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EXPERIMENTAL STUDIES

Hemodynamic Effects of Nitroglycerin in an Experimental Model of Acute Aortic Regurgitation

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Afterload reduction is an accepted therapeutic modality for the treatment of congestive heart failure caused by chronic aortic regurgitation. However, the role of vasodilator therapy in acute aortic incompetence has not been established. To investigate this, left ventricular volume overload was produced in 18 dogs by constructing a valved conduit from the descending thoracic aorta to the left ventricular apex. The time course of aortic, pulmonary and conduit flows was analyzed in eight control studies and established stability of the experimental model.

In the remaining 10 dogs, intravenous nitroglycerin, titrated to reduce mean aortic blood pressure by 40%, and placebo (ethanol) were each infused for 20 min periods. Compared with placebo, nitroglycerin significantly reduced aortic flow (3,945 ± 324 to 3,397 ± 362 ml/min, $p < 0.01$), regurgitant flow (1,304 ± 131 to 764 ± 90 ml/min, $p < 0.001$), septal-lateral end-diastolic diameter (47.5 ± 1.8 to 46.5 ± 1.8 mm, $p < 0.001$), left ventricular end-diastolic pressure (6.9 ± 0.8 to 6.0 ± 0.6 mm Hg, $p < 0.05$), left ventricular stroke work (19.0 ± 2.6 to 10.8 ± 1.7 g-m/beat, $p < 0.001$) and systemic vascular resistance (2,253 ± 173 to 1,433 ± 117 dyne-s/cm^5, $p < 0.001$). In contrast, pulmonary flow, left anterior descending coronary flow and subendocardial pH did not change during infusion of either nitroglycerin or placebo.

These data indicate that by decreasing preload and afterload, and by preserving coronary flow and tissue pH, nitroglycerin effectively reduced ventricular and regurgitant volumes in the setting of acute volume overload. This study supports the clinical use of nitroglycerin in severe acute aortic incompetence.

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Acute aortic regurgitation is most commonly associated with bacterial endocarditis and not infrequently produces severe left ventricular volume overload, leading to congestive heart failure, pulmonary edema and significant mortality (1,2). In this setting, employment of vasodilators has recently been advocated (1) to support patients before aortic valve replacement in order to establish hemodynamic stability and permit a therapeutic course of antibiotic therapy. The rationale for the use of vasodilator therapy in acute aortic incompetence is primarily based on investigations (3–11) that have reported the effects of afterload reduction in chronic aortic regurgitation. However, aside from two clinical reports (12,13), the efficacy of vasodilator therapy in acute aortic incompetence has not been directly assessed. Hence, this study attempts to define the role for vasodilator therapy in this setting by assessing the effects of nitroglycerin in an experimental model of ventricular volume overload.

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Methods

Instrumentation (Fig. 1). Eighteen mongrel dogs weighing between 21 and 42 kg were studied. Animal care was conducted according to the position of the American Heart Association on Research Animal Use, 1984. The dogs were premedicated with intramuscular acepromazine (0.1 mg/kg body weight) and atropine (0.05 mg/kg), and were anesthetized with intravenous sodium pentobarbital (30 mg/kg). Anesthesia was maintained during the course of the studies with supplemental doses of pentobarbital. The dogs were

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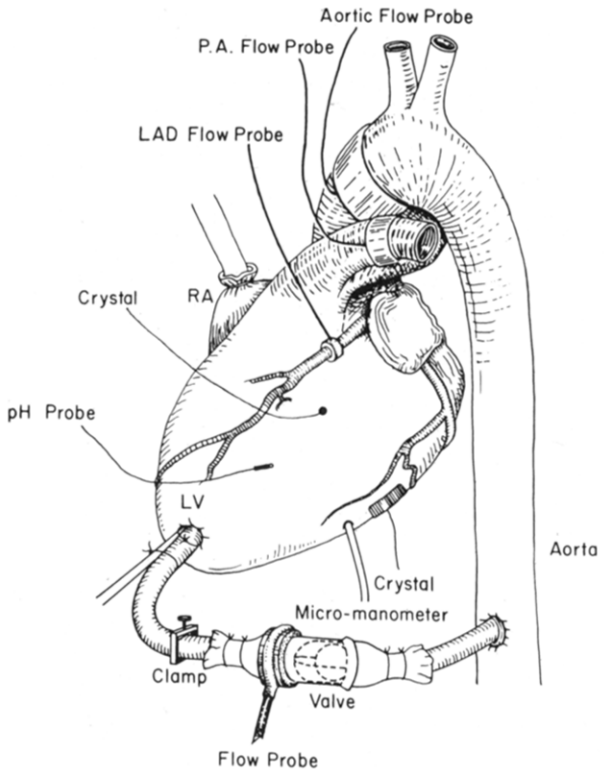

