Effects of Insulin on Experimental Catecholamine Cardiomyopathy

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We have recently shown that insulin attenuates norepinephrine (NE) dose–response curves in both isolated cardiac muscle and intact heart preparations. Accordingly, an intact rabbit model was used to determine if insulin would reduce the extent of myocardial damage following a standard NE infusion. Each animal was given pentobarbital, 30 mg/kg, and heart rate, arterial pressure, glucose, blood gases, and pH were measured. NE (2 μg/min/kg) was given intravenously for 90 minutes. After 48 hours the rabbits were killed and the hearts were examined microscopically and assigned a histologic score. Florid lesions were present in 17 of 24 sections (71%) from 12 animals. They were characterized by myofiber necrosis and an intense cellular reaction. However, only 5 of 40 sections (12.5%) from 20 rabbits given insulin (10 units/kg) 30 minutes before the NE infusion showed advanced lesions ($P < 0.001$). The mean histologic score was reduced from 1.7 to 1.0 ($P < 0.001$). The frequency of advanced lesions increased to 86% in animals given a higher dose of NE (3 μg/kg/min) and was reduced to 53% by pretreatment with insulin. A dosage of 5 units/kg was as effective as 10 units/kg, but rabbits given 1 unit/kg manifested cardiomyopathic changes identical to those in rabbits not pretreated with insulin. No differences in heart rate, arterial pressure, PO_2, or pH were evident between the groups. It is concluded that large doses of insulin reduce myocardial damage produced by NE in this model. This may be linked with the phenomenon of insulin inhibition of the inotropic action of NE. (Am J Pathol 93:339–352, 1978)

IN RECENT STUDIES with isolated cardiac muscle preparations [1] we have demonstrated that pretreatment with insulin sharply reduces the inotropic response of the muscle to norepinephrine (NE). Dose–response curves were drawn from measurements of developed tension and maximal rate of tension development at L max. Responses to a given dose of NE were reduced by approximately 50% in the presence of insulin compared with untreated muscles. Similar findings were obtained in the piglet and the cat. These observations have been confirmed in the intact piglet heart preparation.[2] In the latter, dose–response curves were obtained by recording the change in LV dP/dt max to incremental doses of NE under controlled hemodynamic conditions. Responses were approximately two thirds as great in those animals given insulin.

The foregoing observations suggested the possibility that insulin, in

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Supported in part by Research Grants HL-20401 and HL-08659 from the National Institutes of Health.

Accepted for publication June 22, 1978.

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0002-9440/78/0119-0339/$01.00

addition to modifying the inotropic action of NE, might reduce myocardial injury following exposure to catecholamines. The rabbit model was chosen to test this hypothesis because of its known sensitivity to cardiac damage by NE. Moreover, the lesions are reproducible and have been well characterized by the studies of Schenk and Moss.[3] The methods employed by these workers, with suitable modifications, were used for the generation of NE cardiomyopathy and to evaluate the effects of pretreatment with insulin on the extent and nature of the cardiac damage. A preliminary report on these results has appeared.[4]

Materials and Methods

A total of 82 New Zealand white rabbits were used in this study. In the standard protocol, they were anesthetized intravenously with pentobarbital (30 mg/kg), and polyethylene catheters were placed in a femoral artery and vein. The former was used for continuous measurement of arterial pressure and heart rate, using a Sanborn transducer, cardiotachometer, and recorder (Model 358), and for arterial sampling. Norepinephrine (Levophed, Winthrop) was freshly prepared in a concentration of 5 μg/cc of 0.9% saline and infused intravenously at the rate of either 2 or 3 μg/min/kg for 90 minutes using a Harvard constant infusion pump. In those rabbits given insulin, the hormone (pork insulin, Lilly) was given intravenously 15 minutes prior to initiation of the NE infusion. Doses of 10 units/kg, 5 units/kg, and 1 unit/kg were studied. Arterial samples were drawn at suitable intervals and analyzed for Po_2, Pco_2, and pH with an Instrumentation Laboratories analyzer. Hematocrit and glucose concentration (Glucostat, Worthington Biochemical) were also determined. Body temperature was monitored and maintained with a heating pad. Following the 90-minute infusion period, final samples were obtained, the femoral catheters were removed, and the wounds were surgically closed.

The animals were returned to their cages after recovery from anesthesia. Eleven died of uncertain cause within 24 hours. Seventy-three were killed after 48 hours, and 4 were killed after 24 hours. Two rabbits were given normal saline in lieu of NE and were killed at 48 hours. Four were killed immediately after completion of the NE infusion. Three normal rabbits without studies were used for histologic reference.

