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Long-Term Oral Nitrate Therapy Prevents Chronic Ventricular Remodeling in the Dog

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Objectives. The purpose of this experiment was to assess the long-term effects of oral nitrate therapy on ventricular remodeling in a canine model of discrete myocardial damage.

Background. A progressive increase in left ventricular mass and volume has been documented after experimental and clinical myocardial infarction. This ventricular remodeling has been associated with the development of congestive heart failure. Nitrate therapy, especially when combined with hydralazine, is effective in the management of clinical heart failure. Moreover, nitrates inhibit infarct expansion, one of the earliest manifestations of ventricular remodeling. Whether nitrates can attenuate chronic left ventricular remodeling is unknown.

Methods. Dogs with discrete myocardial necrosis produced 24 h earlier by transmyocardial direct current shock were randomized to receive isosorbide mononitrate, 30 mg twice daily (n = 10), or no treatment (n = 4); the latter group was augmented by 13 control dogs from a prior study in which an identical protocol was used. Ventricular structure was assessed with nuclear magnetic resonance imaging at baseline and at 1 and 16 weeks after myocardial damage.

Results. Left ventricular mass increased at 1 week in the control group (mean ± SD 68.1 ± 10.7 g to 80.1 ± 12.1 g, p = 0.0001) but not in the nitrate-treated group (70.2 ± 7.7 g to 69.6 ± 7.3 g, p = NS). No change in left ventricular volume was observed in either group during the 1st week after myocardial damage. After 16 weeks of follow-up left ventricular mass had increased by 12.7 ± 7.1 g (p = 0.001) in the control group and had decreased by 1.2 ± 7.7 g in the nitrate group. Left ventricular volume was increased at 16 weeks by 14.2 ± 10.3 ml in the control group but was decreased by 3.7 ± 7.5 ml in the nitrate group. Isosorbide mononitrate produced transient hemodynamic effects with a return of most measured variables toward baseline within 2 h after administration of the drug. At 1 week there was no intergroup difference in rest hemodynamic variables assessed 12 h after drug administration. At 16 weeks, pulmonary capillary wedge pressure (15 ± 4 vs. 8 ± 3 mm Hg, p = 0.0001), pulmonary artery pressure (24 ± 5 vs. 16 ± 3 mm Hg, p = 0.0001) and right atrial pressure (10 ± 3 vs. 6 ± 3 mm Hg, p = 0.008) were all higher in the control group.

Conclusions. Long-term oral nitrate therapy attenuates the early and late manifestations of ventricular remodeling after myocardial damage in the dog. Hemodynamic observations suggest the possibility that drug-induced preload or afterload reduction does not completely explain this effect.

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The ventricular hypertrophy (1–4) and dilation (5–7) that are characteristic of chronic heart failure may develop progressively after injury to the myocardium. The mechanisms that account for this process of ventricular remodeling remain elusive despite considerable recent attention, but they probably involve a combination of mechanical factors and specific trophic substances (8). When introduced soon after myocardial infarction, pharmacologic intervention has been demonstrated to inhibit this process in both experimental and clinical settings (6); satisfactory outcomes have included preservation of ventricular function (9), prevention of the development of heart failure (7) and improved 1-year mortality in a rat model of myocardial infarction (10). The converting enzyme inhibitors have been most frequently utilized for this purpose and their efficacy has usually been attributed to their arterial and venous dilating effect reducing left ventricular preload and impedance. A specific antiproliferative effect of these agents may also be relevant in view of data demonstrating an inhibitory effect of converting enzyme inhibitors on increase in left ventricular mass in the presence of minimal or no hemodynamic effect (11,12).

Nitrates also exhibit a vasodilating effect and, when combined with hydralazine, are effective in improving survival in patients with chronic heart failure (13). Moreover, nitrates have been reported to attenuate myocardial infarct expansion (14,15), an early manifestation of ventricular remodeling involving dilation of the infarct zone. The ability of nitrates to prevent chronic structural changes involving

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the remaining viable myocardium after myocardial damage is unknown. Accordingly, we investigated whether isosorbide mononitrate administered over a 16-week period could attenuate progressive ventricular remodeling in the canine model of transmyocardial direct current (DC) shock (16). This model is characterized by a discrete transmural area of necrosis on the anteroapical wall of the left ventricle (16). Ventricular remodeling in this model consists of an early increase in left ventricular mass in the initial week after injury with a later increase in left ventricular volume measured at 16 weeks (17).

