Effect of Captopril on Some Ventricular Contractility Indices in Spontaneously Hypertensive Rats (SHR)

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Summary Two groups of SHR were treated with captopril (Squibb): the first group (1 month old)—30 mg/kg i.p. twice daily for 77 days, and the second group (8 months old)—20 mg/kg p.o. twice a day for 23 days. The recording of electrocardiogram (ECG), systolic blood pressure (SBP), diastolic blood pressure (DBP), and some isometric indices of the left-ventricular contractility indicate that in all treated animals the values of most of the parameters are considerably lowered compared to the controls. The ratio between velocity of pressure increase and intraventricular pressure/equal to 50 mmHg—(dP/dt)/ICP_{50}/does not change significantly. It can be concluded that in SHR, captopril practically does not influence the inotropic condition of the myocardium.

Key words: captopril, SHR, ventricular contractility.

The effect of drugs inhibiting the activity of angiotensin-converting enzyme on the preload, afterload, and frequency of myocardial contractions is well known (FOUAD et al., 1982). It reveals new possibilities for pathogenetic therapy of arterial hypertension (BRAVO et al., 1981; FAGARD et al., 1981), heart failure (CHATTERJEE et al., 1982), pulmonary hypertension (NIACHARS et al., 1979), and other diseases. However, the problem of the likely effect exerted on myocardial contractility as a basic factor determining the magnitude of cardiac output remains unclarified.

In this work, observations on captopril-induced changes in several indicators of the isometric phase of left-ventricular contraction in SHR are described.

Two groups of spontaneously hypertensive rats (SHR) of the Okamoto-Aoki F41 line were used in the study. Group one consisted of 19 animals of both sexes, aged 3(1/2) months, with body mass at the beginning of the experiment 60±4 g, divided up in two subgroups. Subgroup one comprised 7 SHR, treated for 77 days with captopril (Squibb) at a dose of 30 mg/kg intraperitoneally, twice daily. The
second subgroup (12 SHR) was not subjected to treatment, and served as a control.

Group two consisted of 17 male SHR aged 8 months with body mass 33±30 g. Eight of them underwent captopril treatment for 23 days at a dose of 20 mg/kg, twice daily, introduced into the stomach via probe. The remaining nine animals served as controls (untreated). The two control subgroups were treated with physiological saline. Throughout the full observation period, the systolic blood pressure in the tail artery was measured by the indirect method in the morning before, and between the second and fourth hour after the first captopril treatment for the day.

At termination of the experiment, using a 3-channel Biomedica C3e polygraph, under nembutal narcosis the electrocardiogram in the three standard leads, and consecutively the pressure curves in the ascending aorta and left heart ventricle were registered. For the purpose a Venocath 18 catheter (Abbott), introduced through the right common carotid artery, and Gold Statham P23 ID manometer were employed. In all measurements the midpoint of the anteroposterior diameter of the thorax in the animals fixed in supine position was selected as a zero level.

Following analogue-to-digital conversion, the pressure signal from the transducer was fed to a personal "Pravetz 82" microcomputer for processing. The isometric indices of left ventricular contractility were calculated: maximum velocity of intraventricular pressure increase—$dP/dt_{max}$; the quotient of $dP/dt_{max}$ and intraventricular pressure (ICP) at this moment—$(dP/dt_{max})/ICP$; ratio between velocity of pressure increase and intraventricular pressure equal to 50 mmHg—$(dP/dt)/ICP_{50}$. All measurements were done following a 30-min period of adaptation to the conditions of the experiment, between the second and third hour after the last captopril administration. The obtained mean values of the indices for both groups of treated animals were comparatively studied with the untreated age matched SHR by t-criterion of Student-Fisher.

**Group one—3(1/2) months old SHR: preventive effect of captopril in the prehypertensive stage.** Before initiation of captopril treatment, the animals of this group were 1 month of age with body mass 60±4 g, and the arterial pressure, measured by the indirect tail method amounted to 109.3±10.4 mmHg—prehypertensive stage. Throughout the full course of the experiment, the control group of SHR (untreated) invariably exhibited a higher arterial pressure reaching hypertensive values (155±8.3 mmHg) as early as 40 days of age. The results recorded upon reaching 3(1/2) months of age (treated animals and their respective untreated controls) are presented in Fig. 1. The values of the individual indices are as follows. Systolic blood pressure (SBP): untreated 176±9 mmHg, treated 124±9 mmHg ($p<0.01$); diastolic blood pressure (DBP): untreated 137±8 mmHg, treated 89±12 mmHg ($p<0.01$); $dP/dt$ max: untreated 5,921±639 mmHg·s$^{-1}$, treated 3,894±391 mmHg·s$^{-1}$ ($p<0.02$); $(dP/dt_{max})/ICP$: untreated 82±5 s$^{-1}$, treated 78±6 s$^{-1}$ ($p>0.05$); $(dP/dt)/ICP_{50}$: untreated 111±8 s$^{-1}$, treated 99±8 s$^{-1}$ ($p>0.05$).

