Original Article

# Ethanol Ablation of Myocardial Tissue: Early Histo-chemical and Ultra-structural Changes

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## ABSTRACT

**Introduction:** Ethanol ablation has been used in therapy of symptomatic patients with hypertrophic obstructive cardiomyopathy as well as for resistant tachycardia foci associated with re-entrant tachyarhythmias.

**Methods:** We assessed the early effects of 96% ethanol instillation into the second diagonal branch of the left anterior descending coronary artery on the structure and histochemistry of vessels and myocardium in dogs.

**Results:** Ethanol caused coagulation necrosis of intima and media of the affected vessels which lead to a complete thrombosis. Early changes, seen at five minutes, in the peripheral area were characterized by hyper-eosinophilia and the development of darkly stained amorphous densities in mitochondria. At ten minutes, this was followed by a more marked ultra-stuctural destruction resembling severe ischemic damage which included sarcolemmal breaks and swelling of the mitochondria. At 25 minutes, a more pronounced intracellular edema, relaxation of sarcomeres, loss of the mitochondria and a reduction in actin filament density was observed. At 60 minutes, there was a further increase in sarcolemma disruption, severe damage to myocytes in the peripheral region and loss of endothelial lining of the arteries. This was followed by an altered arrangement of miofilaments and loss of actin filaments at 180 minutes. At the same time point, endothelial cells of capillaries were lost and lumen was filled with coagulated blood. At 24 hours, heterogeneity in the intensity of injury was apparent, *i.e.* more pronounced in the areas close to the artery and less in the periphery of the instilled site. Histo-chemically, there was a marked decrease in the ATPase, SDH staining and phosphorylase reactions in the media of the affected arteries.

**Conclusions:** Since infusion of alcohol did not cause any arrhythmia and there was no loss of blood pressure, a localized structural damage due to ethanol is not of any physiological consequence. These findings suggest that ethanol induced focal thrombosis and necrosis is a useful and relatively safe alternative that can save patients from more invasive and expensive surgery.

KEYWORDS: ethanol ablation, histo-chemical changes, myocardial injury, phosphorylase localization

## INTRODUCTION

The persistence of slow conduction in healed infarctions has been suggested to contribute to the occurrence of chronic arrhythmias[1]. During the healing phase of myocardial infarction, areas of slow conduction can develop in the scar, causing late re-entrant ventricular tachycardia[2]. Re-entry circuits are more likely to develop in cases where the infarct is large[3-6].

In patients suffering from atrial fibrillation, flutter or ventricular tachyarrhythmias refractory to antiarrhythmic drugs, alternative nonpharmacological therapies such as cryoablation[7], laser catheter coagulation[8], electrical ablation, defibrillation[9] and cardioversion[10] have rapidly emerged and are being routinely used. The control of arrhythmias by catheter ablation may be the method of choice and was one of the highlights of clinical electrophysiology in the 1980's. Particularly, electrical and radiofrequency catheter ablations of atrioventricular (AV) conduction have been successful[11,12]. This approach has almost replaced the use of surgically created heart block. In some patients however, electrical ablation of the AV conduction system fails to create AV block and does not sufficiently modify AV conduction. In such selected cases chemical ablation by different substances has been used[13-15]. In order to limit diffusion and to deliver the ablation agent to precise target sites, admixture of glycerin and contrast media were experimentally assessed and have been used clinically[16].

Macro- reentrant circuits consisting of a small isolated bundle of surviving cells in the area of the infarct has been reported[17]. An arrhythmogenic area in the heart requires blood supply to preserve electrical activity of the myocardial cells involved in the genesis of arrhythmias. By using recent techniques of cannulation, it is possible to localize

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the arterial blood supply to the site of origin of ventricular tachycardia[18]. Thus, selective embolization of small branches of coronary arteries supplying arrhythmogenic areas may cure re-entrant ventricular tachycardia[19]. Bolus injection of ethanol into the peripheral coronary tree for the treatment of post infarction ventricular arrhythmias or for destruction of the nodal cells, resulted in the prevention of arrhythmias as has been reported by many authors[15, 17,19,20-24].

