

In Vitro Perfusion Studies on Coronary Function of Cardiac Ischemia-Reperfusion in Spontaneously Hypertensive Rat Heart

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고혈압쥐 심장에서 허혈상태-재관류의 관상순환기능에
대한 생체의 관류연구

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Background : Myocardial ischemia in human hypertension and in various animal models of hypertension may be due to abnormal maximal coronary vasodilator reserve and disturbances of coronary vasomotion. The vascular reactivity defects in hypertension have been associated with the defective endothelium and sympathetic neural activation. However, such abnormalities in hypertension need to be elucidated. In the present study the effects of cardiac ischemia-reperfusion on coronary circulation, intramyocytic adenylates and purine nucleosides were examined in Langendorff-perfused Sprague Dawley rat (SD) and spontaneously hypertensive rat (SHR) hearts. Coronary venous and cardiac lactate and cardiac pyruvate were also measured. It should be noted that in the regulation of coronary flow the intrinsic flow autoregulation is highly variable due to coexisting metabolic flow control, and that natural coronary flow and cardiomyocytic energy state are normally reciprocally related in perfused heart.

Methods : For the Langendorff heart perfusion, bicarbonate perfusion buffer (pH 7.40 ± 0.02 , 37°C) was equilibrated with 95% O_2 : 5% CO_2 and contained 5mM glucose (+5U/l insulin) and 2mM pyruvate as energy-yielding substrates. Global hypoperfusion ischemia was induced by lowering coronary perfusion pressure of 100 to 40 cmH_2O , followed by 20 min reperfusion.

Results : During the ischemia and reperfusion, metabolic acidosis and enhanced venous lactate output in SHR were observed with increases in coronary vascular resistance and myocardial oxygen consumption. In addition, coronary reactive hyperemia during reperfusion was depressed. Although ischemia-induced increase in combined adenosine plus inosine were abolished during prolonged reperfusion, SD still exhibited coronary vasodilation. The depressed reactive hyperemia in SHR was associated with decreases in cardiac adenosine triphosphate (ATP) pool and creatine phosphate/inorganic phosphate (CrP/Pi) ratio and an increase in cardiac lactate/pyruvate ratio.

Conclusion : This abnormal vascular reactivity during ischemia and reperfusion in SHR

may be in part due to an alteration in the cardiac energy state and hence to a mismatch between myocardial metabolic demand and supply.

KEY WORDS : Spontaneously hypertensive rat • Ischemia-reperfusion • Coronary circulation • Purine nucleosides • Cardiac adenylates.

Introduction

Previous studies have demonstrated that myocardial ischemia can occur in human hypertension and in various animal models of hypertension^{1,2}). Abnormal maximal coronary vasodilator reserve^{1,3}) and disturbances of coronary vasomotion^{4,6}) may be responsible for myocardial ischemia frequently concurrent with hypertension. The abnormal vascular reactivity in hypertension has been attributed to the defective endothelium and sympathetic neural activation⁷⁻¹⁰). However, the mechanisms for such abnormalities remain to be determined. On the other hand, flow autoregulation and metabolic vasodilation play a major role in coronary flow control. The magnitude of the intrinsic flow autoregulation is highly variable due to coexisting metabolic coronary control^{11,12}), and natural coronary flow and cardiomyocytic energy state are normally reciprocally related in perfused heart¹³⁻¹⁵). No study has performed to correlate the development of myocardial ischemia, impairment of coronary vasorelaxation and the limitation of coronary arterial reactivity with cardiomyocytic energy state in hypertension.

The present study examined parameters of coronary circulation of the spontaneously hypertensive rat (SHR) heart during cardiac hypoperfusion ischemia and reperfusion to correlate direct changes in the cardiac circulatory and oxygen metabolic function with genetic factors in hypertension. Adenosine hypothesis that oxygen supply-demand ratio determines formation of cardiac adenosine¹⁶), was further examined by relating the output of extracellular cardiac adenosine and inosine with coronary vascular resistance at normal and subphysiological coronary perfusion pressure (CPP). Since formation of adenosine and its degradatives may be determined partially by the cellular energy

state^{14,17}), the idea was explored that changes in the myocardial adenylates and glycolytic intermediates can influence coronary flow control in hypertension. All experiments were conducted using fully oxygenated heart preparation : Sprague Dawley rat (SD) was employed as normotensive controls. Such experimental approach can reveal important differential effects of genetic factors in hypertension on cardiac circulatory function, and provide significance in studying the pathogenesis of hypertension.

