Effects of Nitroglycerin on Regional Myocardial Ischemia Induced by Atrial Pacing in Dogs

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SUMMARY The exact mechanism or mechanisms by which nitroglycerin exerts its beneficial effect on pacing-induced regional myocardial ischemia has not been elucidated previously. In an open-chest, anesthetized canine preparation a fixed, flow limiting stenosis was applied to the left anterior descending (LAD) coronary artery and heart rate was increased by atrial pacing. Mass spectrometry was used to measure myocardial oxygen (P_{mo2}) and carbon dioxide (P_{mco2}) tensions. Myocardial blood flow was measured by the radioactive microsphere technique. Application of the stenosis resulted in regional decreases in P_{mo2} and increases in P_{mco2} of greater magnitude in the subendocardial than in the subepicardial layer. Atrial pacing resulted in a further decrease in P_{mo2} and increase in P_{mco2} as well as a reduction in subendocardial blood flow. Nitroglycerin (TNG) infusion reduced mean arterial pressure 20 mm Hg, resulting in a 14 mm Hg reduction in P_{mco2} in the more ischemic subendocardial layer (P < 0.05). Myocardial blood flow decreased in all regions; however, the magnitude of this decrease was less in the ischemic region. Addition of aortic constriction abolished both the afterload and preload lowering effects of nitroglycerin but improved ischemic zone blood flow. These data demonstrate that nitroglycerin reduces the severity of pacing-induced regional myocardial ischemia primarily by reducing the determinants of myocardial oxygen demand. We found that when these effects are counteracted, improvement in myocardial oxygen supply becomes the dominant mechanism.


SUBLINGUAL nitroglycerin has been the time-honored therapy for treatment of angina pectoris (Murrell, 1879). Several recent clinical studies have demonstrated that nitroglycerin can be administered safely to patients with acute myocardial infarction by intravenous infusion with consistently beneficial effects on indices of myocardial ischemia (Borer et al., 1975, Come et al., 1975, Flaherty et al., 1975, Flaherty et al., 1976). The ability of nitroglycerin to relieve ischemia in either clinical situation may result from dilating effects on either peripheral arteries or veins, or both, which might decrease determinants of myocardial oxygen demand, or from direct effects on the coronary circulation which might increase myocardial oxygen supply.

The present study employs a previously well-characterized, anesthetized, open-chest canine model to study the mechanism of nitroglycerin's beneficial effect on regional myocardial ischemia, induced distal to a fixed, flow-limiting coronary stenosis by atrial pacing (O'Riordan et al., 1977). This preparation is designed to model a milder degree of reversible ischemia, such as would be present during angina. Previous studies from this laboratory have demonstrated that mass spectrometry can provide a quantitative index of the severity of regional ischemia (Khuri et al., 1975). It was the purpose of the present study to test the hypothesis that nitroglycerin relieves pacing-induced regional myocardial ischemia by a combination of the two mechanisms mentioned above: (1) peripheral vasodilation of arteries and veins, resulting in a reduction in oxygen demands and (2) central vasodilation of intercoronary collateral vessels, resulting in augmentation of regional oxygen supply.

Methods

Nine mongrel dogs (20-25 kg) were anesthetized with intravenous pentobarbital. The initial dose of 20 mg/kg was followed with intermittent doses as necessary to maintain adequate anesthesia. After endotracheal intubation, ventilation was maintained with a Harvard respirator. A left thoracotomy was performed and the heart was suspended in a pericardial cradle. A 1- to 2-cm segment of the left anterior descending (LAD) coronary artery just distal to the origin of the left circumflex coronary artery was dissected free. An electromagnetic flow probe (Biotronix series 6000 flow probe with a Biotronix model 610 pulse logic flowmeter) was placed...
around the LAD just proximal to a screw-type variable occluder (Fig. 1). Catheters were placed in the femoral arteries for measurement of arterial blood pressure using a Statham P23Db transducer and for withdrawal of blood following injection of radioactive microspheres. A catheter also was placed in the left atrium for subsequent injection of microspheres. Umbilical tape was placed loosely around the descending thoracic aorta to allow aortic constriction to be applied at a later time.