Percutaneous transluminal alcohol necrotization (ethanol induced septal ablation) for reduction of the left ventricular outflow tract in hypertrophic obstructive cardiomyopathy, has also been used as a nonsurgical alternative to left ventricular myotomy, and the method has gained importance as compared to surgical myotomy[16,25-30]. Recently, ethanol in high concentrations has also been used to ablate hepatic tumors[31-33] and hyperplastic prostatic tissue[34]. Although alcohol ablation resulting in myocardial necrosis has been successfully used in a variety of conditions, the detailed early structural changes remain to be described. Thus, the purpose of this study was to assess the early effects of intracoronary administration of 96% ethanol on the ultrastructure and histochemistry of the coronary vessel as well as the surrounding myocardium.

## MATERIAL AND METHODS

Twenty-seven (27) mongrel dogs of either sex, weighing 10-15 kg were anaesthetized with pentobarbital (30 mg/kg body weight). The dogs were ventilated through a cuffed endotracheal tube using a mixture of 95% oxygen and 5% $CO_2$ administered through a constant volume-cycle respirator (Chirana). Left thoracotomy was performed in the fourth intercostal space and the heart was exposed. The left anterior descending coronary artery (LADC) was isolated 0.5 cm from its origin and cannulated. A bolus of 1 ml of ethanol (96%) was injected into the second diagonal branch. A fluid filled cannula was placed in the femoral artery to monitor blood pressure. A femoral vein cannula was used to infuse normal saline solution to replace spontaneous fluid losses. The dog was placed on a warmed pad and the thoracotomy was covered by a plastic sheet. For the 24 hours of the experiment, dogs were sutured and kept conscious, but tranquillized with painkillers. Throughout the experiment, arterial blood gases and pH were maintained within the physiologic range. A bipolar plug electrode was placed in the left atrial wall and two bipolar plug electrodes were inserted in the left ventricular wall, one in the area perfused by the canulated branch of the coronary artery, and the other in the healthy area outside the alcohol injected zone.

After injection of 1 ml of ethanol, experiments were terminated by excising the heart after 5, 10, 25, 60, 180 minutes and 24 hours. Small tissue samples of the heart from each experiment were fixed in paraformaldehyde, dehydrated and embedded in paraffin, cut into six micron thick sections and stained with Hematoxilin-eosin and Masson's trichrome for light microscopic examination.

For electron microscopy, myocardial samples (~1 $mm^3$) were collected from the injected (core) area, periphery and the normal myocardium. The tissue pieces were immersed in 2.5% glutaraldehyde in cacodylate buffer (pH 7.5) and processed using a routine procedure[35].

For histochemistry, transmural samples from the alcohol injected area with a minimum of 5 mm layer of the normal tissue were excised and immediately frozen in liquid hexane cooled by dry ice. Histochemical staining was performed for glucan phosphorylase, succinic dehydrogenase (SDH), -hydroxy butyric dehydrogenase ( -HBDH) and adenosine triphophatase ATPase. The study protocol was completed in accordance with Guidelines on the Care and Use of Experimental Animals.

## RESULTS

During administration of ethanol no changes in blood pressure occurred. In two cases, the heart arrested but this was not attributable to ethanol infusion. However, the myocardial tissue from these animals was also immediately removed for analysis. Transient ventricular tachycardia occurred in some dogs during infusion of alcohol. Arterial pressure was not affected by infusion of ethanol and no arrhythmias were observed.

**Histopathology:** Gross and histo-pathological examination revealed that injection of 1 ml of 96% ethanol into the second diagonal branch of LADC produced coagulation necrosis demonstrated by hypereosinophilic staining of the lesions and contraction bands on the periphery of the affected area. There were focal intramural hemorrhages confined to the tissue directly adjacent to the supplying artery and involving the area of the left ventricular wall supplied by the arterial branch. Nuclei of myocardial cells in the affected area were small and shrunken. Injected diagonal coronary artery, past the injection point showed coagulation necrosis of the intima and media, was completely thrombosed and contained an intravascular (luminal) thrombus and/or fibrin. Adventitial hemorrhage of differing intensity was a frequent finding. The size of necrosis greatly differed; and in three dogs (11%) the necrosis was almost transmural; in 19 dogs (70%) it was wide