Materials and Methods

Langendorff heart perfusion

Hearts were isolated from male SD and SHR of 250–350g body mass as described elsewhere^{18,19}) and immediately perfused with modified Krebs-Henseleit bicarbonate buffer equilibrated with 95% O₂ : 5% CO₂ (pH 7.40 ± 0.02, pO₂ 600 ± 20mmHg, and pCO₂ 36 ± 1 mmHg at 37°C). During the experimental period, all hearts were perfused with the bicarbonate buffer fortified with 5mM glucose and 2mM pyruvate (5U/l bovine insulin, Sigma, St. Louis, MO) as energy substrates. Isolated, perfused hearts were spontaneously empty-beating at CPP of 100cmH₂O. Coronary venous effluent (coronary sinus plus right ventricular thebesian flow, CF) was measured and collected from the cannulated pulmonary artery¹⁵). Retrograde aortic inflow and venous effluent fluids were sampled anaerobically ; pO₂, pCO₂ and pH were measured in a blood pH/gas analyzer (CIBA-Corning, model 238, Orangeburg, NY) to calculate myocardial oxygen consumption (MVO₂). A silastic tubing was inserted across the incised mitral valve to effect left ventricular drainage¹⁵).

When hearts had achieved hemodynamic steady states at CPP of 100 cmH₂O, hemodynamic and oxygen

metabolic parameters were collected for pre-ischemic measurements; spontaneous heart rate, aortic flow, CF, CPP and pO₂ were monitored. Coronary venous effluent was sampled during the last 2 min of this pre-ischemic period. Subsequently, hypoperfusion ischemia was induced by reducing CPP from 100 to 40 cmH₂O for 10 min. In the new steady state, all measurements and sampling were repeated. Thereafter, hearts were reperfused for the next 20 min after raising CPP to the normal pressure of 100 cmH₂O. Measurements were periodically obtained during the 20 min reperfusion.

Analytical measurements

Prior to terminating experiments hearts were freeze-clamped with Wollenberger tongs precooled at a temperature of liquid N₂. Myocardial tissue extraction procedures and energy metabolite measurements were performed as previously detailed^{14,15,17}. Myocardial ATP, creatine phosphate (CrP), creatine (Cr), inorganic phosphate (Pi), pyruvate (Pyr) and lactate (Lac) were assayed with a UVICON Model 930 spectrophotometer (Kontron Instruments, Tegimenta, Switzerland, measuring wavelength 340nm, $\epsilon = 5.782 \text{ cm}^2 \cdot \mu\text{mol}^{-1}$). Coronary venous Pyr and Lac were also enzymatically mea-

sured^{15,17}.

HPLC analyses and measurements of purines

Coronary venous effluents collected were immediately boiled for 8 min to prevent degradation of purines by release adenosine deaminase. Prior to HPLC separation, 1ml portion of boiled venous effluent samples were added to 30 μ l 1N HCl. Purines (adenosine and inosine) in venous effluent samples were measured using C-18 reverse phase HPLC (Waters Associates, Milford, MA) at 4°C as previously described^{14,15}. Identification and quantification of purine peaks were accomplished by comparison with calibrated standards with known retention times in combination with measured absorbance characteristics at four different wavelengths (254, 263, 273, 293nm; Waters model 490 multiple wavelength detector).

Data analysis

Data are presented as means \pm S.E. Single comparison of mean values was accomplished by Student's t-test for unpaired results. For multiple comparisons, an analysis of variance (two-tail) in combination with Tukey's multiple range test was performed. p values <0.05 were taken to indicate statistical significance.

Table 1. Cardiac hemodynamics and myocardial oxygen consumption during cardiac hypoperfusion ischemia and reperfusion in Sprague Dawley and spontaneously hypertensive rats