Figure 1. A flexible conduit that contained a ball-cage valve permitted unidirectional flow from the aorta to the apex of the left ventricle (LV). Flow was measured in the proximal aorta, the main pulmonary artery (P.A.) and the conduit. Left ventricular pressure was recorded with a micromanometer-tipped catheter. The septal-lateral minor axis diameter was measured with a pair of ultrasonic crystals fixed to the septum and the lateral wall of the left ventricle. Left anterior descending (LAD) coronary flow was determined with a pulsed Doppler flow probe. Myocardial pH was monitored with a glass tip electrode inserted into the left ventricular subendocardial region. RA = right atrium.

intubated and mechanically ventilated with a Harvard respirator at a tidal volume of 15 ml/kg. Supplemental oxygen (2 to 3 liters/min) was given. Arterial blood gases were monitored (model 713, Instrumentations Laboratory, Inc.) and maintained in the normal range. A left lateral thoracotomy was performed in the fifth intercostal space, and the heart was suspended in a pericardial cradle. Fluid-filled catheters connected to Statham p23ID transducers were placed into the aortic arch through the right carotid artery and into the right atrial appendage for measurements of aortic and right atrial pressures. Left ventricular cavitary pressure and its first derivative (dP/dt) were recorded with a micromanometer tip catheter (PC 470 Millar Instruments) inserted through the anterior wall of the left ventricle. Electromagnetic flow probes (Biotronex Laboratories Inc.) were placed snugly around the ascending aorta and pulmonary artery. Calibration of the flow probes was performed in situ at completion of each study with autologous blood. A pair of 5 MHz sonomicrometer crystals (Triton Technology Inc.) were fixed to the anterior septum and the lateral wall for determination of left ventricular septal-lateral minor axis dimensions. In 12 dogs, the proximal left anterior descending coronary artery was dissected, and a 20 MHz pulsed Doppler flow probe (Valpey-Fisher Inc.) was placed around the artery before the takeoff of the first major diagonal branch.

Measurement of myocardial pH. Myocardial tissue pH was measured in the subendocardial region of the left ventricular anterior wall with a miniature glass tip electrode developed in our laboratory in conjunction with Ingold Electrodes Inc. The characteristics and calibration of the electrode have been described previously (14,15). Briefly, the electrode was 10 mm in length and 1 mm in diameter. The distal portion of the electrode consisted of lead glass, which contained a silver-silver chloride sensing wire. The electrode was inserted into the myocardium and secured to the epicardium with a fine suture. A reference electrode was placed in a beaker containing 3 *M* potassium chloride (KCl) and connected to the subcutaneous tissue of the dog's hind limb with a 2 *M* KCl bridge. The electrodes were connected by coaxial cables to a Corning voltmeter (model 610 A) set in the millivolt mode. Intramyocardial temperature was measured with a Webster thermistor. Both the millivolt and the temperature readings were recorded on a two channel Soltec recorder. The electrodes were calibrated in standard buffer solutions of pH 4.0 and 7.0 before and after each study. The 95% in vitro response time of the electrode was 3 to 4 s. The stabilization time of the electrode was 3 to 5 min. Myocardial pH was calculated with use of a software program according to the Nernst principle (16).

Aorta to left ventricular conduit. After instrumentation, 200 U/kg of intravenous heparin was administered. Heparin was later supplemented in hourly doses of 100 units/kg. A flexible Dacron graft was anastomosed to the descending thoracic aorta in an end to side fashion (Fig. 1). The graft was connected by plastic tubing to a 22 mm diameter knitted graft that contained a ball-cage Starr-Edwards valve. The distal end of the graft was connected to a 28F plastic tube that was introduced into the left ventricular apex and secured with a tourniquet. The valve was oriented to permit flow from the aorta to the apex. Conduit flow was measured with an intraluminal electromagnetic flow meter inserted distal to the site of the valve. The flow meter was calibrated with autologous blood in situ at the end of each study. Flow through the conduit was controlled by adjusting a clamp placed around the conduit. The valved aortic-apical conduit was a modification of an experimental model of acute aortic regurgitation described by Welch et al. (17).

Protocol. Baseline measurements were obtained before (baseline 1) and after (baseline 2) insertion of the conduit into the left ventricular apex. The conduit was then opened, and conduit flow was gradually increased by adjusting the clamp until a 50% increase in aortic pulse pressure was achieved. Initial pilot studies had indicated that this represented ap-