Myocardial oxygen (PmO₂) and carbon dioxide (PmCO₂) tensions were measured by mass spectrometry. Two 22-gauge Teflon-coated stainless steel probes were placed in the region of myocardium supplied by the stenosed LAD coronary artery, with one probe placed in the deeper subendocardial layer and the second positioned more superficially in the subepicardium. At the end of each experiment, the positions of these probes were confirmed and the left ventricular wall thickness and the distance of the mid-portion of each probe from the epicardial and endocardial surfaces measured and recorded.

Carbonized radioactive microspheres (7-10 μm) labeled with ¹⁴¹Ce, ⁸⁵Sr, ⁹⁵Nb, and ⁴⁶Sc were used to measure regional myocardial blood flow in subendocardial and subepicardial layers. At selected times, approximately one million microspheres were injected into the left atrium while arterial blood was withdrawn simultaneously from the femoral artery by use of a Harvard infusion-withdrawal pump. At the end of each experiment, myocardium perfused by the stenosed LAD was delineated by injection of methylene blue dye into the artery near the site of the stenosis. The stained tissue then was excised and divided into multiple concentric rings parallel to the line of separation between stained and unstained myocardium (Fig. 2). These segments were divided into endo- and epicardial halves, weighed, and counted in a differential well scintillation counter. Computer techniques were used to compute absolute myocardial blood flow in ml/min per 100 g left ventricle.

In each of the nine dogs studied, a stenosis of fixed degree was applied to the LAD coronary artery. The variables constrictor was tightened until a moderate (30-60%) reduction in flow was obtained. In the two animals (#2 and #4) demonstrating the extreme changes in PmCO₂ (least and greatest), the constrictor was readjusted to provide a final flow reduction of 16% (#2) and 86% (#4). The final percent reduction in mean coronary blood flow, expressed as a percent of control, was measured and recorded approximately 30 minutes after placement of the stenosis. Atrial pacing at a rate approximately 40% above each individual animal's resting heart rate was maintained for 30 minutes with no intervention, followed by two subsequent 30-minute intervention periods. The nine dogs then were divided randomly among two protocols. In
four of the nine dogs, nitroglycerin infusion alone was the initial intervention. Nitroglycerin was begun and the infusion rate increased until mean arterial blood pressure was reduced by approximately 20 mm Hg. This infusion rate was readjusted once, if necessary, 15–20 minutes after initiating the infusion. In the remaining five dogs, immediately after the final dose of nitroglycerin had been reached, the aorta was constricted to return mean arterial pressure to pre-nitroglycerin control levels. If necessary, the infusion rate of nitroglycerin was readjusted once, 15–20 minutes into the period, to maintain a constant mean arterial pressure. In the initial four dogs, after 30 minutes of nitroglycerin infusion, a similar degree of aortic constriction was applied and maintained for the duration of the second 30-minute intervention period. The five dogs that had received the combination of nitroglycerin and aortic constriction as the initial intervention had the aortic constriction removed; this allowed the arterial pressure to fall to the level previously attained with nitroglycerin alone for the duration of the second 30-minute intervention period.

The data obtained during each period from all nine dogs then were combined. The data obtained during nitroglycerin infusion alone and during nitroglycerin infusion plus aortic constriction were averaged to neutralize any possible beneficial effect obtained from the order of application of the interventions.

Mean arterial pressure (MAP), mean left atrial pressure (MLAP), PmO\(_2\), and PmCO\(_2\) were recorded 30 minutes after application of the stenosis, after 30 minutes of atrial pacing, and at the end of each of the 30-minute intervention periods, during which either nitroglycerin infusion alone or the combination of nitroglycerin and aortic constriction was administered. Injection of microspheres into the left atrium and simultaneous withdrawal of blood from the femoral artery were also performed at the end of each of these periods. The sequence of injection of each of the four different microspheres was randomized.

Statistical Methods

Repeated measures analysis of variance techniques were used to analyze myocardial blood flow in relation to factors of the experimental procedure (stenosis, pacing, nitroglycerin and nitroglycerin-aortic constriction), layers (subendocardial and subepicardial), and rings (LAD\(_1\), LAD\(_2\), LAD\(_3\), LAD\(_b\), CIRC\(_b\), and CIRC\(_D\)) (Winer, 1971; Dixon and Brown, 1979). A preliminary analysis including all three factors demonstrated significant layer-by-ring and procedure-by-ring interactions. Therefore, separate analyses were performed for each layer and specific pairs of procedures (see Fig. 5, A and B). Unless designated as interactions, all P values for these analyses are derived from the analysis of variance test for procedure differences. In all analyses, the test for differences in myocardial blood flow between rings was highly significant (P < 0.001). Hemodynamic and myocardial gas tension data were analyzed using Fisher’s LSD test for differences between pairs of means within a two-way analysis of variance. Significance was determined at the P ≤ 0.05 level.

