The Effects of Nifedipine on Acute Experimental Myocardial Ischemia and Infarction in Dogs

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SUMMARY We studied 25 anesthetized and thoracotamized dogs before and during 5 hours of acute regional myocardial ischemia. Krypton-81m (81mKr) was infused constantly into the aortic sinuses. The myocardial equilibrium of this tracer was used to image and assess the distribution of regional myocardial perfusion using a gamma camera and digital computer. The epicardial ECG was recorded, S-T segment elevation and the loss of R and appearance of Q waves were measured, and the plasma activity of creatine kinase (CK) was determined in aortic and coronary venous blood throughout these experiments. Ten dogs underwent left anterior descending coronary artery (LAD) narrowing for 5 hours and received no drugs. Five dogs received nifedipine 13 µg/kg, and another five received 1.0 µg/kg intravenously 30 minutes after LAD narrowing. Those dogs receiving nifedipine, 13 µg/kg, showed a 30% fall in aortic pressure, a 12% rise in heart rate, and an extension of regional ischemia. The ECG showed an extension of infarct size, and CK release into the coronary vein appeared earlier than in the controls. Dogs receiving nifedipine, 1 µg/kg, showed a 12% fall in blood pressure, no rise in heart rate, an improvement in regional perfusion, and ECG signs that suggested limitation of infarct size. There also was delayed release of coronary venous CK. The effects of nifedipine on the natural history of regional myocardial perfusion, the electrocardiogram, and enzyme release from the heart were dose related and cannot be generalized. These observations warrant further clinical investigation to improve the use of this agent in man. Circ Res 44: 16-23, 1979

THE extent of ischemic myocardial damage during acute myocardial infarction is one of the important determinants of morbidity and mortality. Recent studies have encouraged a search for interventions that can affect the balance between energy supply and demand during acute infarction of the heart (Maroko et al., 1971; Braunwald and Maroko, 1974). Nifedipine (4-(2'-nitrophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid dimethyl ester) has been shown to retard the transmembrane influx of calcium into ischemic myocardial cells, increase coronary blood flow, delay ischemic contracture, and preserve myocardial creatine kinase activity (Henry, 1975; Fleckenstein, 1975; Vater, 1975; Schmier et al., 1975). These combined pharmacological properties suggest that a favorable effect on acutely ischemic myocardium may be possible.

The purpose of this study was to observe the changes of regional myocardial perfusion, the epicardial ECG, and the appearance of creatine kinase activity in coronary venous blood in dogs during the 5 hours following occlusion of the left anterior descending coronary artery (LAD). The dose-related effects of nifedipine on these parameters were measured, and the use of this drug to protect the ischemic myocardium is discussed.

Methods

Twenty-five mongrel dogs weighing 30-55 kg were anesthetized with intravenous sodium thiopental (Pentothal, 12 mg/kg). Respiration was maintained via a cuffed endotracheal tube and a mechanical ventilator. Anesthesia was maintained by the intermittent intravenous injection of pentobarbital (Sagattal, 2 mg/kg). Care was taken with each administration to ensure that the corneal reflex was not abolished and that heart rate and aortic blood pressure changed by less than 5%.

A left thoracotomy was performed and the heart supported in a pericardial cradle. A reversible snare was placed around the LAD or a major branch thereof. A size 7 French cardiac catheter was introduced via a left femoral arteriotomy and positioned in the thoracic aorta, and another catheter was introduced via a femoral venotomy into the inferior vena cava. Arterial blood pressure was measured continuously (mm Hg) with a Statham P23Db transducer and recorded on a multichannel instrument (Hewlett Packard 7788A).

A modified Paulin catheter was introduced via a right femoral arteriotomy and seated in the aortic sinuses (Paulin, 1964). 81mKr was continuously
eluted in 5% dextrose from a $^{81}$Rb generator and infused into the aortic sinuses of each dog as a constant infusion at between 5 and 10 ml/min (Watson-Marlow MH-RE200, roller pump) (Clark et al., 1976; Turner et al., 1976; Selwyn et al., 1978).

