Influence of Acute Arterial Hypertension on Myocardial Infarct Size in Dogs Without Left Ventricular Hypertrophy

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During acute myocardial infarction an increase in arterial pressure is common in patients who were previously normotensive and, therefore, do not have left ventricular hypertrophy. However, the effect of hypertension on infarct size in the absence of hypertrophy is uncertain. Thus, 32 open chest dogs underwent a 2 hour occlusion of the mid-left anterior descending coronary artery followed by 3 hours of reperfusion. Immediately after occlusion, 14 dogs were randomized to a hypertension group (intravenous phenylephrine infusion starting 5 minutes after occlusion and terminating at the time of reperfusion, with heart rate kept constant by atrial pacing) and 18 dogs to a control group (equivalent volumes of saline solution intravenously). Twelve of the 32 dogs were excluded from analysis because they developed ventricular fibrillation during coronary occlusion or reperfusion.

In the hypertension group (n = 10), the mean arterial pressure increased significantly within 10 minutes of coronary occlusion (146 ± 7 versus 109 ± 11 mm Hg in 10 control dogs, p < 0.01) and was maintained approximately 40 mm Hg higher than in the control group (p < 0.01) throughout the ischemic period. Heart rate was similar in the two groups throughout the experiment. After the dogs were sacrificed, the region normally supplied by the occluded artery (anatomic “region at risk”) was identified by simultaneous perfusion of the aortic root and the coronary artery distal to the occlusion. The heart was sectioned transversely and stained with triphenyltetrazolium-chloride. The infarcted area and the anatomic risk area were determined by video planimetry. Control and hypertension groups did not differ significantly in the percent of left ventricle infarcted (14 ± 2 [mean ± standard error] and 13 ± 3%, respectively) or in the percent of anatomic risk region infarcted (41 ± 5 and 37 ± 7%, respectively).

It is concluded that acute arterial hypertension unassociated with left ventricular hypertrophy has neither detrimental nor beneficial effects on the size of myocardial infarction resulting from a temporary coronary occlusion followed by reperfusion.

Although systemic arterial hypertension is common in acute myocardial infarction (1,2), its influence on ischemic damage is not well understood. Shell and Sobel (3) reported that a reduction in blood pressure by trimethaphan decreases infarct size in hypertensive patients with acute myocardial infarction. However, because trimethaphan also reduces cardiac sympathetic stimulation, the exact mechanism for the limitation of infarct size in that study remains unclear.

Global left ventricular function may improve when afterload is reduced in patients with acute myocardial infarction (4,5), but this effect does not necessarily imply limitation of ischemic damage (5). Studies in experimental animals have not fully clarified this problem. Dogs with chronic arterial hypertension and left ventricular hypertrophy exhibit larger infarcts and higher mortality than do normotensive control dogs (6,7). These results, however, may reflect the enhanced vulnerability of hypertrophic myocardium to ischemia (8) rather than an effect of hypertension as such. In dogs without left ventricular hypertrophy, elevation of arterial pressure favorably affects electrocardiographic (9,10) and metabolic (11,12) indexes of ischemia during brief coronary occlusion, but the impact on infarct size after sustained ischemia has not been ascertained.

The influence of hypertension per se on infarct size is of significant clinical interest as many patients with acute myocardial infarction and hypertension do not have left ventricular hypertrophy. Approximately one-third of normotensive subjects may become hypertensive in the early phase of myocardial infarction as a result of pain, fear and agitation (1,2), release of norepinephrine from damaged myocardium (13) or stimulation of chemoreceptors supplied by the coronary arteries (14). Furthermore, if a hypertensive disorder...
preceeding the infarction was labile, mild or of recent onset, cardiac mass will likely be normal. The appropriate management of these patients with hypertension but without hypertrophy remains largely uncertain for it is unknown whether the influence of the hypertensive state on infarct size is beneficial (because of increased collateral perfusion [12,15,16]), deleterious (because of enhanced oxygen demands) or neither.

In an effort to clarify these problems experimentally, we assessed the effect of elevated arterial pressure on anatomically estimated infarct size in open chest dogs without left ventricular hypertrophy. The study was designed to minimize the interference of such variables as heart rate and size of region at risk. Hypertension was maintained throughout the duration of myocardial ischemia to maximize the likelihood of detecting any effect on infarct size. The elevation of arterial pressure was limited to approximately 40 mm Hg because higher degrees of hypertension are rarely observed in patients (1,2).

