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Localization of the intraventricular conduction defect occurring during coronary arteriography

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LOCALIZATION OF THE INTRAVENTRICULAR CONDUCTION DEFECT OCCURRING DURING CORONARY ARTERIOGRAPHY

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A thesis submitted to the faculties of Diagnostic Radiology and Internal Medicine, Yale University School of Medicine, in partial fulfillment of the requirements for the degree of Doctor of Medicine.

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For Samuel Langhorne Clemens, who first described the salient difference between human and canine hearts; and for Carol, who made it not matter so much.

Heartfelt thanks are due to Richard H. Greenspan, Rene A. Langou and Allan L. Simon, for their kind interest in me and their indispensable help with this work.

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INTRODUCTION

A multiplicity of transient electrophysiologic derangements has been observed consequent upon the injection of angiographic contrast media into the coronary arteries of humans [1-12] and other species [13-18].

Since the description of the electrocardiographic changes associated with intravascular injection of Diodrast [19], the effects of contrast media upon ventricular depolarization have occupied a substantial place in the affections of workers concerned with the physiologic effects of coronary arteriography.

The QRS interval is usually prolonged, although not greatly [5,12,20-23]. The mean frontal plane QRS amplitude is characteristically increased [5,11,12]. Perhaps the most striking effect is the shift in frontal plane QRS axis, which has been extensively discussed in humans [2,5, 10-12,20,21,23-25] and described in dogs [26]. Bundle of His electrograms in humans [27,28] and in dogs [26,29] have demonstrated prolongation of the A-H interval, the H-V interval remaining unchanged. Left bundle-branch electrograms [26] have documented conduction delays in this fascicle.

This monograph describes an attempt to determine the effects of coronary arteriography on the depolarization of

the more distal portions of the conduction system and myocardial muscle, and to relate these to the changes in QRS axis and duration observed in the surface electrocardiogram.

REVIEW OF PREVIOUS WORK

In 1963, Ross [3] described the characteristic pattern of T wave changes following selective injections of roentgen-opaque material into normal and diseased coronary arteries. Continuous recording of lead II revealed inversion of the T waves after selective injection of the normal right coronary artery, while normal left coronary injection resulted in peaking of the T waves. In a patient whose right coronary artery was occluded near its origin, the distal branches being supplied by collaterals from the anterior descending, this pattern was not seen. Instead, injection of contrast into the left coronary artery was followed first by T wave peaking and later by inversion as the medium passed consecutively through the left and right circulation. This pattern was useful in confirming the presence of collateral connections. No mention was made of the analogous QRS changes, although they are clearly evident in Ross' Figure 3.

MacAlpin, et al. [2] studied 107 patients with normal and abnormal coronary arteries by selective coronary or

aortic valve cusp injections using a modified Seldinger technique. Lead III was recorded during the injection of 3-4 cc of Hypaque M-75%. They found the magnitude of the electrocardiographic changes to be positively correlated with the quality of coronary opacification, and their observations confirmed and extended those reported by Ross. In 34 cases with normal and approximately balanced coronary circulation, left coronary injection caused a decrease in amplitude of the R wave, an increase in depth of the S wave, or both, and an increase in positive amplitude of the T wave. Injection of the right coronary artery resulted in an increase in height of the R wave or a decrease in depth of the S wave, or both, and inversion of the T wave (or deeper inversion of a previously inverted T wave). The authors properly pointed out that records of a single lead could not distinguish changes only in direction or magnitude of the vectors from a change in both direction and magnitude, but mentioned that at least a change in direction was evident, since the mean amplitude of the vectors' projections on lead III often inverted its sign.

Interesting exceptions to the usual pattern were noted. In 2 patients there were barely discernible QRS and T wave changes in spite of excellent opacification of both coronary arteries. One patient evidenced increase in R and T wave amplitude during left coronary opacification, and only slight T wave inversion without QRS changes after right

coronary opacification. The cine-arteriogram of this case was not available to the authors for review, although it was said in the official report to be normal. In 3 other patients, the right coronary artery was unusually small, and a disproportionately large amount of the myocardium was supplied from the left. Here, injection of either artery produced minimal electrocardiographic effects.

There were 39 patients with significant, occlusive disease, but sufficient patency of both coronary arteries that similar amounts of myocardium were perfused from each side. This group experienced QRS and T wave changes which were in all respects the same as those produced in patients with normal coronary arteries.

In 1 patient with a congenital single coronary artery, 1 patient with complete left main occlusion, and in 7 of 14 cases with complete right main occlusion, the electrocardiographic changes were attenuated or absent. The remaining 7 patients with right main occlusion had late filling of the distal portions of the right arterial tree from the left coronary system, and a biphasic response of the type described by Ross was observed. In those cases of right main occlusion in which this response was absent, no collateral anastomosis was roentgenographically demonstrable.

These findings illustrate the intimate - and unsurprising - association between myocardial perfusion and electrocardiographic changes. Situations in which an asymmetrical concentration of dye in the electrically active tissue of the heart cannot be achieved, such as congenital or acquired (occlusion of 1 main coronary artery) single coronary artery, or use of the aortic root flooding technique [7,17] yield no QRS or T wave changes.

The experience of Coskey and Magidson [11] confirms that of previous workers. These authors studied 71 patients with various cardiac diseases by the Sones technique, recording only lead II in 43, and simultaneously recording leads I, II, and III in 28. They used warm Hypaque R in concentrations varying from 70% to 90%.

Right coronary opacification resulted in a rightward shift of the mean QRS axis in 89 percent of patients; no shift was appreciable in the remainder. Left coronary opacification produced leftward shift of the mean QRS axis in 68 percent of patients with, again, no shift evident in the remainder. Vector shifts were said to be related to the entire QRS complex or the terminal vector, the initial vector in all instances remaining unchanged.

Right coronary opacification was followed by an increase in mean frontal QRS amplitude in 64 percent of patients. Left coronary injection produced an increase in mean frontal QRS amplitude in 32 percent of patients; none of the 5

patients with arteriographically perceptible left coronary artery disease evidenced a significant increase in mean frontal QRS amplitude. In no case of right or left coronary opacification was a decrease in amplitude observed.