Each dog's chest was positioned under a wide-filed gamma camera (Toshiba GCA 202) and images were recorded on Polaroid or 35-mm film.

Each dog was positioned in the left lateral position at the beginning of the experiment, and the camera was positioned above the thoracotomy site, 4–6 cm from the surface of the heart. The LAD snare was occluded for 30 seconds, and the camera was angled so that the regional defect of $^{81}$mKr activity was on the edge of the image of the heart. This helped to ensure that counts from the posterior aspect of the heart did not interfere with regional count rate analysis in the ischemic zone.

Quantitative high spatial resolution images of total and regional myocardial counts per minute (CPM) of $^{81}$mKr were recorded at 30-second intervals throughout each experiment. The gamma camera was linked to a digital computer (Deltron-Nova 1220), and these images were recorded on a magnetic disc. The resolution of the camera and collimator for $^{81}$mKr was 7 mm, using a line spread function test. The digital computer was programmed to recall and display images recorded on an oscilloscope screen within a 64 × 64 matrix of squares. Corrections were made for the decay of $^{81}$Rb. The background activity was estimated by the simultaneous recording of CPM from an area around the image in the field of the gamma camera. This was the same size as the heart image. CPM of $^{81}$mKr were analyzed at the end of each experiment by constructing areas of interest on the visual display unit with an electronic light pen. The computer calculated the activity recorded in each area of interest for each 30-second interval of the experiment. These areas enclosed (1) the aortic root, (2) the area directly affected by the LAD snare, and (3) the rest of the myocardial image (remote area).

The input impedance of the recorder amplifier was 50 mΩ (Hewlett Packard 7788A, multichannel), and the frequency response of the whole system was less than 3 db from 0.05 Hz to 120 Hz. The tracings obtained were reproducible throughout the 5-hour experiments. Epicardial electrograms were recorded through a single saline-soaked cotton electrode held over the myocardium to include the area affected by the snared LAD (Selwyn et al., 1978). The calibration was 1 mm-1 mV. Two electrode positions were in remote areas and six were positioned within the area supplied by the snared coronary artery.

S-T segment elevation was measured above the T-P segment 20 msec after the end of the QRS complex (Muller et al., 1975). The amplitudes of the R waves were measured in millimeters to the nearest 0.5 mm, using the same isoelectric line. The R wave amplitude at each site was calculated throughout the experiments, and the difference between each R wave at the start of each experiment and at 5 hours was calculated (ΔR). Small Q waves were seen in epicardial leads over the interventricular septum. The development of Q waves was recorded as the difference (in mm) 5 hours after severe coronary narrowing (ΔQ). All electrocardiographic recordings showing a Q to intrinsic deflection interval greater than 40 msec or QRS duration greater than 65 msec were excluded from the study (Muller et al., 1975; Samson and Scher, 1960).

If the R waves in the remote epicardial positions or the limb leads showed progressive changes in axis, (Ettinger and Suter, 1970). The recordings were rejected. Epicardial electrograms recorded during the 20-minute control period, and in the remote areas throughout the experiments, showed no significant change in S-T segments (more than ±2 mV change from the isoelectric), and no significant change in R wave amplitude (more than ±4% variation).

Epicardial electrograms were recorded at 5-minute intervals before and after occlusion of the LAD. Recordings were made at 20-minute intervals for the remainder of each experiment. The effects of respiration were taken into consideration by measuring the mean S-T segment elevation and R wave amplitude from five ECG complexes with each observation.