Methods

Experimental preparation. Thirty-two mongrel dogs of either sex, weighing 14 to 28 kg, were sedated with sodium thiamylal (10 mg/kg intravenously) and anesthetized 10 minutes later with alpha-chloralose (70 mg/kg intravenously). Additional doses of alpha-chloralose were administered during the experiment to abolish the corneal reflex. The dogs were intubated and ventilated with room air. The chest was opened through the left fifth intercostal space and the heart was suspended in a pericardial cradle. The left anterior descending coronary artery was isolated from the surrounding tissues and encircled by a snare. The site of occlusion was chosen to produce ischemic zones of uniform size approximating two-thirds of the anterior surface of the left ventricle, as described previously (17). Polyethylene catheters were inserted through the left atrial appendage into the left atrium and through the left carotid artery into the aorta. Both catheters were connected to a Statham P23Db pressure transducer. A solid state pressure transducer (Konigsberg, model P-20) was positioned in the left ventricular cavity through an incision in the ventricular apex. The first derivative of left ventricular pressure (dP/dt) was obtained by electronic differentiation. Aortic pressure, left ventricular pressure, dP/dt, left atrial pressure and lead II of the electrocardiogram were recorded continuously throughout the study on an eight channel, direct writing oscillograph (Gould Brush, system 200).

Experimental protocol. After baseline data were recorded, the left anterior descending coronary artery was occluded with a bulldog clamp. Immediately after occlusion, dogs were randomized to a hypertension (n = 14) or control (n = 18) group. Animals in the hypertension group received a continuous intravenous infusion of phenylephrine, beginning 5 minutes after occlusion and continuing until reperfusion. The infusion rate was adjusted to increase mean aortic pressure by approximately 40 mm Hg and averaged 88 ± 21 μg/kg per min (mean volume of infusion 72 ± 8 ml/h). Because the elevation of arterial pressure by phenylephrine was associated with a reflex decrease of heart rate, the left atrium was paced throughout the occlusion phase at a rate equal to the pretreatment sinus rate. This permitted assessment of the influence of hypertension on infarct size without the interference of changes in heart rate. Control dogs received equivalent volumes of normal saline solution intravenously. No attempt was made to resuscitate animals that developed ventricular fibrillation.

Two hours after occlusion, the left anterior descending coronary artery was reperfused by removing the clamp. In the hypertension group, phenylephrine infusion and left atrial pacing were discontinued immediately after occlusion release.

Identification and measurement of the anatomic region at risk of infarction. Three hours after coronary reperfusion, dogs were sacrificed by intravenous injection of potassium chloride. The heart was excised and placed in ice-cold saline solution. The anatomic region at risk of infarction (that is, the portion of the left ventricle normally supplied by the occluded artery) was identified by a previously described technique (18). In summary, one cannula was inserted into the left anterior descending coronary artery just below the site of occlusion and a second cannula was inserted into the aortic root. The arterial bed distal to the occlusion was then perfused with 1% brilliant blue dye in normal saline solution while the aortic root was simultaneously perfused with saline solution. Equal physiologic pressures were applied to the aortic and distal left anterior descending coronary artery cannulas to prevent flow across collateral vessels. As a result of this procedure, the myocardium normally perfused by the occluded portion of the coronary artery (anatomic region at risk) was stained blue, while the rest of the heart remained unstained. The risk region, as defined in this study, is an anatomic designation of the collateral-dependent portion of the heart. Our technique does not specify the competence of collateral vessels or the metabolic demands of the myocardium, factors that determine the actual amount of necrosis within the risk region.

The heart was sectioned from apex to base into 1 cm thick slices in a plane parallel to the atroventricular groove, and the border between stained and unstained tissue, which was assumed to be the limit of the region at risk, was marked by a small incision on each cut surface.