Protocols time(min)	SD			SHR		
	CF (ml \cdot min ⁻¹ g wet wt ⁻¹)	CVR (cmH ₂ O \cdot ml ⁻¹ min ⁻¹ g wet wt ⁻¹)	MVO ₂ (μ mol \cdot min ⁻¹ g wet wt ⁻¹)	CF (ml \cdot min ⁻¹ g wet wt ⁻¹)	CVR (cmH ₂ O \cdot ml ⁻¹ min ⁻¹ g wet wt ⁻¹)	MVO ₂ (μ mol \cdot min ⁻¹ g wet wt ⁻¹)
Pre-ischemia	5.80 \pm 0.11	15.50 \pm 0.23	1.94 \pm 0.04	5.97 \pm 0.07	15.16 \pm 0.13	2.48 \pm 0.05 ⁺
Ischemia 10	3.39 \pm 0.06*	11.86 \pm 0.24	1.38 \pm 0.03*	3.16 \pm 0.05* ⁺	12.52 \pm 0.17* ⁺	1.62 \pm 0.03* ⁺
Post-ischemia 0-1	6.80 \pm 0.10*	13.49 \pm 0.19*	2.41 \pm 0.05*	6.18 \pm 0.08* ⁺	14.30 \pm 0.19* ⁺	2.84 \pm 0.05* ⁺
5	6.72 \pm 0.12*	13.28 \pm 0.22*	2.30 \pm 0.04*	6.01 \pm 0.07 ⁺	15.00 \pm 0.14 ⁺	2.68 \pm 0.04* ⁺
10	6.35 \pm 0.11*	14.25 \pm 0.21*	2.14 \pm 0.04*	5.73 \pm 0.07* ⁺	15.56 \pm 0.15* ⁺	2.55 \pm 0.06 ⁺
20	6.17 \pm 0.11*	14.52 \pm 0.23*	2.29 \pm 0.04*	5.58 \pm 0.08* ⁺	16.52 \pm 0.17* ⁺	2.48 \pm 0.06 ⁺

All values are means \pm SE, (n=15 SD, 14 SHR). Cardiac hypoperfusion ischemia was induced by lowering coronary perfusion pressure from 100 to 40 cmH₂O for 10 min, which was followed by 20 min reperfusion. SD, Sprague Dawley rats; SHR, spontaneously hypertensive rats; CF, coronary flow; CVR, coronary vascular resistance; MVO₂, myocardial oxygen consumption.

* p<0.05, relative to corresponding pre-ischemic values

⁺ p<0.05, relative to corresponding SD values

Results

Coronary hemodynamics

Table 1 summarizes coronary circulatory responses

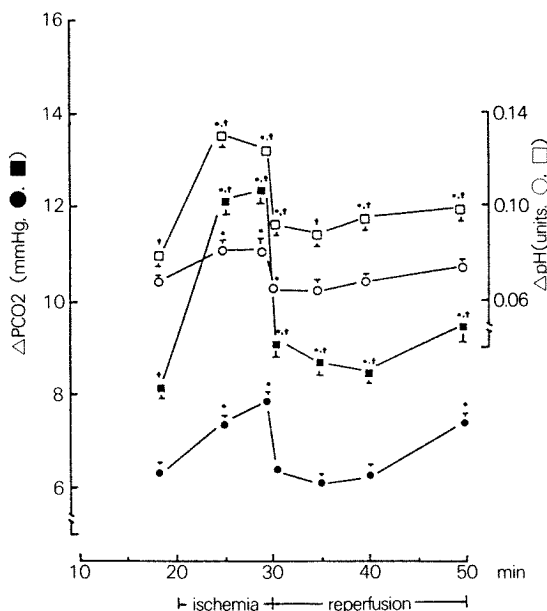


Fig. 1. Graph showing the changes of coronary venous pH (○, □) and pCO₂ (●, ■) during cardiac ischemia-reperfusion in Sprague Dawley and spontaneously hypertensive rats. Mean ± SE, n = 15 SD, 14 SHR. ○ and ●, Sprague Dawley rat; □ and ■, spontaneously hypertensive rat; ΔpH, arterial minus venous pH; ΔpCO₂, venous minus arterial partial pressure of carbon dioxide.

*p < 0.05 vs. corresponding pre-ischemic values.

*p < 0.05 vs. corresponding SD values.

to cardiac hypoperfusion ischemia and reperfusion. As expected, lowering CPP from the physiological pressure of 100 cmH₂O to the subphysiological pressure of 40 cmH₂O produced significant decreases in CF and MVO₂ in both SD and SHR, while coronary vascular resistance (CVR) increased. It should be noted that basal CF and CVR in SHR did not differ from those observed in SD; basal MVO₂, however, increased by 28% when compared with that in SD (p < 0.05). On the other hand, greater coronary vasodilation was exhibited with increased MVO₂ declined with prolonged reperfusion in parallel with a reduction of CF. Nevertheless, MVO₂ in SHR was still greater than that observed in SD even at the 20 min reperfusion, which was due to increased myocardial oxygen extraction (data not shown).

