The Delayed Recovery of Impaired Endothelium-Dependent Vasodilatory Response After Hemodynamic Improvement in Dogs With Congestive Heart Failure

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We investigated whether impaired endothelium-dependent vasodilatory response recovers as heart failure improves. The femoral blood flow responses to intra-arterial administration of nitroglycerin (NTG) and acetylcholine (ACh) were examined in dogs with 2-week pacing-induced chronic congestive heart failure (congestive heart failure group; CHF, $n=12$). Thereafter, pacing was stopped and hemodynamic changes and femoral blood flow responses were re-examined either 1 week (recover 1 week group; Re 1W, $n=6$) or 4 weeks (recover 4 weeks group; Re 4W, $n=6$) after the cessation of pacing. Another group in which a pacemaker was implanted without pacing served as the control group ($n=8$). In CHF, heart rate and pulmonary artery pressure increased, and echocardiography revealed increased left ventricular diastolic dimension and reduced percent fractional shortening compared with those in the control group. In Re 1W, all hemodynamic parameters returned to the basal levels and did not differ from those in the control group. Although there was no significant difference in the blood flow responses to NTG among the 4 groups, the responses to ACh in CHF were significantly reduced compared with those in the control group. Despite the recovered hemodynamics, femoral blood flow responses to ACh were still reduced in Re 1W, but they returned to the levels of the control group in Re 4W. Thus, vascular endothelial dysfunction recovers along with improvement in CHF, however, the recovery of endothelial function is delayed in comparison with improvement in cardiac function.

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Key Words: Congestive heart failure; Endothelial function; Resistance vessel

Congestive heart failure is a systemic disease caused by impaired cardiac function, and changes in the peripheral circulation as well as cardiac function play an important role in the condition. In the presence of depressed cardiac function, peripheral vascular resistance becomes an important determinant of cardiac performance. Heart failure is associated with abnormal vasomotor tone, and it is well known that peripheral vascular tone is increased^{1,2}. It has been known since the report of Kaiser et al³ that a reduction in endothelium-dependent vasodilatory response is partly responsible for such an abnormality in vascular tone. A number of experimental and clinical reports have shown that disturbance in the endothelium-

dependent vasodilatory response is present in the resistance vessels of the skeletal muscle in heart failure. An impaired vasodilatory response has also been observed in other diseases such as hyperlipidemia, atherosclerosis, hypertension, and diabetes mellitus, and revealed to be reversible in these diseases^{4–10}. However, only limited information is available on the reversibility of the impaired endothelium-dependent vasodilatory response in heart failure. As the peripheral circulation as well as cardiac function is the therapeutic target of the treatment of heart failure, it is important to clarify whether the impairment is reversible or not, and, if reversible, to elucidate the time course of recovery in comparison

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Fig 1. Experimental protocol. CHF, congestive heart failure group; Re 1W, recover 1 week group; Re 4W, recover 4 weeks group.

with that of hemodynamic improvement. Complete recovery of heart failure is clinically difficult to obtain, and improvement in the endothelium-dependent vasodilatory responses is often slow compared with the hemodynamic improvement achievable by heart failure therapy. On the other hand, a rapid pacing-induced heart failure model in dogs is known to be reversibly normalized without any pharmacologic interventions by discontinuing pacing.^{11,12} We conducted the following experiment in order to clarify the time course of changes in endothelium-dependent vasodilatory responses during the recovery process from heart failure in hindlimb resistance vessels of dogs with pacing-induced heart failure.

Methods

The investigation conforms to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH publication no. 85-23 revised 1985) and was performed in accordance with the guidelines established by the Rule for Animal Experimentation of the Hyogo College of Medicine.

Experimental Protocol

Chronic heart failure was prepared experimentally in male beagle dogs (weighing 8–12 kg). After the dogs were lightly anesthetized with ketamine hydrochloride (100–150 mg/kg, im) and pentobarbital sodium (10 mg/kg, iv), we inserted a pacing lead into the free wall of the right ventricle from the right external jugular vein under fluoroscopic guidance. The inactive lead was implanted in the connective tissue of the upper neck, and the ends of both leads were connected to a pacemaker generator (SX5984, Medtronic, Minneapolis, MN). The generator was placed in a cervical

subcutaneous pocket. Pacing was performed at 250 beats/min and continued for 2 weeks. Two weeks later, the dogs were again lightly anesthetized and a balloon-directed catheter was introduced into the pulmonary artery via the femoral vein to measure right atrial pressure and pulmonary artery pressure. Echocardiography (SSH-40A, Toshiba, Tokyo) was then performed and left ventricular diastolic dimension (LVDd) and systolic dimension (LVDs) were obtained to calculate percent fractional shortening (%FS). Subsequently, the right femoral artery was separated, and an electromagnetic flowmeter of 3.0 mm in diameter (MFV-1200, Nihon Kohden Instrument, Tokyo) was applied to the artery. A catheter for the measurement of aortic pressure was inserted from the proximal side of the flowmeter into the abdominal aorta, and a catheter for drug injection was inserted into the peripheral side of the flowmeter. Femoral vascular resistance (unit) was calculated by

[mean aortic pressure (mmHg) - mean right atrial pressure (mmHg)] / femoral blood flow (ml/min).