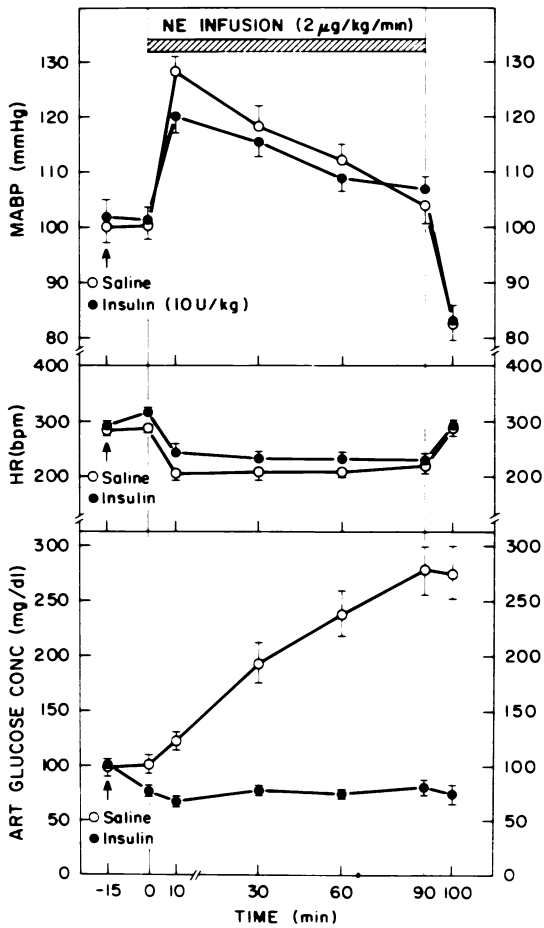
All rabbits were killed by cervical disarticulation, and the hearts were immediately removed. The atria and right ventricle were dissected from the left heart. Transverse sections of the LV + septum were made near the base and mid level and were fixed with a segment of RV in 10% buffered formalin. They were stained with hematoxylin and eosin, and the left ventricular sections were graded according to the extent and intensity of the cellular response, without knowledge of the procedures used in a given animal. A score of 2.0 was given to those with florid and widespread lesions. Those with definite but sparse lesions were scored 1.0. Equivocal focal lesions were scored 0.5. Some sections showed lesions less intense than those graded 2.0, but more frequent or of greater size than those graded 1.0; these were given a score of 1.5. When no evidence for a histologic abnormality was present, a score of 0 was assigned.

All data were analyzed by standard statistical methods using the non-paired t test.[5] Differences were considered significant when P was < 0.05.

Results

Hemodynamic and Metabolic Responses to Norepinephrine and Insulin Infusion

The mean arterial pressure and heart rate changes resulting from norepinephrine (NE) infusion (2 μg/min/kg) in 12 rabbits are shown in



TEXT-FIGURE 1—Mean arterial blood pressure (*MABP*) and heart rate (*HR*) at designated intervals before, during, and following norepinephrine (*NE*) infusion. Simultaneous values for arterial glucose concentration are also shown. Vertical brackets indicate SEM.

the upper and middle panels of Text-figure 1. Saline, 0.5 cc, was given in lieu of insulin 15 minutes prior to NE. Initial mean arterial blood pressure (MABP) was 100 (± 3 SE) mmHg, and heart rate (HR) was 286 (± 6 SE) beats/min. These values were unchanged immediately prior to the onset of NE infusion. The mean values obtained from 18 rabbits given insulin (10 units/kg) are shown by the closed circles in Text-figure 1 and demonstrated no significant differences. Ten minutes after initiation of NE infusion, MABP rose to 128 (± 4 SE) mmHg in the controls (open circles), and 121 (± 3 SE) mmHg in the insulin-treated animals. These values did not differ significantly nor did average values for systolic pressure (159 ± 6 SE and 156 ± 6 SE mmHg, respectively). MABP declined toward control values in both groups during the 90-minute infusion period. HR fell with the onset of NE infusion (Text-figure 1), presumably consequent to baroreceptor stimulation, but the group averages did not differ significantly.

Ten minutes after stopping the NE infusion, the MABP in each group was approximately 83 mmHg and the HR was 290 beats/min. Thus, there was no significant difference in measured hemodynamic parameters between the control group and those given insulin.

