HEMODYNAMIC EFFICACY OF E-1020 IN COMPARISON WITH DOPAMINE ON ACUTE MITRAL REGURGITATION IN ANESTHETIZED DOGS

HITOSHI TANIO, M.D., TOSHIAKI KUMADA, M.D., MASATAKA HAYASHI, M.D.
YOSHIHIRO HIMURA, M.D., YASUYUKI NAKAMURA, M.D.
AND CHUICHI KAWAI, M.D.

To evaluate the effects of a new phosphodiesterase inhibitor, E-1020 (1, 2-dihydro-6-methyl-2-oxo-5-(imidazo [1, 2-a] pyridin-6-yl)-3-pyridine carbonitrile hydrochloride monohydrate), on cardiovascular hemodynamics in acute heart failure, we compared its effects with those of dopamine on experimentally produced acute mitral regurgitation in dogs.

After the production of mitral regurgitation by transmyocardial chordal sectioning and obtaining a stable state, dopamine ($5 \mu\text{g/kg/min}$) was infused until the peak positive dP/dt (peak (+) dP/dt) increased to about 50% of the pre-dopamine value. After complete recovery, E-1020 ($30 \mu\text{g/kg}$) was infused over 5 min and the data were obtained 10 min later.

Both drugs equally increased peak (+) dP/dt , decreased systemic vascular resistance, and increased cardiac output. Left ventricular (LV) end-diastolic pressure, LV end-diastolic segment length (EDL), and mean left atrial (LA) pressure decreased with both drugs. The changes in EDL and mean LA pressure were larger with E-1020 than with dopamine ($p < .01$ and $p < .05$). Although mean inferior vena caval blood flow volume (mIVCF) increased and mean inferior vena caval pressure decreased with both drugs, the increment of mIVCF was smaller with E-1020 ($p < .001$). Thus, E-1020 had not only a positive inotropic effect but also a vasodilatory action both on resistance vessels and on capacitance vessels.

THE primary cause of heart failure is a decrease in myocardial contractility. Improvement of the contractility will therefore restore cardiac pump function and lead to alleviation of heart failure. This is the reason why inotropic agents are used for the

treatment of heart failure. The inotropic drugs most commonly used for this purpose are digitalis glycosides and catecholamines. Digitalis glycosides, however, induce considerable toxicity due to their narrow therapeutic range. In addition, the efficacy of digitalis glycosides in heart failure has recently been questioned^{1,2}. Catecholamines can have an arrhythmogenic effect and increase myocardial oxygen consumption^{3,4}. Moreover, although the usefulness of

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The Third Division, Department of Internal Medicine, Faculty of Medicine, Kyoto University, Kyoto, Japan

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Mailing address: Prof. Chuichi Kawai, M.D., The Third Division, Department of Internal Medicine, Faculty of Medicine, Kyoto University, 54 Kawaracho Shogoin, Sakyo-ku, Kyoto 606, Japan

Fig. 1. Chemical structure of E-1020

catecholamines for the treatment of heart failure has been recognized, the route of administration must be intravenous, and therefore their use is limited to a short period. Thus, new inotropic agents have been sought to replace these drugs^{5,6}

Phosphodiesterase inhibitors, which not only increase cardiac contractility but also cause vasodilation, have recently been developed and their clinical usefulness has been reported^{7,8}. E-1020, one of the imidazopyridinylpyridine derivatives, is a phosphodiesterase inhibitor synthesized in Japan (Fig. 1)^{9,10}. In studies using isolated papillary muscles or intact hearts, E-1020 was shown to increase myocardial contractility by inhibiting the fraction III isoenzyme of phosphodiesterase, and so causing an increase in the myocardial cyclic AMP level⁹. In addition, this drug is a vasodilator with a direct action on vascular smooth muscle¹⁰. However, there are few reports on the effects of E-1020 in heart failure.

In this study, we experimentally produced acute mitral regurgitation to evaluate the efficacy of E-1020 in left heart failure, and compared the effect of E-1020 with that of dopamine, which is a potent positive inotropic agent^{4,11,12}.