Methods

Study dogs. Studies were performed on 27 adult mongrel dogs weighing 17 ± 3 kg. All animals were subjected to repetitive DC shock and then randomized to a treatment group. Fourteen dogs were prospectively studied in the present protocol; 10 were randomized to treatment with isosorbide 5-mononitrate, 30 mg orally twice daily, and 4 to no therapy. Thirteen additional dogs that were randomized to no treatment in a previous protocol using the identical methods were merged with the four control animals to augment the control group. This strategy was utilized because of the consistent hemodynamic and structural response noted in our previous studies with this model (17) and because of the desire, for ethical reasons, to reduce the number of experimental animals subjected to the DC shock procedure. Therefore, although the control group in this experiment consisted of two sets of animals studied at different time points, the methods and protocol used for both sets of control animals were identical. All studies conformed to the "Position of the American Heart Association on Research Animal Use" adopted by the Association in November 1984 and were performed in accordance with guidelines and protocols approved by the Animal Research Committee of the University of Minnesota.

All dogs underwent the same study protocol. One week before induction of left ventricular damage, left ventricular mass and volume were assessed by nuclear magnetic resonance (NMR) imaging. Rest hemodynamic indexes were also assessed before the creation of left ventricular damage. These analyses were repeated 1 and 16 weeks after transmyocardial DC shock. The NMR imaging and hemodynamic studies were separated by 24 to 48 h. During the 16-week period of analysis, dogs in both groups were treated in a similar manner with respect to diet and activity level.

NMR imaging. All NMR imaging studies were performed with a 1·0 tesla magnet. Dogs were anesthetized with sodium pentobarbital (200 mg intravenously followed by a constant infusion of 2 mg/min) and placed in the magnet in the right lateral position. Experience in this laboratory has demonstrated that this agent and level of anesthesia are safe and effective in allowing for optimal control of respiratory excursion during cardiac imaging. Electrocardiographic (ECG) leads were placed for cardiac rhythm monitoring and image-gating purposes. Gated short-axis paracoronal views of the heart were obtained at a repetition time of ≥300 ms as determined by the dog's heart rate and an echo time of 30 ms. These views were obtained 40 ms after the ECG R wave to approximate end-diastole. Six slices, each 1 cm in width with no interslice gap, were used to image the heart from base to apex. Study time ranged from 45 to 90 min depending on heart rate, which varied from 60 to 140 beats/min among these animals.

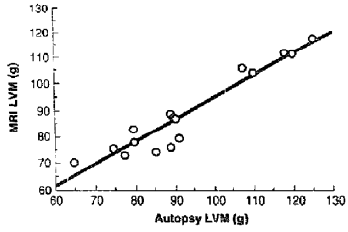

Figure 1. Relation between left ventricular mass (LVM) as measured at autopsy and by nuclear magnetic resonance imaging (MRI) ($r = 0.95$).

The damaged area could be identified as a thin scar on the anteroapical wall on the NMR image at 16 weeks and on autopsy specimens. To measure the surface area of each slice, epicardial and endocardial left ventricular edges were traced with a computer-assisted light pen. Left ventricular mass in each slice was calculated by using a commercially available software package (Siemens). The total area enclosed by the endocardium was subtracted from that enclosed by the epicardium. The resultant figure was multiplied by the slice depth of 1 cm to give volume and then by 1.05 (specific gravity of myocardium) to obtain the mass of each slice. The total left ventricular mass was thus computed by adding the individual mass measurements of all six slices. The accuracy of this technique has been previously documented in this laboratory where the NMR estimate of left ventricular mass has been compared with left ventricular weight obtained at autopsy in 16 dogs (Fig. 1). The left ventricular volume of each slice was represented by the volume enclosed by the endocardium. The total left ventricular volume was computed by summing the volumes of all slices.

A further analysis of left ventricular remodeling was performed by assessing wall thickness and chamber diameter. Septal, anterior, lateral and posterior wall thickness along with anteroposterior and septal-lateral chamber diameters were obtained in the third short-axis slice from the base of the heart. This slice was chosen because it was in the midventricle and did not include the necrotic zone at the apex. All of these measurements were obtained by using a

commercially available software package. The chamber diameter/wall thickness ratio was derived as an estimate of wall stress by dividing the mean of the two values for chamber diameter by the mean of the four regional measurements of wall thickness.