Arterial glucose concentration rose progressively in the saline control animals from 101 (± 8 SE) mg/dl to 255 (± 23 SE) mg/dl after 90 minutes of NE infusion (Text-figure 1, open circles). This may be contrasted with the insulin-treated animals (closed circles) in which glucose concentration initially fell from 102 (± 3 SE) mg/dl to 69 (± 4 SE) mg/dl 10 minutes after starting NE (25 minutes after giving insulin). These values then stabilized in the range of 75 to 80 mg/dl throughout the remainder of the study. Thus, the hyperglycemic action of the NE was prevented by giving insulin, and, conversely, the NE infusion prevented profound hypoglycemia during the infusion period. A few rabbits showed a further fall in glucose to the range of 50 mg/dl after the study period. These were given a single intravenous dose of 10 cc of 5% dextrose, and all survived. Measured changes in other physiologic variables were identical in the two groups. Arterial P_{CO_2} fell slightly and there were only minimal changes in pH (Table 1). Hematocrit fell approximately 4%, presumably due to hemodilution by the saline–NE infusion.

Cardiomyopathic Changes and Quantitative Evaluation

Effects of Insulin Pretreatment

The characteristic histologic findings in rabbits killed 48 hours after the 90-minute NE infusion (2 μg/min/kg) are shown in Figure 1. There was an intense leukocytic reaction, which was most pronounced in the subendocardial and midzonal portions of the left ventricular wall but occasionally extended to the subepicardial region (Figure 1A). The papillary muscles were uniformly involved, but there was no special predilection for the free wall or septum. The dominant cell population was mononuclear, primarily large histiocytic cells, with a smaller representation of polymorphonuclear, and, occasionally, eosinophilic granulocytes. Extensive myofiber damage was present focally and was characterized by segmental destruction, fragmentation, and a foamy cytoplasmic change involving many of the myofibers (Figure 1B). There was moderate separation of the myofibers, suggestive of some degree of interstitial edema, but hemorrhage was not a feature. Identical changes were found in right ventricular myocardium. Changes consistent with myofibrillar degeneration were frequently present in the subendocardial and, occasionally, midzonal myocardium. This was also found in the hearts examined immediately

Table 1—Comparison of Mean Values in Two Groups Subjected to NE Infusion After Saline or Insulin (10 units/kg)

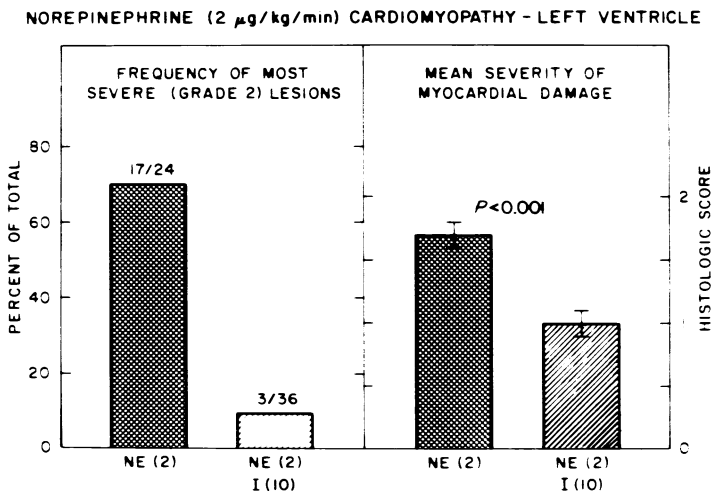
	Norepinephrine and saline*					Norepinephrine and insulin†			
	pH	PO_2	PCO_2	Hct		pH	PO_2	PCO_2	Hct
Control	7.42 ± 0.02	81.5 ± 2.5	37.9 ± 1.9	39.3 ± 0.8	Norepinephrine infusion	7.45 ± 0.01	82.9 ± 1.6	33.8 ± 1.3	37.2 ± 1.0
30-minute	7.43 ± 0.02	74.6 ± 3.2	37.3 ± 1.4	37.4 ± 1.4		7.45 ± 0.01	80.4 ± 1.8	34.1 ± 1.2	36.1 ± 0.8
60-minute	7.44 ± 0.01	75.8 ± 3.0	35.0 ± 1.7	35.2 ± 1.1		7.44 ± 0.02	78.9 ± 1.5	34.5 ± 1.4	35.2 ± 0.7
90-minute	7.45 ± 0.01	80.8 ± 3.1	31.5 ± 1.4	35.2 ± 1.2		7.45 ± 0.02	83.0 ± 1.6	32.0 ± 1.2	34.7 ± 0.7
100-minute	7.45 ± 0.01	86.4 ± 3.2	29.7 ± 1.5	34.8 ± 1.2		7.44 ± 0.02	89.7 ± 1.9	29.0 ± 1.2	33.7 ± 0.7

