Myocardial infarction in experimental hypertension in rats: mechanism of the reduction in blood pressure

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Summary

1. Haemodynamic changes during graded methoxamine infusion have been measured in 16 spontaneously hypertensive rats with healed myocardial infarction produced by left coronary artery ligation and in 15 hypertensive rats without infarction.

2. Arterial pressure of the hypertensive rats was reduced to levels within the normotensive range in animals with moderate and large myocardial infarctions.

3. The peripheral vascular response to methoxamine was similar in rats with and without infarction.

4. The reduction in blood pressure resulted from a combination of lower heart rate and inability to maintain stroke volume at hypertensive pressures.

Key words: cardiac output, cardiac function, spontaneously hypertensive rats, vascular resistance.

Introduction

Hypertensive patients often become normotensive after myocardial infarction (Birkenhager, Schalekamp, Krauss, Kolsters & Zaal, 1972; McCall, Elmfeldt, Vedin, Wilhelmsson, Wedel & Wilhelmsen, 1979). Furthermore, although hypertension before myocardial infarction is a potent risk factor for cardiovascular morbidity and mortality, after myocardial infarction the level of blood pressure is poorly related to survival (Kannel, Sorlie, Castelli & McGee, 1980). One possible explanation is that those patients with the greatest reduction in blood pressure have the most severe cardiac dysfunction (McCall et al., 1979; Kannel et al., 1980). In rats with experimental myocardial infarction we have previously shown that infarct size is a major determinant of cardiac function (Pfeffer, Pfeffer, Fishbein, Fletcher, Spadaro, Kloner & Braunwald, 1979). Left coronary artery ligation in rats with genetic hypertension provides a model in which to study the responses of the hypertensive animal to a myocardial infarction. The present study analyses the haemodynamic mechanisms responsible for the reduction in arterial pressure after myocardial infarction in rats with genetic hypertension.

Methods

Left coronary artery ligation to produce myocardial infarction (16 rats) or a sham operation (15 rats) was performed in 31 female spontaneously hypertensive (SH) rats of the Okamoto–Aoki strain, aged 24 weeks (range 19–31 weeks). Four weeks after the sham operation or coronary ligation, when the infarcts had completely healed (Fishbein, MacLean & Maroko, 1978), cannulae were inserted into the right carotid artery and jugular vein, the trachea and into a femoral vein under ether anaesthesia. Prethoracotomy arterial and venous pressures and heart rate were measured under light ether anaesthesia during spontaneous respiration. Through a small anterior thoracotomy under positive pressure respiration (Harvard Rodent Respirator) a calibrated flow probe was placed around the ascending aorta for measurement of cardiac output by an electromagnetic flowmeter (Statham Inc.) (Pfeffer & Frohlich, 1972). After measurement of base-line haemodynamics, methoxamine was infused into the femoral vein in increasing doses from 0.08 to 3.2 mg min$^{-1}$ kg$^{-1}$.
(Pfeffer & Frohlich, 1973). Repeat haemodynamic measurements were made when blood pressure and cardiac output had stabilized at each dose (approximately 45 s). After these haemodynamic measurements the heart was arrested with potassium chloride and dissected into right and left ventricles, which were weighed separately. The left ventricle was fixed distended in formalin, after which sections were taken at 1 mm intervals from apex to base and stained with modified Masson’s trichrome. The length of fibrous infarct and of muscle were measured by planimetry of epicardium and endocardium from each slice, and infarct size was expressed as a percentage of the total circumference occupied by fibrous scar tissue.

Heart rate was calculated from phasic arterial pressures. Mean arterial pressure (MAP), mean right atrial pressure (RAP) and mean cardiac output (CO) were obtained electronically. Total peripheral resistance was calculated as (MAP−RAP)/CO in mmHg min⁻¹ ml⁻¹. Results are expressed as means ± standard error. Analysis of variance was used for between-group comparisons.

Results
The 16 SH rats with myocardial infarction were divided into those with moderate and large infarcts involving 27–39% (n = 8) and 42–52% (n = 8) of the left ventricular circumference respectively. Prethoracotomy blood pressure was significantly reduced in both groups with myocardial infarction compared with the control group. Infarction reduced both systolic blood pressure (control, 176 ± 4; moderate infarction, 139 ± 6; large infarction, 122 ± 3 mmHg; P < 0.01) and diastolic blood pressure (control, 126 ± 3; moderate infarction, 108 ± 6; large infarction, 96 ± 2 mmHg; P < 0.01), the animals with large infarcts showing the greatest reductions. Arterial pressure of genetically hypertensive rats with myocardial infarction was within the range of pressure observed in normotensive rats without infarction.

