats responded to the load by higher increase in the cardiac function than the control Wistar rats: 60 sec after occlusion the absolute values of developed pressure and Katz index in August rats surpassed the corresponding parameters in Wistar rats by 20% ($p<0.05$) and 51% ($p<0.01$), respectively, and IMF and ME were higher by 84% ($p<0.001$), and 52% ($p<0.001$), respectively. The functional superiority of the control August rats was associated with less pronounced bradycardia, which always accompanies this kind of load [5]. The difference in HR between the groups after 60-sec aortal occlusion was 78 bpm (24%, $p<0.01$). High HR in August rats was preserved due to higher rates of left ventricle contraction and relaxation exceeding the corresponding parameters in Wistar rats by 95% ($p<0.001$) and 51% ($p<0.001$), respectively. The load increased the diastolic pressure to the same extent in both strains.

After MI, the hearts of August rats after occlusion developed higher effort than hearts of Wistar rats. The index of Katz, IMF, and ME in August rats surpassed the corresponding values in Wistar rats by 22-24% ($p<0.05$), 46-60% ($p<0,001$), and 30-45% ($p<0.001$), respectively. This difference was determined not only by more efficient myocardial contractions in August rats, but also by high resistance of their cardiac rhythm to the load: in Wistar rats with MI dramatic bradycardia with HR drop by 83 bpm was observed after 30-sec occlusion, whereas in August rats the decrease in HR was less pronounced (by 38 bpm). At the same time, the rates of myocardial contraction in August rats after 5- and 60-sec occlusion exceeded the corresponding values in Wistar rats by 39% ($p<0.01$) and 46% ($p<0.001$), respectively, and the corresponding rates of myocardial relaxation were higher by 24% ($p<0.05$) and 36% ($p<0.05$), respectively. Thus, in August rats the hearts are more resistant to isometric load than in Wistar rats, which attests to less pronounced disturbances in non-ischemic myocardium.

Another interesting feature of August rats was their relatively low postischemic mortality compared to Wistar rats: 18% within 10-15 min postinfarction and 70% after 3-4 h.

What mechanisms underlay these difference between August and Wistar rats in the resistance to MI? Death within the first hours postinfarction is known to be associated with heart fibrillations caused by stress reaction and catecholamine surge [10]. August rats exhibit less intense stress-response than Wistar rats [7], which can account for their lower postinfarction mortality. On the other hand, their low mortality can be explained by low myocardium adrenoreactivity.

Our experiments showed that the positive inotropic effect of epinephrine in control August rats was twice as low as that in control Wistar rats (Fig. 1, *a*): for the first 15-20 sec after epinephrine administration the developed pressure increased by 76±21 and 14.1±9% ($p<0.05$), respectively, and after 60 sec — by 37±10 and 89±12% ($p<0.01$), respectively. In August rats with MI, the increase in the left ventricular pressure 2 min after epinephrine administration 2-3-surpassed the corresponding values in Wistar rats with

**TABLE 1.** Effect of Acute Myocardial Infarction on Cardiac Contractile Function in Wistar and August Rats at Rest and during Maximum Isometric Load (*M*±*m*, *n*=8-12)

| Indices | | Before aortal occlusion | After aortal occlusion, sec | | |
|---|---|---|---|---|---|
| | | | 5 | 30 | 60 |
| HR, bpm | control | 393±11 | 394±8 | 347±13 | 321±19 |
| | | 416±14 | 405±10 | 399±14*** | 399±15*** |
| | MI | 400±15 | 390±12 | 317±24 | 380±22 |
| | | 417±11 | 409±16 | 379±8$^{+++}$ | 411±5 |
| Developed pressure, mm Hg | control | 76±2 | 127.0±5.7 | 131.0±4.7 | 134.0±8.7 |
| | | 100.0±10.1*** | 146.0±5.7*** | 156.0±4.8*** | 161.0±3.7** |
| | MI | 60.0±3.7 | 117.0±8.7 | 115.0±5.8 | 99.0±6.6 |
| | | 66±4 | 139.0±2.7 | 116.0±2.3 | 111.0±3.1 |
| Katz index | control | 29980±1576 | 51017±2031 | 42094±2917 | 42321±3694 |
| | | 37923±3103*** | 59249±1792** | 62060±1662* | 63937±2152** |
| | MI | 24505±2665 | 45204±3204 | 43372±3329 | 34732±3264 |
| | | 26811±1884 | 56252±1932$^{+++}$ | 44300±1449$^{+++}$ | 42361±1394$^{+++}$ |
| IMF | control | 47.0±2.2 | 83.0±4.3 | 71.0±5.8 | 69.0±6.1 |
| | | 83.0±7.9* | 117.0±5.3* | 123.0±7.9* | 127±7** |
| | MI | 41.0±4.6 | 77.0±1.8 | 58.0±5.6 | 61.0±1.4 |
| | | 53±3.4$^{+++}$ | 117.0±7.1$^{+}$ | 93.0±4.6$^{+}$ | 89.0±5.2$^{+++}$ |
| Left ventricular ME, mm Hg | control | 0.120±0.006 | 0.200±0.009 | 0.21±0.01 | 0.210±0.014 |
| | | 0.180±0.017** | 0.290±0.014* | 0.310±0.015* | 0.32±0.01* |
| | MI | 0.100±0.007 | 0.190±0.008 | 0.180±0.012 | 0.16±0.01 |
| | | 0.130±0.004$^{+}$ | 0.280±0.016$^{+}$ | 0.240±0.008$^{+}$ | 0.230±0.012$^{+}$ |
| Contraction rate, mm Hg/sec | control | 3410±152 | 5478±500 | 4895±422 | 4505±395 |
| | | 4903±494*** | 6418±530 | 7802±430* | 8806±812* |
| | MI | 3289±656 | 3498±250 | 3674±376 | 2800±326 |
| | | 4059±315 | 4850±187$^{++}$ | 4384±201 | 4080±140$^{+}$ |
| Relaxation rate, mm Hg/sec | control | 2297±160 | 2186±204 | 1986±197 | 2227±115 |
| | | 4101±301* | 3147±194* | 3412±139* | 3367±255* |
| | MI | 2957±448 | 2143±42 | 1848±176 | 1970±176 |
| | | 2631±189 | 2882±177$^{+}$ | 2515±78$^{+}$ | 2440±87$^{++}$ |

