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Comparative effects of captopril, nitroprusside, dopamine and lanatoside C on a new model of rabbit congestive heart failure

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ABSTRACT A new animal model of congestive heart failure that mimics failure of coronary heart disease with hypertension was established in rabbits 6-9 d after gradual aortic constriction superimposed on myocardial infarction. The model resulted in significant hypertrophy of the left ventricle and whole heart, an increase of LVEDP (1.7 ± 0.6 *vs* 0.4 ± 0.3 kPa, $p<0.01$), and especially significant decrease of ventricular segmental contraction within the non-infarct area (ΔL, 0.8 ± 0.4 *vs* 1.4 ± 0.5 mm, $p<0.01$) as monitored by a sonomicrometer. Comparative evaluation of captopril, nitroprusside, dopamine and lanatoside C was performed on this model. It was demonstrated that captopril and nitroprusside significantly lowered the dP/dt_{max}, left ventricular pressure (LVP), and enhanced the segmental contraction; dopamine predominantly increased dP/dt_{max}, while lanatoside C manifested significant positive effect on both dP/dt_{max} and segmental contraction. Vasodilators captopril and nitroprusside were also characterized by a significant reduction of the tension-time index (TTI), while dopamine increased it.

KEY WORDS congestive heart failure; myocardial infarction; aortic constriction; myocardial contraction; captopril; nitroprusside; dopamine; lanatoside C

There have been many models of heart failure reported[1], but none mimics congestive heart failure (CHF) originating from coronary heart disease with hypertension, which is a common cause of heart failure[2].

Captopril is an effective oral agent for congestive heart failure refractory to conventional inotropic and diuretic therapy[3]. Some characteristics of captopril, such as the reduction of plasma aldosterone with associated beneficial effects on potassium retention and sodium excretion, may offer advantages over other vasodilators[4]. However, its effects on myocardial contractility especially in comparison with other vasodilators or inotropic drugs have not been differentiated.

The aim of the present paper is to describe a method of producing a new model of CHF that originates from gradual aortic constriction superimposed on myocardial infarction in rabbits, and to discuss the results of comparative studies of captopril, nitroprusside, dopamine and lanatoside C on this model.

MATERIALS AND METHODS

CHF model Rabbits ($3.2 \pm$ SD 0.3 kg) of both sexes were used. Under local anesthesia of 1% procaine, using aseptic technique, the chest was opened through midline sternotomy keeping the pleural cavity intact. Spontaneous respiration was maintained. The heart was exposed and the LAD was ligated near its origin to produce myocardial infarction. Two piezoelectric crystals (2.5 mm in diameter, 3 MHz frequency) were implanted into the subendocardium followed a stab in the non-ischemic area (Fig 1) to monitor the segmental contraction. The implanted ultrasonic crystals were wired and exteriorized for subsequent monitoring of segmental contraction. An aortic constrictor was fixed arround the ascending aorta. The chest was closed. Following sternotomy, the rabbits received penicillin

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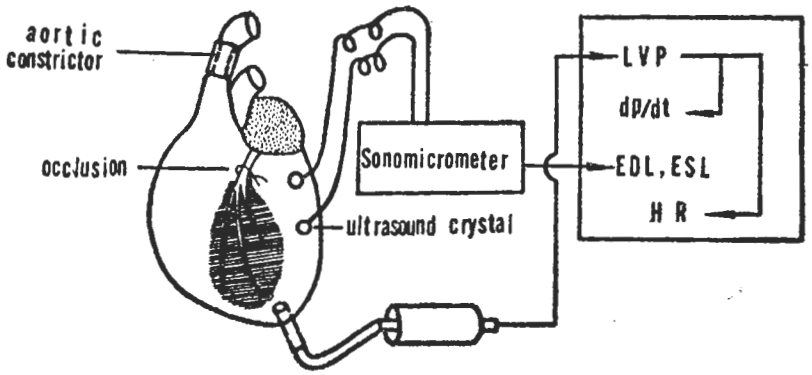

Fig 1. Congestive heart failure (CHF) produced by occlusion of left anterior descending artery (LAD) and gradual aortic constriction by an aortic constrictor. Note a pair of ultrasound crystals was implanted in the myocardium of the non-infarcted area, and segmental contraction was recorded via sonomicrometer. An intracardiac catheter was connected to a pressure transducer and LVP, dP/dt and heart rate were recorded on a polygraph system.

200 000 IU im bid for 4–5 d.