The QRS amplitude in lead II alone was somewhat more variable. Right coronary injection resulted in an increase in 64 percent of patients, no change being found in the remainder. Amplitude increase was more frequent in patients with normal coronary arteries. Left coronary opacification increased the QRS amplitude in 17 percent; decreased it in 37 percent; and effected no change in the remaining 46 percent of cases. The authors made no statement concerning the correlation of coronary artery disease with these results. From the information available it is only possible to speculate concerning the relative roles of vector shifts and amplitude in these patients; similarly, the more variable behavior of the QRS during left coronary arteriography cannot be explained satisfactorily. The authors stated that amplitude increases were greatest when maximal opacification was achieved, and postulated that the higher incidence of QRS amplitude increase consequent upon right coronary artery injection was due to the "sometimes" (p. 516) better opacification of this vessel.

The right and left coronary responses to selective injection of dye described by Coskey and Magidson are comparable to the analogous changes observed by MacAlpin,

et al. The bilateral coronary response described by the former workers was, however, not limited to cases with occlusion of a main coronary artery, and was noted in 14 patients after left coronary artery opacification and in 1 patient after right coronary artery opacification. In no instance did this sequence of response develop with opacification of both coronary arteries. The bilateral response occurred in 2 patients with normal coronary arteries, but 1 of these 2 was found at operation to have marked narrowing of the right coronary ostium. The authors did not indicate whether the other patient came to surgery or post mortem examination, but he had calcific aortic stenosis with a 145 mm Hg systolic pressure gradient across the valve at rest, and both electrocardiographic and roentgenographic evidence of left ventricular hypertrophy. All of the other patients in this group had gross disease with at least 50 percent obstruction of 1 or more major vessels. The authors did not specify if their definition of a major vessel was a main coronary artery or a major branch, although common usage would indicate the latter. The only patient who developed a bilateral coronary response following right coronary opacification had a large intercoronary anastomotic vessel which opacified during right coronary artery injection.

The authors noted that, of the 15 patients with a bilateral coronary response, 14 had marked occlusive disease of at least 1 major vessel, 5 had evidence of

ventricular hypertrophy, and 6 had large collateral vessels evident on cine-arteriography. In all of this group, macroscopic collateral vessels were present, or there were powerful stimuli to collateral formation, or both. The authors suggested that, although they had not observed it, a person with a diminutive right coronary artery and dominant perfusion of the right heart from the left coronary artery might exhibit the bilateral coronary response. Since the temporal sequence of perfusion seems important in this type of response, this suggestion appears untenable; such a person more closely resembles one with a congenital single coronary artery than one with an extensive collateral circulation. In this context it should be recalled that 3 of MacAlpin, et al.'s, patients had this type of anatomy, and had minimal or no electrocardiographic response to opacification of either coronary artery. These considerations underscore the importance of anatomic and temporal myocardial perfusion relationships.

Grendahl, et al. [5], using the Judkins technique and recording leads I and II simultaneously during hand injection of 7 ml of 60% Urografin, described data which is similar to that discussed above. Their data concerning patients with normal coronary arteries and those with aortic stenosis will therefore not be described in detail.

Their series included 9 patients with cardiomyopathy and normal coronary arteries, in whom the control EKG had

low voltage; during angiography only small changes in the QRS complex were observed, while the T wave changes were more marked and followed the usual pattern. The significance of this disparity in reaction is unclear (see, however, page 14-16).

There were 2 patients with congenital single coronary arteries, who exhibited only slight EKG changes during selective coronary injections, again indicating the apparent importance of differential concentrations of angiographic dye in the production of the characteristic electrophysiologic reaction.

Results in patients with coronary artery pathology were similar to those previously noted [2,11]. A total of 42 injections were performed in 40 patients with presumed coronary heart disease. Coronary artery occlusions were demonstrated in 35 patients, of whom only 7 were felt to have extensive disease. In these patients the QRS and T vectors had lower amplitude during selective arteriography than in patients without coronary disease. In 14 patients with ventricular aneurysms after myocardial infarction, the EKG responses to coronary opacification were small or absent. These differences can be viewed in a general way as indicating a smaller than normal mass of electrically active muscle, poorly perfused. A marked deviation from the normal response was characteristic of occlusions in the right or both branches of the left coronary artery, while patients with occlusion in either the anterior

descending or the circumflex artery showed a response only minimally different from the normal. Due to differences in the mode of data presentation it is difficult to compare this finding to Coskey and Magidson's results, but it is compatible with the data offered by MacAlpin, et al. Grendahl, et al., observed angiographic signs of collateral circulation in 9 out of 10 patients with occlusive coronary disease, but only 3 patients exhibited the biphasic response to coronary arteriography. This is not necessarily inconsistent with the results of previous authors. Grendahl, et al., do not specifically state in which patients the biphasic response was observed, but if, as is usual, it was in the group with right coronary artery occlusion, then they elicited the biphasic response in 50 percent of patients, a figure comparable to that observed by Coskey and Magidson. The proportion of bilateral responses to observable collaterals is somewhat lower in Grendahl, et al.'s, series, however; perhaps this can be accounted for by sampling variation.

In 41 cases an increased QRS duration during angiography was noted; in 19 it was observed during injection of both coronary arteries, in 13 only during left and in 9 only during right coronary opacification. In 7 cases the QRS complex was prolonged by 0.03 second or more, and the remaining cases by 0.01-0.02 second. It has been shown [22] that coronary arteriography prolongs all phases

of myocardial electrical activity, but further analysis of Grendahl, et al.'s, results on this basis is impossible without more detailed knowledge of the electrocardiographic and angiographic findings in the individual cases.

The authors stated that, since the EKG changes develop and abate gradually, the most probable location for the causative process is at a distal level, within the myocardial cells or in the most peripheral part of the conductive tissues. Although this statement is open to criticism, there is subsequent work [26] which suggests that the conclusion may be substantially correct (vide infra).