Fig. 1 depicts change curves of arterial minus venous pH (ΔpH) and venous minus arterial pCO₂ (ΔpCO₂) observed during ischemia and reperfusion. In perfused SHR hearts ΔpH and ΔpCO₂ were markedly enhanced. Ischemia-induced increases in both parameters were greater in SHR than those in SD; the post-ischemic ΔpH and ΔpCO₂ did not reach the pre-ischemic levels.

Cardiac adenylates and glycolytic metabolites

Data on levels of cardiac energy metabolite and glycolytic intermediates after the pressure run protocol were shown in Table 2. The ATP pool was depleted by 15% in SHR. Cardiac CrP and Pi in SHR did not differ from those of SD (p > 0.05); CrP/Pi ratio,

Table 2. Cardiac adenylates and metabolites after global cardiac ischemia-reperfusion in Sprague Dawley and spontaneously hypertensive rats

Rats	pH _i	ATP	CrP	Cr	Pi	Lac	Pyr	CrP/Pi	Lac/Pyr
		(μmol · g dry mass ⁻¹)							
SD	7.21 ± 0.01	18.0 ± 0.9	34.4 ± 1.3	22.5 ± 1.7	18.8 ± 1.4	2.3 ± 0.2	3.9 ± 0.3	1.88 ± 0.26	0.57 ± 0.04
SHR	7.13 ± 0.03*	15.3 ± 0.9*	32.6 ± 1.5	24.5 ± 2.4	20.6 ± 1.7	2.8 ± 0.2*	3.5 ± 0.2	1.58 ± 0.07*	0.83 ± 0.05*

All values are means ± SE, (n = 9 SD, 9 SHR). Hearts were freeze-clamped after 20 min reperfusion for myocardial extraction (see Methods). SD, Sprague Dawley rats; SHR, spontaneously hypertensive rats; pH_i, intracellular pH; CrP, creatine phosphate; Cr, creatine; Pi, inorganic phosphate; Pyr, pyruvate; Lac, lactate. Intracellular pH was calculated from measured coronary venous pCO₂ using an operational equation [ref. 17, pH_i = 7.524 × e^{-0.0008786pCO₂}].

*p < 0.05, relative to corresponding SD values

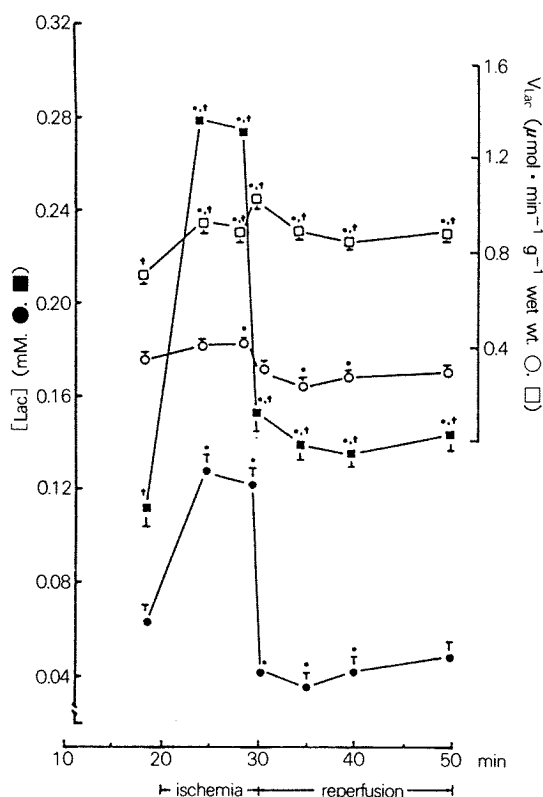


Fig. 2. Graph showing the concentration (●, ■) and release (○, □) of coronary venous lactate during cardiac ischemia-reperfusion in Sprague Dawley and spontaneously hypertensive rats. Mean \pm SE, $n=15$ SD, 14 SHR. ○ and ●, Sprague Dawley rat; □ and ■, spontaneously hypertensive rat; [Lac]_v, coronary venous lactate concentration; V_{Lac} , coronary venous lactate release.
* $p<0.05$ vs. corresponding pre-ischemic values.
* $p<0.05$ vs. corresponding SD values.