Estimation of infarct size. To identify the infarct within the anatomic region at risk, slices were weighed and incubated for 45 minutes in 1% triphenyltetrazolium-chloride solution at 38°C. This agent stains only viable dehydrogenase-containing myocardium dark red (19). Triphenyl-
tetrazolium-chloride has been shown to accurately identify irreversibly injured myocytes as early as 3 hours after coronary artery occlusion (20). When coronary occlusion is followed by reperfusion, clear delineation of necrotic areas by this agent has been observed after even shorter ischemic periods (30 to 35 minutes) (20), possibly because of "washout" of enzymes. The weights of the anatomic region at risk and of the infarct were determined by tracing the portion at risk and the necrotic portion of each slice on transparent plastic sheets. Each area was measured by video planimetry and the masses of the risk region and the infarct expressed as fractions of the weight of each slice (18). Total infarct mass was expressed as percent both of the left ventricle and of the myocardium at risk.

**Statistical analysis.** Values are reported as mean ± standard error of the mean. Regression lines were fitted to the grouped data using the least squares method. The x axis intercepts and their standard errors were calculated by reentering the data with x and y axes reversed. The two-tailed Student’s t test for unpaired data was used to compare means as well as intercepts and slopes of the regression lines of the relations between infarct size and risk region. The chi-square test with Yates’ correction for continuity was used to analyze the differences in mortality rate.

**Results**

**Incidence of ventricular fibrillation.** Arterial hypertension did not significantly affect the incidence of sudden arrhythmic death associated with myocardial ischemia or reperfusion. During the coronary artery occlusion phase, ventricular fibrillation occurred in 5 (28%) of the 18 control dogs and in 3 (21%) of the 14 dogs with hypertension. During the coronary reperfusion phase, 3 (23%) of the 13 control dogs and 1 (9%) of the 11 hypertensive dogs developed the arrhythmia. As a result, 20 dogs completed the protocol (10 in each group) and were included in the analysis of results.

**Hemodynamics.** Heart rate, aortic pressure and mean left atrial pressure were similar in the two groups before coronary artery occlusion as well as 5 minutes after occlusion (that is, immediately before treatment) (Fig. 1 and 2). Systolic and diastolic aortic pressures increased rapidly in treated dogs as phenylephrine infusion was begun, and by 10 minutes of occlusion reached levels significantly (p < 0.01) higher than those in the control group (Fig. 1). Mean aortic pressure remained approximately 40 mm Hg greater in the hypertension group throughout the period of ischemia (p < 0.01 at each time point). After coronary reperfusion, phenylephrine infusion was discontinued and aortic pressure in treated dogs returned to levels comparable with those observed in control dogs. Pacing was performed in hypertensive dogs to prevent the decrease in heart rate associated with the elevation of arterial pressure. As a result, heart rate was similar in the two groups throughout the experimental protocol (Fig. 2). Although left atrial pressure increased during phenylephrine infusion (p < 0.05 versus pretreatment values), it did not differ statistically from that of control dogs (Fig. 2). Thus, the only significant hemodynamic difference between the two groups was an increase in arterial pressure in treated dogs that began 5 minutes after coronary occlusion and persisted until reperfusion.

**Infarct size.** The mass of the left ventricle and that of the occluded coronary bed (anatomic region at risk) were similar in control and hypertensive dogs (Fig. 3). The two groups did not differ significantly in the size of the infarct expressed in grams, as a percent of the left ventricle or as a percent of the anatomic risk region. Even when the risk regions were arbitrarily divided into "small" and "large" (≤ and >32% of the left ventricle, respectively), the percent of risk region infarcted was similar in control and hypertensive dogs: 30 ± 7 (n = 5) versus 27 ± 6% (n = 6).

![Figure 1](https://example.com/figure1.png) **Figure 1.** Systolic (squares), diastolic (triangles) and mean (circles) aortic pressure in control and hypertension groups. Vertical bars represent 1 standard error of the mean. *p < 0.01, **p < 0.001 versus control group at the corresponding time point.
respectively, for small risk regions, and $51 \pm 3$ ($n=5$) versus $53 \pm 9\%$ ($n=4$), respectively, for large risk regions.

The mass of the infarct was directly and closely related to the mass of the anatomic region at risk in both the control ($r = 0.91, p < 0.001$) and the hypertension group ($r = 0.82, p < 0.001$) (Fig. 4). Neither the slope of the regression line nor the intercept for zero infarct was significantly different in the two groups. Thus, arterial hypertension failed to alter the relation between the magnitude of necrosis and the size of the occluded coronary bed over the entire range of occluded beds that we examined (17 to 43% of the left ventricle).