**Note.** *$p$<0.001, **$p$<0.01, ***$p$<0.05 compared to sham-operated Wistar rats; $^{+}p$<0.001, $^{++}p$<0.01, $^{+++}p$<0.05 compared to Wistar rats with MI.

MI (Fig. 1, *b*). Similar interstrain difference in the reaction to epinephrine between strains (both in control rats and in animals with MI) were noted for the rates of myocardial contraction and relaxation. These findings suggest that myocardial adrenoreactivity in August rats (both intact rats and animals with MI) is lower than that in Wistar rats. This mechanism can underlay their high resistance to acute myocardial ischemia, since low adrenoreactivity attenuates the damaging effect of catecholamines on cardiomyocytes and prevents drastic disturbances in $Ca^{2+}$ transport playing an important role in the development of postischemic arrhythmia and myocardial dysfunction.

In summary, the comparison of the heart function in August and Wistar rats at rest, during load, and after MI modelling revealed the following differences. First, the rest level of the cardiac function in August rats is higher than in Wistar rats. This phenomenon

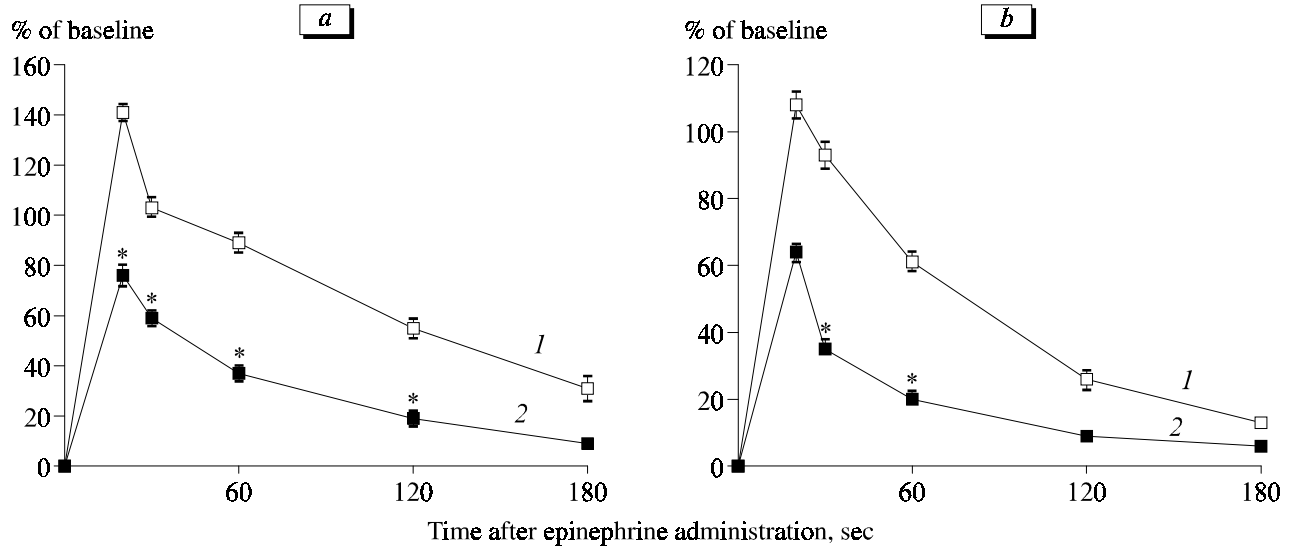


**Fig. 1.** Effect of epinephrine on left ventricular developed pressure in the control (*a*) and after myocardial infarction (*b*) in Wistar (*1*) and August (*2*) rats. *Significant difference with Wistar rats.

can be associated with higher blood content of catecholamines in August rats [2] indicating increased activity of their adrenergic system.

Second, the hearts of August rats are more resistant to load than in Wistar rats. This phenomenon can be attributed to higher resistance of their sinus node to vagal inhibitory effects. The higher load-resistance of the contractile function in August rats suggests that the $Ca^{2+}$-transport systems of their myocardium are more powerful than those in Wistar rats.

Third, in August rats, MI-induced heart dysfunction is less pronounced than in Wistar rats, which attests to less severe damage to non-ischemic myocardium. Since myocardial ischemia is always accompanied by stress-related damage this suggestion is in line with previous data showing that in August rats exposed to severe stress, the outflow of creatine phosphokinase, a cell damage marker, is lower than in Wistar rats [7].

We found that August rats are more resistant to acute MI than Wistar rats, which can be associated with genetically determined low intensity of their stress-response and low adrenoreactivity of their myocardium.

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