Nonuniform Cardiac Sympathetic Nerve Discharge

Mechanism for Coronary Occlusion and Digitalis-Induced Arrhythmia

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SUMMARY This study examined nonuniform postganglionic cardiac sympathetic neural discharge as a possible mechanism involved in the production of coronary occlusion or ouabain-induced arrhythmias. After acute occlusion of the left anterior descending coronary artery in 12 cats, anesthetized with a-chloralose and pretreated with atropine, arrhythmia occurred within 3 min in eight animals; three of these died in ventricular fibrillation. In recordings from 15 nerves in the eight animals with arrhythmia, spontaneous discharge increased in nine nerves, decreased in five nerves, and showed no change in one nerve. This nonuniform neural discharge was associated with the development of arrhythmia after occlusion. In four of the cats, neural discharge did not change within the first 3 min after coronary artery occlusion and arrhythmia did not occur. Development of ouabain-induced arrhythmia was accompanied by a nonuniform pattern in the neural discharge (13 cats). This discharge may alter ventricular excitation and conduction to produce arrhythmia.

IT HAS BEEN RECOGNIZED for some time that the cardioexcitatory action of digitalis can be produced by an action directly on the heart. Recently several observations have suggested that an action on the sympathetic nervous system might contribute, at least in part, to the cardioexcitatory effects. Reports indicating that sympathectomy and adrenalectomy1 or reserpine pretreatment2 reduced the cardiac toxicity of digitalis appeared in the early 1960s. However, a relationship between the adrenergic nervous system and digitalis toxicity was not clearly indicated until Roberts et al.3 showed that agents which reduced adrenergic nervous activity also decreased the capacity of digitalis to produce arrhythmia. These observations were confirmed subsequently by Erlij and Mendez,4 Boyajy and Nash,5 Takagi et al.,6 and by a series of studies by Roberts and his group.7-10

A direct effect of ouabain on sympathetic neural discharge was established in 1969 by McLain11 and Gillis12 and this effect was associated with arrhythmia. In 1970 Roberts reported that the action of ouabain on the adrenergic innervation of the heart is complex, consisting in part of receptor blockade and in part of facilitation and/or inhibition of pre- and postganglionic neural effects.13 He advanced the hypothesis that ouabain produces a nonuniform effect on cardiac adrenergic neural activity by producing different effects in individual nerve filaments within the same nerve fiber; these nonuniform effects may alter myocardial excitability and conduction in a nonuniform manner and result in arrhythmia. It was later shown by Lathers et al.14 that ouabain did indeed cause nonuniform neural discharge which was associated with arrhythmia.

Nonuniform neural discharge may also be involved in arrhythmias resulting from acute coronary artery occlusion since it has been reported that adrenergic nervous activity is altered during the first hour after experimentally produced occlusion.15-18 Autonomic imbalance is also thought to be an important factor in the genesis of arrhythmias occurring in patients during the first hour after myocardial infarction.19 Webb et al.20 found that the presence of anterior infarction after occlusion of the left anterior descending coronary artery often involves the adrenergic division of the autonomic nervous system and results in tachyarrhythmias of ventricular origin.

The present study was initiated to determine if both acute coronary artery occlusion and digitalis toxicity produce nonuniform sympathetic neural discharge and whether this is a mechanism involved in the production of arrhythmias.

Methods

Adult conditioned cats* weighing between 2.5-4.5 kg were anesthetized with a-chloralose, 80 mg/kg, i.v. which was prepared by dissolving 720 mg of purified a-chloralose in 45 ml of warm 0.9% saline; 5 ml/kg was injected. The trachea was cannulated and the animals were ventilated with a mixture of O2 and room air using a respirator set at a rate of 18 breaths/min. The femoral arteries were cannulated to monitor mean arterial blood pressure and to collect arterial blood samples at 10 min intervals. Arterial blood pH was monitored with a blood gas analyzer (Instrumentation Laboratories, Model 113). The pH was maintained between 7.4 and 7.5; blood pO2 above 100; and blood pCO2 between 10 and 30. The femoral vein was cannulated for drug administration. Atropine (2 mg/kg) was infused slowly to prevent vagal efferent activity; this dose of atropine has been shown to abolish the effects of vagal stimulation on heart rate.21 Gallamine (2 mg/kg, i.v.) was given periodically to prevent spontaneous muscle movement from interfering with the electrical recordings. Body temperature was