In each dog, Portex tubing, outer diameter 0.63 mm, was introduced into a coronary vein lying parallel to the LAD. The tubing was advanced until the end was distal to the coronary snare and within a coronary vein draining the area supplied by the snared artery. One-milliliter blood samples were drawn every 30 minutes from the aortic and coronary venous catheters simultaneously. The tubing was flushed with heparinized dextrose after sampling, and care was taken to remove the dextrose before each sample was taken. The blood samples were stored in heparinized tubes on ice for up to 3 hours before centrifuging. The plasma was separated by centrifuging at 2500 g for 10 minutes. Plasma samples were kept overnight at 4°C before assaying for creatine kinase (CK) activity. CK activity was determined kinetically at 25°C in a Cecil CE 275 spectrophotometer linked to a Servoscribe recorder. The reaction mixture was prepared from Boehringer CK-activated UV test systems. Samples with activity greater than 250 m-units ml⁻¹ were diluted with heat-deactivated dog plasma to reduce the activation effect of dilution (Oliver, 1965; Hearse et al., 1973).

Twenty-five dogs were divided into four groups.

Group 1

In 10 dogs, quantitative $^{81}$mKr cardiac scintigrams, the epicardial ECG, blood pressure, and also arterial and coronary venous blood samples were
collected during a 20-minute control period. The LAD was occluded and all these observations were continued for 5 hours.

**Group 2**

In five dogs, the observations were recorded as in group 1 during a 20-minute control period. The LAD was occluded and all the observations were continued for 5 hours. Thirty minutes after LAD narrowing, nifedipine, $13.0 \pm 3.1 \mu g/kg$ (mean $\pm$ SD), was given intravenously (iv) over 15 minutes.

**Group 3**

In five dogs, the observations were recorded as in group 1 during a 20-minute control period and for 5 hours after LAD occlusion. Thirty minutes after LAD occlusion, nifedipine, $1.0 \mu g/kg$, was administered iv over 15 minutes.

The drug was not exposed to light before administration and was dispensed in a solution of polyethylene glycol and ethanol containing nifedipine, $0.1 \mu g/ml$ (Bayer).

**Group 4**

In five dogs the coronary arteries were not occluded. All the observations were recorded as in group 1 for 5 hours. The $^{81}$m Kr scintigrams, epicardial ECG, and blood pressure showed no abnormalities and were stable.

At the end of each experiment in all the groups, the right and left coronary arteries were selectively injected with Patent Blue 5 dye. The unstained myocardium was dissected out and weighed.

The changes in the regional and total myocardial activity of $^{81}$m Kr and in plasma CK activity during the experiments were analyzed with an analysis of variance. The ECG signs were analyzed using linear regression, and $F$ test of slopes, and a Wilcoxon rank sum test to compare the slopes.

**Results**

The following observations did not vary beyond the stated ranges through the experiments: arterial pH, 7.33–7.45; $P_{o_2}$, 94.5–119.2 mm Hg; $P_{cO_2}$, 30.75–44.2 mm Hg. The mean aortic pressure was $90.7 \pm 7.5$ mm Hg (mean $\pm$ 7.5 mm Hg (mean $\pm$ SD)) and the heart rate was $126 \pm 16.5$ beats/min. These varied by less than $\pm 3\%$ during the 20-minute control periods in the dogs of groups 1, 2, and 3 and throughout the experiments in the “sham-operated” dogs in group 4. There were no significant changes ($< \pm 3\%$) for 20 minutes following LAD occlusion in all the dogs and throughout the 5-hour experiments in the 10 dogs of group 1 that received no intervention. In the five dogs of group 2, nifedipine, $13 \mu g/kg$, given iv over 15 minutes produced a fall in mean aortic pressure from $90.0 \pm 9.0$ to $63.0 \pm 10.5$ mm Hg and a rise in heart rate from $124 \pm 15$ to $139 \pm 18.3$ beats/min. These parameters returned to control after $2.2 \pm 0.6$ hours. In the five dogs from group 3, nifedipine, $1.0 \mu g/kg$, given iv over 15 minutes produced a fall in mean aortic pressure from $92.2 \pm 9.75$ to $81.0 \pm 8.2$ mm Hg lasting $58 \pm 14.5$ minutes. There was no significant change in heart rate following the administration of this dose of the drug.