Gradual aortic constrictor A special ring-form band (which was pressed and closed around the aorta) was designed for gradual constriction of the ascending aorta. It was composed of two layers: the outer layer, a 1.2 mm thick aluminum band, was strong enough to constrict the aorta and maintain the constriction once it was compressed according to the desired diameter; the inner layer, a thin plastic bag enclosing approximately 2 mm of kelp as an absorbant. Openings in the plastic bag permitted tissue fluid to gradually pass into the bag and be absorbed by the kelp, which in turn swelled and compressed the aorta gradually. The initial diameter of the aortic constrictor was designed to be 1/3 less than the original diameter of the individual aorta. The original circumferential length was measured by circling a thread around the aorta where constrictor was to be fixed. 1/3 of the circumferential length was cut off, and the remaining 2/3 was used as the standard circumferential length of the constrictor. In this way, after fixing the constrictor around the aorta, the diameter of the aorta was initially reduced by 1/3 of its original size. Upon gradual swelling of the absorbant layer, the aorta was further constricted to less than 1/2 of the original diameter. The after load of the jeopardized myocardium increased in the following 24 h, heart function deteriorated and CHF resulted.

Measurement of segmental contraction The segmental length change of the myocardium monitored by a sonomicrometer (Triton Technology Inc, San Diego) as described previously[5]. The ultrasound transit-time between the 2 implanted crystals provided the basis for segment length measurement, which served as a parameter of segmental contractility. Its accuracy was better than 0.01 mm for relative change in segment length and better than 0.2 mm for absolute changes[6]. The segmental contraction is expressed as segmental shortening (ΔL), calculated as the differences in mm between end distolic length (EDL) and end systolic length (ESL). The EDL was identified as the point just before the onset of the positive dP/dt_{max}, and ESL was defined as the maximum systolic excursion occurring within 20 ms of the negative dP/dt_{max}[7].

Experimental protocol 6–9 (8.1 ± 1.6) d after the operation, the chests of the rabbits were re-opened under procaine anesthesia. A polyurethane nylon catheter was introduced into the apex of the left ventricle

for measurement of the LVP and dP/dt_{max}. Heart rate was triggered by LVP and was monitored by HR counter. The wires connecting the previously implanted ultrasonic crystals were secured to monitor the segmental contraction via a sonomicrometer. LVP, dP/dt, segmental contraction and heart rate were recorded on a Polygraph System (Nihon Kohden). Tension-time index (TTI) was estimated by the area under the LVP curve, an integration of ejection time and LVP projected from dP/dt_{max} to the turning point of dP/dt[8]. TTI is assumed to be a measurement of myocardial work and oxygen consumption. Effects of drugs on these parameters were tested in the following sequence: 1. sodium nitroprusside 10 μg/(kg • min) for 10 min followed by 20 μg/(kg • min) for another 10 min; 2. Dopamine 0.2 and 0.4 mg/kg; 3. Captopril 2 and 4 mg/kg; and 4. Lanatoside C 0.13 mg/kg. Each drug was administered only after the effect of the previous drug had subsided (see Fig 2).

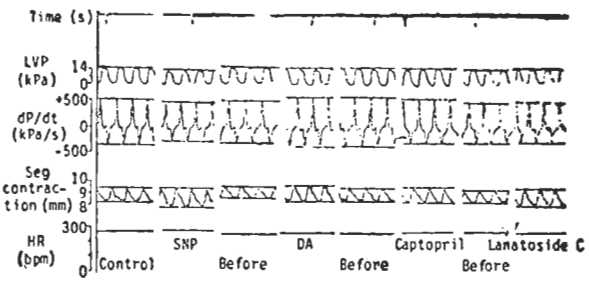

Fig 2. Representative example (rabbit wt 3.1 kg) showing the effect of sodium nitroprusside (SNP) 10 μg/(kg·min), dopamine (DA) 2 mg/kg, captopril 2 mg/kg and lanatoside C 0.13 mg/kg on LVP, dP/dt, segmental contraction and heart rate (HR). Note the reduction of LVP and dP/dt_{max} with concomitent increase of segmental contraction after SNP and captopril injection. Note also DA and lanatoside C increase both dP/dt_{max} and segmental contraction. Paper speed 50 mm/s

In order to compare the possible differences between drug effects on the failing heart and the normal heart, a control group of 11 rabbits without CHF were operated on and processed according to the same protocol described above.

Drugs Captopril (Squibb), lanatoside C (Shanghai 13th Pharmaceutical Factory) and dopamine (Shanghai 10th Pharmaceutical Factory) were injected by iv bolus. Sodium nitroprusside (Pharmaceutical Industry Institute of Beijing) solution prepared just before use and protected from light, was infused by Murphy's drip at a constant rate.