All NMR measurements were made by two of us (K.M.M., J.M.), who were unaware of the treatment status of the dogs at the time of analysis. The mean of these two sets of values was used as the final estimate of left ventricular mass and volume.

Hemodynamic studies. Hemodynamic studies were carried out in awake dogs, lightly sedated with Innovar (2 ml consisting of fentanyl, 0.8 mg and droperidol, 80 mg). Percutaneous catheterization was performed under local lidocaine anesthesia. A balloon flotation catheter was positioned in the pulmonary artery from the external jugular vein and an aortic catheter was advanced into the root of the aorta from the femoral artery. Mean aortic pressure, pulmonary capillary wedge pressure, pulmonary artery pressure and right atrial pressure were monitored using Statham P23db transducers and a Hewlett-Packard 77588 eight-channel physiologic recorder. Cardiac output was determined by thermodilution from the pulmonary artery utilizing a Lexington cardiac output computer and 5 ml of iced saline solution injected into the right atrium. Stroke volume was calculated by dividing the cardiac output by the ECG-recorded heart rate. Systemic vascular resistance was calculated from the formula Mean aortic pressure × 80 ÷ Cardiac output. Hemodynamic studies were performed in dogs at baseline and again 7 days and 16 weeks after DC shock. Therapy was withheld in the treated group on the morning of these studies.

To document the magnitude and persistence of the hemodynamic response to isosorbide mononitrate, six dogs in the treatment arm of this study underwent measurements for 2 h after nitrate administration at the time of scheduled hemodynamic studies at baseline and at 1 and 16 weeks after left ventricular damage. After baseline measurements were made, isosorbide mononitrate (30 mg dissolved in 5% dextrose in water) was administered by mouth. The dogs were immediately anesthetized with sodium pentobarbital and maintained on an intravenous infusion of this anesthetic agent to maintain a stable hemodynamic state for an extended period of observation. Hemodynamic variables were remeasured within 5 min of the institution of anesthesia and taken to represent baseline readings under anesthesia at the time of nitrate administration. Measurements were then obtained 30, 60, 90 and 120 min after these baseline readings. Readings were continued beyond 2 h in the first four studies. Because the majority of hemodynamic variables had returned to baseline after 2 h, subsequent studies were confined to 120 min of monitoring.

Left ventricular damage. Discrete left ventricular necrosis was produced by transmyocardial DC shock. A previous study has shown that this method produces a reproducible moderate-sized area of necrosis on the anteroapical wall of the left ventricle involving 17 ± 6% of the total left ventricular myocardium (16). The dogs were anesthetized with sodium pentobarbital, intubated and prepared for the transmyocardial DC shock procedure after hemodynamic measurements were made under light sedation. Animals were placed in the right lateral position. A small area of the left side of the chest over the maximal precordial impulse was shaved. A pigtail catheter was placed across the aortic valve and then advanced 1 cm farther to displace it from conduction tissue at the base of the heart. A premeasured soft metallic guide wire was then passed through the catheter with 5 mm of wire extended beyond the catheter tip into the left ventricular cavity. One electrode paddle was placed on the left chest at the point of maximal cardiac impulse (fourth to sixth intercostal space); the second electrode was connected to the proximal end of the guide wire in the left ventricle. Moderate left ventricular damage was produced by one shock of 80 J/kg body weight repeated at 20- to 60-s intervals. This protocol was previously found through a process of trial and error to produce the stated amount of damage. Heart rhythm was monitored by ECG throughout the DC shock procedure. Each shock of 80 J was invariably followed by a rhythm disturbance, usually a short run of nonsustained ventricular tachycardia that did not result in hemodynamic compromise. Rarely, cardioversion (80-J shock) was needed to break ventricular tachycardia when it was associated with low blood pressure. In these situations this therapeutic cardioversion was counted as one of the individual shocks for the dog. Temporary bradyarrhythmias occasionally occurred, but they did not persist and required no therapy. A brief period of hypotension, occasionally associated with bradyarrhythmias, often followed an individual shock. After the completion of the shock procedure the guide wire and catheter were removed and hemostasis was achieved at the puncture site by pressure. The procedure usually took 30 to 45 min to perform. Approximately 24 h after the transmyocardial DC shock procedure 10 dogs were randomly assigned to receive isosorbide mononitrate, 30 mg orally twice daily, and 4 to receive no treatment.