When the hemodynamics was stabilized by iv injection of aspirin (25 mg/kg) to exclude participation by the prostaglandin system,³ 10^{-12} to 10^{-6} mol/min acetylcholine (ACh), an endothelium-dependent vasodilatory substance, and 2×10^{-7} to 4×10^{-5} mol/min nitroglycerin (NTG), an endothelium-independent vasodilatory substance, were administered (each concentration for 1 min) through the catheter for drug injection, and the femoral blood flow was measured during congestive heart failure (congestive heart failure group; CHF, $n=12$). Measurement of vascular responses and hemodynamic parameters was carried out when femoral blood flow changes were at their peak. After measurement, the catheters were removed and pacing was discontinued. The skin was

Table 1 Hemodynamic Variables

	HR (beats/min)	MAoP (mmHg)	MPAP (mmHg)	BFBF (ml/min)	BFVR (unit)	LVDd (mm)	%FS (%)
Control (n=8)	107±7	101±8	16±3	24±11	4.0±0.4	31±3	40±4
CHF (n=12)	147±15*	92±7	30±3*	20±10	4.5±0.6	45±4*	16±6**
Re 1W (n=6)	114±12	97±8	17±4	21±9	4.2±0.5	33±4	36±4
Re 4W (n=6)	112±10	96±6	16±4	21±6	4.1±0.6	32±3	38±3

Control, control group; CHF, congestive heart failure group; Re 1W, recover 1 week group; Re 4W, recover 4 weeks group; HR, heart rate; MAoP, mean aortic pressure; MPAP, mean pulmonary artery pressure; BFBF, basal femoral blood flow; BFVR, basal femoral vascular resistance; LVDd, left ventricular diastolic dimension; %FS, percent fractional shortening. Values are means±SD

* $p < 0.05$ vs controls, Re 1W and Re 4W. ** $p < 0.01$ vs controls, Re 1W and Re 4W.

Fig 2. Femoral blood flow responses to cumulative doses of intra-arterial nitroglycerin in the control, CHF, Re 1W, and Re 4W groups. No significant difference in the femoral blood responses to nitroglycerin at any concentration could be detected among these 4 groups. Values are means±SD. CHF, congestive heart failure group; Re 1W, recover 1 week group; Re 4W, recover 4 weeks group.

then sutured, and the dogs were returned to the cages. The dogs were randomly divided into 2 groups according to the re-examination period after the first study during heart failure. Hemodynamic parameters and vascular responses were re-examined 1 week after cessation of pacing (an examination at 1 week recovery: recover 1 week group; Re 1W) in 1 group of dogs (n=6) and 4 weeks after cessation of pacing in the other group (n=6; an examination at 4 weeks recovery: recover 4 weeks group; Re 4W) (Fig 1). Improvement in wall motion was confirmed by echocardiography at each stage. The femoral artery opposite to that used during the period of heart failure was separated and an electromagnetic flowmeter was applied to the artery. The catheters for drug injection and measurement of aortic pressure were inserted into the artery in a way similar to that of the protocol for CHF. After iv injection of 25 mg/kg aspirin, the femoral blood flow response was also measured after

administration of ACh and NTG as in the protocol for CHF and compared with the data measured in CHF. Another group of dogs, in which pacemaker generators were implanted but pacing was not performed, were used as the control group (n=8). The femoral blood flow responses to NTG and ACh were also measured in the control group and compared with the responses at each stage.

Drugs

The drugs used in this study were acetylcholine hydrochloride (Daiichi Seiyaku), nitroglycerin (Nihon Kayaku), and aspirin DL-lysine (Green Cross).

Statistics

All values are expressed as means±SD. Statistical differences among groups were tested by 1-way analysis of variance with Scheffé's multiple comparison test. A p value of less than 0.05 was considered statistically significant.

Results

Hemodynamic Variables at Each Stage

Hemodynamic variables in each period are shown in Table 1. Heart rate, left ventricular diastolic dimension (LVDd), and mean pulmonary artery pressure were increased and %FS was decreased in CHF compared with the controls. Although mean aortic pressure and basal femoral blood flow tended to be decreased and basal femoral vascular resistance tended to be increased in CHF, they showed no statistical differences between the CHF and control groups. As early as 1 week after cessation of pacing, heart rate, LVDd, pulmonary artery pressure, and %FS returned to the control levels. There were no differences in hemodynamic parameters between the Re 1W and Re 4W groups.