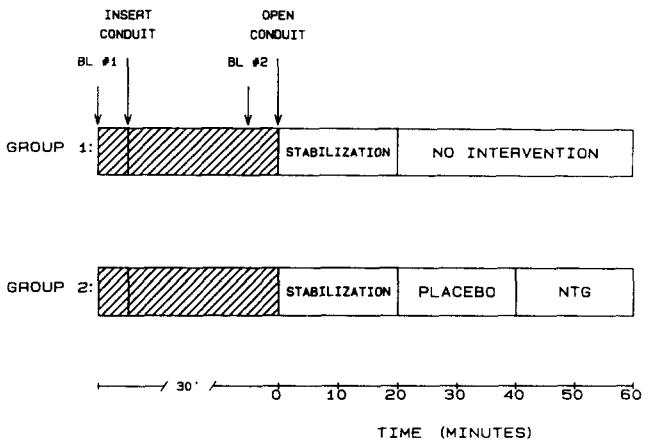

Figure 2. Group 1 comprised eight control dogs that did not receive pharmacologic intervention during the 60 min period after opening of the aorta-apical ventricular conduit. Group 2 comprised 10 dogs that received a 20 min infusion of placebo (ethanol) followed by a 20 min infusion of intravenous nitroglycerin (NTG). BL #1 and #2 = baseline 1 and 2 (measurements made, respectively, before and after conduit insertion into the left ventricular apex).

proximately a 30% to 40% regurgitant fraction (conduit flow/aortic flow) that could be tolerated for up to 90 min under stable conditions. Attempts to increase conduit flow such that regurgitant fraction exceeded 40% invariably resulted in the rapid onset of ventricular failure and cardiovascular collapse.

The conduit was opened for a period of 60 min (Fig. 2). Conditions were allowed to stabilize during the initial 20 min, and measurements were subsequently made at 5 min intervals. To investigate the stability of the model, no pharmacologic intervention was performed in eight dogs (Group 1) during the period when the conduit was opened. In the remaining 10 dogs (Group 2), placebo (ethanol) was administered by continuous intravenous infusion for 20 min after the stabilization period. The infusion of placebo was terminated at the 40 min interval after opening of the conduit. Nitroglycerin (Nitro-Bid, Marion Laboratories Inc.) was then administered by a continuous intravenous infusion for 20 min. The dose of nitroglycerin was titrated to reduce mean aortic pressure by 40%. Systolic aortic pressure was not allowed to decrease to <100 mm Hg. The effects of alcohol infusion were studied because nitroglycerin was diluted in an ethanol base, which is a known vasodilator substance (18). The quantity and rate of ethanol administration were equivalent to those delivered during an infusion of 100 μg/kg per min of nitroglycerin.

Data analysis and measurements. All data are reported as mean values ± SEM. Measurements were averaged over 8 to 10 cardiac cycles. Coronary flow was measured in two Group 1 dogs and in all Group 2 dogs, and is expressed as a percent of the baseline 2 value. Minor axis left ventricular end-diastolic (LVEDD) and end-systolic (LVESD) diameters were determined from the sonomicrometer signals. End-diastole was defined as the beginning of the upstroke of the left ventricular dP/dt tracing. End-systole was defined as the point 20 ms before the minimal dP/dt.

Percent systolic shortening (%SS) of the minor axis was then calculated:

$$\%SS = \frac{(LVEDD - LVESD)}{LVEDD} \times 100\%.$$

Systemic vascular resistance (SVR) was calculated using mean arterial pressure (MAP), right atrial pressure (RAP) and pulmonary flow (Pul Flow):

$$SVR = \frac{(MAP - RAP) \times 80}{Pul\ Flow}\ (dyne\text{-}s/cm^5).$$

Left ventricular stroke work (LVSW) was calculated with use of MAP, LVEDP and the stroke volume (SV):

$$LVSW = (MAP - LVEDP) \times SV \times 0.0136\ (g\text{-}m/beat).$$

Statistics. Statistical significance of the time course of the variables was performed using Friedman's analysis of variance (19). Paired and unpaired data were analyzed using the two tailed Students *t* test. Correlations between various variables were established using linear regression. A probability (p) value of ≤0.05 was considered statistically significant.

Results

Impact of the model on ventricular mechanics. Data before (baseline 1) and after (baseline 2) implantation of the aorta to left ventricle conduit (before opening) are shown in Table 1. Insertion of the conduit created decreases in mean and diastolic aortic pressures, peak dP/dt and left ventricular stroke work. In contrast, heart rate, systolic aortic pressure, left ventricular end-diastolic pressure, aortic and pulmonary flows, systemic vascular resistance, coronary flow and myocardial pH did not change after conduit insertion. Comparisons of left ventricular end-diastolic and end-systolic diameter and systolic shortening were not made until after introduction of the conduit.

Data obtained at 20 min after opening of the conduit are also shown in Table 1. The mean regurgitant (conduit) flow was 1,200 ± 91 ml/min, which corresponded to a mean regurgitant fraction (conduit flow/aortic flow) of 36 ± 3%. This produced significant decreases in diastolic and mean aortic pressures, pulmonary artery flow (effective cardiac output) and myocardial pH. In contrast, systolic aortic pressure, left ventricular end-diastolic pressure and diameter, aortic flow, systolic shortening, peak dP/dt and left ventricular stroke work all significantly increased. Heart rate, systemic vascular resistance, left ventricular end-systolic diameter and coronary flow did not change after opening of the conduit.