**Discussion**

This study demonstrates that in the absence of left ventricular hypertrophy, acute elevation of arterial pressure, albeit marked and maintained throughout the period of ischemia, does not significantly affect the extent of myocardial necrosis resulting from a temporary coronary artery occlusion followed by reperfusion.

**Modeling considerations.** In our study, arterial pressure was elevated by administering the alpha-adrenergic agonist phenylephrine. Compared with other experimental techniques, this mechanism of hypertension more closely resembles the increased alpha-adrenergic activity that is thought to cause the acute increases in blood pressure during the early phase of myocardial infarction in human beings (1,2,13,14). However, the possibility that different results might be obtained with other types of acute hypertension (for example, aortic constriction) cannot be excluded.

A temporary coronary occlusion was preferred to a permanent obstruction for several reasons. First, it appeared more suitable for detecting infarct extension. The 2 hour ischemic period followed by reperfusion resulted in a subendocardial infarction limited to approximately 40% of the anatomic risk region, whereas a permanent coronary occlusion in open chest dogs produces transmural necrosis extending to approximately 80% of the risk region (18). Clearly, if hypertension increases infarct size, such an effect...
Effect of hypertension on the relation between infarct size and occluded bed (anatomic region at risk). The importance of our data indicating failure of hypertension to alter the relation between extent of necrosis and size of occluded bed needs to be emphasized. The close relation between mass of infarct and mass of anatomic region at risk is due to variation in the size of the occluded coronary bed. Normalizing mass of infarct to mass of anatomic risk region minimizes this variability and enhances the ability of the technique to detect differences (18,25,26). Furthermore, expressing infarct mass as a percent of myocardium at risk affords determination of whether the effect of a given intervention on infarct size varies with the size of the occluded coronary bed. This analysis is necessary in light of recent data (27) indicating that infarct-sparing interventions are more effective when the region at risk is small. In our study, no effect of hypertension on the percent of necrosis within the anatomic region at risk was detected, even when the analysis was limited to the smaller risk regions.

Previous studies of hypertension and infarct size. The impact of arterial hypertension on infarct size is difficult to predict because hypertension may increase both oxygen demands and perfusion (12,15,16) of ischemic myocardium. Relatively few studies have addressed this problem. Koyanagi et al. (6,7) demonstrated that chronic hypertension associated with left ventricular hypertrophy increases infarct size (6) and mortality (7) after permanent coronary occlusion in conscious dogs. However, the relative contributions of hypertension and hypertrophy to these deleterious effects remain to be determined. Conceivably, left ventricular hypertrophy may exacerbate ischemic injury because of the fundamental abnormalities of the coronary circulation inherent in this condition (increased diffusion distance from capillaries to center of myocytes [28,29], reduced coronary vascular reserve [8]). Furthermore, the tendency for collateral flow to be lower in hypertensive dogs despite higher coronary perfusion pressures (6) suggests that collateral development may also be impaired in the hypertrophic heart. Hence, the difference between the results of Koyanagi et al. (6,7) and ours may be accounted for by the absence of left ventricular hypertrophy and the associated perfusion abnormalities in our dogs. This would imply that hypertrophy is, at least, a necessary cofactor in the exacerbation of ischemic damage by chronic hypertension.

In a clinical investigation of hypertensive patients with acute myocardial infarction, Shell and Sobel (3) observed a reduction in infarct size (estimated from serum creatine kinase time curves) in the cohort in which blood pressure was lowered with trimethaphan, suggesting a deleterious influence of hypertension on ischemic myocardial necrosis. Our data are not in contrast with these results. The beneficial effects reported by Shell and Sobel may have resulted, at least in part, from the diminished myocardial sympathetic stimulation associated with trimethaphan rather than from afterload reduction. Furthermore, most patients had chronic hypertension and, therefore, were likely to have left ventricular hypertrophy. Thus, the difference between our results and those of Shell and Sobel may be accounted for by the absence of hypertrophy in our experimental preparation.