Fig 3. Femoral blood flow responses to cumulative doses of intra-arterial acetylcholine in the control, CHF, Re 1W, and Re 4W groups. In the CHF and Re 1W groups, femoral blood flow responses to ACh were significantly depressed at high concentrations compared with the control group. There was no difference in blood flow response between the control group and the Re 4W group at any concentration. Values are means $\pm$ SD. * $p < 0.05$ vs the control group and the Re 4W group. CHF, congestive heart failure group; Re 1W, recover 1 week group; Re 4W, recover 4 weeks group.

Fig 4. Changes in femoral blood flow from baseline in response to acetylcholine in the control, CHF, Re 1W, and Re 4W groups. In the CHF and Re 1W groups, ACh-induced increases in femoral blood flow were significantly depressed compared with the control group. There was no difference in blood flow response between the control group and the Re 4W group. Values are means $\pm$ SD. * $p < 0.05$ vs the control group and the Re 4W group. CHF, congestive heart failure group; Re 1W, recover 1 week group; Re 4W, recover 4 weeks group; Δ FBF, peak femoral blood flow (ml/min)/basal femoral blood flow (ml/min).

Changes in the Femoral Blood Flow After Administration of ACh and NTG at Each Stage

Although the higher concentrations of NTG or ACh

Fig 5. Reductions in femoral vascular resistance in response to cumulative doses of intra-arterial nitroglycerin in the control, CHF, Re 1W and Re 4W groups. There were no differences in the responses among 4 groups at any concentrations. Values are means $\pm$ SD. CHF, congestive heart failure group; Re 1W, recover 1 week group; Re 4W, recover 4 weeks group.

Fig 6. Reductions in femoral vascular resistance in response to cumulative doses of intra-arterial acetylcholine administration in the control, CHF, Re 1W and Re 4W groups. In the CHF and Re 1W groups, the reductions in femoral vascular resistance in response to ACh were significantly attenuated at high concentrations compared with the control group. There was no difference in blood flow response between the control group and the Re 4W group at any concentration. Values are means $\pm$ SD. * $p < 0.05$ vs the control group and the Re 4W group. CHF, congestive heart failure group; Re 1W, recover 1 week group; Re 4W, recover 4 weeks group.

induced slight and gradual reductions in systemic arterial pressure, there were no significant changes in systemic arterial pressure at the time of peak femoral blood flow measurements. The blood flow responses

to NTG of each concentration did not differ among these 4 groups (Fig 2). Femoral blood flow responses to ACh were significantly attenuated in the CHF group compared with the control group (10^{-8} mol/min, 98 ± 20 in CHF vs 141 ± 15 ml/min in the control group, $p < 0.05$; 10^{-6} mol/min, 100 ± 22 in CHF vs 158 ± 20 ml/min in the control group, $p < 0.05$). There were no differences in the responses to ACh between the Re 1W and CHF groups. However, the femoral blood flow responses to ACh were significantly improved in the Re 4W group and returned to the same levels as in the control group (Fig 3). ACh-induced changes in femoral blood flow from the baseline were also attenuated in the CHF and Re 1W groups, but not in the Re 4W group, compared with the control group (Fig 4). Along with these blood flow responses, the reduction in femoral vascular resistance in response to ACh, but not to NTG, was attenuated in the CHF groups (Figs 5 and 6). Animals in the Re 1W group showed a similar attenuation of ACh-induced response in femoral vascular resistance to that in the CHF group. In contrast, in the Re 4W group, ACh reduced femoral vascular resistance to a level similar to that in the control group.

Discussion

The present study demonstrated that impaired endothelium-dependent vasodilatory response to ACh in the resistance vessels of the hindlimb was reversibly improved in dogs with pacing-induced heart failure. The improvement of the vascular response was observed later than the overt hemodynamic recovery attained by the discontinuation of pacing.

It is well recognized that heart failure is associated with impaired endothelium-dependent vasodilation in peripheral vessels.¹³⁻¹⁶ The impaired vasodilatory response in heart failure is not restricted to the muscarinic agonist-mediated response.¹⁷ We have previously shown that the vasodilatory responses to ADP, another endothelium-dependent vasodilatory substance, were also reduced in the hindlimb resistance vessels of the same canine model of pacing-induced heart failure as used in the present study.¹⁸ The pacing-induced heart failure model in dogs is shown to mimic closely congestive heart failure in humans in terms of hemodynamic changes and neurohumoral factors.¹⁹ It is demonstrated that the depressed cardiac function is reversibly normalized in this model by discontinuing pacing.^{11,12,19} Moe et al¹² reported that the dilated left ventricle was not completely restored within 4 weeks of pacing, although left ventricular wall motion was rapidly normalized by

cessation of pacing in dogs with heart failure induced by rapid ventricular pacing at 250 beats/min for 5 weeks. In our model, dogs underwent pacing for 2 weeks and the left ventricular diastolic dimension was normalized within 1 week after pacing was stopped, probably because of the short period of pacing. This pacing-induced heart failure model enables us to study the reversibility of endothelial dysfunction in heart failure independently of the influence of medication, such as angiotensin-converting enzyme (ACE) inhibitors, which may itself change endothelial function.²⁰

Although it was desirable to perform a longitudinal study in which changes in vascular responses were studied within each animal, we subdivided the animals into 2 groups because of the difficulty in re-using a femoral artery.