Hct = hematocrit.
* N = 12.
† N = 18.

after the NE infusion and was accompanied by little or no leukocytic reaction. It is noteworthy that the intramyocardial arterial vessels manifested no significant pathologic alterations, and thrombi were never encountered (Figure 1A). These findings may be contrasted to the minimal changes characteristic of sections obtained from rabbits given insulin prior to the NE infusion (Figure 2).

A basal and mid-level transverse slice from each heart was assigned an individual histologic score, as defined in *Materials and Methods*. With one exception, each slice from a given heart received an identical score, suggesting a uniformity of lesion distribution throughout the ventricular myocardium. In the 12 animals given NE alone, 17 of 24 sections, or 71%, manifested the most severe lesions and were scored 2.0 (Text-figure 2). Three additional sections were scored 1.5. Two hearts (four sections) showed only focal and questionable (0.5) changes. One of these latter animals failed to show a hyperglycemic reaction characteristic of NE infusion. The other showed myofibrillar changes characteristic of hearts removed immediately after NE infusion but no significant leukocytic response. The mean histologic score for this group was 1.69 (± 0.11 SE) (Text-figure 2, right panel).

A similar analysis was carried out on 36 LV sections from the 18 rabbits pretreated with insulin before the NE infusion. Only three sections from 2



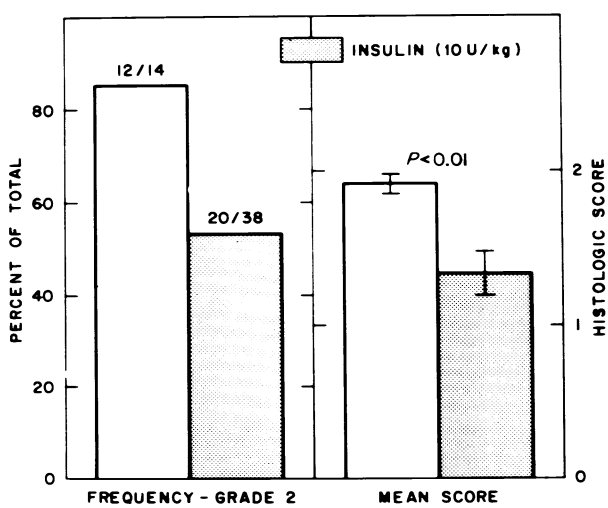
TEXT-FIGURE 2—Comparison of frequency of most severe lesions (*left panel*) and mean histologic score (*right panel*) in animals subjected to NE (2 μg min kg) infusion with or without insulin pretreatment (10 units kg). Numbers over columns (*left panel*) indicate ratio of sections examined. Vertical brackets show SEM.

animals, or 8.3%, manifested lesions which were scored 2.0. An additional eight sections were scored 1.5. The remaining 25 sections (69.5%) showed sparsely scattered (Figures 2A and B), questionable, or no identifiable lesions. The mean histologic score was 1.01 (± 0.10 SE) (Text-figure 2, right panel), and the difference from the untreated group was highly significant ($P < 0.001$).

Dose-Response Relations and Lesion Development

An additional 26 rabbits were studied as described above, but the NE infusion was increased to 3 μg/min/kg to determine if the protective action of insulin could be overridden. Twelve of 14 sections from animals not given insulin (85.7%) were scored 2.0 (Text-figure 3, left panel). The remaining two sections (from 1 animal) were scored 1.5. The mean histologic score was 1.93 (± 0.05 SE) with the greater NE dose, which may be compared with 1.69 (± 0.11 SE) in those given 2 μg/min/kg. In the rabbits pretreated with insulin (10 units/kg), only 20 of 38 sections (52.6%) were assigned the highest score. The mean score was 1.34 (± 0.13 SE) and was significantly lower ($P < 0.01$) than in those not given insulin. This may be compared with the score of 1.01 (± 0.01 SE) obtained in the group given the same insulin dose but a lesser amount of NE (2 μg/min/kg). Thus, insulin reduced the extent of myocardial damage produced by the larger dose of NE by an equal amount (differences in each score, approximately 0.6) but not to the level found with the lower NE dosage. These relationships are depicted in Text-figure 4.