METHODS

Ten adult mongrel dogs (body weight 19.0–31.5 kg; average 24.3 kg) were anesthetized with sodium pentobarbital (25 mg/kg i.v. and then an infusion of 4 mg/kg/hr). Respiration was maintained by an artificial ventilator delivering room air (Harvard apparatus NSH34RH). A left thoracotomy was performed via the fifth intercostal space. After the pericardium was opened fully, a high-fidelity micromanometer (Konigsberg P-7) and a polyethylene

Fig. 2. Hemodynamic effects of E-1020 on mitral regurgitation. The arrow shows the beginning of E-1020 infusion. Note that E-1020 increases peak (+) dP/dt, AoF, and IVCF, and decreases LAP and SL. LAP=left atrial pressure; LVP=left ventricular pressure; dP/dt=first derivative of left ventricular pressure; SL=left ventricular segment length in the anterior free wall; IVCF=inferior vena caval blood flow volume; AoF=aortic blood flow volume.

tube were introduced into the left ventricle through the ventricular apex to measure left ventricular (LV) pressure and the first derivative of LV pressure (dP/dt). The tube was connected to a Statham P23ID transducer, and the zero level was standardized at the mid-chest. The micromanometer was calibrated by adjusting its output to the measured pressure using the fluid filled method. NIH catheters (8F) were placed in the ascending aorta via the femoral artery and in the inferior vena cava (IVC) via the femoral vein, and were connected to Statham P23ID transducers for measuring the pressures in these vessels. A microtip-catheter (Millar SPC-484A) was inserted into the left atrium through the left atrial appendage. An electromagnetic flow probe (Narcomatic Model RT-500) was attached to the ascending aorta to measure cardiac output. An ultrasonic transit-time flow probe (Transonic Model

TABLE 1 EFFECTS OF DOPAMINE AND E-1020 ON ACUTE MITRAL REGURGITATION (N=10)

	HR b/min	mLAP mmHg	EDP mmHg	LVPP mmHg	peak (+) dP/dt mmHg/sec	TSR dyn·s·cm ⁻⁵	EDL mm	mean VSS circ/sec	CO L/min	SV ml	mIVCF L/min	mIVCP mmHg
Control	164 ± 16	7.6 ± 1.6	7.5 ± 4.2	124 ± 18	2432 ± 619	3963 ± 1325	10	1.11 ± 0.35	2.01 ± 0.62	12.2 ± 3.6	1.29 ± 0.29	5.8 ± 1.5
MR 1	172 ± 17	12.7 ± 3.2	14.2 ± 7.4	116 ± 20	2586 ± 736	4110 ± 1516	10.9 ± 0.5	1.53 ± 0.62	1.77 ± 0.56	10.3 ± 3.3	1.05 ± 0.17	6.4 ± 1.6
Dopamine	175 ± 21	10.3 ± 2.6	10.2 ± 6.8	125 ± 21	4031 ± 1584	3224 ± 1047	10.5 ± 0.6	1.96 ± 0.86	2.15 ± 0.65	12.4 ± 3.5	1.48 ± 0.30	5.6 ± 1.6
p 1	NS	<.001	<.001	<.01	NS	NS	<.001	<.01	<.05	<.001	<.01	<.05
p 2	NS	<.01	<.01	<.01	<.001	<.001	<.05	<.01	<.01	<.01	<.001	<.05
MR 2	170 ± 17	12.5 ± 2.7	12.3 ± 6.1	114 ± 20	2569 ± 696	4208 ± 1438	10.7 ± 0.4	1.47 ± 0.61	1.69 ± 0.55	10.0 ± 3.2	1.06 ± 0.23	6.7 ± 1.6
E-1020	175 ± 16	8.8 ± 2.2	8.0 ± 5.4	126 ± 21	4095 ± 1270	3312 ± 1094	10.0 ± 0.5	1.95 ± 0.83	2.01 ± 0.55	11.6 ± 2.9	1.23 ± 0.28	5.3 ± 1.4
p 3	NS	<.001	<.01	<.001	<.001	<.001	<.001	<.01	<.01	<.01	<.01	<.001
p 4	NS	<.05	NS	NS	NS	NS	<.01	NS	NS	NS	<.001	NS

Control=before MR (mitral regurgitation); MR1=MR before Dopamine; MR2=MR before E-1020; HR=heart rate; mLAP=mean left atrial pressure; EDP=left ventricular end-diastolic pressure; LVPP=left ventricular peak systolic pressure; peak (+) dP/dt=peak positive dP/dt; TSR=total systemic vascular resistance; EDL=left ventricular end-diastolic length; mean VSS=mean segment shortening velocity; CO=cardiac output; SV=stroke volume; mIVCF=mean inferior vena caval blood flow volume; mIVCP=mean inferior vena caval pressure; p1=MR1 vs Control; p2=Dopamine vs MR1; p3=E-1020 vs MR2; p4=E-1020 vs Dopamine; No significant difference was noted between MR2 and MR1.