A recent preliminary report by Ksiezycka and Maroko (30) indicates reduction of infarct size in open chest dogs subjected to acute phenylephrine-induced hypertension. These results are not in conflict with ours, since several
differences in model are present. First, in the aforementioned study (30), arterial pressure was increased by approximately 90 mm Hg, compared with approximately 40 mm Hg in our investigation. It is conceivable that moderate and extreme hypertension may have different effects. Second, in that study, hypertension was associated with a modest decrease in heart rate, which might have contributed to reduce infarct size. Third, Kiezycky and Maroko used a sustained coronary occlusion resulting in transmural infarction, whereas we produced a temporary occlusion resulting in subendocardial infarction. The increase in collateral flow produced by hypertension may be sufficient to salvage myocardium in the outer but not in the inner half of the risk region. According to this interpretation, extreme arterial hypertension may limit the extent of transmural infarction, whereas moderate hypertension has no beneficial effect on subendocardial infarction. The influence of moderate hypertension (which is more common in patients [1,2]) on transmural infarction remains to be determined. 

Studies of hypertension and indexes of ischemia. Previous studies employing indirect assessments of ischemic damage, such as measurements of ST segment shifts (9,10), lactate production (11) and intramyocardial carbon dioxide tension (12), have suggested that acute elevations of arterial pressure may exert a beneficial effect in dogs without left ventricular hypertrophy. The apparent discrepancy between these data and ours may reflect the different severity of the ischemic insults examined. The aforementioned indexes of ischemia were evaluated a few minutes after coronary occlusion, before irreversible damage occurs (31), whereas we assessed the necrosis resulting from 2 hours of ischemia followed by reperfusion. Thus, although acute hypertension may alleviate a reversible ischemic insult, it does not appear to limit myocardial death produced by sustained flow deprivation. Our findings are consistent with the results of Roan et al. (12) demonstrating that in dogs without left ventricular hypertrophy, acute hypertension maintained for 24 hours of coronary occlusion does not significantly affect contractile function of ischemic myocardium.

Lack of effect of hypertension on infarct size: possible explanations. The failure of hypertension to affect infarct size in the present study may be due to the fact that hypertension increases collateral flow to the ischemic region, but this beneficial effect is offset by a concomitant increase in oxygen consumption. Alternatively, hypertension may not significantly affect either collateral perfusion or oxygen consumption in the inner half of the risk region, which is the portion undergoing necrosis in our model. Phenylephrine-induced hypertension has been suggested to augment collateral flow to the subepicardium but not to the subendocardium (15), presumably because the latter is compression by the elevated systolic and diastolic left ventricular pressures. It is also possible that subendocardial oxygen consumption may not increase despite afterload elevation because of the severe loss of contractile function that occurs with acute coronary occlusion (32).

Theoretically, the failure of hypertension to reduce infarct size in our study might be attributed to an alpha-adrenergic-mediated vasoconstriction that limited the increase in collateral perfusion. Such a possibility is unlikely because alpha-adrenergic stimulation appears to have relatively little influence on native collateral vessels (15,33,34); however, it cannot be ruled out. From this standpoint, a model like ours of alpha-agonist-mediated hypertension might have greater clinical relevance than others, because hypertension complicating acute myocardial infarction in human beings appears to result from exaggerated alpha-adrenergic activity (1,2,13,14).

Clinical implications. Extrapolation of our experimental results to human beings must be done with great caution. In particular, our data should not be applied to patients with left ventricular hypertrophy, because this condition may impair the response of ischemic myocardium to pressure overload with respect to the oxygen supply/demand ratio. Nevertheless, cardiac hypertrophy is either absent or minimal in many patients who exhibit elevated arterial pressures during the early phase of myocardial infarction. Our findings suggest that hypertension is unlikely to have a major impact on infarct size in this common clinical subset. Accordingly, antihypertensive therapy aimed solely at limiting ischemic necrosis may not be warranted. In summary, previous investigations (6,7) have shown that chronic arterial hypertension associated with left ventricular hypertrophy increases myocardial infarct size. Our study demonstrates that hypertension not associated with hypertrophy does not affect infarct size. Thus, hypertension may not be deleterious in itself. The exacerbation of ischemic damage observed in chronically hypertensive dogs might depend on the coexistence of left ventricular hypertrophy. Further investigation of this hypothesis is warranted.

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