To determine the effects of reducing the insulin dosage, 13 rabbits were

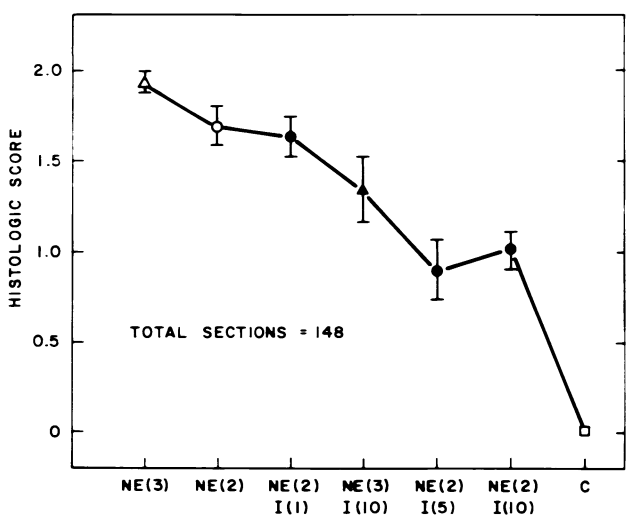


TEXT-FIGURE 3—Effects of insulin on cardiac lesions resulting from infusion of larger dose of norepinephrine (3 μg min/kg). Numbers over columns (*left panel*) indicate ratio of sections examined. Vertical brackets show SEM.

studied with infusion of NE (2 μg/min/kg) after giving insulin, 5 units/kg (4 animals) or 1 units/kg (9 animals). The histologic score of the former group was 0.88 (± 0.15 SE) and did not differ from that of the group given 10 units/kg (1.01 ± 0.10 SE). However, 1 unit/kg of insulin was without effect. The mean histologic score of this group was 1.64 (± 0.10 SE). This did not differ significantly from the value of 1.69 (± 0.11 SE) obtained in animals not given insulin (Text-figure 4).

Five animals were used for histologic controls. Three were killed, and the hearts were removed and sectioned for morphologic analysis. None showed identifiable lesions, and all were graded 0. Two rabbits were anesthetized and prepared for infusion and circulatory measurements. They were subjected to a 90-minute infusion of 0.9% saline and were killed 48 hours later. All heart sections were completely normal histologically and were graded zero (Text-figure 4).

Four rabbits were killed immediately after the 90-minute NE infusion (2 μg/min/kg). Two had been given insulin (10 units/kg) prior to infusion. All showed changes consistent with myofibrillar degeneration, most pronounced in the inner one third of the left ventricle, and minimal subendocardial fresh hemorrhage. None showed a significant leukocytic response. Of 4 animals killed 24 hours after the NE infusion, 1 of 2 not given insulin showed the characteristic advanced lesions (2.0), but the other showed only myofibrillar degeneration, mild subendocardial hemorrhage, and scattered polymorphs. Those given insulin showed sparse or no leukocytic response. Thus, more than 24 hours appears necessary for



TEXT-FIGURE 4—Relationship of norepinephrine (*NE*) and insulin (*I*) dosages to histologic score. Numbers in parentheses indicate μg/min/kg for NE and units/kg for insulin. *Open symbols*, no insulin; *closed symbols*, insulin given. Vertical brackets show SEM. *C*, normal control rabbits (*open square*). See text for further discussion.

uniform generation of the characteristic cellular reaction under the conditions of these experiments.

Discussion

The administration of large doses of catecholamines has long been known to produce myocardial damage in several animal species,[3,6-11] and this may also be true in humans.[9,11] The morphologic features of the lesions vary substantially, as do their extent and localization. These differences may relate in part to species-specific factors and dosage.[6,9] This study, the primary objective of which was to determine if insulin would reduce or modify myofiber injury produced by norepinephrine, required a model in which biologic variability was not excessive. The work of Schenk and Moss [3] suggested that the rabbit model would fill this requirement. Using a modification of their approach, we found that infusion of NE at the rate of 3 μg/min/kg for 90 minutes produced severe cardiomyopathic changes in all 8 rabbits studied. With a lower dosage (2 μg/min/kg for 90 minutes), 10 of 12 animals showed similar lesions. These observations are reflected by the mean histologic scores of 1.93 and 1.69, respectively, in a possible maximum of 2.00. None of the control rabbits had myocardial lesions. Although a spontaneous, possibly viral, myocarditis is known to occur in the rabbit, and was found in 8% of those reported by Schenk and Moss, this has a very different histologic pattern of uniform interstitial lymphocytic infiltration. It has been seen in only one of our preparations, which was not part of this study.