Experimental design and statistics Rabbits of the CHF group and the control group were operated on alternately. Both group comparisons and individual comparisons were calculated by *t*-test to estimate the differences between the test and control group, as well as the effects of different drugs within the same group.

RESULTS

CHF model Symptoms and signs of CHF-cyanosis of the ear and mouth area, edema of the feet, general weakness, usually appears 6-9 d after the occlusion of the LAD and constriction of aorta. 13 out of 25 rabbits (52%) died with 6 d (among them 9 died within 24 h). Among the 12 survivals, one showed no apparent symptoms and signs of CHF and was discarded from the experiment. 11 rabbits were used in the drug study. Two of the 11 rabbits died of severe CHF on the table before finishing the drug tests.

Criteria of CHF 1) Segmental contraction was decreased after the modelling process, a significant lengthening of ESL (8.7 ± 2.1 *vs* 7.6 ± 1.7 mm, $p < 0.05$) and a decrease of ΔL (0.8 ± 0.4 *vs* 1.4 ± 0.5 mm, $p < 0.01$) up to $42 \pm 38\%$ (Tab 1). 2) In heart failure rabbits, LVEDP was significantly higher, (1.7 ± 0.6 kPa 13.0 ± 4.5 mm Hg), in constrast with 0.4 ± 0.3 kPa (3.3 ± 2.6 mmHg) in control rabbits. As shown

in Tab 2, dP/dt_{max} was less than the control, although statistically the difference is not significant ($p=0.1$). 3) Weights of the whole heart and left ventricle as well as the ratio of heart wt/body wt were significantly higher in failing heart than the control group (Tab 2).

Tab 1. Change of segmental contractility after heart failure in rabbits. $n=10$, $\bar{X}\pm SD$. $^*p>0.05$, $^{**}p<0.05$, $^{***}p<0.01$

Indices	Before failure	After failure	Change
EDL(mm)	9.0±2.0	9.4±2.3	+0.5±0.9*
ESL(mm)	7.6±1.7	8.7±2.1	+1.0±1.0**
ΔL(mm)	1.4±0.5	0.8±0.4	−0.6±0.5*** (42±38%)

Tab 2. Comparison of heart weight, LVEDP and dP/dt in failing group and sham-operated group. $^*p>0.05$, $^{**}p<0.05$, $^{***}p<0.01$

Indices	Sham-operat (n=11)	Failing heart (n=10)
Body wt (kg)	3.2±0.5	3.22±0.29*
Heart wt(g)	8.1±1.8	10.9±1.5***
Left ventricle wt(g)	5.2±1.2	6.3±0.9**
Heart wt/body wt(%)	0.25±0.03	0.34±0.03***
dP/dt_{max}(kPa/s)	387±35	317±144*
LVEDP(kPa)	0.4±0.3 (n=6)	1.7±0.6*** (n=5)

Effects of captopril, dopamine, sodium nitroprusside and lanatoside C on segmental contraction and hemodynamics of sham-operated heart and CHF of rabbits

1. Captopril lowered LVP and dP/dt_{max} significantly in doses of 2 mg/kg in both sham-operated and CHF rabbits (Tab 3). It reduced segmental shortening (ΔL) 5–13% in 2 and 4 mg/kg, in both groups of rabbits. At dose of 4 mg/kg it also reduced TTI. It did not affect heart rate in any dose. It reduced LVEDP from 1.1±0.4 to 0.6±0.3 kPa ($p<0.01$) in CHF rabbits (Tab 3).

2. Sodium nitroprusside in doses of 10 and 20 μg/(kg • min) lowered LVP and dP/dt_{max} significantly in both groups. Only at 20 μg/(kg • min) did it significantly improve the segmental contraction of CHF rabbits. It also reduced TTI, but HR was not affected. It normalized LVEDP from 1.7±0.5 to 0.4±0.6 kPa ($p<0.01$) in CHF rabbits (Tab 3).

3. Dopamine significantly enhanced LVP and dP/dt_{max} at doses of 0.4 mg/kg. Though it increased segmental shortening 6–15% in 2 doses in both groups, it only attained statistically significant levels in the CHF group receiving doses of 0.2 mg/kg. It increased HR and TTI in the CHF group (Tab 3).

4. Lanatoside C manifested enhancement of both dP/dt_{max} and segmental shortening in both groups. It also significantly reduced HR in both groups (Tab 3).