Statistics. The significance of changes in left ventricular mass and volume and hemodynamic variables during the 16-week period was assessed with one-way analysis of variance (ANOVA). If the ANOVA was significant, multiple *t* tests were performed and interpreted by using the modified Bonferroni method (18). An ANOVA using two variables (time after DC shock and time after administration of drug) was also performed to assess the pattern, duration and extent of the hemodynamic response to isosorbide mononitrate in six treated dogs. Unpaired *t* tests were used to compare temporally matched points from control and treatment groups. Data are expressed as mean value ±1 SD.

Table 1. Absolute Values for Left Ventricular Mass and Volume at Baseline and at 1 and 16 Weeks After Myocardial Damage in Control and Isosorbide Mononitrate-Treated Dogs

Group	Left Ventricular Mass (g)			Left Ventricular Volume (ml)		
	Baseline	1 Week	16 Weeks	Baseline	1 Week	16 Weeks
Control	68.1 ± 10.7	80.1 ± 12.1*	80.8 ± 10.4*	55.8 ± 10.3	58.0 ± 10.0	70.0 ± 8.2*
Treatment	70.2 ± 7.7	69.6 ± 7.3†	68.9 ± 8.4†	53.0 ± 9.8	50.5 ± 6.6	49.4 ± 6.1†

*$p < 0.01$ compared with baseline value. †$p < 0.025$ compared with temporally matched value in the control group.

Results

Data from 27 dogs are reported in this study. Three deaths occurred during the shock procedure among the 17 new dogs entered into the protocol. Ten of the surviving dogs were randomized to receive isosorbide mononitrate and four to receive no treatment. The other 13 dogs were a previously studied control group.

Ventricular remodeling. The absolute values for left ventricular mass and volume are presented in Table 1. There was a significant increase in left ventricular mass in the control group in the week after transmyocardial DC shock (68.1 ± 10.7 to 80.1 ± 12.1 g, $p = 0.0001$); there was little further change between 1 and 16 weeks. Although there was no significant change in left ventricular volume during the 1st week after myocardial damage, chamber size had increased by 16 weeks as compared with the baseline value (55.8 ± 10.3 to 70.0 ± 8.2 ml, $p = 0.0001$).

Nitrate therapy significantly altered the natural history of ventricular remodeling in this canine model. After 1 and 16 weeks left ventricular mass in the isosorbide mononitrate group was unchanged (−0.6 and −1.2 g, respectively) compared with an increase of 12 ($p = 0.0001$) and 12.7 g ($p = 0.0001$) in the control group (Table 1). Left ventricular volume was essentially unchanged at 1- and 16-week follow-up in the nitrate group (−2.5 and −3.7 ml, respectively) whereas it increased by 2.2 and 14.2 ml ($p = 0.0001$) in the control group.

Figure 2 displays the effect of isosorbide mononitrate in comparison with no treatment on ventricular mass and volume. A marked attenuation of ventricular remodeling is noted in the nitrate-treated group.

Wall thickness increased significantly between baseline and 1 week in the control group at all four measured areas (Table 2). By 16 weeks these values had returned toward baseline and remained significantly increased only in the lateral wall (8.22 ± 0.65 vs. 7.72 ± 0.76 mm, $p = 0.01$). Chamber diameter did not change significantly during week 1 and this, coupled with the increase in wall thickness, resulted in a significant decrease in the chamber diameter/wall thickness ratio (4.81 ± 0.34 to 4.33 ± 0.49, $p = 0.0001$). Septal-lateral chamber diameter increased significantly by 16 weeks ($p < 0.05$) with a similar trend in the anteroposterior measurement (37.94 ± 2.3 to 41.65 ± 5.18 mm, $p = 0.13$).

Baseline wall thickness and chamber diameter measurements were not significantly different between the two groups except in the posterior wall where wall thickness was significantly less in the isosorbide mononitrate-treated group. Neither wall thickness nor chamber diameter changed significantly over the 16-week period in the nitrate-treated group apart from the significant reduction in the lateral wall thickness at 16 weeks.