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*Conditioned cats refer to animals which were freed of internal and external parasites, received 1-M. antibiotic treatments for three consecutive days and vaccines for both feline distemper and pneumonitis and were then placed in isolation for at least seven to fourteen days before delivery to the investigators.
monitored on a Yellow Springs telethermometer, using a rectal temperature probe, and was maintained at 37–38°C by a hot water pad (K-Aquamatic).

In all cats, the clavicle and the first five ribs were resected to allow identification of the right stellate ganglion. The right cardiac postganglionic sympathetic nerves were isolated to allow electrical recordings of nerve activity in desheathed small nerve branches. A pool of oxygenated mineral oil, maintained at 37.5°C by an appropriate thermoregulator, was formed by retracting the cut ends of the ribs, the clavicle, and the skin flaps and tying them to a support.

The nerve branches were identified as sympathetic by determining their discharge response to a fall in blood pressure produced by an injection of histamine (5 μg/kg, i.v.). This method for identifying sympathetic fibers has been described previously by Kelliker and Roberts22 and is based on the observation by Bronk et al.28 that a fall in blood pressure elicits an increase in sympathetic activity by means of the baroreceptor mechanism. Those nerves not responding in this manner were discarded. The histamine was injected before the onset of each experiment to identify the nerve branches as sympathetic; thereafter it was not employed. The nerve was crushed distal to the recording electrode to reduce the possibility that afferent discharge was included in the efferent discharge recording. It should be emphasized that crushing the nerve distal to the recording electrode did not alter the neural response to the blood pressure fall induced by histamine. This indicates that afferent neural discharge did not contribute to the recordings.

Since changes in blood pressure affect cardiac sympathetic neural discharge29 it is important to correlate changes in spontaneous nerve activity with fluctuations in blood pressure which occur during the experiment by computing a ratio between neural activity and blood pressure (nerve activity ratio, NAR). Our method of calculating NAR is depicted in figure 1. The NAR was calculated by dividing the mean of the range of the spontaneous discharge during a 1 min interval by the existing mean arterial blood pressure. A 1 min period was selected to calculate the NAR because the range of spontaneous discharge during this interval is constant; very high or low discharge rates lasting only a few seconds were not evident in the integrated recordings. There was a marked increase in spontaneous discharge seen in most nerves as the blood pressure fell in association with ventricular fibrillation; NAR values were not calculated for the fibrillation period and are not shown in any of the figures. The calculation of NAR values takes into account experimentally induced changes in blood pressure (whether due to ouabain toxicity or coronary occlusion) which would also alter neural discharge. In the control period, the fall in blood pressure induced by histamine always elicits a concomitant increase in neural discharge in the postganglionic cardiac sympathetic nerve branches while a rise in blood pressure induced by norepinephrine causes a decrease in neural discharge. However, after ouabain toxicity or occlusion, a fall in blood pressure does not always elicit an increased neural discharge, nor does an increase in blood pressure always elicit a decrease in neural discharge.