DISCUSSION

Many experimental models of heart failure have been devised using either an increase of pre-load or after-load of heart, or by jeopardizing the myocardium by ischemia or cardiotoxic chemicals[1]. Most models are useful in evaluating particular aspects of failure, and can provide information not otherwise available from the patients. However, so far no reported model can mimic CHF of coronary heart disease and hypertension. The present paper reports for the first time such a model produced by occlusion of the LAD and superimposed by gradual aortic constriction. The following criteria justified the establishment of CHF: 1) Segmental contraction other than the infarct area was reduced significantly; 2) LVEDP was remarkably increased, and dP/dt_{max} tended to decrease; 3) Both the left ventricle and whole heart hypertrophied as indicated by increase of weight. It was shown that constriction of aorta to about 1/4 of the original diameter produced heart failure in most rabbits[8]. In our experiment, neither constriction of the aorta to about 2/3 of the original diameter, nor occlusion of LAD itself causes congestive failure. However, superimposing gradual

Tab 3. Effects of captopril (CAP), sodium nitroprusside (SNP), dopamine (DA), and lanatoside C (LNC) on segmental contraction and hemodynamics in sham-operated (Sham) and failing (Fail) hearts, change after drug (ΔA) compared with before drug (Bef). n = 8. *p > 0.05, **p < 0.05, ***p < 0.01

Drug	Dose	Experiment		LVP (kPa)	$+dP/dt_{max}$ (kPa/s)	EDL (mm)	ESL (mm)	ΔL (mm)	TTI (mm^2)	HR (bpm)
CAP	2*	Sham	Bef	12.0±2.0	306±67	8.8±1.3	7.5±1.2	1.28±0.25	55±15	242±19
			ΔA	−1.2±1.4**	−33±35**	−	−	0.07±0.12* (5±9%)	−5±9*	−5±24*
		Fail	Bef	14.0±3.1	327±106	9.5±2.1	8.7±2.1	0.83±0.29	70±34	246±32
			ΔA	−0.8±0.9**	−24±25**	−	−	0.05±0.04*** (7±5%)	−5±8*	−3±15*
	4*	Sham	Bef	12.8±1.6	316±54	8.8±1.4	7.6±1.3	1.23±0.27	64±14	241±22
			ΔA	−1.2±0.9***	−20±32*	−	−	0.15±0.18** (12±14%)	−10±10**	−8±14*
		Fail	Bef	13.7±3.5	313±79	9.3±2.3	8.6±2.2	0.77±0.32	71±12	243±27
			ΔA	−0.8±1.7*	−20±31*	−	−	0.23±0.27** (30±35%)	−5±3**	−7±12*
SNP	10†	Sham	Bef	13.6±2.0	338±70	8.6±1.2	7.5±1.1	1.07±0.27	57±14	240±30
			ΔA	−1.3±0.9***	−12±23*	−	−	0.14±0.20* (12±18%)	−8±8**	4±14
		Fail	Bef	14.1±3.5	355±132	9.4±3.0	8.6±2.2	0.79±0.36	58±25	258±25
			ΔA	−0.8±2.3*	−36±26***	−	−	0.01±0.1* (1.3±13%)	−9±17	5±6*
	20†	Sham	Bef	13.0±2.3	328±63	8.7±1.3	7.5±1.1	1.27±0.32	48±8	240±27
			ΔA	−2.3±1.2***	−45±47	−	−	0.01±0.10* (1.1±8%)	−9±5***	5±24*
		Fail	Bef	13.3±4.1	324±131	9.2±2.3	8.5±2.2	0.73±0.33	46±16	267±28
			ΔA	−2.0±1.5***	−58±41***	−	−	0.10±0.09*** (14±13%)	−6±8*	2±11*
DA	0.2*	Sham	Bef	12.1±2.1	320±75	8.7±1.3	7.4±1.1	1.24±0.35	54±17	228±30
			ΔA	1.2±1.5*	61±49***	−	−	0.08±0.18* (7±22%)	4±15*	8±10**
		Fail	Bef	13.1±3.6	304±116	9.5±2.2	8.7±2.1	0.77±0.28	55±24	250±34
			ΔA	1.1±1.7*	35±45*	−	−	0.07±0.08** (10±11%)	4±6*	9±6***
	0.4*	Sham	Bef	12.6±2.0	352±73	8.8±1.2	7.5±1.2	1.26±0.26	57±10	232±28
			ΔA	1.2±0.9***	54±39***	−	−	0.19±0.3* (15±24%)	5±15*	9±10*
		Fail	Bef	13.6±2.5	330±120	9.5±2.2	8.7±2.1	0.80±0.28	63±20	255±22
			ΔA	0.7±0.8**	34±40**	−	−	0.05±0.09* (6±11%)	6±6**	7±10*
LNC	0.13*	Sham	Bef	11.6±2.8	276±87	8.8±1.4	7.6±1.2	1.24±0.34	55±17	230±27
			ΔA	0.8±1.0*	32±33*	−	−	0.12±0.15** (10±12%)	−2±9*	−12±8**
		Fail	Bef	12.6±3.7	266±94	8.7±1.7	8.0±1.6	0.68±0.30	71±24	237±30
			ΔA	1.2±0.8***	51±35***	−	−	0.04±0.03** (6±4%)	10±16*	−14±12**