Electrocardiographic changes did not develop during the intracoronary injections of Ringer's solution, indicating that hypoxia cannot be the cause of the electrophysiologic response when blood is displaced by contrast medium, unless, as the authors suggest, the high viscosity of the contrast agent causes an additional impedance of the microcirculation.

An interesting variation on the theme under discussion was provided by Benchimol, et al. [10], who studied the aortocoronary bypass grafts of 20 patients, using a modified Sones technique. These workers simultaneously recorded leads I, II and III during hand injections of 6 to 8 ml of 75% Hypaque.

Patients with occluded or significantly stenosed grafts had minimal or no electrocardiographic changes during graft angiography.

Right aortocoronary graft injection elicited a rightward shift of frontal plane QRS axis in all 14 patients with patent grafts (mean, 32.7°; range 5°-104°), in 3 of whom the resultant axis was greater than +90°. Patients with a more leftward control frontal plane QRS axis had greater magnitudes of right axis shift during right graft opacification.

Injection of patent left anterior descending aorto-coronary grafts resulted in no axis shift in 1 patient (in whom injection of the left coronary artery with a patent anterior descending also caused no axis shift), and a leftward frontal plane QRS axis shift in 1 subject (control +8°; post-injection, -20°). The 6 other patients with patent left anterior descending grafts manifested rightward axis shifts during graft opacification (mean, 22.6°; range, 10°-62°). There was, in these cases, no intermediate leftward axis shift. Of these patients, 3 had arteriographically demonstrable collateral vessels between their distal left anterior descending and right coronary arteries.

Patients with a control frontal plane QRS axis greater than -30° or +90° did not develop any significant change during graft injection. In those subjects with the most marked QRS axis shifts, the QRS duration increased no more than 0.03 second, and in no instance did the QRS duration exceed 0.12 second. This is in accord with

previously cited data [6]. If an intramyocardial conduction deficit were responsible for the increased QRS duration, then, considering the probably smaller amount of myocardium supplied by a graft relative to a normal coronary artery, it would not have been remarkable had the increase in QRS duration been smaller. This data also does not clearly indicate the converse conclusion that an effect on the right or left bundle branches is responsible for the increase in ventricular depolarization time.

The mean right axis shift induced by patent right coronary arterial graft injection compares well with average rightward shifts of 23° [21] and 28° [20] previously noted during right coronary arteriography. The preponderance of right axis shifts during left graft opacification is unusual in the absence of a preceding "left coronary response" despite obvious collaterals between the right and left circulations in 3 cases. The authors proposed 3 possible mechanisms to account for this: (1) bypass of the perforating arterial branches which supply the left anterior fascicle; (2) fibrosis of the left ventricular myocardium supplied by the distal left anterior descending coronary artery; and (3) extensive left-right coronary collateral vessels. Of these, only the first and second seem plausible in the absence of a biphasic response, although such a result might conceivably occur if all of the flow through the anterior descending graft was shunted directly to the right heart

and septum.

This study is also of interest in its declared purpose as a method for assessing the physiologic efficacy of aortocoronary bypass grafts.

Smith, et al. [12], studied the vectorcardiographic changes consequent upon intracoronary injections of Hypaque M-69%, Renovist, saline solutions of from 0.9 percent to 3 percent, hypertonic mannitol, Ringer's solution, hypoxemic blood, plasma, and 5 percent dextrose in water. Using the Sones technique, they made simultaneous recordings of the Frank leads X, Y and Z during intracoronary injections in a group of 19 patients with normal or abnormal coronary arteries. Recordings were analyzed with an electronic integrator, an oscilloscope, and directly from photographic tracings. Although most of their report was concerned with the repolarization process, some interesting data regarding depolarization were discussed.

Changes in the QRS complex were less marked and more inconstant than the T wave changes in 18 of the 19 patients. In each patient developing a QRS vector change there was an increase in the QRS duration, which did not exceed 0.02 second in any patient. On the scalar recordings, the characteristic response to left coronary artery opacification was an increase in the peak QRS amplitude in lead X and decrease of the peak QRS amplitude in leads Y and Z. The maximum instantaneous vector increased in approximately the

same direction as the maximum QRS vector of the control loop. There was usually slight deviation toward the region injected. The electronically derived spatial mean QRS vectors of the patients without bundle-branch block showed a slight increase in magnitude in 4 cases and a slight decrease in 1. Of the 2 patients with left bundle-branch block, 1 had responses to left and right coronary opacification that were similar to the typical vector changes, although his control QRS vector was grossly abnormal. The other patient with left bundle-branch block showed prolongation of the QRS duration with right and left coronary injections and decrease in the T vector magnitude, an atypical response. Although these reponses seem to indicate an additional effect distal to a blocked left bundle-branch, it is impossible to be sure that the control block was complete. As Brest [30] has emphasized, patterns of complete block may be produced by sufficient delays without any conduction "block". With intracoronary injections of saline solutions, although T vector changes developed similar to those observed with injections of angiographic contrast media, the analogous QRS changes were not observed. The other test substances produced no vectorcardiographic changes at all.

Although the application of the technique of vectorcardiography did not materially increase our understanding of the electrocardiographic effects of coronary arteriography,

the isolation of sodium concentration as a major factor in the effect on repolarization is of interest, and is in agreement with previous [13] and subsequent research [22]. The lack of relationship between sodium concentration and the depolarization changes is germane to the investigation described herein, and has also been confirmed by subsequent work [22].

Maytin, et al. [21], studied 29 patients by the Sones technique, opacifying the coronary arteries with 4-6 ml of warm Hypaque 75. Simultaneous recordings of lead I, II and III were registered during each injection. The QRS axis and duration, and the patterns of "ischemic" ST-T changes, were studied in all patients. Variations in the initial 0.02 second QRS vectors could be analyzed in only 6 cases.