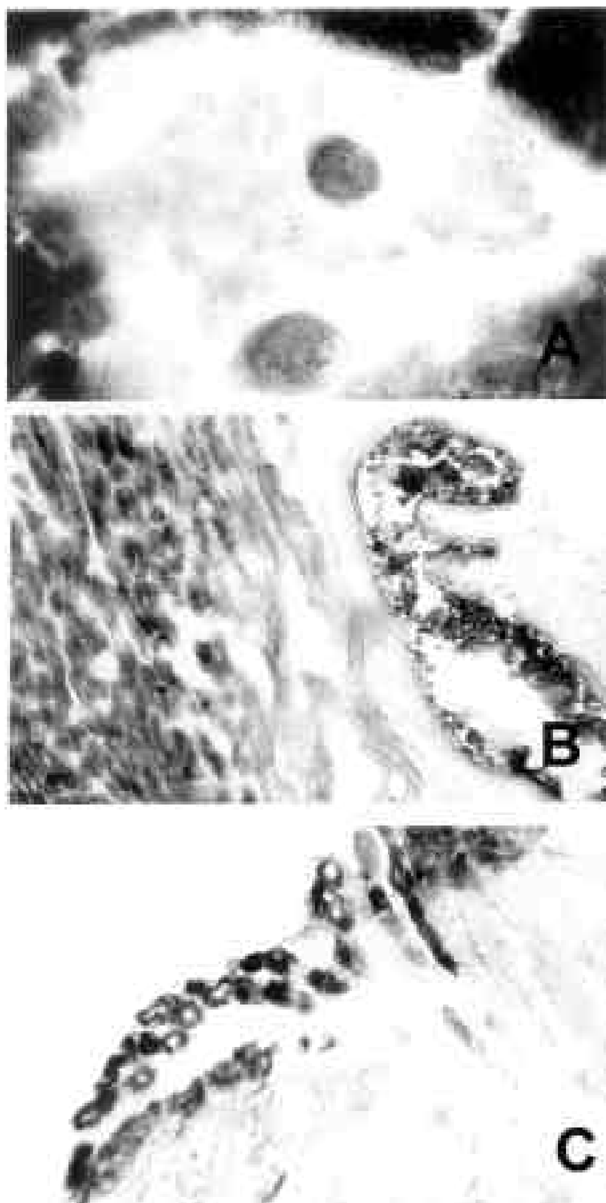


**Fig. 1:** Histochemical localization of - glucan phosphorylase after five minutes of ethanol infusion: A) Two branches of thrombosed coronary artery in a cross section. Surrounding myocardium is completely devoid of the reaction. Relatively sharp demarcation between the positively reacting and non reacting areas can be seen; B) Reaction in the peri-coronary area is absent and the intensity of the reaction increases with the distance from the coronary. Thrombosed contents in the coronary lumen are apparent; and C) Foci of positively stained cardiac myocytes for - glucan phosphorylase can be found next to cells devoid of reaction. (Magnification in all cases is 400 X)