The measured background activity did not exceed $2.5\%$ of the total myocardial activity of $^{81}$m Kr in any of the experiments. The activity in the area enclosing the aortic root did not vary by more than $\pm 3\%$ throughout all the experiments. The initial value of CPM of $^{81}$m Kr in each region has been treated as $100\%$ and changes calculated as time-activity graphs.

In the 10 dogs of group 1 that received no drugs, the total and regional activity of $^{81}$m Kr varied by less than $\pm 5\%$ during the 20-minute control period. On occlusion of the LAD, a diminution of regional myocardial perfusion was demonstrated as a defect seen in the images and in the sudden loss of activity in the LAD area of interest (Fig. 1). The images and the time-activity graphs showed a spontaneous improvement that occurred in all the dogs during the 5 hours of regional myocardial ischemia (analysis of variance of the regional counts showed this to be significant, $P < 0.001$).

In the five dogs of group 2 that received nifedipine, $13 \mu g/kg$ the total and regional activity of $^{81}$m Kr varied by less than $\pm 5\%$ during the 20-minute

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**Figure 1** The $^{81}$m Kr cardiac scintigrams show a typical example of A) the uniform distribution of perfusion during the control period, B) regional ischemia 1 minute after LAD narrowing, and C) and D) the natural history showing spontaneous diminution in regional ischemia at 45 minutes and 5 hours after LAD narrowing, respectively.
control period. On occlusion of the LAD, a regional decrease of activity appeared in each scintigram (Figs. 2 and 3). On administration of nifedipine, there was a marked fall in mean aortic pressure (MAP). This was followed within 3 minutes in all five dogs by a 32% (mean) increase in activity of $^{81m}$Kr in the remote myocardium not directly affected by the coronary snare. The area directly affected by the LAD narrowing showed a further 19% (mean) decrease in activity (analysis of variance, $P < 0.001$). The changes in the images showed an extension of the regional defect in perfusion that lasted for 80–110 minutes.

In the five dogs of group 3 that received nifedipine, 1.0 $\mu$g/kg, the total and regional myocardial activity of $^{81m}$Kr varied by less than ±5% during the 20-minute control period. On occlusion of the LAD, the diminution in regional perfusion resulted in defects in the images (Fig. 4), and in the sudden loss of activity in the LAD area of interest (Fig. 5). On administration of nifedipine, a smaller fall in MAP was followed within 3 minutes in all five dogs by 25% mean increase in the myocardial activity of $^{81m}$Kr in the areas of the heart directly affected by the LAD snare and the rest of the myocardial image (analysis of variance, $P < 0.001$) seen in Figures 4 and 5. The images in Figure 4 show a typical example of the regional improvement in myocardial

**Figure 2** The $^{81m}$Kr cardiac scintigrams show a typical example of A) the uniform distribution of perfusion during the control period, B) regional ischemia 1 minute after LAD narrowing, C) the extension of ischemia when nifedipine, 13 $\mu$g/kg, was given (45 minutes), and D) the distribution of perfusion at 5 hours.

**Figure 3** The graph shows the percentage changes in the regional activity of $^{81m}$Kr from the area directly affected by the LAD narrowing (ischemic) and the rest of the myocardium (remote). The stable control period, the onset of ischemia, the results over 5 hours for the control group, and the effects of nifedipine 13 $\mu$g/kg on regional ischemia are shown. The loss of regional activity and the differences comparing the nifedipine and control groups were significant ($P = < .001$). (IVI = intravenous)

**Figure 4** The $^{81m}$Kr cardiac scintigrams show a typical example of A) the uniform distribution of perfusion during the control period, B) regional ischemia 1 minute after LAD narrowing, C) the decrease in the regional ischemia when nifedipine, 1.0 $\mu$g/kg, was given (45 minutes), and D) the distribution of perfusion at 5 hours.
perfusion that lasted for 40-50 minutes in this group.

Group 4 ("sham operated") showed no significant variation (<±5%) in the total or regional myocardial activity of $^{81}$Kr throughout these experiments.