Hemodynamic results. The absolute values for hemodynamic variables in the control group are presented in Table 3. Over the 16-week period, there was a significant increase in pulmonary artery pressure (18 ± 5 to 24 ± 5 mm Hg, $p = 0.0002$), pulmonary capillary wedge pressure (9 ± 4 to 15 ± 4 mm Hg, $p = 0.003$) and right atrial pressure (7 ± 4 to

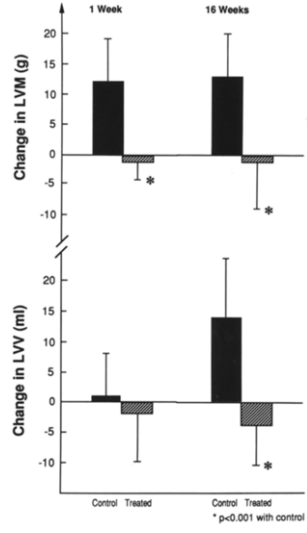

Figure 2. Absolute change from baseline in left ventricular mass (LVM) and volume (LVV) at 1 and 16 weeks after myocardial damage in control and nitrate-treated groups. Values represent mean value ±1 SD.

Table 2. Wall Thickness and Chamber Diameter Variables in Control and Isosorbide Mononitrate–Treated Dogs at Baseline and at 1 and 16 Weeks After Myocardial Damage

Group	Interventricular Septum (mm)	Left Ventricular Wall (mm)			Chamber Diameter (mm)		Diameter/Wall Thickness Ratio
		Anterior	Lateral	Posterior	Septal-Lateral	Anteroposterior	
Control							
Baseline	7.64 ± 0.76	8.04 ± 0.64	7.72 ± 0.76	8.27 ± 0.76	38.06 ± 3.13	37.94 ± 2.30	4.81 ± 0.34
1 Week	8.71 ± 1.13*	8.81 ± 1.18*	8.73 ± 0.88*	9.28 ± 1.02*	38.24 ± 3.21	38.24 ± 3.20	4.33 ± 0.49*
16 Weeks	7.95 ± 0.87	8.08 ± 0.71	8.22 ± 0.65*	8.69 ± 1.06	41.65 ± 3.41*	41.65 ± 5.18	5.09 ± 0.75
Treatment							
Baseline	7.45 ± 0.70	7.58 ± 0.73	7.74 ± 0.78	7.61 ± 0.6†	39.2 ± 4.08	39.1 ± 3.25	5.17 ± 0.47
1 Week	7.45 ± 0.61†	7.62 ± 0.68†	7.62 ± 0.72†	7.62 ± 0.63†	38.6 ± 3.75	35.6 ± 11.7	4.86 ± 0.74
16 Weeks	7.37 ± 0.59	7.51 ± 0.64†	7.50 ± 0.77*	7.51 ± 0.6	38.4 ± 3.78†	38.7 ± 3.89	5.16 ± 0.32

*p ≤ 0.025 compared with baseline value. †p ≤ 0.05 compared with the temporally matched value in the control group.

10 ± 3 mm Hg, p = 0.0036). Although there was a downward trend in cardiac output, stroke volume and systemic vascular resistance, none of these measurements demonstrated a significant difference at 16 weeks from baseline values.

In the nitrate-treated group there was a significant decrease in pulmonary artery pressure (20 ± 4 to 16 ± 3 mm Hg, p = 0.002), pulmonary capillary wedge pressure (13 ± 4 to 8 ± 3 mm Hg, p = 0.0004) and right atrial pressure (10 ± 3 to 6 ± 3 mm Hg, p = 0.006) at 16 weeks compared with baseline. Mean aortic pressure was not significantly reduced at 16 weeks in the treated group (93 ± 13 to 89 ± 9 mm Hg).

At baseline, cardiac output was significantly greater in the control group than in the nitrate-treated group. The heart rate was also slightly higher in the control group but stroke volume values were similar in the two groups. There were no other significant baseline differences between the two groups. At 1 week there was no significant difference between groups in any of the hemodynamic variables studied. At 16 weeks the dogs treated with isosorbide mononitrate had a significantly lower pulmonary artery pressure (16 ± 3 vs. 24 ± 5 mm Hg, p = 0.0001), pulmonary capillary wedge pressure (8 ± 3 vs. 15 ± 4 mm Hg, p = 0.0001) and right atrial pressure (6 ± 3 vs. 10 ± 3 mm Hg, p = 0.0084) than the control group. Mean aortic pressure was not significantly different between the two groups at either of these time points.