Table 1. Comparisons of Baseline Conditions and the 20 min Interval of Conduit Flow (n = 18)

				Conduit	
	Baseline 1	Baseline 2	p Value	Open 20 min	p Value
Ao pressure (mm Hg)					
Systolic	137 ± 5	128 ± 5	NS	156 ± 9	0.001
Diastolic	63 ± 4	49 ± 4	0.001	35 ± 3	0.001
Mean	80 ± 3	70 ± 4	0.001	69 ± 4	0.05
LVEDP	5.1 ± 0.4	5.5 ± 0.5	NS	7.2 ± 0.6	0.01
HR	177 ± 5	170 ± 6	NS	172 ± 6	NS
Flow (ml/min)					
Ao	2,679 ± 205	2,622 ± 218	NS	3,532 ± 239	0.001
PA	2,673 ± 205	2,645 ± 218	NS	2,414 ± 210	0.01
Regurg	0	0	—	1,200 ± 91	—
Regurg %	0	0	—	36 ± 3	—
LVEDD	—	44.3 ± 1.8	—	45.1 ± 1.7	0.001
LVESD	—	40.2 ± 1.7	—	39.7 ± 1.7	NS
% SS	—	9.1 ± 0.9	—	12.1 ± 0.8	0.001
SVR	2,688 ± 183	2,443 ± 212	NS	2,558 ± 226	NS
Peak dP/dT	1,788 ± 72	1,513 ± 78	0.001	1,632 ± 106	0.05
LVSW	16.5 ± 2.0	13.3 ± 1.5	0.05	17.8 ± 2.0	0.001
Myocardial pH	7.33 ± 0.04	7.38 ± 0.05	NS	7.33 ± 0.05	0.05
LAD flow (n = 12)	116 ± 14	100	NS	104 ± 6.5	NS

Ao = aortic; Baseline 1 and 2 = measurements made, respectively, before and after conduit insertion into the left ventricular apex; HR = heart rate (beats/min); LAD flow = left anterior descending coronary flow (percent of baseline 2 measurement); LVEDD = left ventricular end-diastolic diameter (mm); LVEDP = left vetricular end-diastolic pressure (mm Hg); LVESD = left ventricular end-systolic diameter (mm); LVSW = left ventricular stroke work (g-m/beat); Peak dP/dT = maximal first derivative of left ventricular pressure (mm Hg/s); PA = pulmonary artery; % SS = percent systolic shortening; Regurg % = regurgitant flow/aortic flow × 100; SVR = systemic vascular resistance (dyne-s/cm^5).

Effect of volume overload in Group 1. Data for Group 1 (no pharmacologic intervention; n = 8) at 10 min intervals after opening of the conduit are shown in Table 2. Throughout the period of observation, there were no significant changes in the measured variables, attesting to the stability of the model over a 60 min period.

Comparability of the two groups. Comparisons of hemodynamic data were made between dogs in Group 1 and

Table 2. Hemodynamic Measurements in Group 1 During Conduit Flow (n = 8)

	20 min	30 min	40 min	50 min	60 min	p Value
Ao pressure (mm Hg)						
Systolic	151 ± 12	148 ± 12	148 ± 10	149 ± 14	146 ± 9	NS
Diastolic	29 ± 4	28 ± 4	27 ± 4	29 ± 5	26 ± 5	NS
Mean	56 ± 5	56 ± 5	56 ± 6	58 ± 5	56 ± 4	NS
LVEDP	7.5 ± 1.0	7.8 ± 1.1	7.7 ± 1.1	7.8 ± 1.2	7.8 ± 1.2	NS
HR	158 ± 10	156 ± 10	156 ± 11	162 ± 8	155 ± 11	NS
Flow (ml/min)						
Ao	3,069 ± 284	3,085 ± 315	3,072 ± 295	3,033 ± 237	3,035 ± 249	NS
PA	2,124 ± 322	2,170 ± 343	2,146 ± 329	2,055 ± 268	2,143 ± 313	NS
Regurg	1,064 ± 123	1,034 ± 119	1,022 ± 116	1,131 ± 99	990 ± 108	NS
Regurg %	37 ± 5	37 ± 6	36 ± 5	39 ± 5	35 ± 5	NS
LVEDD	41.3 ± 3.1	41.3 ± 3.0	41.4 ± 3.0	41.3 ± 3.1	41.3 ± 3.1	NS
LVESD	36.5 ± 2.7	36.5 ± 2.6	36.5 ± 2.6	36.5 ± 2.7	36.5 ± 2.7	NS
% SS	11.6 ± 0.6	11.5 ± 0.6	11.7 ± 0.6	12.9 ± 0.9	11.7 ± 0.6	NS
SVR	2,410 ± 365	2,342 ± 371	2,405 ± 366	2,452 ± 352	2,309 ± 322	NS
Peak dP/dT	1,444 ± 156	1,385 ± 155	1,425 ± 151	1,508 ± 136	1,331 ± 98	NS
LVSW	13.3 ± 2.5	11.8 ± 1.7	11.6 ± 4.3	12.0 ± 1.6	11.8 ± 1.3	NS
Myocardial pH	7.36 ± 0.06	7.34 ± 0.06	7.35 ± 0.06	7.35 ± 0.08	7.35 ± 0.08	NS

Abbreviations as in Table 1.