Results

Following Application of the LAD Stenosis

Mean flow in the LAD coronary artery following the application of the stenosis was reduced to 42 ± 4% of control. Application of this degree of fixed stenosis resulted in no significant change in mean arterial pressure, mean left atrial pressure, or heart rate (Fig. 3) but did result in significant increases in regional myocardial carbon dioxide tension in subendocardial layers (Table 1). Subendocardial PmCO\(_2\) rose from 39 ± 2 to 70 ± 6 mm Hg (P < 0.05) and subepicardial PmCO\(_2\) increased from 38 ± 1 to 55 ± 4 mm Hg (Fig. 4). Myocardial oxygen tension decreased in both subendocardial and subepicardial

![Figure 3](http://ahajournals.org)
The Addition of Atrial Pacing

Atrial pacing at a rate of 192 ± 7 beats/min resulted in no significant change in mean arterial pressure. Although previous application of the stenosis had not increased mean left atrial pressure (MLAP), the subsequent addition of atrial pacing resulted in a significant increase in mean left atrial pressure from 6.3 ± 0.5 to 9.1 ± 0.9 mm Hg (P < 0.05) (Fig. 3). In the region of myocardium supplied by the stenosed LAD, Pmco₂ in the subendocardial layer increased during pacing from 70 ± 6 to 96 ± 13 mm Hg (P < 0.05), and Pmco₂ in the subepicardial layer increased from 55 ± 4 to 74 ± 9 mm Hg (P < 0.05) (Fig. 4). Concomitantly, with addition of pacing subendocardial Pmo₂ decreased from 9 ± 3 to 5 ± 2 mm Hg (P < 0.05) whereas the subepicardial Pmo₂ decreased from 12 ± 2 to 10 ± 2 mm Hg (P < 0.05).

The addition of atrial pacing dramatically changed the myocardial blood flow relationship across the LAD- and circumflex-supplied regions in both subendocardial and subepicardial layers, as indicated by highly significant procedure by region interaction (P < 0.001) (Fig. 5A). In the border ischemic ring a lesser decrease in flow was observed. On the other hand, subendocardial flow in circumflex-supplied regions demonstrated a significant increase with the addition of atrial pacing. In contrast to the decreases in flow noted to the subendocardial layers within the ischemic region, flow to the subepicardial layers increased slightly with the addition of atrial pacing (Fig. 5A). In adjacent circumflex-supplied myocardium, subepicardial flow increased to a degree comparable to that noted in the subendocardial layer in the same region.

The Administration of Intravenous Nitroglycerin

A reduction in mean arterial pressure of 20 ± 4 mm Hg (P < 0.001) was obtained with nitroglycerin infusion (Fig. 3). The mean infusion rate required was 64 ± 9 μg/min. The mean final infusion rate, after all necessary readjustments, was 71 ± 13 μg/min. Mean left atrial pressure was simultaneously decreased from 9.1 ± 0.9 to 7.3 ± 0.9 mm Hg (P < 0.05). Myocardial carbon dioxide in the subendocardial layer of the ischemic zone decreased from 96 ± 13 to 82 ± 13 mm Hg (P < 0.05) while subepicardial Pmco₂ decreased from 74 ± 9 to 71 ± 9 mm Hg (Fig. 4). Myocardial oxygen tension in the subendocardial layer of the ischemic zone decreased from 96 ± 13 to 82 ± 13 mm Hg (P < 0.05) while subepicardial Pmco₂ decreased from 74 ± 9 to 71 ± 9 mm Hg (Fig. 4). Myocardial oxygen tension in the subendocardial layer of the ischemic zone remained at 5 mm Hg whereas subepicardial Pmo₂ decreased from 10 ± 2 to 7 ± 2 mm Hg (P < 0.05).