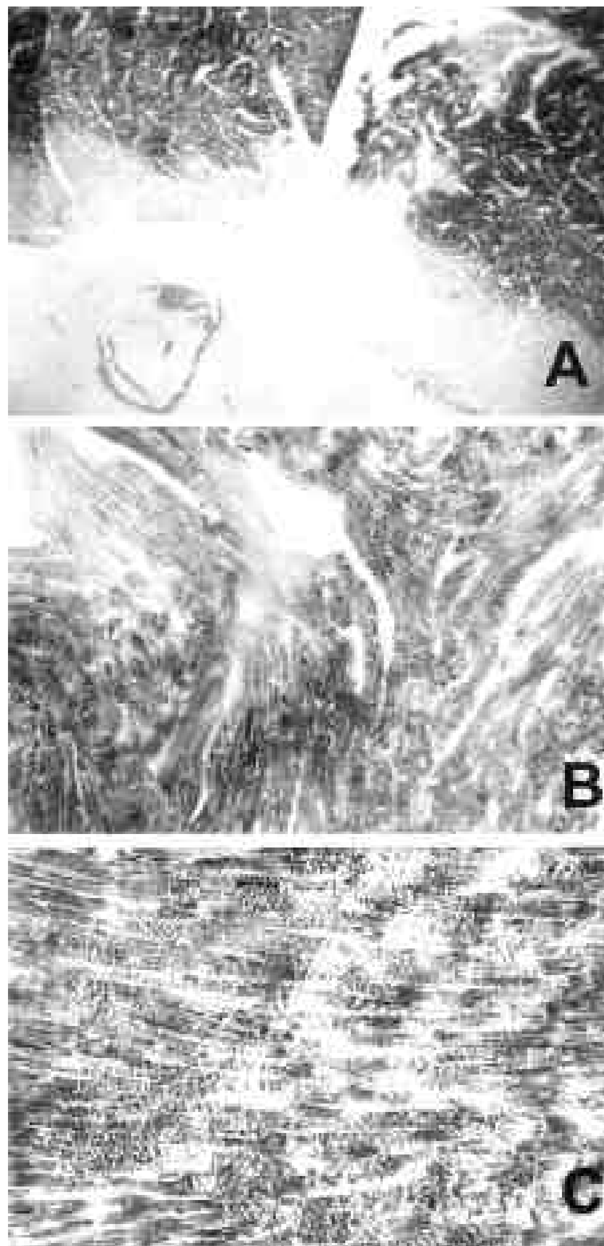


**Fig. 2:** Histochemical localization of succinic dehydrogenase after 25 min of ethanol infusion: A Core area around the thrombosed coronary artery shows no reaction; A) A normal reaction is seen in the distant areas. Note the absence of reaction around the arteriole in a remote area (top right); B) Areas with decreased reaction containing irregular hypercontracted fibers; and C) Hypercontracted myofibers in the transition zone in between the necrotic and normal myocardium. (Magnification 400 X)

periarterial with occasional small islands of normal tissue; and in five dogs (19%) there was a narrow periarterial necrosis. In border zones of larger necrosis, islands of almost normal myocytes with mild hemorrhage and a few neutrophils and mononucleocytes were observed in samples at the later stages (24 h). Vascular lumen in the core of the alcohol treated area was free of polymorphonuclear and mononuclear infiltrate. In fact, infiltration, that can usually be seen in early stages of infarction was missing. Foci with normal muscle bundles varied markedly in size and shape within the same heart.

**Histochemistry:** There was a decrease in ATPase and SDH staining in the wall of affected arteries, and in surrounding tissue. Phosphorylase reaction (Fig. 1A-C) was the most sensitive indicator of injury in comparison with ATPase or SDH (Fig. 2A-C). The reaction for phosphorylase always revealed larger area which was negatively stained as compared to the area for the other enzymes (Fig.1A). Macroscopically, the size of the affected area was larger after 10 minutes. In the 25 min