* mg/kg, † μg/(kg·min)

aortic constriction (to about 1/2-1/3 of original diameter) on myocardial infarct of rabbits constantly produced CHF. In some of the rabbits, CHF was so severe that they died on the operation table before finishing the drug experiment. Only one of the 12 rabbits resisted the injuries. Since the mortality rate was relatively low (60%) and rate of success was high, we would recommend this clinically oriented and stable CHF model for the evaluation of drugs on CHF.

We reported previously that angiotensin converting enzyme (ACE) inhibitors captopril and enalapril protected myocardial ischemia and reperfusion damage in the rat[10] and enalapril protected reperfusion arrhythmia and preserved segmental contractibility of infarcted areas in anesthetized dogs[5]. In this paper we demonstrated that captopril at doses of 2 and 4 mg/kg significantly improved the segmental contractibility of non-infarcted area of CHF rabbits as well as in the normal heart. Sodium nitroprusside at dose of 20 μg/(kg·min) and 0.2 mg/kg shared similar beneficial effects in the CHF model but not in the normal heart.

The first derivative of LVP, dP/dt_{max} is often used as an index of myocardial contractility. However, its fidelity is limited by alteration of after-load and pre-load of heart. It is also limited to the extent that non-uniformities exist in the ventricular wall[11]. We demonstrated in the present work that there was a dissociation of these two indices of heart function: dP/dt_{max} and segmental contraction in the response to vasodilators, captopril and nitroprusside. Segmental contraction increased, while dP/dt_{max} decreased. It was interesting to find that nitroprusside at doses of 20 μg/(kg·min) lowered dP/dt_{max}, which was correlated with the decrease of LVP ($r = 0.58$). However, previous reports did not find a significant change in dP/dt_{max} with either enalapril in dogs with acute heart failure[12], or with nitroprusside in CHF patients[13]. The discrepancy between our data and the literature may be attributed to either the difference of animal species and/or dose schedule of drugs. At any rate, the beneficial effect of vasodilators on CHF cannot be evaluated by dP/dt_{max}. However, their therapeutic efficacy can be estimated by segmental contraction. Our data also indicated that dP/dt_{max} correlated well with the measurement of segmental contraction in those inotropic agents without major vasoactivity, such as lanatoside C. In addition, our rabbit model confirmed the finding that nitroprusside significantly reduced TTI in CHF patients[14].

No significant difference in cardiac function or hemodynamic effect was found between the rabbits of the sham-operated and heart failure groups, except that an apparently better effect was noticed as an increase in dP/dt_{max} induced by lanatoside C ($p = 0.2$). This theoretically unexpected result may be attributed to the relatively short duration of CHF formed in our experiment.

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卡托普利、硝普钠、多巴胺与毛花甙 C 对兔充血性心衰新模型的作用比较[1]

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提要 结扎兔冠脉造成心肌梗塞, 附加主动脉逐渐缩窄, 6-9 d 后形成拟似冠心病高血压导致充血性心衰的新动物模型. 确认本模型的指标是: 全心和左室肥大, LVEDP 显著升高达 1.7±0.6 kPa (13±4 mm Hg), 与对照组 (0.4±0.3 kPa) 比较 $p<0.01$. dP/dt_{max} 趋于降低, 特别是用超声微测距仪 (sonomicrometer) 测定非缺血区心肌节段收缩显著降低 (收缩幅度 ΔL 由心衰前 1.4±0.5 降为 0.8±0.4 mm). 用本模型比较各药作用显示: 卡托普利与硝普钠显著降低左室内压与 dP/dt_{max} 并显著增强非梗塞区节段收缩; 多巴胺主要升高 dP/dt_{max} 而毛花甙 C 则表现为对心肌节段收缩与 dP/dt_{max} 均显著增加; 卡托普利与硝普钠并显著减低"张力时间指数", 而多巴胺则使之升高.

关键词 充血性心力衰竭; 心肌梗塞; 主动脉缩窄; 心肌收缩; 卡托普利; 硝普钠; 多巴胺; 毛花甙 C

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