Sympathetic nerve activity was recorded from 1–3 postganglionic cardiac sympathetic nerve branches placed on platinum bipolar recording electrodes connected to a Tektronix 122 differential preamplifier. The output of the preamplifier was displayed on an oscilloscope (Tektronix 521) and passed through a differential amplitude discriminator. The discriminator was set at 0.4 mV above the baseline, so that only action potentials with an amplitude greater than 0.4 mV were counted. This method does not record single fiber activity but it does filter out the discharge of some nerve fibers and reduces the background noise. The output of the differential amplitude discriminator then entered an integrating circuit which converted the electrical impulses into a varying DC voltage. The integrated neural discharge was displayed on a polygraph (Grass Model 7A), along with mean arterial blood pressure, at a paper speed of 0.25 mm/sec. Lead II of the electrocardiogram (ECG) was taped using a suitable tape recorder, and at a later date, was printed on polygraph paper using a speed of 25 mm/sec. The signal from the differential amplitude discriminator was also taped during the experiment and later entered into a data retrieval computer (Nuclear Chicago, Model 7100). The computer analyzed the time, in milliseconds, between

![Figure 1. Method for determining the nerve activity ratio (NAR). In the upper graph neural discharge monitored from one postganglionic sympathetic branch (impulses/sec) is illustrated. Mean arterial blood pressure (mm Hg) is shown in the lower graph. The brackets indicate a representative 60 sec period during which the mean of the range of the spontaneous discharge was determined and divided by the mean arterial blood pressure when calculating the NAR value.](https://circ.ahajournals.org/content/full/1059/1/1059/F1.large.jpg)
successive action potentials. Only action potentials occurring within 125 msec after the preceding action potential were recorded; all those occurring after this interval were not included in the histogram. Interspike interval histograms were constructed for 1 min intervals of spontaneous discharge during the control and designated experimental times after ouabain or coronary occlusion and printed out on the polygraph.

Nerve activity was recorded from ten nerves in a control group of four cats for 60 min. This is longer than the period of neural recordings in either the ouabain or the coronary occlusion experiments. Statistical analysis of the data was performed by establishing the 95% confidence interval for the NAR values of the control group every minute for the first 15 min. Subsequent confidence intervals were computed every 5 min for a total of 60 min. In the experimental groups, NAR values determined in the minute before arrhythmia which were above or below the limits of the confidence interval for the same time period in the control group were considered to be significantly different from control. These NAR values were then placed in either the increased or decreased category of neural activity, while those which fell within the control confidence intervals were classified in the "no change" category.

In the digitalis toxicity studies, spontaneous discharge was monitored for a 10 min control period; thereafter ouabain (25 μg/kg) was administered intravenously every 15 min until death. For the coronary occlusion experiments, the chest was opened on the left side between the fourth and fifth ribs. The pericardium was opened, the left anterior descending coronary artery (LAD) was isolated, and a tie was placed under the artery at its origin. After monitoring spontaneous discharge for a 10 min control period, the artery was abruptly occluded by tying the ligature.

In the coronary artery occlusion experiments, the hearts were removed from animals after death by ventricular fibrillation or one hour after occlusion in those animals which survived for this time in order to determine the completeness of occlusion and to allow visualization of the arterial branching pattern. The surviving animals were sacrificed by rapid injection of saturated potassium chloride. The hearts were placed in either a normal saline solution or in a 10% solution of formalin for anatomical study. A microsyringe (1 ml) with a fine (30 gauge) needle was secured in the trunks of the coronary arteries proximal to the occluding tie in order to introduce a suspension of latex.* When the latex suspension was introduced into the coronary arteries, the occluding tie prevented the latex from filling the coronary arteries distal to that point. The portion of the arterial tree that did not contain the latex was studied with the aid of a dissecting microscope. One of two procedures was used to study the vascular patterns below the ties. Some hearts were placed in xylene to give translucency to the tissue and to allow visualization of the arterial branching pattern while other specimens were studied by using a dissecting needle and fine (jeweler's) forceps. The course and branching pattern of the injected vessels was studied by stripping away the epicardium and fat. Both procedures provided good results that allowed a clear record to be made of the coronary arterial scheme.

The drugs used in this study were ouabain octahydrate (Lilly); histamine phosphate (Lilly); atropine sulfate (K and K Labs); α-chloralose (Fisher), and Gallamine (Flaxedil, Davis and Geck). The doses of histamine and atropine are expressed in terms of their salts.