Impairment of endothelium-dependent vasodilation in the resistance vessels in heart failure is well accepted, but its mechanisms remain unknown. Disturbance in the production or release of NO in endothelial cells, increase in degradation by superoxide anion produced from endothelial cells, and disturbance in diffusion of endothelium-derived relaxing factor owing to the accumulation of sodium chloride and water in the vascular wall have all been proposed as mechanisms.²¹⁻²³ The possibility of the reduced response of vascular smooth muscle to NO cannot be completely denied, but the vasodilatory response to NTG, which is an endothelium-independent vasodilator, was maintained. Thus, the response of smooth muscle is unlikely to be diminished in the present study.

Kubo et al²⁴ examined the effect of heart transplantation on endothelium-dependent vasodilatory response. They found that forearm blood flow responses to methacholine and peak reactive hyperemia were improved after transplantation. Our results are consistent with theirs and suggest that the endothelium-dependent vascular response of resistance vessels of skeletal muscle is a potential therapeutic target. Kubo et al²⁴ did not measure the time course of endothelium-dependent vascular responses after transplantation. In contrast, we measured the time course of recovery of attenuated endothelium-dependent vascular responses during the process of improvement of heart failure.

Teerlink et al²⁵ performed an isometric tension experiment in the aorta of rats with heart failure induced by myocardial infarction and investigated the time-dependent worsening of the endothelium-dependent vasodilatory response after the onset of myocardial infarction. They demonstrated that the vasodilatory response had not decreased 1 week after

the onset of myocardial infarction when hemodynamic changes showed findings characteristic of heart failure. The endothelium-dependent vasodilatory response started to decline 4 weeks after the onset of myocardial infarction, and worsened progressively thereafter. They concluded that endothelial dysfunction in heart failure is not merely the distinct result of hemodynamic insufficiency. Consideration of present findings along with those of Teerlink et al²⁵ suggests that endothelial dysfunction is a delayed phenomenon that evolves over time after hemodynamic deterioration and that, once it occurs, a certain period is needed for recovery. We did not correlate the vascular responses with hemodynamic parameters or the extent of neurohumoral activation during the period of recovery from heart failure. Also, the present study was not directed toward the mechanism(s) of the impairment of endothelium-dependent vasodilatory response and its recovery in heart failure. However, it seems possible that endothelial damage occurs during the process of heart failure and repair of the damaged endothelium requires a certain period after hemodynamic improvement²⁶. As neurohumoral factors such as sympathetic nervous system, the renin-angiotensin system and cytokines may play important roles in endothelial dysfunction, future studies assessing the relation between changes in of these factors and endothelial dysfunction may elucidate the mechanisms of recovery of endothelial function.

The present results have some clinical relevance. Patients with congestive heart failure exhibit decreased exercise tolerance, which is partly due to the inadequate increase in blood flow to the skeletal muscle during exercise^{27,28}. Some reports have suggested that the decrease in endothelium-dependent vasodilatory response in resistance vessels of the skeletal muscle is related to a disturbance in the increase of blood flow during exercise^{29,30}. In recent years, percutaneous transluminal mitral commissurotomy (PTMC) has been commonly used in treating mitral stenosis, and exercise tolerance before and after PTMC has been investigated. It has increasingly become clear that exercise tolerance is improved some time after PTMC³¹. Vascular endothelial dysfunction in heart failure is thought to be correlated closely with the morbidity of heart failure. Enhancing cardiac function by inotropic drugs is not directly related to the reduction in morbidity in patients with heart failure. This finding is also noted in patients who undergo cardiac transplantation, and suggests that it takes some time pathologic conditions to resolve after cardiac function has improved³². A time lag between improvement in hemodynamic changes and improvement in endothelial

dysfunction, as shown by the present study, may be involved in the phenomenon observed after PTMC or cardiac transplantation.

In summary, we found that the impaired endothelium-dependent vasodilatory response in hindlimb resistance vessels of dogs with pacing-induced heart failure could be reversed with the improvement of hemodynamics attained by discontinuation of pacing. A certain period is needed after hemodynamic improvement until the recovery of vascular response. The present results provide useful information on the strategy to be adopted in heart failure therapy.

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