The hemodynamic response to isosorbide mononitrate was monitored in six dogs for 2 h after the administration of 30 mg of this medication at baseline and at 1 and 16 weeks. Isosorbide mononitrate significantly reduced mean aortic pressure, pulmonary artery pressure, pulmonary capillary wedge pressure and right atrial pressure during this 2-h period but had no significant effect on cardiac output or heart rate. There was no statistical difference in the pattern of response in mean aortic pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, right atrial pressure, heart rate and cardiac output at the three time points, although the effect was somewhat less marked at 16 weeks. Comparison of the 120-min data with baseline values revealed that the hemodynamic effect of isosorbide mononitrate had largely waned within 2 h of its administration except in the case of pulmonary artery pressure, which remained significantly below the baseline value at 2 h. The response of mean arterial pressure, pulmonary capillary wedge pressure, right atrial pressure and pulmonary artery pressure are displayed graphically in Figure 3.

Table 3. Absolute Values for Hemodynamic Variables in Control and Isosorbide Mononitrate–Treated Groups at Baseline and at 1 and 16 Weeks After Myocardial Damage

	Baseline		1 Week		16 Weeks	
	Control	Treatment	Control	Treatment	Control	Treatment
AoP (mm Hg)	97 ± 14	93 ± 13	96 ± 15	92 ± 11	95 ± 12	89 ± 9
PAP (mm Hg)	18 ± 5	20 ± 4	21 ± 4	20 ± 4	24 ± 5*	16 ± 3*†
PCWP (mm Hg)	9 ± 4	13 ± 4	13 ± 4*	13 ± 4	15 ± 4*	8 ± 3*†
RAP (mm Hg)	7 ± 4	10 ± 3	7 ± 4	9 ± 4	10 ± 3*	6 ± 3*†
HR (beats/min)	89 ± 25	74 ± 15	94 ± 22	82 ± 10	96 ± 24	77 ± 15†
CO (liters/min)	3.83 ± 1.11	2.91 ± 0.71	3.76 ± 1.01	3.05 ± 0.53	3.65 ± 1.02	3.19 ± 0.73
SV (ml/s)	44 ± 9	40 ± 7	41 ± 10	38 ± 8	39 ± 7	42 ± 7
SVR (dynes·s·cm^5)	2,011 ± 513	2,374 ± 633	1,989 ± 484	2,188 ± 456	1,988 ± 521	2,157 ± 502

*p < 0.01 compared with baseline value. †p < 0.05 compared with the temporally matched value in the control group. AoP = aortic pressure; CO = cardiac output; HR = heart rate; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; SV = stroke volume; SVR = systemic vascular resistance.

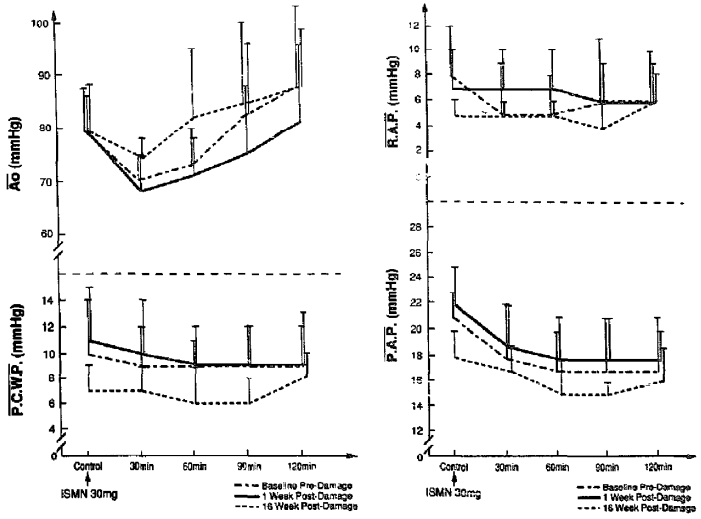

Figure 3. The response of mean aortic pressure ($\overline{Ao}$), pulmonary capillary wedge pressure ($\overline{P.C.W.P.}$) (A) and pulmonary artery pressure ($\overline{P.A.P.}$) and right atrial pressure ($\overline{R.A.P.}$) (B) in six dogs over a 2-h period after oral administration of 30 mg of isosorbide mononitrate (ISMN 30 mg, arrow) at baseline and at 1 and 16 weeks after myocardial damage. Values represent mean value ±1 SD.