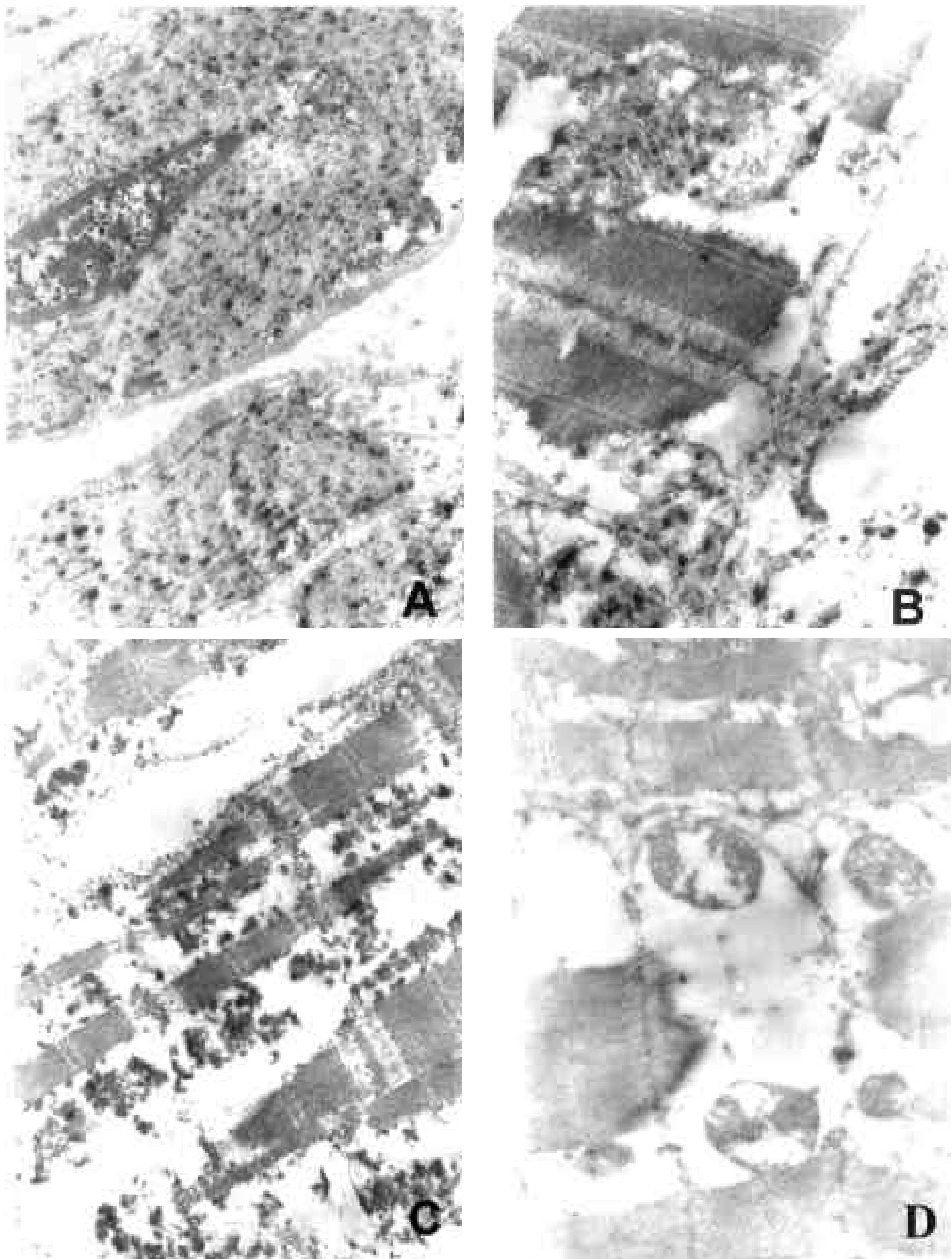


**Fig. 3:** Ultrastructural changes due to ethanol at different post-treatment duration: A) Five minutes after infusion. Fixative effect of alcohol on the myocardium next to the thrombosed artery. Ultrastructure of myocytes can hardly be recognized; B) 25 minutes after infusion. Electron micrograph of the peri-arteriolar area, a small distance away from the thrombosed artery. Although myocytes are severely damaged, some myofibers and mitochondria can be recognized. Electron dense granules in the mitochondria are apparent; C) 60 minutes after infusion. Core area of alcohol treated myocardium show severe damage evidenced by the protein denaturing; and D) 60 minutes after infusion. Near the periphery of the affected area mitochondrial swelling and edematous changes in the myocytes resembling severe ischemic injury are apparent. (Magnification in all cases 10,000 X)