Pretreatment of these preparations with insulin resulted in a striking reduction in the intensity of the cardiomyopathic changes associated with NE infusion. This conclusion was based on the morphologic differences demonstrated by light microscopy (Figures 1 and 2) and is supported by additional studies to establish dose–response relations (Text-figure 4). Thus, the effect of giving 10 units/kg of insulin to rabbits infused with the lower NE dose was to reduce the histologic score from 1.69 to 1.01. However, in those given the same amount of insulin but the higher NE dose, the score was 1.34. The same protection was found with 5 units/kg of insulin. But with 1 unit/kg, no effect could be demonstrated. The mean score in this group infused with the lower NE dose was 1.64, virtually identical with those given no exogenous insulin (1.69).

Changes in the inotropic state of cardiac muscle which result from the exogenous administration of insulin are complex. On one hand, insulin elicits a substantial positive inotropic response in the lamb [13] and an even greater and more prolonged response in the pig.[14] These responses are independent of arterial glucose concentration, glucagon contamination,

or adrenergic activity [13] and are demonstrable in isolated cardiac muscle systems.[1] On the other hand, we have shown that after the addition of insulin, the responsiveness of isolated cardiac muscle to norepinephrine is sharply reduced,[1] and this has been confirmed in the intact preparation.[2] It was this observation which prompted us to pursue the present study. The results have verified our hypothesis that insulin would be expected to modify the tissue response to injurious doses of NE. But the difficult task remains of determining the underlying mechanisms which may account for these observations.

It would seem most reasonable to conclude that in the rabbit model the myofiber damage and associated cellular response are the result of direct injury to subcellular organelles and membrane systems. This is to be contrasted with notions of ischemic damage in which metabolic demand exceeds the supply capability or vascular obstruction by platelet thrombi or endothelial swelling may be invoked. No evidence for the latter was identified in these studies (Figure 1). It is also noteworthy that during NE infusion there was a modest elevation of LV afterload, but cardiac frequency fell substantially (Text-figure 1). It is therefore unlikely that minute MVO_2 was greatly enhanced, even in the face of maximal inotropic stimulation.[15] Moreover, the measured hemodynamic responses following insulin were identical with those in animals not given the hormone (Text-figure 1). For these reasons, excessive hemodynamic loading or altered supply–demand relations cannot fully explain the pathogenesis of the myocardial lesions.

Norepinephrine, acting on cardiac muscle, increases cAMP generation, with a parallel augmentation of contractility.[16] Intracellular sodium concentration [Na+] also increases,[17] and this is accompanied by an elevation in [Ca^{2}+]. The latter change results from release of Ca^{2}+ from competitive intracellular membrane binding sites and/or by utilization of the Na+–Ca^{2}+ exchange system.[18] The increase in [Ca^{2}+] inactivates the troponin–tropomyosin system and permits enhanced interaction of the actin and myosin fillaments. Excessive concentrations of Ca^{2}+ in the sarcoplasm may lead to irreversible supercontraction, which is a characteristic feature of the myofibrillar degeneration lesion in catecholamine cardiomyopathy.[9] It is likely that sarcotubular membrane damage and loss of the Ca^{2}+ transport function of SR is an important contributory factor. Mitochondrial damage is also substantial, but it is not known if this is a direct toxic effect of NE or a secondary change. Disruption of the sarcoplasmic membrane was frequent in the advanced lesions and is probably necessary for release of chemotactic substances which incite the leukocytic responses

(Figure 1). Although this probably follows lethal cell damage, direct injury to the cell membrane cannot be excluded.

There is limited information which might explain why insulin reduces the severity of myocellular damage by NE. It is clear that the inotropic response is sharply reduced,[1,2] possibly by activation of an insulin-sensitive Na+ pump,[19] although this has only been demonstrated in skeletal muscle. It has also been shown that insulin may limit cAMP production [20] and enhance phosphodiesterase activity.[21] However, it would seem unlikely that these effects are sufficient to prevent the severe myofiber damage which was observed. It is noteworthy that doses of 1 unit/kg, which should be sufficient to saturate the insulin receptors, did not appear to alter the extent of myocardial damage. The possibility that this hormone in larger doses exerts other effects, perhaps similar to the membrane stabilizing action of steroids, must be considered. Of particular interest, however, is the possibility that insulin lack, as in the insulin-deficient diabetic subject, may permit excessive catechol stimulation from endogenous sources and lead to myofiber damage. This hypothesis is under investigation.