In the presence of a reduction in both myocardial oxygen demands and of coronary perfusion pressure, nitroglycerin infusion was observed to result in a significant lowering in blood flow to all regions (P = 0.065). Myocardial blood flow again was found to vary continuously across myocardial rings, increasing progressively from the center ischemic to the distant non-ischemic regions.
TABLE 1  Ischemic Zone Subendocardial Carbon Dioxide Tensions (PmCO₂) and Blood Flows (MBF) in Ring LAD₂* in the nine Experiments

<table>
<thead>
<tr>
<th>Experiment no.</th>
<th>Control PmCO₂ (mm Hg)</th>
<th>PmCO₂ MBF (ml/min per 100 g)</th>
<th>PmCO₂ MBF (ml/min per 100 g)</th>
<th>Aortic constriction (AC) + TNG + P + S</th>
<th>Post-control PmCO₂ (mm Hg)</th>
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<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>NS</td>
</tr>
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* The position of the mass spectrometry probe was approximated most closely by the LAD-2 ring.
† P values obtained by paired Student's t-test vs. the comparable data in the adjacent column to the left.

non-ischemic regions. From examination of this flow relationship it appears that, following the administration of nitroglycerin, subendocardial blood flow in center ischemic zones tended to fall less than in non-ischemic circumflex-supplied zones. Although not reaching the 95% level of significance, this tendency for subendocardial ischemic zone flow to be maintained is indicated by the level of the region by procedure interaction (P = 0.122).

Restoration of Mean Arterial Pressure to Control Levels by Aortic Constriction

Constriction of the descending thoracic aorta returned mean aortic pressure to the level present prior to the administration of nitroglycerin. In response to this increase in afterload, however, mean left atrial pressure rose from 7.3 ± 0.9 to 8.4 ± 1.0 mm Hg, a level not significantly different from that.
noted prior to initiation of nitroglycerin therapy (Fig. 3). Following restoration of mean arterial pressure, subendocardial and subepicardial Pmco2 in the ischemic zone fell slightly (7-8 mm Hg) but these changes failed to reach statistical significance (Fig. 4). Subendocardial Pmco2 remained at 5 mm Hg whereas subepicardial Pmco2 increased slightly from 7 to 9 mm Hg (P < 0.05).

With restoration of aortic pressure in the continued presence of nitroglycerin, significant increases in flow were observed in both deep and superficial layers across all ischemic and nonischemic regions (P = 0.017 for subendocardial layers and P = 0.008 for subepicardial layers) (Fig. 5A). Subepicardial flow increases were of comparable magnitude in central ischemic, border, and non-ischemic regions. If one compares the effect of nitroglycerin and maintenance of aortic pressure with atrial pacing alone, one finds that mean flows in the ischemic zone rings were 10-16 ml/min per 100 g greater than mean flows measured during pacing alone, in both the deep and superficial layers (Fig. 5A). Nonischemic zones' flows, in contrast, were essentially unchanged.

**Discontinuation of Pacing and Removal of Stenosis**

To confirm that the changes in myocardial gas tensions were reversible, subendocardial Pmo2 and Pmco2 were measured again. Fifteen minutes after removal of the LAD stenosis, PmO2 rose to 25 ± 3 mm Hg and PmCO2 fell to 37 ± 2 mm Hg. These final levels were not significantly different from those measured during the pre-stenosis control period.

**Discussion**

The results of the present study demonstrate the usefulness of mass spectrometry for assessing the effect of an intervention such as nitroglycerin on the balance between myocardial oxygen supply and demand. Application of a flow-reducing coronary stenosis resulted in the development of regional ischemia as evidenced by an increase in myocardial carbon dioxide tension and a decrease in myocardial oxygen tension. Both of these changes were of greater magnitude in subendocardial than in subepicardial layers. The addition of atrial pacing resulted in a further increase in the severity of the regional ischemia, as evidenced by further changes in both oxygen and carbon dioxide tensions. Increasing myocardial oxygen demands by atrial pacing was associated with the expected proportional rise in blood flow to regions supplied by unstenosed coronary arteries. In contrast, flow to myocardium supplied by the stenosed artery fell markedly in deeper layers and increased only slightly in superficial layers. Redistribution in coronary flow away from the deeper layers resulted in worsening of the subendocardial ischemia already present prior to the initiation of pacing.