Fig. 3. Representative tracings before and after dopamine and E-1020 infusions. MR 1=MR (mitral regurgitation) before dopamine; MR 2=MR before E-1020; IVCP=inferior vena caval pressure.

T201) was positioned around the IVC at about 4–5 cm below the junction of the right atrium to measure IVC blood flow volume. The calibration curves of this flowmeter *in vivo* established an absolute accuracy of 5.1% with a 4 ml/min zero offset, and a linearity within the range of error for the calibration technique (1% of full scale)¹³ We used a filter at 10 Hz. For the accurate measurement of venous flow volume we used a transit-time flowmeter. The transit-time flowmeter allows accurate flow volume to be obtained independent of the vessel dimensions or the blood flow velocity¹³ A pair of ultrasonic crystals (2 mm in diameter, 5 MHz) were implanted 1–2 cm apart in the subendocardial layer of the left ventricular anterior free wall in a circumferential plane for the measurement of left ventricular segment length¹⁴ The measured values were normalized to a 10 mm initial dimension by dividing the observed length by the control LV end-diastolic segment length (EDL) and multiplying by 10. The mean segment

Fig. 4. The effects of dopamine and E-1020 on EDP and EDL. EDP=left ventricular end-diastolic pressure; EDL=left ventricular end-diastolic segment length; C=Control before MR; D=Dopamine; E=E-1020; *= $P < .05$; **= $P < .01$; ***= $P < .001$.

shortening velocity was calculated using the formula $(EDL - ESL)/(EDL \times ET)$, where ESL=end-systolic segment length and ET=ejection time. The left anterior brachial vein was used for drug infusion.

After control recordings, mitral regurgitation (MR) was produced by sectioning the chordae tendineae as described previously^{15,16} In brief, a stab incision was made in the anterior wall of the left ventricle, and a small hook was inserted to cut the chordae tendineae. When a systolic thrill was noted by palpation of the anterior surface of the left atrium, the wound was closed with a purse-string suture.

When the MR reached a stable state, control recordings (pre-dopamine study) were made. Then dopamine was infused at a rate of 5 $\mu\text{g/kg/min}$ until the peak (+) dP/dt increased to about 50% above the pre-dopamine value (from 2586 ± 736 to 4031 ± 1584 mmHg/sec). After an adequate recovery period, E-1020 was infused at a rate of 30 $\mu\text{g/kg}$ for 5 min (Fig. 2), and data were recorded 10 min later.

All data were recorded on an eight-channel, forced-ink oscillograph (San-Ei Instruments, Model 142-8) at a paper speed of 100 mm/sec, and stored simultaneously on magnetic tape (TEAC, Model SR-30). All data points were an average of ten consecutive beats during end-expiratory apnea and

Fig.5. The effects of dopamine and E-1020 on cardiac output and total systemic vascular resistance.
CO=cardiac output; TSR=total systemic vascular resistance.

Fig.6. The effects of dopamine and E-1020 on capacitance vessels.
mIVCF=mean inferior vena caval blood flow volume; mIVCP=mean inferior vena caval pressure.

were expressed as the mean $\pm$ S.D. Statistical analysis was performed using the Newman-Keuls multiple comparison test with two-way analysis of variance. The level of statistical significance was $p < .05$.

RESULTS

Hemodynamic data are summarized in Table I, and tracings illustrating the variables measured are reproduced in Fig. 3.

With the production of MR after sectioning of the chordae tendineae, LV end-diastolic pressure (EDP) rose from 7.5 ± 4.2 to 14.2 ± 7.4 mmHg ($p < .001$) and EDL increased from 10 to 10.9 ± 0.5 mm ($p < .001$, Fig. 4). Mean left atrial (LA) pressure rose from 7.6 ± 1.6 to 12.7 ± 3.2 mmHg ($p < .001$). LV peak systolic pressure decreased from 124 ± 18 to 116 ± 20 mmHg ($p < .01$) and cardiac output decreased from 2.01 ± 0.62 to 1.77 ± 0.56 liter/min ($p < .05$, Fig. 5). Stroke volume decreased from 12.2 ± 3.6 to 10.3 ± 3.3 ml ($p < .001$).