There were 9 patients with rheumatic valvular disease, 8 had coronary heart disease, and 9 had primary myocardial disease. There was 1 case with typical angina, a positive exercise test, and normal coronary arteries. There was 1 patient with idiopathic hypertrophic subaortic stenosis, and 1 patient with Paget's disease and high-output failure. Patients were divided for purposes of analysis into 3 groups according to their control QRS axis: normal (23 cases, axis between 0° and +100°), left axis deviation (5 patients), right axis deviation (1 patient). Criteria for diagnosis of left anterior and posterior hemiblocks (LAHB and LPHB)

were established: an axis between -30° and -90° without presence of known causes of left axis deviation [31] was considered indicative of LAHB, and LPHB was diagnosed when the axis was between +100° and +180° in the absence of other causes of right axis deviation [31].

In 20 patients with a normal control QRS axis, left coronary injections produced a leftward axis shift from +88.6° ± 12.2° (mean ± S.D.) control to +8.2° ± 49.1° post-injection ($P < 0.001$). Left axis deviation beyond -30° resulted from dye injection in only 7 patients. In these, the leftward shift relative to control ranged from 117° to 158°. In 5 additional cases the post-injection axis was between 0° and -30° with a leftward shift ranging from 47° to 114°. The post-injection axis did not go beyond 0° in 8 patients; in this group the leftward shift varied from 7° to 50°. Of the patients with pre-existing LAHB, 6 did not evidence any change in QRS axis during injection, and 1 developed a leftward axis shift of 15°.

The characteristic right axis deviation following right coronary injection averaged +89.3° ± 16.7°, relative to the control axis of +66.5° ± 17.2° ($P < 0.001$). The magnitude of right axis shift with right coronary injections was less than that of left axis shift with left coronary injections ($P < 0.001$). The patients with LAHB manifested marked right axis shift (93° to 192°) relative to control, without the appearance of complete left bundle-branch block.

The patient with LPHB in the control state experienced no change of QRS axis after right coronary opacification.

The biphasic response occurred in 3 patients after right coronary injection. There was no description of the arteriographic findings in these cases.

QRS prolongation over 0.02 second was seen only once; the authors do not describe the patient's control state.

The initial QRS vectors could, for technical reasons, be studied only during right coronary arteriography. At the time of maximal right axis deviation a q wave was increased (2 cases), decreased (1 case) or not brought out (3 cases). The authors gave no correlations with the control electrocardiograms.

The authors ascribed left axis deviation after left coronary injections to complete (post-injection axis beyond -30°) or incomplete (post-injection axis between 0° and -30°) block in the anterior division of the left bundle-branch. Similarly, they related the right axis shifts to block in the posterior division of the left bundle-branch. The authors attributed the greater magnitude of the axis shifts with left coronary opacification to the single vascular supply of the anterior fascicle and the double vascular supply of the posterior fascicle. This anatomic feature has since been disputed [32], but a relative difference in perfusion from each side could still

be postulated. It should also be noted that experimental production of LPHB, albeit in dogs, results in a smaller axis deviation than production of LAHB [33-35].

That the patients with pre-existing LAHB and LPHB did not manifest a change in QRS axis upon injection of the relevant artery is compatible with the locus of action of the angiographic dye being at the fascicular level, either in the main fascicle or in the more peripheral ramifications. If the site of action were in the ventricular muscle, one might reasonably expect an additional conduction delay and an additional axis deviation upon coronary opacification. However, it is somewhat inconsistent that coronary opacification did not produce complete left bundle-branch block. The authors offer several explanations for this: (1) the arteriographically produced block could have been incomplete, preventing a complete post-divisional left bundle-branch block; (2) the divisional block induced by the procedure might have been distal enough to initiate ventricular depolarization without the classical pattern of complete left bundle-branch block (LBBB); (3) a combination of these factors; and (4) the changes attributed to transient divisional block could be due to other causes.

Points embarrasing to a hemiblock theory are the absence of changes in the initial 0.02 second QRS vectors [23,36,38] and the failure of any patient to develop right bundle-branch

block (RBBB) coincident with the putative LAHB [37,39]. However, the first might be explained by an incomplete block, wherein the normal pathway of activation is maintained but the impulse is desynchronized and regional activation prolonged. The relatively privileged position of the main bundle branches might be invoked to explain the second (note, however, the work of Nakhjavan [26], discussed below). The authors provide suggestive but inconclusive evidence for a fascicular genesis of the QRS changes.

A less tolerant stance was adopted by Fernandez, et al. [20], who, in a study of 29 patients during selective coronary arteriography, simultaneously recorded leads I and II or II and III. No QRS changes were observed in 9 patients, all of whom had abnormal control electrocardiograms (6 cases with complete LBBB, 1 case with complete RBBB, 1 case with third-degree atrioventricular block, and 1 case with "diaphragmatic peri-infarction" block). Characteristic QRS changes were observed during coronary injections in 20 patients, whose control tracings were normal (6 cases), or showed ischemic T waves (4 cases), old anteroseptal infarction (4 cases), left ventricular hypertrophy (5 cases), or incomplete LBBB (1 case). This group comprised 17 males and 3 females, with arteriographic findings of normal coronary arteries (8 cases) or coronary arterial irregularities or stenosis (12 cases). The authors studied the duration and

shape of the QRS complex and the frontal plane direction and magnitude of the initial 0.02 second, initial and terminal 0.04 second, and overall QRS vector.

Left coronary artery opacification typically resulted in the following changes: (1) a mean increase of QRS duration of 0.013 second ($P < 0.001$), with no increase in 5 patients and increase up to an overall duration of 0.12 second in 2 cases; (2) leftward shift of the QRS axis by a mean of 33.8° ($P < 0.001$), with the resultant axis remaining within normal limits in all but 4 cases (in which it was equal to or beyond -30°); (3) increase in average magnitude of the QRS ($P < 0.01$); (4) leftward deviation of the mean initial and terminal 0.04 second QRS vectors ($P < 0.01$), without significant modification of the angle between them; (5) significant increase ($P < 0.05$) in magnitude of the mean initial 0.02 second QRS vector, without significant change of its frontal plane direction. Changes in QRS patterns in leads I and III were noted. In lead I, the R wave increased in size and the S wave diminished or disappeared. In lead III, the Q or S waves increased and the R wave diminished. The QRS patterns in lead I changed from qR or qRs to qR and from R or Rs to R. In lead III, the patterns changed from qR, qRs or QR to QS and from R or RS to rS.