Results

Effect of Ouabain on Blood Pressure and Heart Rate

Ouabain did not influence the blood pressure and the heart rate prior to arrhythmia. The mean arterial blood pressure in 13 cats during the control period prior to the injection of ouabain was 137 ± 8 mm Hg; in the minute prior to initial arrhythmia (defined as a change in the P-R interval or a loss of the P wave) it was 138 ± 6 mm Hg (NS). The heart rate in these animals at the corresponding period was 164 ± 8 and 152 ± 8 beats/min (NS, paired Student's t-test), respectively.

Effect of Ouabain on Spontaneous Neural Discharge

Nerve activity was monitored for 60 min in a control group of four animals (10 nerves). These animals were anesthetized for a period of time comparable to the animals that received ouabain. Two nerves were recorded from each of two cats while three nerves were monitored in the other two cats. In all cases, the NAR values varied slightly with time, but arrhythmia did not develop. The 95% confidence limits of the mean NAR for the control group were calculated and are represented by the shaded area in figs. 2, 3, 5. The onset of initial arrhythmia is indicated by the arrows on the graphs.

The next series of experiments examined the effect of ouabain on spontaneous neural discharge and cardiac

*The latex suspension used was microfil #117 with a curing agent (Dibutyl tin dilaurate).

![graph](image-url)  
**Figure 2.** Effect of ouabain on spontaneous neural discharge in one nerve. The nerve activity ratio is expressed as a percent of control and is graphed as a function of time in minutes. Data from each of three different cats in which neural discharge was recorded from one postganglionic cardiac sympathetic branch are depicted by circles, squares and triangles. The arrows along the abscissa indicate intravenous injections of ouabain 25 μg/kg. The arrows in the graph indicate the occurrence of initial arrhythmia. The shaded area represents the 95% confidence limits of the mean NAR in a control group of four animals.
rhythmicity. The data obtained in these experiments were compared with the data obtained in the control group (represented by the shaded area of fig. 2).

Neural recordings obtained from one postganglionic sympathetic branch in ten different cats revealed that just prior to arrhythmia ouabain induced an increase in the spontaneous activity in three of ten nerves, a decrease in three of ten, and no change in four of ten nerves. It should be noted that recordings from one postganglionic branch in each of ten cats does not imply the same branch was used in each experiment. The results obtained from three different cats, in which neural discharge was recorded from one postganglionic cardiac sympathetic branch (circles, squares and triangles, respectively) are depicted in figure 2. The results indicate that ouabain produced a nonuniform effect on sympathetic neural discharge, since neural activity increased in one nerve (circles), decreased in a second nerve (squares), and showed little or no change in the third nerve (triangles). It should be noted that initial arrhythmia occurred along with the nonuniform effect on the neural discharge. These initial arrhythmias, characterized by a change in the P-R interval or by a loss of P wave, were transient but were consistently seen from animal to animal. With the continued administration of ouabain (25 µg/kg, every 15 minutes), ventricular tachycardia eventually developed. The animals died in ventricular fibrillation. Nonuniform neural discharge was also associated with the latter.

The response of the postganglionic sympathetic nerves to ouabain is not always in the same direction. It is possible that this pattern of response may also develop among the various postganglionic branches in the same cat. Therefore, spontaneous neural discharge was monitored in two or three postganglionic cardiac branches in the same cat to determine if altered neural discharge among the various postganglionic branches coincided with the development of arrhythmia. Experiments were performed in four cats in which ouabain (25 µg/kg, i.v.) was given every 15 min and the data are depicted in figure 3. The graphs show that when neural activity is monitored from more than one branch in each cat, some nerves increase above their controls, others decrease, and/or others show no change just prior to the onset of arrhythmia. These observations further support the contention that nonuniform activity in the cardiac sympathetic branches is associated with the development of rhythm disturbances following ouabain administration. Another important finding was that neural recordings obtained from only one postganglionic cardiac sympathetic branch do not reflect the effect of ouabain on all branches in the same cat.