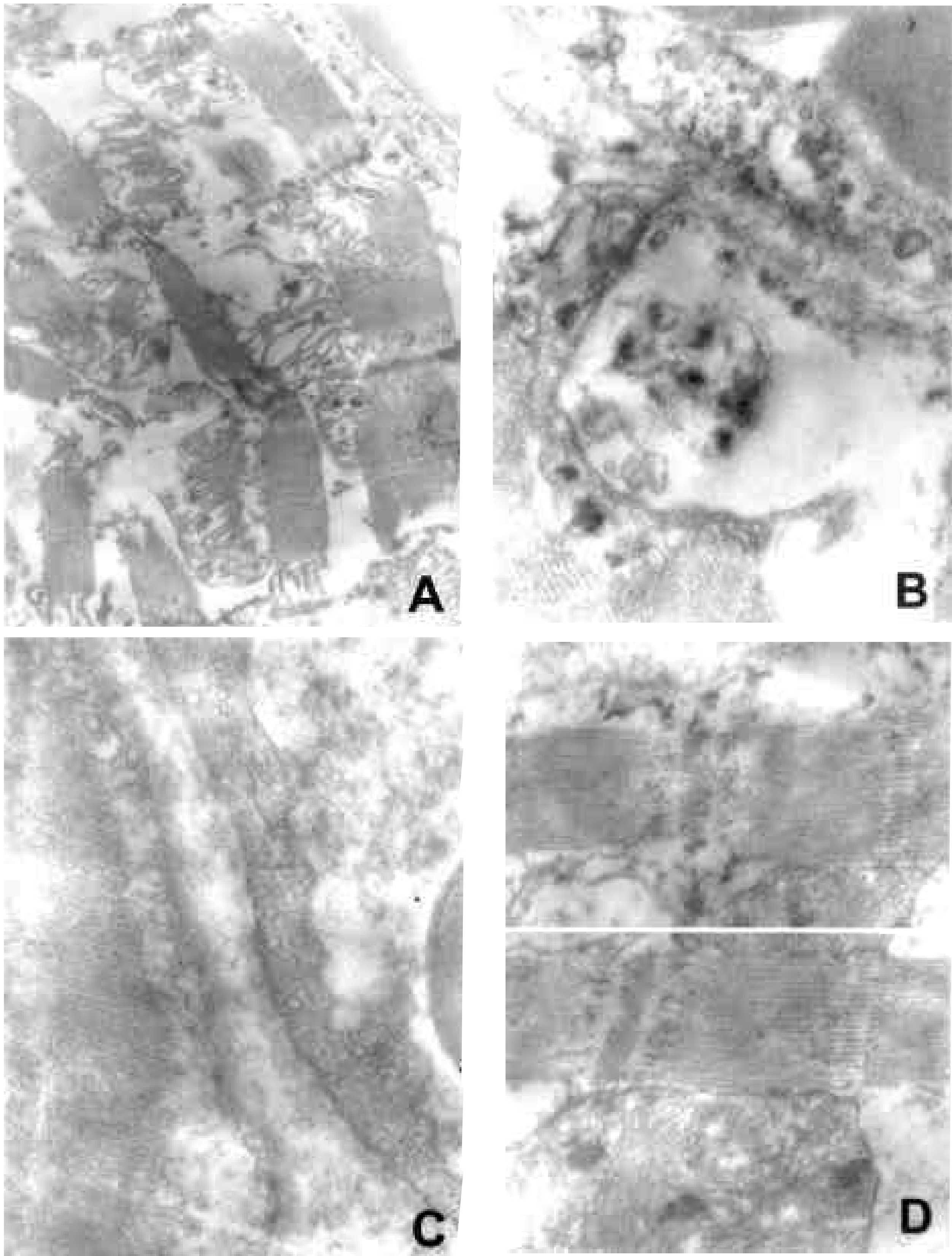


**Fig. 4:** A and B) 180 min after infusion. Irreversibly damaged myocytes with severe disruption of mitochondria and contractile elements. Intracellular edema is prominent (10000 X); B) Membranaceous and proteinaceous debri can be seen. Endothelial cells of capillaries are destroyed but pinocytotic vesicles in some capillaries can be recognized (upper right). (23000 X); C and D) 24 h after infusion. Peripheral areas of the border zone contain almost normal capillaries and myocytes.Very minimal electron dense granules were seen. Prominent feature is a large amount of pinocytotic vesicles in endothelial cell as well as in the subsarcolemmal region. (24000 X); and D) Two damaged myocytes in the border zone as documented by amorphous densities in mitochondria (24000 X).

group, the affected area was smaller by about 10-15%. This reduced size did not change later and it represented the final size of necrosis as revealed by the glucan phosphorylase histochemical reaction (Fig. 1B). The border zone and the area surrounding irreversibly damaged tissue usually revealed foci of viable myocardium with normal activity for phosphorylase and/or hypercontractions of different sizes and shapes (Fig. 1B and 1C).

**Electron Microscopy:** Nominal ultrastructural pattern and cross striations disappeared at 5 min in alcohol treated tissue close to the core area of the injected artery. Mitochondria were seldom discernible and a number of darkly stained amorphous densities and clumps of precipitated darkly stained material of different sizes were a hallmark of the early effect of alcohol administration on myocytes (Fig. 3A). Nuclei were shrunk and nuclear chromatin was marginated.

After 10 minutes, the core area of the treated zone showed highly disrupted myofibres but the cellular membranes were still visible. The typical ultrastructural pattern in some myocytes was frequently found in the periphery of the lesions. Sarcomere showed a wide range of injury including hypercontraction and stretching in some myocytes with well preserved structure. Intracellular edema was present in severely damaged myocytes. Changes in the periphery resembled severe ischemic damage with ruptured sarcolemma and edematous mitochondria. Numerous amorphous densities occurred in the mitochondria of endothelial cells as well as extracelluarly. Endothelial cells were frequently necrotic and lysed.

After 25 minutes, the intracellular edema was even more pronounced, sarcomeres were disrupted, the usual structure of mitochondria was completely lost and instead, amorphous electron dense material in the remnants of mitochondrial membranes was present (Fig. 3B). Instead of well defined endothelial cells, membranous and proteinaceous remnants were found in the lumen of capillaries in the core region.