Administration of intravenous nitroglycerin resulted in a reduction in the severity of subendocardial ischemia as evidenced by a significant decrease in regional myocardial carbon dioxide tension. By dilating peripheral arteries and veins, nitroglycerin reduced mean arterial pressure and left ventricular filling pressure, thereby decreasing left ventricular wall tension, a major determinant of myocardial oxygen demand. Although myocardial blood flow in the ischemic region did not increase during nitroglycerin infusion, the observed reduction in PmCO2 clearly demonstrated that nitroglycerin exerted a favorable effect on the balance between oxygen supply and demand.

Previous studies have demonstrated that, under certain experimental conditions, nitroglycerin can be shown to exert a more positive effect on blood flow to ischemic myocardium (Becker et al., 1971; Smith et al., 1973; Bache et al., 1975; Chiariello et al., 1976; Cohn et al., 1977, Bache, 1978) Redistribution of transmural coronary flow, with an increase in subendocardial relative to subepicardial flow, as well as an absolute increase in flow as a result of a direct vasodilating effect on intercoronary collateral vessels, has been demonstrated (Cohen et al., 1976; Cappuro et al., 1977a, 1977b). However, studies demonstrating an absolute increase in ischemic zone blood flow with nitroglycerin have employed a coronary ligation, rather than a coronary stenosis, to induce ischemia. When Forman et al. (1973) employed a stenosis rather than a ligation, they found a reduction in ischemic zone blood flow with nitroglycerin. Coronary ligation would be expected to result in more severe regional ischemia than a flow-reducing stenosis. Furthermore, a greater degree and extent of ischemia would result in more pronounced left ventricular dysfunction (Salisbury et al., 1963; Bache, 1978; Ellis and Klocke, 1978). Under these conditions, nitroglycerin could improve subendocardial perfusion not only by increasing collateral flow, but also by reducing the elevated left ventricular end-diastolic pressure and, thereby, lowering intramural pressure. In our model that used a stenosis plus pacing, the minor elevation in observed end-diastolic pressure during ischemia might limit the potential benefit to be obtained from preload reduction.

The results of the present study suggest that, whereas nitroglycerin may be capable under certain circumstances of causing an absolute increase in ischemic zone blood flow, this is not a prerequisite for the reduction of ischemia. It is likely that, in the presence of a large enough reduction of myocardial oxygen demand, nitroglycerin might not need to increase ischemic zone flow in order to reduce ischemia. A reduction in the severity of ischemia might require only a relative maintenance of subendocardial flow in the ischemic zone. In the present study, while flow to non-ischemic myocardium was falling approximately 15%, flow in more ischemic subendocardial layers distal to the coronary
stenosis was falling by only 5%. Within the ischemic region the magnitude of the decrease in flow similarly was less in the subendocardial than in the subepicardial layer. In the presence of this apparent preferential effect on ischemic zone subendocardial perfusion, a decrease in Pmco2 in the ischemic zone was found that was greater in deeper than in superficial layers. These Pmco2 data suggest that nitroglycerin may have its most beneficial effect in the most severely ischemic subendocardial layers.

A direct effect of nitroglycerin on coronary collateral blood flow was made more apparent when its peripheral effects were abolished by aortic constriction. It is important to note that the reduction in Pmco2 obtained with nitroglycerin in the absence of any significant afterload or preload lowering was not different from that obtained with nitroglycerin alone. Previous studies, again employing more severe degrees of ischemia, had suggested that a greater beneficial effect could be obtained by restoring arterial pressure in the presence of nitroglycerin (Borer et al., 1975; Miller et al., 1977; Ellis and Klocke, 1978).

The extent of pre-existing intercoronary collateral channels is known to vary from dog to dog. Therefore, the severity of the ischemic response to a given degree of stenosis and/or to the addition of atrial pacing also would be expected to vary. The effect to be obtained from a vasodilating drug such as nitroglycerin, therefore, also might be expected to depend on the extent of each dog’s pre-existing collaterals. This could be inferred from the variability from dog to dog in the magnitude of the Pmco2 response following the initiation of atrial pacing. Animals that showed the greatest increases in Pmco2 distal to a given degree of stenosis with the addition of pacing were found to decrease ischemic zone subendocardial flow with the addition of nitroglycerin. In contrast, animals that previously had demonstrated only a small increase in Pmco2 following the addition of atrial pacing to a given degree of stenosis were found to increase ischemic zone subendocardial flow with nitroglycerin. Thus, the magnitude of an individual animal’s Pmco2 response to the addition of atrial pacing could be seen to correlate with, if not predict, a given animal’s ischemic zone blood flow response to the initiation of nitroglycerin therapy. The development of a milder degree of ischemia distal to a given degree of coronary stenosis following addition of atrial pacing might suggest that the animal had better developed pre-existing collateral vessels. The presence of such well-developed collaterals would predispose such an animal to respond optimally to an agent such as nitroglycerin, which can not only reduce determinants of oxygen demand but also dilate intercoronary collateral channels.