Discussion

The prevention of ventricular remodeling after myocardial damage is assuming increasing importance (6). As many as 25% of patients surviving myocardial infarction develop heart failure in the subsequent 5 years (19). It is likely that the progressive structural changes that constitute ventricular remodeling contribute to the development of this syndrome (6,7).

Ventricular dilation and an increase in ventricular mass are the structural changes that occur in remodeling. Dilation may be due to a combination of myocardial infarct expansion (20), myocyte slippage (21) and eccentric hypertrophy (1) of remaining viable myocytes. Ventricular chamber enlargement can be progressive (7,22,23) and is associated with the development of heart failure (7) and a poor short- and long-term prognosis (24,25).

Left ventricular mass increases as a result of myocyte hypertrophy (1,2) and growth of the cardiac interstitium (26). It is generally believed that the increase in left ventricular mass that occurs after infarction is an adaptive response whose purpose is to reduce wall stress, which increases as a result of chamber dilation (27). Recently, however, a primary increase in left ventricular mass, not stimulated by prior chamber dilation, has been described in experimental (17,28) and clinical (3) settings after myocardial damage. The prognostic implications of increased mass in response to left ventricular damage, whether or not this structural change is preceded by chamber dilation, is unclear (3,17,28). Morphometric (1), biochemical (29) and regional blood flow data (30) suggest that, at least in the long term, increased ventricular mass may be maladaptive.

Accordingly, increasing efforts are being directed to the pharmacologic attenuation of these structural changes (6). Ideally such interventions should be based on knowledge of the mechanisms responsible for remodeling. However, these remain unclear. Both hypertrophy and dilation could represent a structural response to a nonspecific increase in myocardial load after myocardial damage (31,32). Alternatively, trophic substances, such as angiotensin II (33,34), norepinephrine (35,36) and aldosterone (37) may contribute to myocyte hypertrophy and growth of the cardiac interstitium. Pharmacologic studies have confirmed the effectiveness of angiotensin-converting enzyme inhibitors in attenuating ventricular remodeling (6,38,39). Other load-reducing agents such as hydralazine (40) and furosemide (7) have not

been successful in this regard. Preliminary data from this laboratory have illustrated the effectiveness of the alpha$_1$-adrenoceptor blocking agent terazosin in attenuating early but not later left ventricular mass increase after myocardial damage in the dog (41). Although it is difficult to separate the relative effects of load and specific trophic influences in vivo, these data do suggest that reduction in load alone may not be sufficient to attenuate remodeling.

Role and mechanisms of nitrate therapy in preventing left ventricular remodeling. The results of this study demonstrate that long-term oral nitrate therapy with isosorbide mononitrate can attenuate both early and late manifestations of left ventricular remodeling in this canine model. The treated dogs displayed neither the early increase in left ventricular mass nor the delayed increase in left ventricular volume evident in the control dogs. The beneficial effect of nitrates in attenuating myocardial infarct expansion, an early manifestation of remodeling, has been demonstrated by Jugdutt (14) and Jugdutt and Warnica (15). However, nitrate therapy has not previously been shown to attenuate an increase in myocardial mass. Moreover, the data presented here demonstrate that long-term ventricular remodeling can be prevented by nitrate therapy. To date, only angiotensin-converting enzyme inhibitors have been shown to be successful in preventing the long-term manifestations of ventricular remodeling in both experimental and clinical settings (7,26,38,39). Our data support the concept that nitrates may also be effective in this regard.