1) Effects of dopamine on acute MR (Table I):

Dopamine did not change the heart rate. LV peak systolic pressure increased from 116 ± 20 to 125 ± 21 mmHg ($p < .01$), while peak (+) dP/dt and mean segment shortening velocity increased from 2586 ± 736 to 4031 ± 1584 mmHg/sec ($p < .001$) and from 1.53 ± 0.62 to 1.96 ± 0.86 circ/sec ($p < .01$),

respectively. Total systemic vascular resistance (TSR) decreased from 4110 ± 1516 to 3224 ± 1047 dynes·sec·cm⁻⁵ ($p < .001$). EDP and mean LA pressure also decreased from 14.2 ± 7.4 to 10.2 ± 6.8 mmHg ($p < .01$) and from 12.7 ± 3.2 to 10.3 ± 2.6 mmHg ($p < .01$), respectively. EDL decreased from 10.9 ± 0.5 to 10.5 ± 0.6 mm ($p < .05$, Fig. 4). Cardiac output increased from 1.77 ± 0.56 to 2.15 ± 0.65 liter/min ($p < .01$), and stroke volume from 10.3 ± 3.3 to 12.4 ± 3.5 ml ($P < .01$, Fig. 5).

Mean IVC pressure decreased from 6.4 ± 1.6 to 5.6 ± 1.6 mmHg ($p < .05$). Mean IVC blood flow volume increased from 1.05 ± 0.17 to 1.48 ± 0.30 liter/min ($p < .001$, Fig. 6).

2) Effects of E-1020 on acute MR (Table I):

After the E-1020 infusion, heart rate remained unchanged. LV peak systolic pressure increased from 114 ± 20 to 126 ± 21 mmHg ($p < .001$). Peak (+) dP/dt and mean segment shortening velocity increased from 2569 ± 696 to 4095 ± 1270 mmHg/sec ($p < .001$) and from 1.47 ± 0.61 to 1.95 ± 0.83 circ/sec ($p < .01$), respectively. TSR decreased from 4208 ± 1438 to 3312 ± 1094 dynes·sec·cm⁻⁵ ($p < .001$). EDP and mean LA pressure decreased from 12.3 ± 6.1 to 8.0 ± 5.4 mmHg ($p < .01$) and from 12.5 ± 2.7 to 8.8 ± 2.2 mmHg ($p < .001$), respectively. EDL decreased from 10.7 ± 0.4 to 10.0 ± 0.5 mm ($p < .001$, Fig. 4). Cardiac output and

stroke volume increased from 1.69 ± 0.55 to 2.01 ± 0.55 liter/min ($p < .01$) and from 10.0 ± 3.2 to 11.6 ± 2.9 ml ($p < .01$), respectively (Fig. 5).

Mean IVC pressure decreased from 6.7 ± 1.6 to 5.3 ± 1.4 mmHg ($p < .001$), while mean IVC blood flow volume increased from 1.06 ± 0.23 to 1.23 ± 0.28 liter/min ($p < .01$, Fig. 6).

3) Comparison between dopamine and E-1020:

Both drugs increased LV peak systolic pressure, peak (+) dP/dt, and mean segment shortening velocity, and decreased TSR, to an equal degree.

The increase in mean IVC blood flow volume with dopamine was greater than with E-1020 ($p < .001$), while the increase in cardiac output and stroke volume was similar with both drugs. The decrease in mean IVC pressure with both drugs was also the same. The decrease in EDL and mean LA pressure with E-1020 was greater than with dopamine ($p < .01$ and $p < .05$, respectively).