After 60 minutes, myocytes of the core area contained fragmented fibrils with membranous debris and amorphous densities. Occasionally, membranous remnants of mitochondria could be seen. Even though there were discontinuities in the sarcolemma, cell boundaries were still recognizable (Fig. 3C). The endothelial lining of small arterioles was destroyed. Myocytes on the periphery of the affected area were edematous and revealed structural changes resembling severe ischemic injury (Fig. 3D).

After 180 minutes, the center of the affected area revealed changes similar to that seen after 60 minutes. Cell boundaries were still recognizable. Myosin filaments were preserved but actin filaments were almost completely lost (Fig. 4A). The mitochondrial cristal membranes were almost absent and instead only amorphous proteinaceous material was present (Fig. 4B). In the periphery of the affected area, advanced ischemic changes with disarray of myofilaments and partial loss of actin filaments were a characteristic feature. Mitochondrial inner as well as outer membranes were disrupted, amorphous densities and intracellular edema were present (Fig. 4A and B). Endothelial cells of capillaries were destroyed and lumen was filled with coagulated blood (Fig. 4B).

After 24 hours, heterogeneity in the intensity of injury was apparent. In several cases even in the areas close to injected arteriole, less injured myocytes as well as capillaries (Fig. 4C and D) could be found next to irreversibly damaged ones. In well preserved cells the main feature was numerous lipid droplets, frequently associated with mitochondria. Endothelial cells of capillaries were frequently well preserved in border areas. Large number of pinocytotic vesicles were a prominent feature of endothelial cells and sarcolemma in the boundary region (Fig. 4C). Electron dense material seen at earlier time points was relatively infrequent at 24 hrs (Fig. 4C and D).

## DISCUSSION

With improved techniques of cannulation even small blood vessels, supplying arrhythmogenic areas within an infarction can be selectively cannulated and sclerosed with an injection of alcohol[18]. It is difficult to separate the cytotoxic and denaturizing effect of ethanol from the pathologic changes that result from the vascular occlusion and subsequent ischemia. Efficacy of myocardial ablation using direct intramural injection of ethanol via ventricular catheter[36], and retrograde coronary venous infusion of ethanol, for ablation of ventricular myocardium associated with reentrant tachyarhythmias[37], were examined experimentally and were proven useful for nonsurgical ablation. Based on the present study, it can be inferred that the coronary artery in which ethanol is injected occludes immediately making the treated area of the myocardium completely nonfunctional, a conclusion also reached by other studies[21,24,38].

A major risk of intracoronary embolization can be the reflux of the ethanol proximal to the injection site which could extend the area of infarction[19]. We suggest that by using a small

amount of high percentage alcohol bolus, the possibility of getting alcohol into the circulation through large collaterals seems to be diminished. Effect of increased ethanol concentration in the circulation, with its negative inotropic effect on cardiac muscle, must have been negligible, since no persistent arrhythmia or loss of blood pressure was noted.

Surgical removal of a reentry focus may destroy more myocardium than is necessary and besides, that requires large and invasive preparation of the patient. If ethanol ablation of an arrhythmogenic pathway is selected for treatment, the size of necrosis can be restricted by limiting the volume and precisely positioning the catheter. As demonstrated in this work and also in the work of others, following instillation of highly concentrated ethanol into a coronary vessel or directly intramuscularly, one can find two effects. First, the direct chemical and dehydrating effect of highly concentrated ethanol acting as a fixative and/or protein denaturing agent[39,40] and second, an ischemic effect after thrombolization of the coronary artery and/or its branches. Therefore the injury that can be seen in the periphery of treated areas is probably a combination of both mechanisms and is also dependent on the extent of the collateral circulation.

As known from studies of experimental infarction, the subendocardial or subepicardial layer of several cells or intramurally located islands of ventricular cardiomyocytes usually survive after the ischemic injury progresses from the epicardium to the endocardium following obstruction of coronary artery[1,17, 41-44]. Similarly, in the periphery of the ethanol treated area in our experiments on dogs, partially damaged, dead and normal cells interdigitated with each other. Such a heterogeneity is not desirable and has to be limited by using a high concentration, and a low amount of ethanol. Alcohol ablation is suitable for situations when separate zones of viable myocardial fibers are located intramurally in infarcted areas and reentry occurs via bundles of isolated myocytes connecting subendocardial muscle. Advantage of alcohol instillation in such cases is that it can ablate more than one exit from the area and eliminate the possibility of recurrence of tachycardia.

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