During the control periods in all the dogs and throughout the experiments in group 4, S-T segment changes were <±2 mV and R wave changes were <±4%. Epicardial S-T segment elevation was noted within 45 seconds of LAD occlusion in the dogs of groups 1, 2, and 3. This ECG sign increased to a maximum of 48 ± 8.1 mV at 18 ± 1.9 minutes, and in the 10 dogs in group 1 (no intervention) it decreased significantly during the 5 hours that followed (analysis of variance showed $P < 0.001$.) In the five dogs of group 2, (nifedipine, 13 µg/kg, iv), epicardial S-T segment elevation followed the same natural history; however, on administration of the drug, this ECG sign increased from 44 ± 4.7 to 76 ± 8.4 mV and decreased slowly thereafter during the 5-hour experiments. In the five dogs in group 3 (1.0 µg/kg), the natural history of the epicardial S-T segment elevation was the same as in group 1 until the intervention. Epicardial S-T then decreased more rapidly than in group 1 (no drug). The analysis of variance showed $P < 0.01$ at 1 and 5 hours.

An increase in epicardial R wave amplitude was noted within 45 seconds of LAD narrowing, and this reached a peak of 38 ± 9 mV at 17 ± 2.0 minutes. All of the dogs in groups 1, 2, and 3 then showed a progressive loss of R wave amplitude and appearance of Q waves during the 5 hours at those epicardial sites within the area affected by the LAD snare. The sham-operated dogs in group 4 showed no S-T segment elevation and no progressive loss of R wave amplitude.

In each dog, the S-T segment elevation in millivolts recorded from each epicardial site at 18 minutes was related to the final loss of R wave (AR mV) plus the appearance of Q waves (ΔQ mV), using linear regression analysis. All the 20 dogs in groups 1, 2, and 3 showed r values > 0.89 and $P < 0.01$. The slopes of the 10 regression lines in group 1 were significantly different ($F$ test, $P < 0.01$), and they were used to calculate a median slope and interquartile range. The ECG signs in the five dogs in group 2 receiving nifedipine, 13 µg/kg were analyzed in the same way, and showed the same r and $P$ values for each dog. A median slope and interquartile range was calculated. The ECG signs in the five dogs in group 3 receiving nifedipine, 1.0 µg/kg, analyzed in the same way, showed the same r and $P$ values, and were used to calculate a median slope (Fig. 6). A Wilcoxon rank sum test showed that the slopes of groups 1 and 2, also groups 1 and 3, were significantly separated and different ($P < 0.01$ for both). This showed that for sites with similar S-T segment elevations 18 minutes after occlusion, group 2 showed more QRS changes and group 3 less QRS changes than did group 1.

Figure 7 shows that the plasma activity of CK in the aortic samples of all the dogs increased throughout the experiments. The plasma activity of CK in the coronary venous samples in group 1 (no nifedipine) was similar to the aortic samples at up to 90 minutes after LAD narrowing. The analysis of var-
By guest on May 1, 2017

The changes in plasma CK activity in the aorta and coronary vein (within the ischemic area) showed that the arteriovenous difference was positive up to 90 minutes in the control group. Thereafter, the venous CK activity increased and was released from the heart (A). The graph also shows that the release of CK activity from the heart in the group receiving nifedipine, 1.0 μg/kg, appeared later (P < 0.001) than in the control group (C). The earlier release of CK activity is shown for the group receiving 13 μg/kg of the drug (B). The results for the sham-operated group are shown (D).

**Figure 7**

Discussion

A constant infusion of \(^{81m}\text{Kr}\) into the aortic sinuses will result in the accumulation of this tracer in the myocardial water space and an equilibrium of activity within the heart (Selwyn et al., 1978; Kaplan and Mayron, 1976). This inert, freely diffusible radionuclide has been developed for the continuous assessment of changes in regional myocardial perfusion in dogs.