At least two mechanisms could be involved in this nitrate effect. The beneficial effects of isosorbide mononitrate could be mediated by a nonspecific reduction in myocardial load. Raya and colleagues (40) have demonstrated the efficacy of captopril and the failure of hydralazine in attenuating left ventricular dilation in a rat model of infarction. They concluded that venodilation was an important factor in attenuating ventricular remodeling. The results of our study are consistent with that observation, as isosorbide mononitrate significantly reduced pulmonary artery pressure, pulmonary capillary wedge pressure and right atrial pressure at 16 weeks compared with temporally matched control values. However, at 1 week after myocardial damage there was little difference between the groups in any of the measured hemodynamic variables. Despite this lack of major hemodynamic difference between nitrate-treated and control dogs, the myocardial mass increase documented in the control group at 1 week was prevented by isosorbide mononitrate. Moreover, the acute hemodynamic effect of the nitrate on measured hemodynamic variables appeared to be transient. All measurements were returning toward baseline within 2 h after administration of the drug, thus implying that the preload- and afterload-reducing effects of this agent were short-lived throughout a 24-h period. However, because the isosorbide mononitrate for this pharmacodynamic study carried out on a subset of the study dogs was dissolved in dextrose solution rather than administered as a tablet, this dosage form may have exhibited more rapid absorption and shortened duration of action than those of the study drug. Furthermore, a full analysis of ventricular loading conditions was not performed in this study. Consequently, a sustained reduction in impedance or preload induced by isosorbide mononitrate cannot be excluded by these data.

If load reduction does not fully explain the ability of isosorbide mononitrate to attenuate ventricular remodeling, it is interesting to speculate that this agent may have a direct antigrowth effect (42). Experimental data have revealed that nitrates and other endogenous vasodilators such as atrial natriuretic peptide have a direct antiproliferative effect on several tissues (42,43) in vitro. Cyclic guanosine monophosphate could mediate this effect. Whether these effects are relevant in vivo will require further study.

Limitations of the study. Certain specific features of the design of this study should be addressed. Mild Innovar sedation was used for the catheterization procedures so as to obtain hemodynamic measurements in the awake state. Sodium pentobarbital general anesthesia was used for the NMR imaging studies. This agent represents the most practical approach to anesthesia in the setting of NMR imaging as it allows for maintenance of a constant level of anesthesia with good control of respiratory movements. The known cardiodepressant effect of the barbiturates will not alter the estimate of ventricular mass but could influence ventricular volume. However, this possible influence on chamber volume would have affected all studies in a similar manner.

Morphometric analysis of tissue was not performed because killing the animals at three different time points to obtain pressure-perfused tissue would have been impractical. Moreover, a large number of animals would have been needed because of the modest increase in left ventricular mass and the known variability in size of normal myocytes. The increase in left ventricular mass observed in the control group is therefore presumed but not proved to represent a combination of myocyte hypertrophy and growth of the cardiac interstitium. Previous studies (1,26) using many different experimental models have demonstrated that such an assumption is well founded. It may be argued that edema could have contributed to the early increase in ventricular mass. However, previous data from this laboratory (17) have demonstrated that the T_2 relaxation times, an NMR-derived index of tissue fluid, do not prolong in the 1st week after myocardial damage. Moreover, wall thickness increases in areas remote from the damaged zone where edema should not be a factor. Accordingly, prevention of the increase in mass by isosorbide mononitrate probably represents an antiproliferative effect of this agent on cardiocyte and noncardiocyte myocardial tissue, but this hypothesis will need to be confirmed by quantitative morphometric studies.

The purpose of this study was to assess the long-term efficacy of oral nitrate therapy in inhibiting ventricular remodeling. Whether the successful inhibition of remodeling improves ventricular function remains unclear from these data. Left ventricular function at rest, as assessed by simple hemodynamic variables, suggests that the inhibition of re-

modeling has a salutary effect on ventricular function. However, more elaborate testing of ventricular function, including pressure-volume loop analysis, would be required to more fully investigate the functional consequences of remodeling and its prevention.

The extent of myocardial damage in each animal was not directly assessed. At the time of death, scar size would probably not correlate with percent damage to the left ventricle because of the subsequent chamber remodeling and scar shrinkage over the 16-week period of observation. Previous studies with this model have identified a reproducible area of damage involving 17 ± 6% of the left ventricular myocardium (16), producing a consistent pattern of ventricular remodeling (17). Random assignment to the control and isosorbide mononitrate–treated arms of this study coupled with the reproducibility of the remodeling response in the control group suggests that it is highly unlikely that a systematic difference in animal selection could account for the apparent response to therapy.

Conclusions. In summary, isosorbide mononitrate prevents early mass increase and later chamber dilation in the canine model of transmyocardial DC shock. This inhibitory effect may reflect either subtle hemodynamic effects or a direct antiproliferative action of this drug.

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