In summary, we used a canine model of regional myocardial ischemia induced by pacing in the presence of a fixed coronary stenosis, and were able to analyze in detail the mechanisms responsible for the modification of ischemia by a specific pharmacological agent. Mass spectrometry provided the needed quantitative index of the severity of ischemia. The microsphere technique provided detailed information as to the distribution of blood flow to both subendocardial and subepicardial layers, in regions supplied by stenosed as well as unstenosed vessels. Intravenous nitroglycerin was shown to exert its beneficial effects on regional ischemia by a combination of peripheral and local mechanisms. The peripheral effects reduced determinants of oxygen demand. The local or cardiac effects tended to maintain preferentially subendocardial blood flow in the ischemic region, and this mechanism became more dominant when the peripheral effects of the drug were abolished. Thus, it would appear that the beneficial effects of nitroglycerin on a degree of ischemia comparable to that obtained during angina result primarily from its ability to decrease myocardial oxygen demand and only to a lesser extent from its ability to have a direct effect on myocardial oxygen supply. This latter effect would appear to be dependent on the presence of significant pre-existing collateral channels.

Acknowledgments
We wish to acknowledge Louis Jackson for his technical assistance in the performance of these experiments.

References
Come PC, Flaherty JT, Baird MG, Rouleau JR, Weisfeldt ML,
Hypertension following Arterial Baroreceptor Denervation in the Unanesthetized Dog

Cyril S. Ito and Allen M. Scher

SUMMARY Studies were conducted on unanesthetized dogs (1) in the control state, (2) after carotid sinus denervation plus section of the cervical aortic nerves (SCAD), and (3) after carotid sinus denervation plus section of intrathoracic vagal branches which innervate arterial and cardiopulmonary baroreceptors, the heart, lungs, and other structures (STD). Mean values and standard deviations of blood pressure and heart rate were measured during many 75-minute recording sessions. The control mean arterial pressure was 94.8 ± 8.9 mm Hg. The mean pressure after SCAD was 105.5 ± 9.5 mm Hg, 10.0 mm Hg higher (P < 0.05) than in the control state, whereas, after STD, the mean pressure was 119.5 ± 16.8 mm Hg, 25.3 mm Hg higher (P < 0.001) than in the control state. The standard deviation of pressure was increased (P < 0.01) by either denervation procedure. The mean pressure after STD was higher than after SCAD (P < 0.05). Ten of 12 animals with SCAD showed residual baroreceptor reflexes (seven from intrathoracic receptors) whereas, after STD, six of 11 animals showed reflexes (one from intrathoracic receptors). SCAD only occasionally produces denervation as complete as that produced by STD. A larger increase in arterial pressure follows a more complete denervation of vagally innervated baroreceptors. We believe that our procedures do not denervate all arterial baroreceptors. Chronic denervation of arterial baroreceptors leads to a widely varying, elevated arterial pressure. The increase in pressure has persisted more than 1½ years. Circ Res 48: 576-586, 1981

According to the classic view of blood pressure control, reflexes initiated by the arterial baroreceptors maintain arterial pressure at its normal level. A decrease in impulses travelling from these receptors into the medullary cardiovascular control centers causes vasomotor and cardiac changes which raise arterial pressure. Thus, chronic denervation of arterial (carotid and aortic) baroreceptors should produce maintained hypertension (Heymans and Neil, 1958). The effects of chronic baroreceptor denervation have been studied in rats (Krieger, 1964), rabbits (Green et al., 1935; Boyd and McCullagh, 1938; Alexander and DeCuir, 1966), cats (Kremer et al., 1933; Guazzi and Zanchetti, 1965), and dogs over several decades. In the dog, hyper-