Right coronary artery injections were accompanied by the following electrocardiographic changes: (1) a mean

widening of the QRS complex by 0.014 second ($P < 0.001$), no change being observed in 6 cases and a resultant duration of 0.12 second seen in 3 patients; (2) rightward QRS axis shift by a mean of 27.7° ($P < 0.001$), the post-injection axis remaining within normal limits in all but 3 cases (in which it reached or exceeded +90°); (3) significant rightward deviation of mean initial and terminal 0.04 second QRS vectors ($P < 0.001$) without significant change in the angle between them; (4) "significant" increase of the average magnitude of the QRS (P not given); (5) "significant" increase in magnitude of the initial 0.02 second QRS vector (P not given), without significant modification of its frontal plane direction. Changes in QRS patterns in leads I and II were essentially the inverse of those noted above. In lead I, the R wave diminished in amplitude, and the S wave increased; in lead III, the amplitude of the S wave was reduced, but that of the R wave increased. The QRS pattern in lead I changed from qR or qRs to qRS and from R or Rs to Rs or RS; in lead III, QR, qRs or qRS patterns changed to qR, and R or Rs patterns to R.

In all cases, deviation of the terminal 0.04 second QRS vector was more pronounced than that of the initial 0.04 second vector.

The authors assumed a priori that the changes described above resulted from forms of LAHB and LPHB, and drew the following conclusions on that basis: (1) that left intra-

ventricular hemiblock alone may widen the QRS duration to 0.12 second and that a QRS duration of 0.12 second is not an absolute criterion of left bundle-branch block; (2) that there are, between the control QRS and the most abnormal post-injection tracings, a gamut of intermediate patterns corresponding to various degrees of hemiblock, and that these probably constitute a normal variant of the electrocardiogram; (3) that left intraventricular hemiblock can be present without significant change of the initial 0.02 second QRS vector.

In the frame of reference adopted by the authors, it is impossible to fault their conclusions. However, they give no evidence, save for the resemblance of their results to those obtained in experimental studies in dogs [33-35,37] that the electrocardiographic changes they describe represent left intraventricular hemiblocks. As Rosenbaum has convincingly demonstrated [36], the differences observed in dogs from the classical human pattern of left hemiblocks are due to the different anatomic axes of the heart in the dog and the human and cannot be ascribed to physiologic differences or, as Fernandez, et al. [20], propose, to differences in functional lesions. Hence the basic assumption made by Fernandez, et al., is unsupported, and their conclusions must be regarded as unproven.

In a subsequent publication, Fernandez, et al. [24], used vectorcardiographic techniques during selective intracoronary injections of the contrast agent Vasurix-38. They

divided their 26 cases into 4 groups based principally on the control electrocardiograms: group I, 13 patients with normal ventricular depolarization and a frontal plane QRS axis between +10° and +70°; group II, 6 patients with a frontal plane QRS axis of -10° to -90°; groupIII, 5 patients with old myocardial infarction or left to right coronary anastomoses, or both; groupIV, 2 patients with bundle-branch block (1 intermittent complete left, and 1 incomplete right combined with right ventricular hypertrophy).

In group I, left coronary arteriography caused the QRS loop to deviate towards the left and become largely open in the frontal plane. The initial QRS vector was unchanged in the frontal plane. The maximal QRS vector rotated to the left superior quadrant ($P < 0.001$), and its timing was delayed ($P < 0.01$); the terminal vector deviated to the left and superiorly. The initial 0.02 second QRS vector was unchanged in the horizontal plane. The maximal QRS vector rotated toward the left posterior quadrant (not significant), and the terminal vector deviated to the left and posteriorly ($P < 0.01$). Right coronary opacification did not change the initial 0.02 second vectors in the frontal and horizontal planes. In the frontal plane the QRS loop deviated to the right and inferiorly and became largely open, encircling a wide area with an isolated or predominantly counterclockwise inscription of the QRS loop. In the horizontal plane the QRS loop remained counterclockwise in all but 2 cases. In

the latter, the loop showed a figure-of-eight (incomplete RBBB) pattern. In the frontal plane, the maximal QRS vector deviated to the right ($P < 0.02$) and the terminal vector rotated to the right inferior quadrant. In the horizontal plane the maximal QRS vector deviated anteriorly ($P < 0.05$), and the terminal vector rotated toward the right posterior quadrant.

In group II, left coronary injection resulted only in deviation of the terminal QRS vector toward the left superior quandrant ($P < 0.05$). Right coronary injections resulted in a clockwise inscription of the frontal plane QRS loop in 2 cases. In the horizontal plane, the QRS loop remained counterclockwise in all but 1 case, in which it showed a figure-of-eight pattern with clockwise rotation of the anteriorly deviated terminal vectors (incomplete RBBB pattern). In the frontal plane the maximal QRS vector deviated to the right ($P < 0.05$), while the terminal vector rotated to the right superior quadrant.

The results in group III are less pertinent to this discussion. These patients demonstrated the characteristic biphasic pattern.

The patient in group IV with intermittent complete LBBB demonstrated, on left coronary injection, an increase in QRS duration from 0.13 to 0.15 second; the frontal plane QRS loop deviated to the left and showed a figure-of-eight configuration; the QRS axis rotated from +5° to -20°.

Right coronary injection increased the QRS duration from 0.13 to 0.14 second; the frontal plane QRS loop was deviated to the right, but the inscription remained counter-clockwise; the QRS axis changed from +5° to +75°. The patient with incomplete RBBB evidenced mild superior deviation of the frontal QRS loop figure-of-eight pattern and mild leftward deviation of the maximal QRS vector, the terminal vectors pointing to +180° in both planes, consequent to left coronary artery opacification. Right coronary artery opacification caused rightward rotation of the frontal QRS loop, which became largely open in its counterclockwise inscription. The maximal QRS vector rotated rightward, and the terminal vector changed from +120° to +100°.