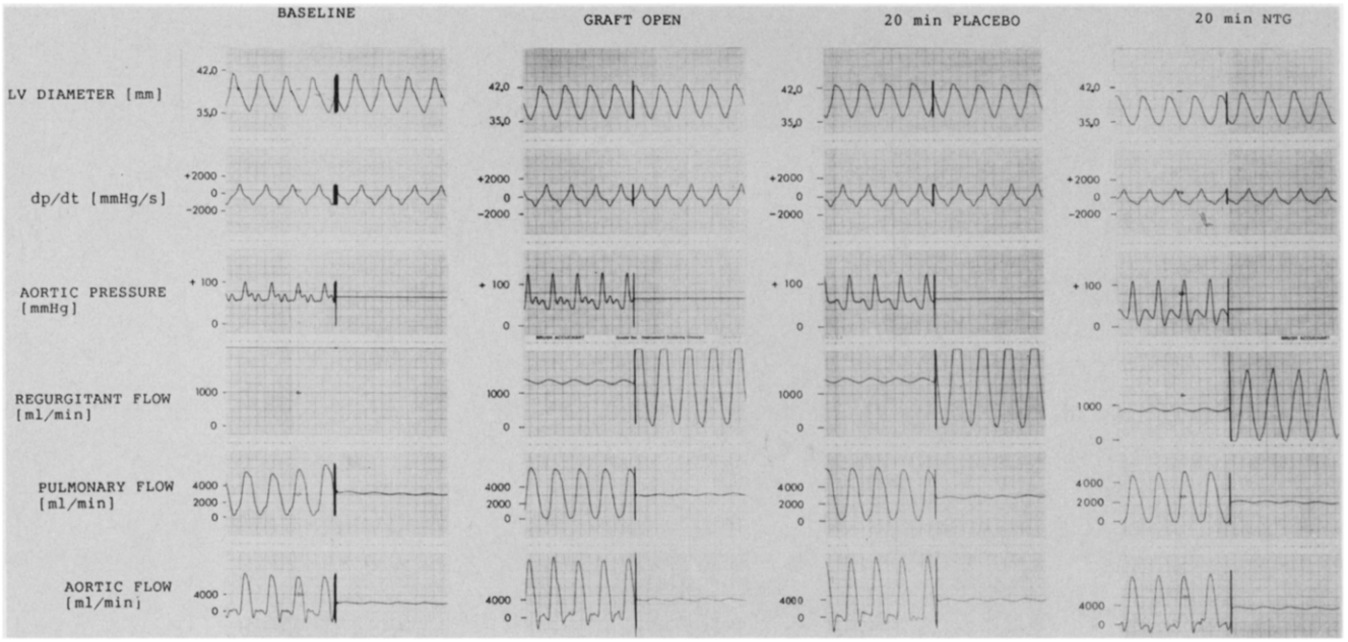

Figure 3. Strip chart recordings from a representative case. Opening of the conduit (graft open) produced 1,431 ml/min of regurgitant flow and increased aortic pressure and aortic flow. There were no further hemodynamic changes during infusion of placebo. In contrast, nitroglycerin (NTG) infusion resulted in reductions in left ventricular (LV) end-diastolic and end-systolic diameter, peak dP/dT, aortic pressure, regurgitant flow and aortic flow.

Group 2 (pharmacologic intervention; n = 10) at the end of the 20 min interval after opening of the conduit. Though the variances and the differences in the mean values between the two groups were relatively large for some of the hemodynamic variables (including heart rate, aortic flow, pulmonary flow, regurgitant flow and stroke work), these differences did not achieve statistical significant (p = NS).

Effects of placebo and nitroglycerin. Illustrated strip chart recordings of a Group 2 dog before and during nitroglycerin administration are shown in Figure 3. All hemodynamic variables were unchanged during infusion of placebo (ethanol). Compared with placebo, nitroglycerin reduced left ventricular end-diastolic and end-systolic diameters, regurgitant and aortic flows, aortic pressures and peak dP/dt.