however, decreased by 16%. Marked increases in cardiac Lac and Lac/Pyr ratio were obtained in SHR despite only a small fall in cardiac Pyr compared with those of SD (Table 2); this was consistent with an increase in the venous Lac production (Fig. 2). Ischemia-induced increase in venous Lac was abolished in SD during reperfusion, while it was still enhanced in SHR. Comparisons of the cardiac Lac data with the hemodynamic data indicate that increased cardiac and venous Lac in SHR were associated with enhanced MVO_2 ; cellular acidification was associated with sti-

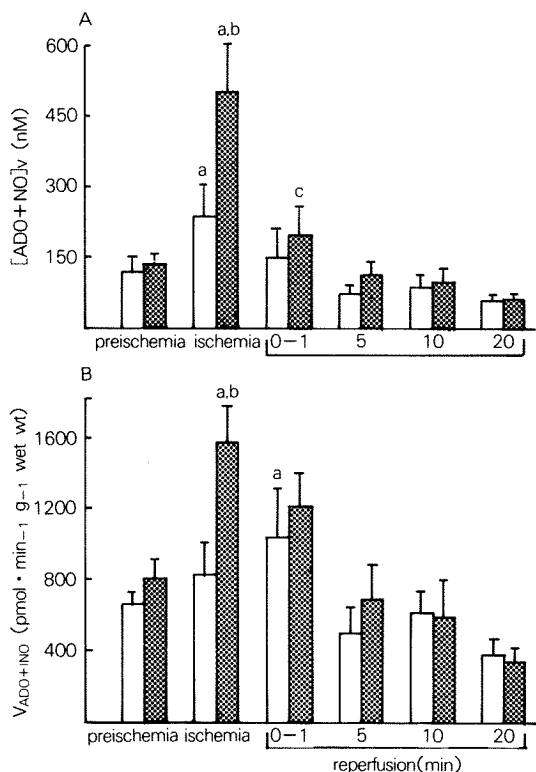


Fig. 3. Coronary venous adenosine plus inosine concentration (A panel, [ADO+INO]_v) and release (B panel, $V_{ADO+INO}$) of Sprague Dawley rat (open bars) and spontaneously hypertensive rat (hatched bars) during cardiac ischemia-reperfusion. Each bar represents means \pm SE ($n=15$ SD, 14 SHR).
^a $p<0.05$ vs. corresponding pre-ischemic values.
^b $p<0.05$ vs. corresponding SD values.
^c $p<0.05$ vs. corresponding ischemic values.

mulated oxidative metabolic rate (Table 1, 2, Fig. 2).

Coronary venous purine nucleoside production

Fig. 3 presents data for coronary venous concentration ([ADO+INO]_v) and release ($V_{ADO+INO}$) of the combined adenosine plus inosine during ischemia and reperfusion. The basal purine production was not modulated in SHR. Cardiac ischemia increased markedly the [ADO+INO]_v in both SD and SHR ($p<0.05$); SD did not increase $V_{ADO+INO}$ due to ischemia-induced decrease in CF (Table 1). When CPP was restored to the physiological pressure, [ADO+INO]_v immediately to the pre-ischemic levels in both groups;

$V_{ADO+INO}$ was still significantly enhanced during 1 min reperfusion, which was associated with simultaneous increases in CF.

Discussion

Differential effects of cardiac ischemia-reperfusion on coronary circulation and myocardial energy metabolites were examined in perfused SD and SHR hearts. The findings of this study demonstrate that genetic factors in hypertension can influence coronary vascular reactivity, myocardial oxygen metabolism and cardiac energy pool under these conditions. These abnormal effects seemed to be in part associated with an alteration in the myocardial cellular energy state. The implication is that in patients with essential hypertension maximal coronary vasodilator reserve and coronary vasomotion could be altered under pathophysiological conditions.

Coronary flow response to ischemia and reperfusion

The present study demonstrates that an increase in coronary vascular smooth muscle tone in SHR during ischemia and reperfusion produced remarkable differential effects on the rate of post-ischemic recovery and the magnitude of coronary circulation. Coronary vasoconstrictor action was activated in the hypertensive rat heart under this pathological condition. The temporal recovery of coronary circulation in this study is noteworthy. At the end of reperfusion a fully-recovered CF response maintained in SD, while CVR was augmented and oxygen uptake reduced in SHR in parallel with a decrease in CF. Although coronary vasoconstriction was elicited in SHR, the oxidative metabolic rate were invariably enhanced: an increase in oxygen demand associated with elevated oxidative metabolic rate appeared to be adjusted by an increase in oxygen extraction. The oxygen-extracting property of the coronary vasculature in SHR seemed to be unaltered. From these results it should be noted that natural CVR response of SHR must have been partially antagonized owing to metabolic vasodilation during ischemia and reperfu-

sion.