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Acknowledgments

The authors wish to express their appreciation for the expert technical assistance of Victor Hardaswick, Ronald Gordon, and Carol Mertens.

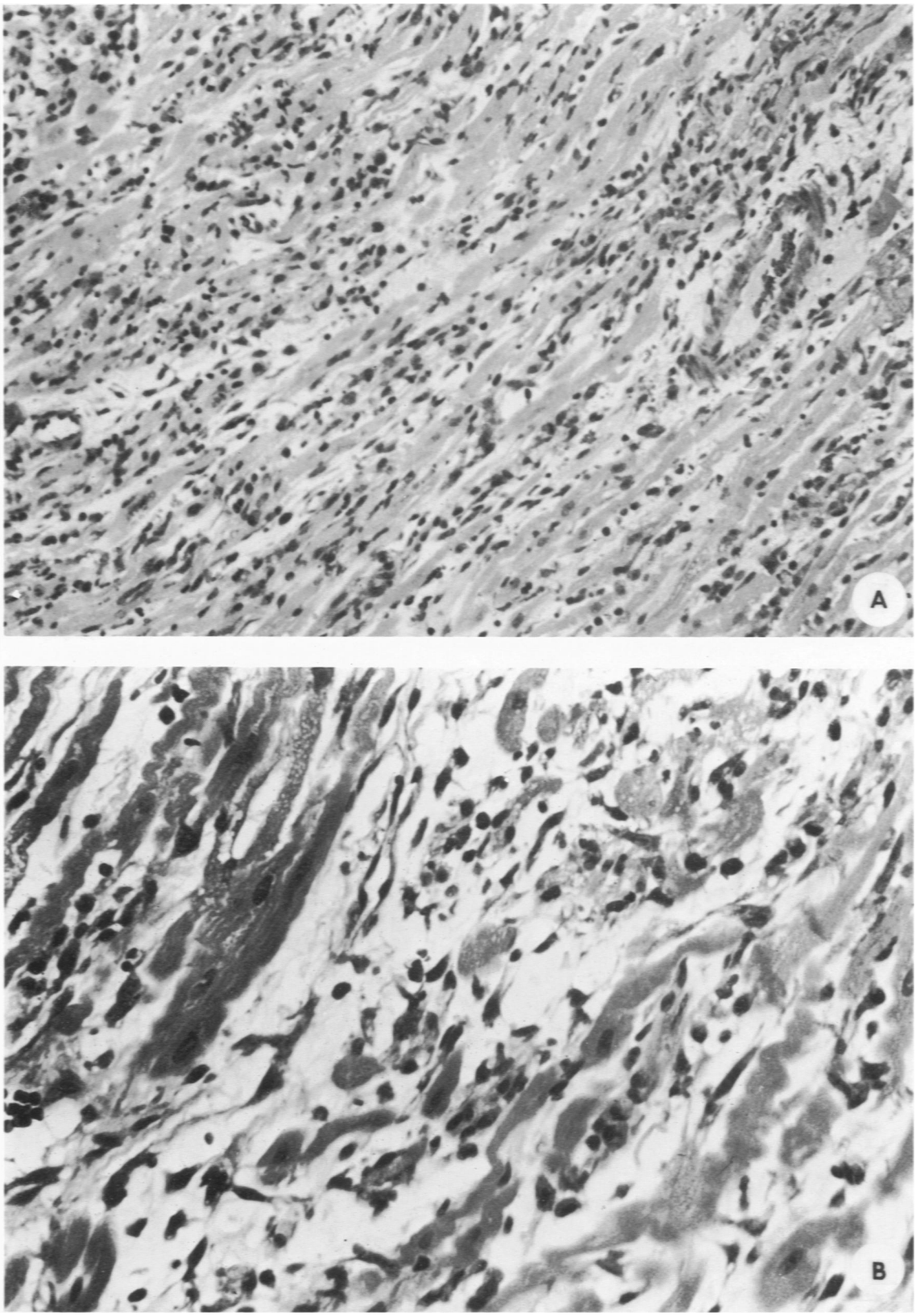

Figure 1A—Representative histologic section of left ventricular myocardium from rabbit killed 48 hours after standard NE infusion. There is extensive leukocytic infiltration and myofiber damage characteristic of lesions scored 2.0. B—Higher magnification showing myofiber destruction, interstitial edema, and mixed population of leukocytes. (H&E; A, × 125; B, × 310)