These findings extend somewhat and confirm those of Smith, et al. [12]. The vectorial approach of itself contributes no further understanding of the mechanism of the QRS changes. However, the authors modified their earlier analysis. They postulated, to explain the discrepancy in initial QRS forces between classical hemiblocks and the arteriographically induced "hemiblocks", that the latter are "parietal" hemiblocks, resulting from the action of the angiographic dye on nonspecific myocardiac cells. This was, indeed, the most reasonable explanation of the available data. In this schema, activation via the fascicles would proceed normally, and the later portions of the QRS complex, representing the contribution of the myocardial mass, would

be slightly delayed, accounting for the slight QRS widening and axis shift. This hypothesis is circumstantially supported by the observation that patients with a control axis compatible with LAHB developed similar but less marked changes following left coronary arteriography. However, the criteria for LAHB in the control were rather loose. Further, it is impossible to say how complete the control blocks were.

The authors offered, as further evidence in support of their explanation, the occurrence of incomplete RBBB in 2 patients during right coronary injections. They proposed that this pattern resulted from delayed activation of the right ventricular myocardium due to direct action of the opaque material on the ventricular muscle. This is, of course, possible, but is in no way demonstrated by their data. Since at least the proximal portion of the right bundle-branch may receive blood from the right coronary artery [32,40,41], and since an effect of angiographic dye on the specialized conduction tissue has been demonstrated [26,42], their conclusion is premature.

Rosenbaum, et al. [23], in a paper submitted for publication almost simultaneously with the later of the articles by Fernandez, et al. [24], reported a series of 16 patients in whom the 3 standard limb leads were recorded during catheterization of the left ventricle and selective opacification of the coronary arteries with Hypaque 75.

The usual electrocardiographic changes of left anterior and posterior "hemiblocks" were observed during intracoronary injections of contrast medium. They were considered not to be true hemiblocks by virtue of the lack of change in the initial forces of the QRS.

During the cannulation of the coronary arteries in 1 patient, however, the catheter tip slipped into the left ventricular outflow tract and 2 bursts of ventricular ectopic beats, separated by a short interval in which a sinus beat was present, were recorded. Most of the ectopic beats had the pattern of RBBB and LPHB, as expected when ectopic activity arises from the outflow tract of the left ventricle. During the second burst and immediately thereafter, several sinus beats were recorded which showed the characteristics of classical LAHB. Compared to the control state: (1) the QRS axis changed from +90° to -50°; (2) an $S_I Q_{III}$ pattern became a $Q_I S_{III}$ pattern; (3) the QRS duration increased from 0.07 second to 0.09 second. After a few beats showing the LAHB pattern, it diminished gradually and had disappeared after about 10 beats. Although one might ascribe the block to the residual effect of numerous extrasystoles, the authors' interpretation was that it was due to transient injury of the left anterior fascicle by the catheter. This is probably correct, as ventricular extrasystoles provoked in the same manner in other patients did not reporduce this phenomenon. Opacification of the

left coronary artery in this patient produced the usual result: the QRS axis shifted from +90° to -30°, the QRS duration increased by 0.01 second, to 0.08 second, and there was no change in the direction of the initial QRS forces.

The authors concluded that, since the QRS changes during coronary arteriography could not be considered bundle-branch blocks or divisional blocks as they defined them, they must represent conduction disturbances in the Purkinje networks (arborization block) or myocardium (parietal block). They felt that a conduction disturbance involving the Purkinje network of the anterior division of the left bundle-branch would result in an electrocardiographic pattern of LAHB [36]. Conversely, if the functional lesion were limited to the anterolateral wall of the left ventricle without involvement of the Purkinje network, the initial portion of ventricular activation could not be affected, since it would begin simultaneously in the uninvolved anterior and posterior Purkinje networks. By this logic, the absence of initial 0.02 second QRS changes was considered evidence that parietal block is the cause of the QRS changes during coronary arteriography. Although a parietal block was not demonstrated by direct measurement, this formulation has the virtue of explaining all of the data then available.

There are 2 flaws in this theory. First, a parietal block produced by intracoronary injection should involve, in a balanced circulation without gross occlusive disease, approximately the entire mass of the appropriate ventricle. A pattern of complete or incomplete bundle-branch block would be more likely than a pattern of divisional block. Second, there is evidence that angiographic contrast media directly affect the specialized cardiac pacemaker and conduction tissues. On the strength of this evidence, which will now be described, it appears unlikely that an isolated pharmacologic lesion of the myocardium, without involvement of the Purkinje network, can be induced by coronary opacification.

Betriu, et al. [25], 2 years after the exchange of views by Fernandez and Rosenbaum, published 2 examples of classical LAHB during right coronary arteriography. These were included in a series of 60 patients who were studied during coronary arteriography with 12-lead electrocardiograms. The coronary arteries were opacified with 4 to 5 ml of Renografin 76 injected by hand. All patients save the 2 to be discussed below showed responses within the range of previously described cases and will not be mentioned further.

The criteria for diagnosis of LAHB were: (1) presence of a deep S wave in leads II, III and aVF; (2) QRS axis beyond -30°; (3) terminal r wave in lead aVR; (4) S wave

in leads V_5 and V_6; (5) QR or R waves in lead aVL with intrinsicoid deflection greater than 0.045 second [43].

The resting electrocardiogram of the first patient showed an old infero-lateral myocardial infarction, with QRS duration 0.10 second and QRS axis 0°. During left coronary opacification the QRS axis shifted to -20°, terminal slurred r waves in leads III and aVF disappeared and the R wave increased in voltage in lead aVL. Right coronary opacification led to a QRS axis shift to -45°, with a new $Q_I S_{III}$ pattern, appearance of a terminal r wave in lead aVR and deep S waves in the left precordial leads. The intrinsicoid deflection in lead aVL was 0.06 second. There was no significant increase in QRS duration during right or left coronary injections. The ciculation was right dominant, with moderate or marked narrowing in all major vessels and no visible collaterals.