Experiments in dogs have measured regional blood flow by means of a reference technique. This was used to calibrate the control regional CPM according to \(^{81m}\text{Kr}\). The systematic and random errors showed adequate agreement between measured and calculated perfusion. These experiments suggested that the delivered arterial concentration and mixing of \(^{81m}\text{Kr}\) were stable over a wide range for heart rate, blood pressure, and cardiac output (Selwyn et al., 1978). This may be explained in part by the particular vortex pattern of blood flow in the aortic sinuses (Bellhouse et al., 1968; Bellhouse and Bellhouse, 1969).

The gamma camera represents the heart in two dimensions. This is a severe limitation when trying to assess the effects of nifedipine. The images may be affected by heart size, shape, and wall thickness. In addition, this technique cannot separate the distribution of blood flow to endocardium and epicardium. Areas of ischemia greater than 3 cm\(^2\) were used because of the resolution of \(^{81m}\text{Kr}\). The geometrical relationship between each heart and the gamma camera was carefully fixed throughout each experiment so that the area of interest was isolated on the edge of the image. Only large areas were analyzed to allow for heart motion, and no attempt was made to interpret changes in CPM in the border zones between ischemic and normal myocardium.

Considerable controversy surrounds the use of S-T segment elevation in the epicardial or precordial ECG for the assessment of therapies aimed at the salvage of active myocardium (Hollands and Brooks, 1977). Recent research has shown that in individual experiments there is a close relationship between the early manifestations of ischemia (S-T segment elevation) and the later signs of cell death (R waves lost plus Q waves gained) (Hillis et al., 1976). This study has used that relationship to see if nifedipine can preserve electrically active myocardium. The results showed that more electrically active myocardium was lost at 5 hours for any given level of ischemia (S-T elevation at 18 minutes) in the dogs that received the larger dose of nifedipine. This group also showed an extension of regional ischemia with a marked fall in blood pressure. The group that received the smaller dose showed improved regional perfusion and diminished ECG evidence of cell death.

The analysis of ECG signs in this study has considered the relationship between the early signs of ischemia (S-T segment elevation) and the later signs of cell death (R wave loss plus appearance of Q waves) as individual in each dog. This approach, with nonparametric statistical analysis, provided a consistent qualitative assessment of extent and limitation of myocardial infarction in the different groups of dogs. This qualitative approach may overcome some of the spatial and electrophysiological problems of using one ECG sign in dogs or in man to assess myocardial salvage (Holland and Brooks, 1977).

Changes in the coronary venous activity of CK can be expected because of the surgical procedure. The simultaneous measurement of the arterial plasma enzyme activity permits some separation of events and an assessment of the pattern and time course for the release of CK from damaged cells within the region of ischemic myocardium.

Any measure of the total CK released would have
to measure venous blood flow in the ischemic myocardial segment. A number of studies using isolated perfused hearts have shown that acceleration or delay of CK release is associated with changes in the time course of myocardial injury (Hearse et al., 1975; Nayler et al., 1976). This study has shown marked differences in the time course of CK release in a coronary vein draining the ischemic area, and this is consistent with an alteration in the time course of ischemic myocardial damage associated with the different doses of nifedipine.

The survival of working myocardium will depend on both available coronary perfusion and metabolic state. There is good evidence to suggest that nifedipine can decrease cardiac work by reducing aortic pressure and increase myocardial blood flow by dilating coronary arteries (Vater, 1975). It is also possible that this drug can decrease ventricular volume by diminishing venous return, and this probably assists metabolic demand and myocardial perfusion by decreasing wall tension (Henry, 1975; Fleckenstein, 1975; Vater, 1975).

Fleckenstein (1975) has shown that nifedipine restricts the transmembrane calcium influx during excitation in cardiac and smooth muscle fibers. Interference with Ca-dependent myofibrillar ATPase may help preserve phosphate-bound energy, and diminish the tone of vascular smooth muscle fibers (Fleckenstein, 1975). In addition, Henry (1975) has shown that it can preserve myocardial CK activity during acute regional ischemia of the heart.