Effect of Ouabain on Interspike Interval Histograms

Examination of the distribution and total number of action potentials included in the interspike interval histograms in a given nerve branch obtained in all four of the control cats revealed that the histograms remained remarkably constant over a period of time well beyond the duration of the ouabain experiments (data not shown). When the effect of ouabain on the interspike interval histograms for the spontaneous discharge recorded from the nerve branches dis-
discussed in the upper left graph of figure 3 was examined, it was found that the histogram constructed for the nerve depicted by the squares contained less than 10% of the action potentials included within the control histogram 14 min after ouabain 25 \( \mu \)g/kg, (4 min before the development of arrhythmia). The distribution pattern was also altered from that seen in the control period. However, the histogram for the nerve depicted by the triangles in the upper left graph of figure 3 differed only 10% from its control at this time. This indicates that nonuniform neural discharge has occurred. Furthermore, since arrhythmia developed 3 min after 50 \( \mu \)g/kg ouabain had been injected, it seems that this nonuniformity is associated with the development of rhythm disturbances. With the development of sustained ventricular tachycardia after 75 \( \mu \)g/kg ouabain, the histogram collected for the nerve depicted by triangles showed a decrease in the total number of action potentials with respect to its control; however, with the development of ventricular fibrillation the total number of action potentials increased above control. The histograms collected for the nerve depicted by the squares at the time of ventricular tachycardia and fibrillation exhibited a progressive decrease in the total number of action potentials. Similar nonuniform interspike interval changes were observed in the histograms constructed for all four cats in which neural discharge was monitored simultaneously in two or three postganglionic branches (see figure 3).

A limitation of the interspike interval histograms is that they were not constructed continuously, thus nonuniform changes in the histogram may have occurred undetected prior to arrhythmia. Furthermore, it is not possible to determine whether an increase in the total number of action potentials included in the interspike interval histogram is due to increased firing of the original population of nerve fibers or whether it is due to recruitment of additional fibers since recordings from single fibers were not obtained. This increase in frequency may also be explained by shorter interspike intervals or by an increased duration in the discharge pattern of neural activity. In this regard, it should be noted that Ten Eick and Hoffman found an increase in fibers responding after ouabain in the superior cervical ganglion-nititating membrane preparation. Decreases in the total number of action potentials in the histograms may be due to decreased firing rates in the original population of nerve fibers or due to a decrease in the number of fibers firing due to some combination of the two. The interspike interval histograms also do not tell us whether the number of action potentials occurring during a burst is altered.

**Effect of Coronary Artery Occlusion on Blood Pressure, Heart Rate and Cardiac Rhythm**

The left anterior descending coronary artery was occluded abruptly in 12 cats; eight of these animals developed arrhythmia, i.e., premature ventricular contractions, at 0.9 \( \pm \) 0.4 min after occlusion. In the eight animals which developed arrhythmia, three died in ventricular fibrillation (at 2.5 \( \pm \) 0.3 min after occlusion). Before occlusion, the mean blood pressure was 147 \( \pm \) 7 mm Hg (N = 8). In the five animals that survived for 1 hour after occlusion, the...
maximum fall in blood pressure (from control values) occurred approximately 3 min after occlusion and was 26 ± 3 mm Hg ($P < 0.05$). The blood pressure remained 19 ± 3 mm Hg below control levels ($P < 0.05$) for 15 min after the occlusion. The heart rate in the five animals that survived for 1 hour after occlusion did not change from the preocclusion values. In the three cats which died, the mean blood pressure and heart rate were 74 ± 6 mm Hg and 184 ± 22 beats/min, respectively, 1 min before ventricular fibrillation developed.