The second patient had only non-specific ST-T wave changes on her control electrocardiogram, with a QRS axis shift of +45° (by my reading it is +75°). Left coronary injection shifted the QRS axis to 0°. Right coronary injection shifted the QRS axis to -20°; the R wave in lead aVL became taller, a terminal R wave appeared in lead aVR, S waves were seen in leads V_5 and V_6, narrow q waves appeared in leads V_2 and V_3 while previously demonstrated q waves in leads V_5 and V_6 disappeared, and a $Q_I S_{III}$ pattern became evident. The circulation was right dominant with mild premarginal narrowing of the right coronary artery and moderate stenosis of the main branches of the left.

There was no apparent collateral circulation.

These 2 cases demonstrate changes in the initial 0.02 second QRS vector. These cases unarguably demonstrate the pattern of LAHB except for the insufficient axis shift in the second. Following Rosenbaum's reasoning, this might represent a divisional or an arborization block; the latter seems unlikely, since the block was produced during right coronary artery injection in patients who did not develop a bilateral response to injection of either artery and who had no obvious collateral vessels or ventricular hypertrophy [2,11]. Frink and James [32] have demonstrated perfusion from the right coronary artery of the proximal portion of the anterior fascicle in 5 of 10 human post-mortem specimens, and this route seems a more plausible one to conduct the contrast agent to a target tissue. In either event, an effect of angiographic dye at a heretofore privileged site was demonstrated. Perhaps reflecting the global confusion attending this subject, the left axis shift in these patients after left coronary injections was ascribed by the authors to "an incomplete type of divisional block" and to a "parietal block" at different points in their discussion.

Nakhjavan [25] had previously shown a delay in conduction in the main left bundle-branch in dogs. He studied 5 dogs with simultaneous recording of left bundle-branch (LB) and bundle of His (H) potentials, as well as

leads I and II. Renografin 76 (5-12 ml) was hand-injected into the left coronary artery.

QRS axis shifts occurred in 3 dogs; in 2 dogs there was a significant left axis shift (90° and 62°), in 1 dog there was a slight right axis shift (12°), and in 1 dog a slight left axis shift (6°). There was no axis shift in 1 dog. QRS widening, varying from 5 to 35 msecond, was observed in all dogs.

Three dogs developed conduction delay in the left bundle-branch, as evidenced by gradual merging of the LB potential into the cavity potential (V) with prolongation of the H-LB interval. There was no change in the H-V interval at any time during the experiment. This observation and the disappearance of the left bundle potential may be explained by assuming that conduction in the right bundle-branch was not affected, and that activation of the septum occurred from the right at the normal time. This would be rather surprising, in that the interventricular septum, including the bundle of His and the right bundle-branch, is thought to be perfused in the dog entirely by the left coronary artery [44-48] (see Discussion, however). One can only plead the lack of an alternate explanation. Transient injury to the left bundle-branch by the electrode catheter seems unlikely, since in all cases the block occurred only within the time period during which the characteristic QRS changes of contrast injection were seen in leads I and II.

The author felt the dilemna could be resolved by postulating non-simultaneity of conduction disturbance in the right and left bundle-branches; thus, the normal H-V interval reflects conduction thorough the "yet unaffected bundle". This explanation is substantiated by the depth-electrode studies of Durrer, et al. [49], in which the isotropy of the interventricular septum and nearly simultaneous activation of both its surfaces were convincingly demonstrated.

The 2 dogs who evidenced the largest left axis deviation upon coronary opacificaton both developed conduction delay in the left bundle-branch. In these dogs onset of the QRS axis shift and increase in QRS duration (5 msecond and 19 msecond, respectively) preceded the left bundle-branch delay, which disappeared before the QRS changes abated. The third dog who developed H-LB prolongation manifested no axis shift, although developing the greatest increase in QRS duration (from 70 msecond to 105 msecond).

In 2 dogs, QRS widening (5 msecond and 11 msecond) and minor left and right axis shifts occurred without change in conduction in the left bundle-branch.

This study is the only direct demonstration of an effect of angiographic dye on the intraventricular conduction tissue. It also indicates that the functional lesion responsible for the axis changes is, at least in the dog, distal to the main left bundle-branch.

Although conduction delay in the left bundle-branch has been documented, in neither the dog [29] nor in man [27,28] has an effect of coronary arteriography on the main bundle of His been observed. There is no immediately apparent explanation for this. In the dog study 1 out of 20 dogs developed transient complete heart block (after right coronary artery injection of Renografin M-76) and this was shown by bipolar electrogram to occur proximal to the bundle of His deflection, probably within the atrio-ventricular node. In the human studies [27,28], although sinus bradycardia and prolongation of the A-H time were common in a group of 37 patients, in no instance was the H-V interval prolonged, even in patients with an abnormally long control H-V time. One might postulate that this order of precedence is a reflection of the functioning of the "gating" mechanism (see Discussion and references therein).

Elucidation of the mechanisms of the sinus node depression has been accomplished by Adams and Paulin [42] and by Frink, Merrick and Lowe [50].

Adams and Paulin cannulated the sinus node artery and perfused the sinoatrial node with various test solutions. The portion of their results which is relevant to this discussion disclosed an osmolality-related depression of the sinoatrial node by contrast agents (Hypaque 50; Hypaque M-75; Angio-conray; Conray 60), saline and dextrose.

There was no significant difference between the effects generated by different contrast media; their effects were in turn the same as those elicited by saline of equal osmolality, and somewhat greater than those of equiosmolal dextrose solutions. Injection of contrast agents in concentrations and volumes used in clinical examinations usually resulted in severe bradycardia, often followed by transient atrail flutter or fibrillation. Cervical vagotomy did not alter the sinus node response; however, intravenous atropinization of the animal (1 mg/kg) decreased or abolished the response to slow intra-arterial infusion of test solutions (rapid infusions are a separate matter [51,52]). A direct toxicity of hyperosmolal contrast media on pacemaker tissue was proposed on the basis of this evidence. It is interesting that, like ventricular depolarization but unlike repolarization [22], the pacemaker tissue is not sensitive to sodium ion *per se*.