A significant alteration in the magnitude of cardiac adenylates were observed in SHR. Cardiac ATP content decreased and the CrP/Pi ratio increased despite relatively unaltered CrP. The depletion of the ATP pool could be explained by stimulated oxidative metabolic rate and increased glycolytic process when CF and oxygen supply were limited. Thus, changes in coronary function could be partially responsible for an alteration in the cellular energy level of the coronary smooth muscle in this study. On the other hand, it has been reported that CF response and cardiomyocytic energy state are conversely related in perfused hearts^{13,14}). It was hypothesized that adenosine metabolism might be altered in SHR. At the subphysiological perfusion pressure $[ADO+INO]_v$ increased significantly, which was obvious in SHR due to a marked decrease in CF. However, prolonged reperfusion did not increase $V_{ADO+INO}$ despite decreased myocardial energy pool in SHR. These findings are in agreement with other studies which concluded that the major determinant for adenosine formation was an imbalance between oxygen supply and demand and not metabolic rate *per se*^{16,21,22}). All in all, coronary adenosine could not be attributed to mediating CF response of SHR when ATP pool became depleted.

Myocardial metabolism of energy-yielding substrates during ischemia and reperfusion

Myocardial metabolic acidosis and increased venous lactate output occurred in SHR due to stimulated oxidative metabolic rate despite decreased CF during ischemia and the late phase of reperfusion (Fig. 1, 2). These data suggest that myocardial glycolytic metabolism of exogenous glucose and pyruvate must have been altered and some pathological significance of cardiac lactate assigned in SHR. It should be noted that noticeable changes in the perfusate gases and pH were not induced by the present experimental interventions and no lactate was contained in the perfusate buffer. In the current study cardiac Lac/Pyr ratio and lactate formation from cardiac pyruvate pool increased in

SHR, which must have been also associated with enhanced myocardial oxidative rate during ischemia and reperfusion. An imbalance between oxygen demand and supply would increase anaerobic oxidation and hence the futile glycolytic process to favor the lactate formation in the hypertensive heart. Therefore, genetic factors in hypertension can alter energy utilization and myocyte respiration, and activities of some glycolytic enzymes involved. In our laboratory the basal activity of cardiac lactate dehydrogenase has been shown to be stimulated in SHR (unpublished data). It has been also demonstrated that cardiac lactate dehydrogenase is regulated by prevailing energy-yielding substrates²³⁾.

Related implications for abnormal coronary vasoconstriction in spontaneously hypertensive rat

The vascular endothelium plays important roles in regulating vascular tone. Arachidonic acid-derived prostaglandins, short-lived superoxides and other vasoconstricting factors are shown to be endogenously released by the vascular endothelium under physical stretching^{ref. 24)}. Pressure-induced vascular stretching in the hypertensive heart could release these constrictors at the level of the coronary resistance vessels. If these constrictors at the level of the coronary resistance vessels. If these unknown factors evoke the coronary vasoconstriction in SHR, ischemia-induced reactive hyperemia would be inadequate in the aspect of a mismatch between myocardial metabolic demand and supply. Moreover, releases of endothelium-derived factors which are known to mediate vasorelaxant actions of various exogenous and endogenous substances might be reduced in the hypertensive heart, which leads to an increase in coronary vascular smooth muscle tone. In hypertensive patients, impairment of endothelium-dependent dilation of coronary epicardial and resistance vessels has been evidenced^{6,7)}. In experimental hypertension, morphological changes develop in arterial endothelial cells²⁵⁾. Loss of relaxation to acetylcholine occurs in vessels from individuals with diseases associated with endothelial damage^{8,26,27)}. From these observations, it is assumed that enhanced liberations of un-

known vasoconstricting factors and blunted releases of endothelium-derived relaxing factors in the heart may contribute to the abnormal vasomotion of coronary arteries in SHR.