In the four animals which did not develop arrhythmia after coronary occlusion, there was no significant change in blood pressure at 3 min after occlusion (NS), while at 15 min after occlusion it was significantly below (114 ± 13 mm Hg) the preocclusion level of 119 ± 15 mm Hg ($P < 0.05$). Conversely, the heart rates for the above four nonarrhythmic animals were significantly different at 3 min postocclusion (197 ± 21 beats/min vs a control of 193 ± 22 beats/min; $P < 0.05$) and not significantly different at 15 min postocclusion.

Neural Activity and Coronary Occlusion-Induced Arrhythmia

Spontaneous discharge was monitored in one postganglionic cardiac sympathetic branch in four of the eight animals which developed arrhythmia after the LAD was occluded. The pattern of response after coronary occlusion was not uniform in that some of the nerves showed a decrease while others showed an increase or no change in neural activity just prior to arrhythmia. This finding was similar to that obtained in the ouabain experiments in which only one postganglionic nerve branch was used for recording. The results obtained in three of the four cats are illustrated in figure 4. The NAR values (obtained for the first 10 min) following LAD occlusion are expressed as a percentage of the NAR values obtained 10 min before the occlusion. The coronary vessel was occluded at zero time. The triangles represent the NAR values obtained in a cat which died in ventricular fibrillation 2 min after occlusion. The cat not represented in figure 4 died 2.5 min after the LAD occlusion. The other values were obtained from two cats that developed arrhythmia after occlusion but did not die. The NAR value increased in one nerve (circles). It also increased in another nerve (recorded from a different cat and indicated by squares) for the first 3 min after occlusion. In the latter cat, arrhythmia developed 2 min, 28 sec after the occlusion and coincided with the elevated neural discharge. The nerve activity then began to decrease over the next 7 min even though the blood pressure was 14 mm Hg lower than control.

In the other four cats developing arrhythmia after occlusion, neural activity was recorded from two or three cardiac sympathetic branches in the same cat to determine if a non-uniform pattern also exists among the various postganglionic branches within a given cat. The data showed that a nonuniform pattern did occur and that this pattern was associated with the development of arrhythmia. Results obtained from three of the animals are presented in figure 5. The top graph of figure 5 illustrates an experiment in which nerve activity increased in two branches and decreased in a third at the time of arrhythmia. In the experiment depicted in the middle graph, it can be seen that the NAR values increased in only one of the nerves while it decreased in the other two. This coincided with the development of arrhythmia. In the lower graph, the NAR values for both nerves decreased at the time of arrhythmia, although the magnitude of the response was quite different. In the animal illustrated in the bottom graph, the branch depicted by the squares stopped discharging 2 min after the occlusion but began to discharge as the cat’s blood pressure fell during the development of fatal ventricular fibrillation at 2 min and 40 sec after the coronary occlusion. The neural discharge which occurred during ventricular fibrillation is not shown in figure 5 since a 1 min interval is used to calculate an NAR value (see Methods section); however, it does indicate that the nerve was still functioning.

Further evidence that neural activity becomes nonuniform is provided by the fact that all of the nerve branches recorded showed an increase in discharge in response to a lowering in blood pressure induced by histamine during the control phase of the experiment but only seven of 15 nerves recorded showed an increase when the blood pressure fell spontaneously after coronary occlusion. Two nerves showed no change and six nerves showed a decrease.

Effect of Coronary Occlusion on Interspike Interval Histograms

Interspike interval histograms were constructed for neural activity recorded before and after coronary occlusion in seven of the cats which developed arrhythmia after the occlusion. It should be noted that in each of the eight cats, the total number of action potentials included within each histogram varied after occlusion but the distribution of these action potentials did not appear to be altered. When interspike interval histograms were constructed for branches for which NAR values were depicted in the middle graph of figure 5, in the minute following coronary occlusion, the total number of action potentials in the nerves depicted by the circles and the squares decreased to 88 and 66% of control, respectively, while that of the nerve depicted by the triangles increased to 144% of control. Arrhythmia developed in the minute after coronary occlusion. The distribution of these action potentials was not altered.