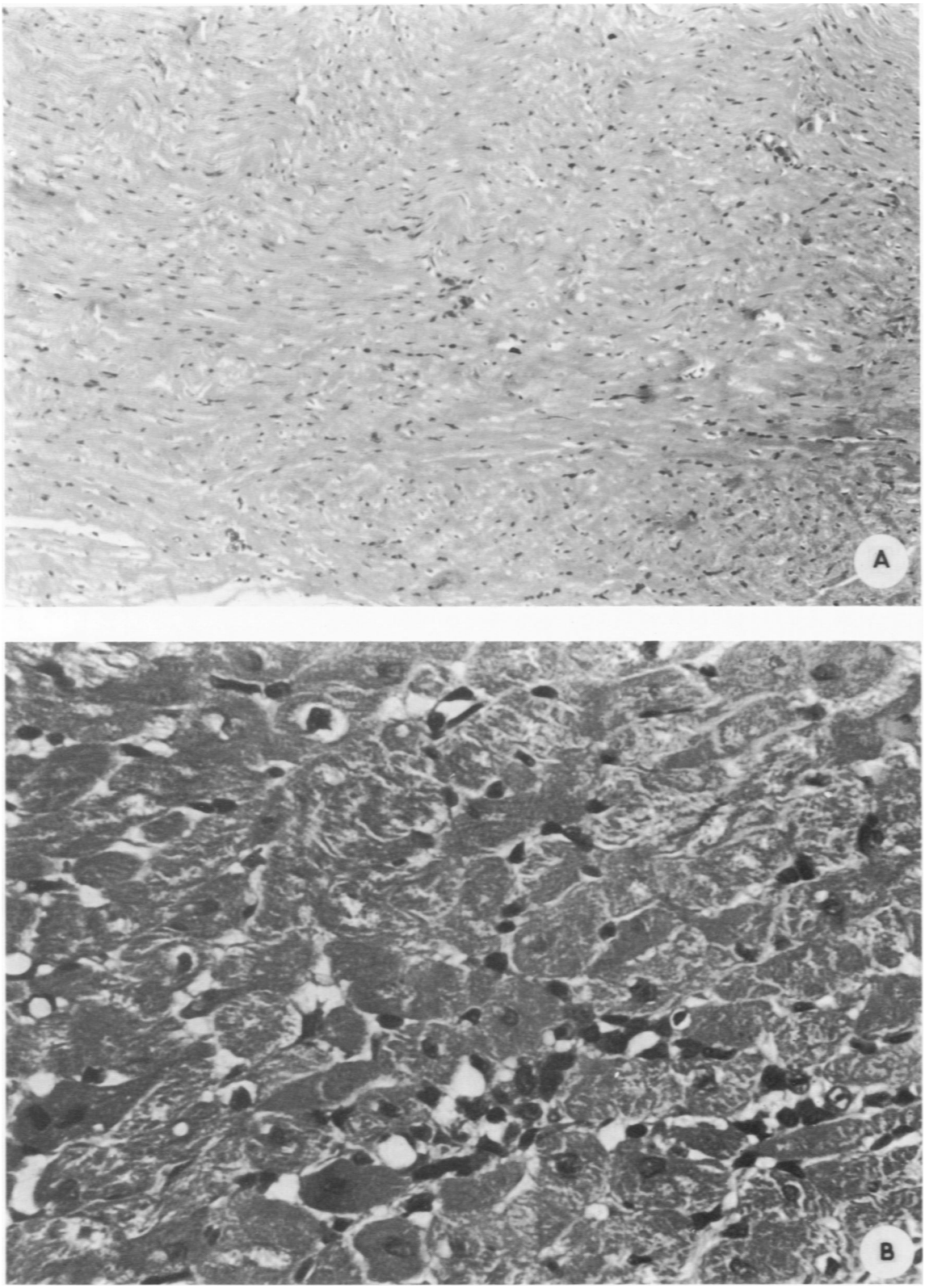

Figure 2A—Representative section of LV myocardium from rabbit subjected to standard NE infusion following pre treatment with insulin (10 units/kg). Rabbit was killed after 48 hours. Only scattered foci of leukocytes are present characteristic of changes scored 1.0. **B**—Higher magnification showing a few mononuclear cells, probably repre senting cardiac histiocytes. Myocytes are intact and show no definite cytologic changes. (H&E; **A**, × 125; **B**, × 500)