Methoxamine infusions were used to provide a wide range of arterial pressure. At each infusion rate mean arterial pressure was significantly lower in both groups with infarction, reflected in the maximum pressure achieved by each group (control, 207 ± 3; moderate infarction, 181 ± 4; large infarction, 155 ± 3 mmHg; P < 0.01). Calculated total peripheral resistance was the same in groups with and without myocardial infarction at each dose of methoxamine. For example, at a methoxamine infusion rate of 0.4 mg min⁻¹ kg⁻¹, total peripheral resistance in the three groups was: control, 2.42 ± 0.22; moderate infarction, 2.54 ± 0.17; large infarction, 2.97 ± 0.20 mmHg min⁻¹ ml⁻¹.

The reduction in mean arterial pressure was the result of a lower cardiac output at any level of total peripheral resistance. The response of cardiac output and stroke volume to the increase in afterload differed between groups (Fig. 1). SH rats without myocardial infarction maintained both cardiac output and stroke volume until mean arterial pressure exceeded 175 mmHg. In contrast, SH rats with large myocardial infarctions had reduced cardiac output and stroke volume at rest, which decreased progressively with even small increases in mean arterial pressure above 100 mmHg. SH rats with moderate myocardial infarctions had near-normal initial blood flow, but with an increase in mean arterial pressure above 140 mmHg both cardiac output and stroke volume decreased, with loss of the ‘plateau’ seen in the control SH rat (Fig. 1). Heart rate was also significantly slower in both groups with myocardial infarction at any given level of arterial pressure and therefore contributed to the lower cardiac output at each level of arterial pressure. For example, at a common mean arterial pressure of 150 mmHg, heart rate was: control, 396 ± 14; moderate infarction, 360 ± 8; large infarction, 280 ± 7 beats/min (P < 0.01).
Discussion

In the present study, SH rats with healed myocardial infarction had substantial reductions in blood pressure, to levels found in normotensive rats. Infusion of the α-adrenergic agonist, methoxamine, was used to produce graded increases in vascular resistance and left ventricular afterload. In rats with myocardial infarction this manoeuvre revealed progressive impairment of flow-generating ability in proportion to infarct size over a wide range of blood pressure. The inability of rats with myocardial infarction to maintain cardiac output at hypertensive blood pressures was due largely to lower stroke volume. However, lower heart rate at comparable blood pressures also contributed to the lower cardiac output. The observation that calculated total systemic resistance was similar in rats with and without myocardial infarction during each dose of the methoxamine infusion suggests that the peripheral vasculature retained its 'hypertensive' response characteristics despite lower blood pressure and cardiac output.

The present findings during graded increases in afterload are consistent with our previous studies demonstrating impaired cardiac function in proportion to infarct size during maximal preload and afterload stress in both normotensive and hypertensive animals (Fletcher, Pfeffer, Pfeffer & Braunwald, 1979; Pfeffer et al., 1979). In the former study hypertensive rats had more than twice the reduction in blood pressure found in normotensive rats with comparable infarct size and their maximal cardiac performance was also more severely impaired. However, at each infarct size blood pressure was still significantly higher in previously hypertensive rats than in normotensive rats. The present observation that vascular responsiveness is unchanged by infarction is consistent with these findings. Therefore, in contrast to the heart of a normotensive animal, the heart of a hypertensive animal after sustaining a myocardial infarction has an additional disadvantage in that it is still coupled to a peripheral vascular bed which appears to retain the characteristics of the initial hypertensive state.

Finally, our data offer an explanation for the reduction in blood pressure observed in some hypertensive patients after myocardial infarction (Birkenhager et al., 1972; McCall et al., 1979) and for the lack of relationship of post-infarct blood pressure to mortality in previously hypertensive patients (Kannel et al., 1980). As suggested by both McCall et al. (1979) and Kannel et al. (1980) the largest reductions in blood pressure are associated with the most severe degrees of post-infarct cardiac dysfunction, which presumably becomes the major predictor of mortality.

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References