DISCUSSION

In the present study, we produced MR in order to evaluate the efficacy of E-1020 in heart failure. After sectioning the chordae tendineae, EDP, EDL, mean LA pressure, and mean segment shortening velocity increased, while LV pressure, cardiac output, and stroke volume decreased. These findings imply the occurrence of acute volume overload in the left atrium and the left ventricle, an increase of fiber shortening in the left ventricle due to afterload reduction, and reduction of effective forward flow. Such hemodynamic alterations confirmed the production of MR.¹⁵

Heart rate is known to affect cardiac performance. The present data showed that neither dopamine nor E-1020 had a significant effect on heart rate (Table I). A similar finding was reported in anesthetized dogs, in which there was little increase in heart rate with E-1020.¹⁰ The positive chronotropic effect of dopamine is dose-related, and dopamine at a dose of $5 \mu\text{g/kg/min}$ causes little change in heart rate.¹¹ These previous data support the present result that the influence of heart rate on the hemodynamic

effects of both drugs was negligible, although heart rates with both drugs in our study were relatively high because of anesthetization by pentobarbital. The chronotropic effect of E-1020 under the physiological range of heart rate remains to be further investigated in the diseased heart. In addition, there was no significant difference between the two drugs in the reduction in TSR (Table I, Fig. 5). Thus, the afterload was considered to be reduced to the same level by both drugs.

Peak (+) dP/dt¹⁷ and mean segment shortening velocity¹⁸ reflect left ventricular contractility. The former depends on preload and heart rate,^{19,20} and the latter is independent of preload but dependent on afterload and heart rate.^{20,21} In the present study, peak (+) dP/dt and mean segment shortening velocity increased significantly with E-1020 as well as with dopamine, while EDP and EDL (preload) decreased. The reduction in preload is known to decrease peak (+) dP/dt. In addition, there were no significant differences between the effects of dopamine and E-1020 on heart rate and afterload (Table I). Though the extent to which MR influenced peak (+) dP/dt or mean segment shortening velocity was unclear in our study, the fact that both peak (+) dP/dt and mean segment shortening velocity increased equally with both drugs indicated that E-1020 had a positive inotropic action equivalent to that of dopamine. Thus, the results indicated that E-1020 could enhance myocardial contractility in the failing heart.

It has been demonstrated that the positive inotropic effect of E-1020 is not mediated through stimulation of β -, α -, H_1 -, or H_2 -receptors, endogenous catecholamine release, cholinergic nervous transmission, or through prostaglandin synthesis.¹⁰ In addition, this drug has no inhibitory effect on Na^+ , K^+ -ATPase.⁹ On the other hand, its inotropic effect is attenuated by carbachol.⁹ E-1020 is reported to inhibit phosphodiesterase type III, which has a high affinity for cyclic AMP^{9,22} and increases the cyclic AMP content in isolated guinea-pig papillary muscles. The increase in cardiac intracellular cyclic AMP causes the activation of cyclic AMP-dependent protein kinase, leading to an increase in the intracellular Ca^{++} concentration associated with membrane protein

phosphorylation²³ When increased Ca^{++} is bound to troponin C, myosin interacts with actin, and consequently cardiac contractility increases²⁴ It is thought to be by this mechanism that E-1020 produces a positive inotropic effect.

Dopamine increases cardiac contractility by a direct action upon β_1 receptors. Moreover, when dopamine is administered at a low dose, activation of both dopamine₁ receptors on post ganglionic vascular effector cells and dopamine₂ receptors on prejunctional sympathetic nerve terminals causes vasodilation. The vasodilation due to activation of dopamine₂ receptors is a result of the inhibition of norepinephrine release from sympathetic terminals.¹² Such vascular effects of dopamine were considered responsible for the decrease in TSR seen in the present study (Table I). In contrast, E-1020 inhibits phosphodiesterase III and causes an increase in cyclic AMP, resulting in activation of protein kinase. Protein kinase causes the phosphorylation of phospholamban with activation of the Ca^{++} pump of the sarcoplasmic reticulum, stimulates Ca^{++} uptake into the sarcoplasmic reticulum, and finally decreases the intracellular Ca^{++} concentration.²⁵ Furthermore, protein kinase causes the phosphorylation of troponin I and produces a decrease in the Ca^{++} sensitivity of troponin.²⁴ By these mechanisms, E-1020 inhibits the interaction between actin and myosin to produce muscle relaxation and consequently vasodilation. This mechanism accounts for the significant decrease in TSR seen with E-1020 (Table I).