The results obtained in these experiments differ from the interspike interval histograms obtained when arrhythmia was induced by ouabain, since in the latter case the histograms exhibited a change in both the total number and distribution of potentials. The same limitations in interpreting the histograms, as indicated in the discussion of ouabain-induced changes, also apply to those collected after coronary occlusion. In any case, a nonuniform change in the number of action potentials included in the interspike interval histograms was seen only in the animals exhibiting arrhythmia after coronary occlusion.

Neural Activity in Animals Which Did Not Develop Arrhythmia After Coronary Occlusion

Electrocardiographic evidence of ischemia was not apparent in three of four cats that did not develop arrhythmia after coronary occlusion. An elevated ST segment was seen in the fourth cat. Postganglionic cardiac sympathetic discharge was monitored in these cats; neural discharge within the first 3 min after occlusion was relatively unchanged as it remained within the confidence limits calculated for the control series. When arrhythmia did develop after coronary occlusion, it generally occurred within this time period.
Interspike interval histograms were also constructed for the postganglionic cardiac sympathetic nerves monitored in the nonarrhythogenic cats. In general, the total number of action potentials did not change markedly and arrhythmia did not develop. Since nonuniform changes did not occur, this again suggests that inhomogeneity in neural responses is associated with the development of occlusion-induced arrhythmia.

Anatomy of the Coronary Collateral Vasculature

Examination of three of the hearts obtained from cats which did not develop arrhythmia and were sacrificed 1 hour after occlusion revealed that extensive collateral circulation existed between the circumflex and left anterior descending arteries. In one cat the tie occluded the left anterior descending artery of the heart, but a branch extending from the left circumflex artery appeared to be large enough to deliver a sufficient blood supply to the area of the myocardium and may have prevented the development of arrhythmia. In cats that developed arrhythmia the ties included the left anterior descending artery and its collaterals. The production of arrhythmia after coronary occlusion is also related to the number and size of collaterals which are occluded by the tie.

Discussion

Evidence that sympathetic innervation to the heart is involved in the genesis of arrhythmia after coronary occlusion was provided by Harris in 1951.24 Randall et al.25 noted that stimulation of the splanchnic ventrolateral cardiac nerve produced a shift in the origin of the pacemaker and tachyarrhythmias. They explained this observation by the fact that the nerves are not uniformly distributed to the various regions of the heart but is specifically localized to the atrioventricular junctional and ventricular regions. The results of the present study indicate that, in addition to the nonuniform distribution of sympathetic nerves, nonuniformity in the neural discharge would predispose the heart to arrhythmia. Indeed, when recordings were obtained simultaneously from two or three postganglionic nerve branches in the same cat, the onset of occlusion- or ouabain-induced arrhythmias coincided with nonuniform changes in the direction and/or magnitude of spontaneous discharge. Furthermore, in the cats in which nonuniform postganglionic neural discharge did not develop after acute occlusion, arrhythmia also did not occur. It is suggested that if discordant activity occurs in the various filaments of each nerve branch which innervate a given area of the heart, i.e., the ventricular muscle, the Purkinje system, or the junction between the two, nonuniform excitability and conduction could be imposed within discrete areas of the myocardium which ultimately would make the heart more susceptible to the development of arrhythmia26 produced by coronary occlusion or ouabain administration.

There are several reports in the literature which support this contention. Han and Moe27 showed that sympathetic nerve stimulation, ouabain administration, or coronary occlusion causes increased temporal dispersion of recovery of ventricular excitability. Furthermore, Nagy et al.28 reported that after occlusion of the left anterior descending coronary artery, there was greater inhomogeneity of the repolarization time at four neighboring points in the ischemic area. More recently, Ramanathan et al.29 reported that immediately after partial coronary occlusion in the dog, refractoriness in the ischemic zone was significantly reduced and resulted in an inhomogeneity of ventricular refractoriness between the ischemic and the nonischemic zone. These and other authors30-35 suggested that this leads to an underlying electrical instability which predisposes the ventricular myocardium to re-entrant arrhythmias.