It is also well known that regional perfusion to ischemic myocardium can be aggravated by a fall in mean aortic pressure and a rise in heart rate (Shine et al., 1977; Brazier, 1974). Nifedipine is capable of producing marked changes in these two factors. There is also the more debatable possibility that large doses of this drug may markedly dilate normal coronary vessels in the heart. The fall in resistance to blood flow in the normal vessels may compete with the limited ability of collateral vessels to do the same. The effect will be to increase the inhomogeneous distribution of myocardial blood flow.

A variety of interventions have been used in experimental work to protect ischemic myocardium (Maroko 1971; Braunwald and Maroko, 1974). These results have shown that nifedipine can produce beneficial or harmful effects on acutely ischemic myocardium. The anesthetized and open-chest dog cannot provide results that can be applied directly to patients suffering acute infarction. However, Epstein (1973) and others (Greenberg et al., 1975; Banka et al., 1975) have shown that nitroglycerine and nitroprusside can exert beneficial and deleterious effects on acute regional myocardial ischemia. It seems necessary to consider the relationship between dose and effects on pathophysiology when making interventions to salvage ischemic myocardium.

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Effects of Inotropic and Arrhythmogenic Digoxin Doses and of Digoxin-Specific Antibody on Myocardial Monovalent Cation Transport in the Dog

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SUMMARY The effects of digoxin on monovalent cation active transport were determined in cardiac tissue obtained from dogs given inotropic, toxic, or lethal doses of digoxin. In hemodynamically monitored dogs, active uptake of the K⁺ analogue Rb⁺ was determined in vitro in a control myocardial biopsy, and then in serial biopsies from the same dog after the infusion of [3H]digoxin in doses sufficient to cause a sustained positive inotropic effect in the absence of toxicity, and finally after additional doses to induce overt toxicity. Nontoxic digoxin doses producing a mean increase of 20% in left ventricular (LV) dP/dt significantly reduced Rb⁺ active transport by 25% below control values. At the onset of digoxin-induced arrhythmias, maximal LV dP/dt was 53% above control whereas active Rb⁺ transport was reduced by 60% below baseline values (P < 0.001). Control dogs given vehicle alone showed no significant change in contractility or in monovalent cation active transport. In another group of dogs given a lethal dose of digoxin, Rb⁺ active transport was reduced 59% below control levels at the onset of overt toxicity and was further reduced 80% below control at the time of onset of a fatal rhythm disturbance. When dogs were given high affinity digoxin-specific IgG or Fab fragments at the onset of overt toxicity, toxicity was rapidly reversed, and monovalent cation active transport increased to 51% of control at the time of restoration of sinus rhythm. Twenty-four hours after antibody reversal of arrhythmias, monovalent cation transport values approximated normal control levels. These data provide quantitative estimates of the extent of inhibition of monovalent cation transport by digoxin at inotropic, toxic, and lethal endpoints. Similar degrees of transport inhibition were present at the time of onset of digoxin-induced arrhythmias and at the time of arrhythmia reversal by digoxin-specific antibodies. Circ Res 44: 23–31, 1979

SCHATZMANN in 1953 first demonstrated that cardiac glycosides inhibit the active transport of monovalent cations across cell membranes. In the decades since this observation, numerous studies have shown changes in potassium (and less commonly in sodium) concentrations in cardiac tissue exposed to cardiac glycosides (Grupp and Charles, 1964; Muller 1965; Akera and Brody, 1978; Langer, 1977; Ettinger et al., 1977; Ku et al., 1977), presumably brought about by the inhibitory effect of cardiac glycosides on monovalent cation transport. Ten years after Schatzmann’s observation, Repke (1963) advanced the hypothesis that cardiac glycoside inhibition of the monovalent cation transport enzyme complex sodium- and potassium-activated adenosine triphosphatase (Na⁺,K⁺-ATPase) is responsible for the therapeutic and toxic effects of digitalis. However, the relationship of cardiac gly-
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