Cumulative data comparing the effects of nitroglycerin and placebo in Group 2 are shown in Table 3 and Figure 4. The average dose of nitroglycerin required to reduce mean aortic pressure by 40% was 100 ± 28 μg/kg per min. In addition to reducing systolic, diastolic and mean aortic pressures, nitroglycerin significantly decreased left ventricular end-diastolic pressure, aortic flow, regurgitant flow, regurgitant fraction, peak dP/dt, left ventricular end-diastolic and end-systolic diameters, systemic vascular resistance and stroke work. In contrast, apparent changes in mean heart rate, pulmonary flow, systolic shortening, coronary flow and myocardial pH were insignificant during nitroglycerin infusion.

The diminution in regurgitant flow during nitroglycerin infusion correlated with changes in left ventricular end-diastolic pressure ($r = 0.74$, $p < 0.02$). In addition, there was a significant correlation between the diminution in left ventricular end-diastolic diameter and the decrease in systemic vascular resistance ($r = 0.67$, $p < 0.05$). The reduction in systemic vascular resistance during nitroglycerin infusion correlated with the initial value of systemic vascular resistance ($r = 0.80$, $p < 0.01$).

Discussion

Effects of nitroglycerin on volume overload. The acute left ventricular volume overload produced by the aortic-ventricular conduit in this model simulated the changes in systemic hemodynamics and ventricular loading conditions commonly associated with clinical aortic regurgitation. The Group 1 experiments (no pharmacologic intervention) indicated that volume overload was able to be maintained under stable conditions for a period of 60 min. In this setting, infusion of nitroglycerin resulted in a 40% reduction in regurgitant flow, significant decreases in left ventricular end-diastolic and end-systolic diameters and a 43% decrease in left ventricular stroke work. The absence of changes in systemic hemodynamics, minor axis dimensions and regurgitant flow during infusion of placebo indicated that the potential vasodilator effects of the alcohol base of the nitroglycerin solution were negligible. The volume load-reducing effects observed during the administration of the

Table 3. Comparison of the Effects of Nitroglycerin and Placebo in Group 2 (n = 10)

	5 min	10 min	15 min	20 min
Ao pressure				
Systolic				
Placebo	159 ± 13	159 ± 13	163 ± 15	164 ± 15
NTG	120 ± 9	127 ± 10	128 ± 11	130 ± 10
p	0.001	0.001	0.001	0.001
Diastolic				
Placebo	41 ± 4	41 ± 4	42 ± 4	39 ± 4
NTG	16 ± 2	14 ± 2	15 ± 2	15 ± 3
p	0.001	0.001	0.001	0.001
Mean				
Placebo	72 ± 4	72 ± 5	73 ± 5	71 ± 4
NTG	44 ± 3	44 ± 3	44 ± 3	44 ± 3
p	0.001	0.001	0.001	0.001
LVEDP				
Placebo	6.9 ± 0.8	7.1 ± 0.8	7.2 ± 0.7	6.9 ± 0.8
NTG	6.2 ± 0.7	6.3 ± 0.7	5.9 ± 0.6	6.0 ± 0.6
p	NS	0.05	0.05	0.05
HR				
Placebo	184 ± 7.0	184 ± 7.0	183 ± 7.3	182 ± 7.3
NTG	181 ± 7.0	183 ± 7.0	184 ± 7.3	183 ± 7.3
p	NS	NS	NS	NS
Flow				
Ao				
Placebo	3,945 ± 320	3,918 ± 298	3,937 ± 305	3,945 ± 324
NTG	3,205 ± 311	3,375 ± 336	3,402 ± 360	3,397 ± 362
p	0.001	0.01	0.01	0.01
PA				
Placebo	2,694 ± 254	2,678 ± 250	2,690 ± 249	2,710 ± 270
NTG	2,503 ± 270	2,599 ± 294	2,681 ± 289	2,701 ± 322
p	NS	NS	NS	NS
Regurg				
Placebo	1,307 ± 127	1,287 ± 127	1,302 ± 132	1,304 ± 131
NTG	801 ± 108	783 ± 98	780 ± 100	764 ± 90
p	0.001	0.001	0.001	0.001
Regurg %				
Placebo	34 ± 2	33 ± 3	33 ± 3	33 ± 3
NTG	26 ± 3	24 ± 2	24 ± 2	23 ± 3
p	0.001	0.001	0.001	0.001
LVEDD				
Placebo	47.5 ± 1.7	47.4 ± 1.8	47.5 ± 1.8	47.5 ± 1.8
NTG	46.4 ± 1.8	46.5 ± 1.8	46.4 ± 1.7	46.5 ± 1.8
p	0.01	0.001	0.001	0.001
LVESD				
Placebo	41.4 ± 2.0	41.5 ± 1.9	41.5 ± 1.9	41.6 ± 1.9
NTG	40.9 ± 1.9	40.8 ± 1.9	40.8 ± 1.9	40.8 ± 1.9
p	0.05	0.01	0.01	0.01
% SS				
Placebo	12.9 ± 1.4	12.8 ± 1.3	12.8 ± 1.3	12.6 ± 1.3
NTG	12.0 ± 1.1	12.4 ± 1.2	12.1 ± 1.1	12.5 ± 1.1
p	NS	NS	NS	NS
SVR				
Placebo	2,275 ± 190	2,296 ± 174	2,314 ± 155	2,253 ± 173
NTG	1,518 ± 110	1,494 ± 128	1,428 ± 107	1,433 ± 117
p	0.001	0.001	0.001	0.001
Peak dp/dT				
Placebo	1,765 ± 139	1,740 ± 134	1,765 ± 126	1,774 ± 131
NTG	1,225 ± 129	1,275 ± 135	1,295 ± 130	1,320 ± 134
p	0.001	0.001	0.001	0.001
LVSW				
Placebo	19.6 ± 2.6	18.7 ± 2.5	19.0 ± 2.4	19.0 ± 2.6
NTG	10.5 ± 1.7	11.0 ± 1.6	10.6 ± 1.7	10.8 ± 1.7
p	0.001	0.001	0.001	0.001
Myocardial pH				
Placebo	7.29 ± 0.07	7.28 ± 0.07	7.28 ± 0.07	7.27 ± 0.07
NTG	7.29 ± 0.05	7.28 ± 0.06	7.26 ± 0.06	7.23 ± 0.06
p	NS	NS	NS	NS
LAD flow				
Placebo	106.3 ± 6.6	104.6 ± 8.3	108.6 ± 9.4	104.0 ± 8.3
NTG	99.2 ± 10.0	99.8 ± 9.4	110.9 ± 7.3	112.9 ± 13.9
p	NS	NS	NS	NS