Compared with dopamine, E-1020 significantly decreased both mean LA pressure and EDL. In previous studies, E-1020 was shown to decrease EDP,¹⁰ while pulmonary wedge pressure remained unchanged with dopamine.¹¹ Our results are compatible with these studies. Dopamine has a venoconstrictor action,^{26,27} and both the mean circulatory filling pressure and the pressure gradient between peripheral veins and the right atrium are increased by venoconstriction. Consequently, venous return is increased.^{28,29} In contrast, venodilation cannot increase venous return as much as cardiac output increases, because of blood pooling in capacitance vessels.³⁰ Therefore, the greater reduction in mean LA pressure and EDL seen

with E-1020 was considered to be caused mainly by the dilation of capacitance vessels by E-1020, and strongly suggested that preload reduction was greater with E-1020 than with dopamine.

Since the circulatory system is a closed circuit, venous return must be equal to cardiac output at equilibrium. In the present study, the increase in mean IVC flow volume was less with E-1020 than with dopamine, while the increase in cardiac output was the same (Figs. 5, 6). It was unclear why there was a difference in the increase of mean IVC flow volume between the two drugs despite the equivalent increase in cardiac output. It may have been because the peak effect of E-1020 (30 $\mu\text{g/kg}$) appears ten minutes after administration and its action lasts for more than two hours.¹⁰ We evaluated the effect of E-1020 ten minutes after injection. At the time of measurement E-1020 had already increased cardiac output but its venodilatory action may not have reached a maximum. If this was the case, part of the increase in cardiac output would have been stored in the dilating veins, resulting in a smaller mean IVC flow volume with E-1020 than with dopamine. The finding that cardiac output increased equally with both drugs despite the smaller IVC flow volume with E-1020 indicated that some of the blood which had accumulated in the lungs due to MR was added to the forward stroke volume, resulting in the maintenance of cardiac output; however, IVC flow volume was still smaller than that with dopamine because of venous dilatation with E-1020, although the IVC flow with E-1020 was slightly greater than that before E-1020. Such a phenomenon would persist until the venodilatory action of E-1020 reached a stable state, but after blood pooling in capacitance vessels stabilized, IVC flow and cardiac output should become equal. Secondly, venous return to the right atrium is the sum of superior vena caval, inferior vena caval, and coronary sinus blood flow, but we measured only IVC flow volume in the present study. Therefore, we can estimate the change in the venous return as a whole from the change in IVC flow volume only if the blood volume in each venous system is altered equally by drugs such as E-1020. However, our estimate of the change in venous return would be in-

accurate if the responses of the individual venous systems to the drugs were different, but there is no evidence to support this. Despite these limitations, however, it is obvious from the present results that E-1020 can increase cardiac output in association with a decrease in the preload due to venodilation.

The factors which determine the degree of regurgitant flow in MR are the size of the regurgitant orifice, the duration of the period of regurgitation or the duration of ventricular systole, and the systolic pressure gradient between left ventricle and left atrium.³¹⁻³⁴ The mitral regurgitant area in acute MR decreases during ventricular ejection as the volume of the left ventricle decreases.³⁴ Inotropic agents therefore might reduce the regurgitant flow in MR, since the enhancement of myocardial contractility by inotropic agents could reduce LV size and augment contraction of the mitral annular muscle fibers, thus decreasing the size of the mitral annulus.³² This kind of mechanism is considered to have operated in our experimental model with dopamine and with E-1020. In addition, a decrease in preload due to the dilation of capacitance vessels by E-1020 also could have helped to decrease the size of both the left ventricle and the regurgitant orifice. Though we did not directly measure the regurgitant volume, the fact that both drugs reduced preload while increasing cardiac output suggested a reduction in regurgitant volume and an increase in forward output. This was supported by the increase in stroke volume (Table I).

Positive inotropic agents increase myocardial oxygen consumption. Therefore, the use of these drugs for congestive heart failure due to ischemic heart disease may worsen myocardial ischemia and heart failure. However, E-1020 has been shown to cause only a small increase in myocardial oxygen consumption in anesthetized dogs.¹⁰ Moreover, in dogs with heart failure due to coronary occlusion, E-1020 improved cardiac performance.¹⁰ In our study, E-1020 decreased TSR and EDL while heart rate remained unchanged, suggesting that E-1020 can reduce myocardial oxygen consumption in the failing heart. This was in agreement with the results of the previous study.¹⁰

E-1020 has a positive inotropic effect combined with a vasodilatory action on both re-

sistance and capacitance vessels, and has been called an "inodilator".⁵ It reduced pulmonary congestion while increasing cardiac output. Accordingly, the present data strongly suggests that E-1020 is useful in the treatment of left heart failure.

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