The effect of cardiac glycosides to produce nonuniform neural discharge may result from numerous actions on 1) the autonomic centers within the central nervous system,24 2) baroreceptors,30 3) ganglionic transmission,30 30 and/or 4) pre- and postganglionic fiber activity. The extent of the contribution of each of these sites to ouabain-induced arrhythmias probably varies. The final common site is the nerve terminal, and recent supporting evidence36 showed that ouabain-induced nonuniform changes in isolated cat left ventricular repolarization times when monitored simultaneously from four separate areas. In addition, two weeks after sympathectomy produced by regional neural ablation,40 the amount of ouabain necessary to produce nonuniform changes in ventricular repolarization times as well as the dose to produce arrhythmia was increased. This indicated that the postganglionic sympathetic nerve terminal was involved in the production of ouabain-induced arrhythmia.

The effect of coronary occlusion to produce nonuniform neural activity may also involve several different mechanisms of action. It is well established that a fall in blood pressure normally elicits an increased neural discharge in cardiac sympathetic nerves.29 Since a fall in blood pressure occurs after coronary occlusion, it is likely that some of the increased neural responses associated with arrhythmia may be explained by baroreceptor reflexes. Since many of the nerves did not increase in activity in spite of the fall in blood pressure, the response of the postganglionic cardiac sympathetic nerves to hypotension is obviously altered by occlusion: it becomes nonuniform.

The mechanism(s) responsible for the development of the nonuniformity in the neural response associated with occlusion-induced arrhythmia may be related to changes in cardiac sympathetic afferent activity, ventricular stretch receptor discharge, the activity of sympathetic centers in the central nervous system, and/or pre- and postganglionic sympathetic and vagal fibers neural discharge. One might attribute the nonuniform neural effect which coincides with occlusion-induced arrhythmia to the local cardiac reflex described by Malliani et al.,41 cardiac sympathetic afferent activity initiated by an ischemic response which travels to the stellate ganglia and then directly back to the heart via the postganglionic sympathetic nerves. Indeed, Malliani et al., recording from single preganglionic fibers, found that coronary occlusion increased neural discharge in most of the nerves while few fibers exhibited no change or decreased discharge. Since we eliminated the afferent neural discharge only in those branches from which we recorded, the local cardiac reflex could still be intact. Thus, the extent of the contribution of this reflex to our results cannot be assessed.

Modification of central neural activity may also explain the development of nonuniformity in sympathetic activity.
associated with coronary occlusion-induced arrhythmia. Lown and Verrier\textsuperscript{16} have demonstrated that certain hearts may be electrically unstable because of ischemic heart disease and that central neural factors may alter the excitabile properties of the myocardium and trigger ventricular fibrillation. Indeed, it has been reported that central neural modification of both pre-\textsuperscript{17} and postganglionic\textsuperscript{18} neural discharge occurs after coronary occlusion.

Nonuniform neural discharge could also be explained by increased end-diastolic volume following occlusion. Costantin et al.\textsuperscript{19} found after coronary occlusion that postganglionic sympathetic nerve activity in decerebrate cats decreased (often followed by an increase) or did not change. They concluded that cortical or hypothalamic centers were not involved in the neural pathway. It was suggested that ventricular stretch receptors and/or "ischemic receptors," responding to abnormal stimuli of systolic expansion of the infarcted portion of myocardium and dilatation of the remainder of the heart, might initiate the occlusion-induced change in postganglionic sympathetic nerves via a vagal afferent reflex mechanism. In the present study the vagal afferent reflex is operative, even though atropine was employed, since this agent blocks only the effects of vagal afferents.

Regardless of the mechanisms involved, it is clear that nonuniform neural discharge is associated with both occlusion- or ouabain-induced arrhythmias, suggesting that discordant neural activity may be a basic factor in the development of arrhythmias.

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