Abbreviations as in Table 1.

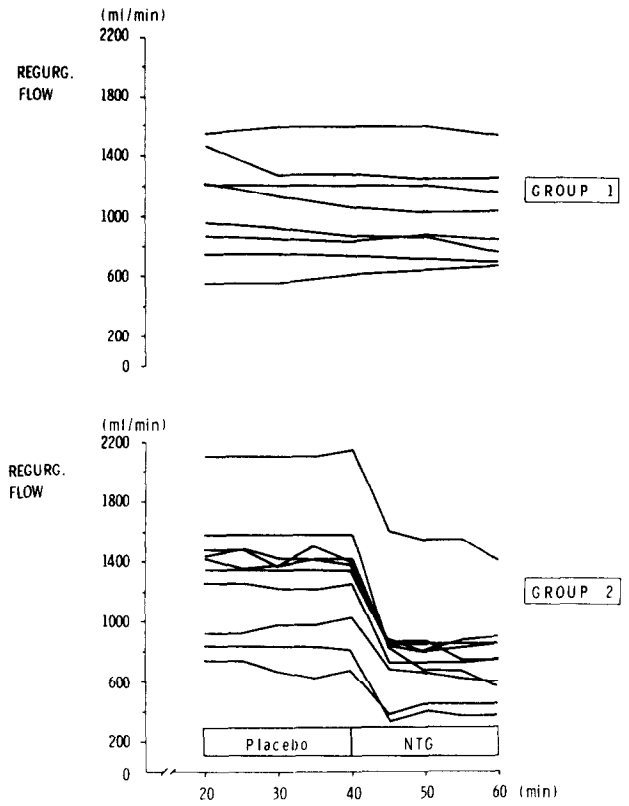

Figure 4. Regurgitant (REGURG.) flow in Group 1 (n = 8, **upper panel**) was constant after opening of the conduit. In Group 2 (n = 10, **lower panel**), regurgitant flow did not change during placebo (ethanol) infusion. In contrast, regurgitant flow decreased considerably in all dogs during nitroglycerin (NTG) infusion. **Each line** represents data from an individual experiment.

nitroglycerin solution thus stemmed solely from the vasodilator properties of nitroglycerin.

The therapeutic benefits of oral and sublingual nitrates in patients with chronic aortic regurgitation are produced by reductions in left ventricular afterload and preload (20–22). The prolonged volume overload state associated with chronic aortic regurgitation results in ventricular dilation and an increase in diastolic compliance (23). These adaptive responses permit greater tolerance of volume overload. Thus, the effects of therapeutic intervention in chronic aortic regurgitation cannot be readily extrapolated to the acutely decompensated volume-overloaded ventricle. The present investigation establishes the efficacy of vasodilator therapy in the uncompensated volume-overloaded ventricle.

In the present investigation, the venodilator properties of nitroglycerin were manifested by reductions in left ventricular end-diastolic pressure and diastolic septal-lateral dimensions. The relatively small decrease in the minor axis dimensions may have, in part, stemmed from the structural constraints imparted by the stiff conduit, thus preventing optimal relaxation of the ventricle. Though the 2% reduction in the septal-lateral diameter during infusion of nitroglycerin was relatively small, the global decrease in ventricular volume probably approached 6 to 8% of the initial volume, assuming that changes in chamber size were uniform (24,25). The importance of the venodilator effects was illustrated by the significant correlation between the change in regurgitant flow and the decrease in left ventricular end-diastolic pressure.