**Group two—8 months-old SHR: antihypertensive effect of captopril in the Japanese Journal of Physiology
Fig. 1. Preventive action of the captopril in prehypertensive stage of SHR.

Fig. 2. Antihypertensive effect of the captopril in SHR.
presence of hypertension. At the beginning of the experiment, the body mass of the animals in accordance with age was \(339 \pm 30\) g, while arterial pressure in the tail artery was rather elevated—\(191 \pm 20\) mmHg. Captopril treatment produced a decrease in blood pressure \((147.1 \pm 2.7\) mmHg\) between the second and fourth hour after giving the consecutive dose, but the morning measurement disclosed a higher value \((167.7 \pm 5\) mmHg). Figure 2 illustrates the results of assessment of the indices under study following treatment lasting 23 days (3h after giving the last dose). They are as follows: systolic blood pressure: untreated \(170 \pm 13\) mmHg, treated \(129 \pm 8\) mmHg \((p < 0.02)\); diastolic blood pressure: untreated \(116 \pm 8\) mmHg, treated \(73 \pm 11\) mmHg \((p < 0.01)\); \(dP/dt\ max\): untreated \(5,741 \pm 561\) mmHg \(\cdot s^{-1}\), treated \(3,365 \pm 527\) mmHg \(\cdot s^{-1}\) \((p < 0.01)\); \((dP/dt)\ max/ICP\): untreated \(97 \pm 9\) s\(^{-1}\), treated \(61 \pm 12\) s\(^{-1}\) \((p < 0.05)\); \((dP/dt)/ICP_{50}\): untreated \(122 \pm 19\) s\(^{-1}\), treated \(95 \pm 12\) s\(^{-1}\) \((p > 0.05)\). The heart rate in both groups of SHR subjected to treatment did not show regular statistically significant changes, by comparison with the respective untreated controls. The electrocardiogram in all rats of both experimental groups (treated and untreated alike) was of the left type. No rhythm and conduction disorders were documented.

In both groups of our experimental animals captopril similarly brought about a decrease in arterial pressure, both after single treatment and long-term administration. The most strongly pronounced effect was recorded about the third hour after giving the consecutive dose, which is consistent with the data established by Rubin et al. (1978). By comparison with the respective controls, the decrease at the end of our experiments for both groups of treated SHR proves to be more pronounced for diastolic pressure (average 36%), as compared to systolic pressure (average 27%)—a fact readily explainable by the mechanism of hypotensive action of the drug: vascular tone reduction.

By continuous, 12-month-long treatment of SHR per os with large doses (100 mg/kg) of captopril, some authors (Sen et al., 1980) succeeded in preventing the development of myocardial hypertrophy. The electrocardiographic finding at termination of the observation period points to the presence of left-ventricular hypertrophy in the animals treated by us. This may be attributed to the circumstance that the doses employed by us, and the duration of treatment failed to keep the animals normotension in the intervals between the drug applications. In most of the animals the measurement of arterial pressure in the morning, prior to the first captopril injection, once again showed hypertensive values.

In reference to the goal of this work, the changes in isometric indices of the left-ventricular contractility deserve special attention. A multitude of indices for assaying the inotropic state of the myocardium in the event of an intact heart have been described in the literature. Out of the isometric indices, the maximum velocity of intraventricular pressure increase \((dP/dt\ max)\) is the most frequently evaluated. Its elevated value is interpreted as an expression of enhanced contractility (Siegel and Sonnenblick, 1963; Mason et al., 1970). The \(dP/dt\ max\) is particularly sensitive
to the inotropic state of the myocardium (SONNENBLICK and DOWNING, 1963; POLLACK, 1970), although it is strongly dependent on pre- and afterloading of the respective heart ventricle (VAN DEN Bos et al., 1973; BRAUNWALD et al., 1974). The remainder of contractile indices are likewise dependent on the condition of pre- and afterload (MASON et al., 1970), although to a lesser degree.

The magnitude of afterload exerts practically no effect on the ratio between velocity of pressure increase and intraventricular pressure, the latter at a value of 50 mmHg—(dP/dt)/ICP50. Along with that, this particular index is sufficiently sensitive (MASON et al., 1970). What is the state of pre- and afterload of the left ventricle of the heart in our experimental setup? As it is well known the inhibitors of the angiotension-converting enzyme dilate the resistant and capacity vessels (FRANCIOSA and SCHWARTZ, 1982), reduce the total peripheral and pulmonary vascular resistance, respectively the systemic arterial pressure and the one of the pulmonary artery (CODY, 1982; Fouad et al., 1982). The pre- and afterload of the left heart ventricle is likewise reduced (FRANCIOSA and PIERPONT, 1981; Fouad et al., 1982). Hence, the statistically significant changes in the contractile indices observed in our experiment subsequent to captopril treatment should be linked to the altered hemodynamic conditions. In support of the latter explanation we found that the afterload decreases (decreased BP) and also the index (dP/dt)/ICP50 which is virtually unaffected by the conditions of loading, does not undergo statistically significant changes.

In the experimental setup used (doses and duration of treatment) captopril exerts practically no effect on the inotropic state of the myocardium in spontaneously hypertensive rats.

REFERENCES