The sympathetic nervous system is also involved in the vasomotion of arterial vessels. Increased reactivity of resistance vessels to sympathetic stimulation has been demonstrated in hypertensive patients^{9,28)}. In addition, the endothelium modulates the contractile agonist effects of sympathetic activation. In isolated coronary arteries, norepinephrine is a more powerful vasoconstrictor in the absence of endothelium¹⁰⁾. We have also observed that coronary functional hyperemic response to isoproterenol, a β -receptor agonist, is attenuated in the hypertensive rat heart (unpublished data). In the present study isolated Langendorff-perfused hearts were experimentally employed. Since neuro-humoral and blood-borne influences were devoid in this preparation, involvement of the sympathetic stimulation in a mechanism for enhanced vascular resistance and defective reactive hyperemia during ischemia-reperfusion can be ruled out in the current study.

In conclusion, enhanced myocardial oxygen uptake, coronary metabolic acidosis and elevated cardiac lactate formation were observed in SHR during cardiac ischemia and reperfusion. Nevertheless, reactive hyperemia during reperfusion were depressed in SHR. This abnormal coronary function during ischemia-reperfusion may be attributed a depletion of myocardial high energy phosphate pool and an alteration in myocardial cellular energy state, and may have implications regarding myocardial perfusion abnormalities reported in hypertensive patients. However, further investigations should be undertaken to elucidate the mechanisms involved.

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= 국문 초록 =

연구배경 : 인간이나 여러가지 동물모델의 고혈압 형태에서 심근의 허혈상태는 비정상적인 maximal coronary vasodilation reserve와 coronary vasomotion의 혼란에 기인하는 것 같다. 또한 고혈압에서 초래되는 혈관활동의 결함은 혈관 내피세포와 교감신경성 활성작용의 결함과 연관성이 있다고 알려져 있다. 그러나, 그러한 고혈압에서의 비정상 상태는 여전히 규명되어야 할 필요성이 있다. 본 연구에서는 langendorff 관류방식을 이용하여 sprague dawley rat의 일 반백서와 고혈압쥐 (spontaneously hypertensive rat)의 적출된 심장에서 관상순환기능과 심근 내의 adenylates 그리고 purine nucleosides에 대한 심근의 허혈상태와 재관류의 효과를 조사 하였다. 또한 관상혈관내의 lactate와 심근의 lactate 및 pyruvate를 측정하였다. 여기서 주목할 것은, 관상혈류량의 조절작용에서 내재적인 혈류 자동조절기능은 공존하는 대사적인 혈류조절 현상 때문에 상당히 변할 수 있으며 관류된 심장에서 자연적으로 나타나는 관상혈류량과 심근내의 에너지 상태는 정상적으로 상반된 관계를 형성한다는 것이다.

방 법 : langendorff 심장관류를 위해 사용된 bicarbonate buffer는 37°C에서 95% 산소와 5% 이산화탄소의 혼합 gas로 equilibrate 시켜 pH를 7.40 ± 0.02 의 범위내로 하고, 여기에 5U/l insulin과 함께 5mM의 glucose와 2mM pyruvate가 에너지원으로 첨가되었다. 관상내압을 100에서 40cmH₂O의 정수압으로 낮추어 국소적 저관류 허혈상태를 지속시킨 다음, 20분간의 재관류를 실시하였다.

결 과 : 허혈상태와 재관류의 기간동안에 고혈압쥐에서 대사적인 acidosis와 관상내 lactate output의 증가는 관상혈관저항과 심근의 산소소비량의 상승과 함께 관찰되었다. 또한, 재관류 기간동안에 나타난 관상혈관의 reactive hyperemia는 감소되었다. 비록 허혈상태로 인한 combined adenosine plus inosine의 증가현상이 재관류의 기간동안에 소멸되었다 할지라도 정상 백서에서의 관상 관류량의 상승은 지속되었다. reactive hyperemia의 감소와 아울러, 고혈압 쥐에서는 심근의 adenosine triphosphate (ATP) pool 및 inorganic phosphate에 대한 creatine phosphate 비율 (CrP/Po ratio)이 감소한 반면에 pyruvate에 대한 lactate 비율 (lactate/pyruvate ratio)은 증가하였다.

결 론 : 고혈압쥐에서 재관류 기간동안의 이러한 비정상적인 관상혈관의 활동은 심장내 energy 상태의 변화에, 그리고 나아가서 심근의 대사적 수급의 불균형에 부분적으로나마 기 인된다고 할 수 있을 것이다.