The correlation between the diminution in left ventricular end-diastolic diameter and the change in systemic vascular resistance indicates the importance of afterload reduction during nitroglycerin infusion. That the decline in systemic vascular resistance was most pronounced in dogs with the highest initial values of peripheral resistance is consistent with findings described in previous studies (7,20), and suggests that the afterload-reducing effects of nitroglycerin may be clinically most useful in patients with elevated systemic resistance. Despite the significant reduction in afterload, administration of nitroglycerin did not improve cardiac output in the setting of acute volume overload. The arterial-dilating effects of nitroglycerin may have been offset by its predominant venodilator properties, thus preventing a net increase in forward flow. It is conceivable that more potent arterial-dilating agents such as hydralazine (3,5,9,11) and sodium nitroprusside (13) would generate an increase in cardiac output in this setting.

Effects of nitroglycerin on coronary flow. During nitroglycerin infusion, myocardial oxygen demands were diminished by the reductions in stroke work and ventricular afterload. Nitroglycerin also decreased aortic diastolic pressure and, therefore, coronary driving pressure (26). The simultaneous reductions in oxygen demand and coronary driving pressure would have been expected to reduce coronary flow during nitroglycerin infusion. However, the lack of change in coronary flow despite the marked reduction in aortic pressure suggests the presence of intact autoregulatory mechanisms. This condition may have, in part, resulted from the direct vasodilator effect of nitroglycerin on the coronary resistance vessels (27,28). The absence of a change in myocardial pH during nitroglycerin infusion indicates preservation of adequate tissue perfusion in the subendocardial regions (29) and corroborates the coronary flow findings.

The direct vasodilator effects of nitroglycerin are known to stimulate sympathetic activity (30,31). However, in our model, the absence of significant changes in heart rate and percent systolic shortening indicates that the potential effects of increased sympathetic tone during the study protocol were not appreciable. In addition, at least one report (32) has indicated that nitroglycerin may directly inhibit cardiac afferent sympathetic discharge.

Clinical correlates. Two clinical reports (12,13) in addition to the present study, suggest that vasodilator therapy may be effective in acute aortic incompetence. An isolated case report (12) showed that sublingual isosorbide dinitrate

improved cardiac output and reduced pulmonary capillary wedge pressure in a patient with congestive heart failure and acute aortic incompetence secondary to bacterial endocarditis. A study by Miller et al. (13) demonstrated that, in a small group of patients with either chronic or acute aortic regurgitation, afterload reduction with sodium nitroprusside decreased left ventricular end-diastolic pressure and regurgitant flow while increasing cardiac index and ejection fraction. The small number of patients investigated in these two studies and the imprecise methods used to assess ventricular function diminish the impact of their findings. Nevertheless, they provide support for the expanded use of vasodilator therapy in acute aortic regurgitation.

Limitations of the study. Several limitations of the present investigation are recognized. Because the aortic valve was competent, the model did not anatomically simulate clinical aortic regurgitation. However, the significant increases in pulse pressure, aortic flow and left ventricular end-diastolic diameter and the decrease in cardiac output produced by the aorta-ventricular conduit characterized the physiologic changes associated with clinical aortic insufficiency. It should be noted that pertubations in coronary flow associated with diastolic volume overload in this model do not necessarily simulate those associated with clinical aortic regurgitation produced by an incompetent aortic valve because the latter is often associated with reverse or negative coronary directional flow during diastole (33). The absence of an intact pericardium in our study was probably responsible for the relatively small, though significant, changes in left ventricular end-diastolic pressure during volume overload and may have prevented potential changes in diastolic compliance, which can accompany infusion of nitroglycerin (34,35). However, the presence of an open pericardium did not preclude the salutory preload- and afterload-reducing effects of nitroglycerin. The dose of nitroglycerin used in this study was considerably higher than that associated with use of this drug in patients. This large dose may have reflected either an effort to produce a large (40%) reduction in mean arterial pressure or a species difference in the pharmacologic response to nitroglycerin (36). Finally, the potential development of tolerance to nitroglycerin therapy (37,38) was not assessed in this study because nitroglycerin was infused for a relatively short period of time. The presence and the importance of nitroglycerin tachyphylaxis in the setting of acute aortic incompetence can only be properly addressed in clinical studies.

Conclusions. This study indicates that nitroglycerin effectively reduces regurgitant and ventricular volumes during acute volume overload in the uncompensated ventricle. This reduction was accomplished by significant decreases in both preload and afterload and by the preservation of coronary flow and tissue pH. These findings warrant the clinical investigation of intravenous nitroglycerin in acute aortic incompetence.

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