Frink, *et al*. [50], divided their 25 patients into 2 groups, based on the origin of the sinoatrial and atrioventricular node arteries. In patients with type A anatomy, both the sinus and atrioventricular node arteries arose from the right coronary artery. In those with type B anatomy, only the atrioventricular node artery arose from the right coronary artery. The heart rate response to right and left coronary artery opacification was observed (in all patients without valvular disease, cardiomyopathy, congenital heart

disease or greater than 50 percent coronary artery occlusion) before and after selective right intracoronary infusion of 0.2 mg atropine in 10 cc of normal saline solution.

In type A patients the sinus rate decreased by 33 percent during right coronary opacification before and by 17 percent after atropine infusion. Type A patients manifested a 25 percent increase in sinus rate after atropine infusion alone.

Type B patients evidenced a 24 percent decrease in sinus rate after right coronary injections of dye. Atropine infusion uniformly resulted in a junctional rhythm faster than the control sinus rate. Right coronary opacification after atropine infusion resulted in junctional bradycardia at about the same rate as the sinus bradycardia elicited before atropine infusion.

The infusion of autologous blood into the right coronary artery produced a mean decrease in heart rate of 2 percent in the 5 patients studied in this manner. A total of 7 type A patients were studied during left coronary opacification; the decrease in heart rate observed was identical to that noted during right coronary injections, but was completely abolished by prior right coronary artery infusion of atropine.

The authors considered and rejected sinoatrial node artery distension and the Bezold-Jarisch effect as possible mechanisms for these results. The arteriographically induced

bradycardia of type A patients was explained by an equal contribution of reflex and directly toxic effects. In type B patients, the pre-atropine bradycardia produced by the dye was attributed to a reflex effect, since the dye did not circulate to the sinus node. The heart rate response after atropine was highly suggestive of a direct effect of the contrast agent on the atrioventricular junction.

For all its variability, and despite the differing mechanistic interpretations placed upon some individual sets of data, the literature described above permits certain definite conclusions.

The indirect [2,5,7,10,11,17,21,25] and direct [42,50] evidence sustains the common-sense hypothesis that the electrophysiologic effects of coronary opacification are intimately related to coronary artery anatomy and the regional perfusion of the heart. Consequently, any attempt to elucidate the mechanisms of these changes must include description, and correlation with the electrocardiographic changes, of the vascular supply to possible sites of action of the angiographic dye.

It is clear that, although true hemiblocks can rarely occur [25] as a result of selective intracoronary injections of contrast media, in almost all cases the changes do not represent acceptable hemiblocks as the latter are currently defined [21,23-25,36-38]. The most

popular theory at present ascribes these changes to intra-myocardial ("parietal") blocks [23-25]. It is of interest, however, to examine the sites at which an action of angiographic dye on depolarization has been proven. These include the left bundle-branch [25] and the specialized tissue of the sinoatrial node [42,50] and atrioventricular junction [50]. The only study of the myocardium *per se* [22] did not utilize techniques capable of studying depolarization (as noted by the authors), and its conclusions were limited to repolariztion. It has been demonstrated [17], however, that depolarization and repolariztion are differently affected by angiographic dye; so one cannot extrapolate from the results of Simon, *et al*. [22]. The evidence most suggestive of myocardial involvement is the existence of the biphasic or bilateral coronary response; but, although well-documented, this is poorly understood. Similarly, the necessity of producing an asymmetrical concentration of dye for clear effects would support an effect on the myocardium, as a parietal block. However, differential perfusion of the conduction system might equally well account for this. We find ourselves, then, with the definitions in one camp and the evidence in another. Clearly, any further study of the electrocardiographic changes had to test all of the possible sites of conduction delay.

METHODS AND MATERIALS

ELECTROPHYSIOLOGIC STUDIES

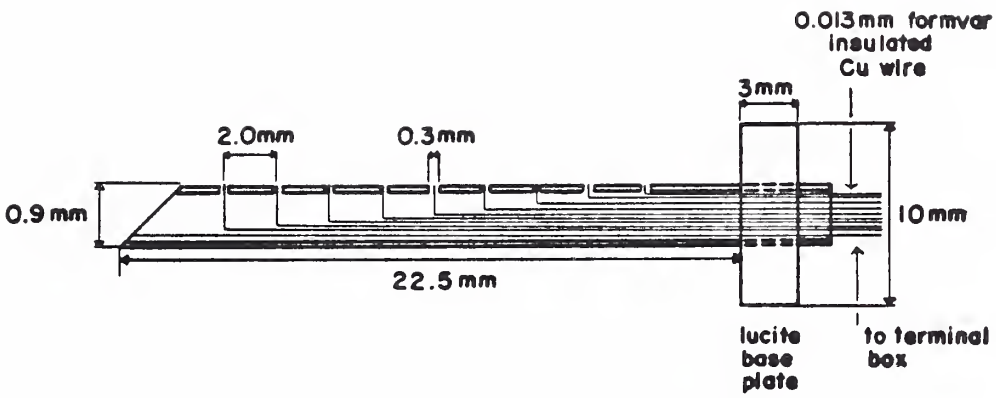
Preparation: Studies were performed on adult mongrel dogs of both sexes weighing 15-31 kg. Each dog was anesthetized with sodium pentobarbital (25 mg/kg, i.v.), intubated, atropinized (0.4 mg/kg, i.v.) and placed on a respirator on room air in the supine position.

Both carotid arteries and the right femoral artery were isolated. A catheter was advanced from the femoral artery into the central aorta for withdrawal of arterial blood samples for blood gas and pH analysis and measurement of aortic pressure during the procedure by means of a fluid-filled system consisting of the catheter and a Statham P23Db pressure transducer in linkage with an Electronics for Medicine DR-8 photographic recorder. A tripolar electrode catheter was introduced through the right common carotid artery and positioned in the left ventricular cavity against the interventricular septum for measurement of the left bundle-branch electrogram (LBE) and ventricular cavity potential (V). In 1 experiment, a tripolar electrode catheter was advanced from the right femoral vein and positioned across the tricuspid valve to record the bundle of His electrogram (HBE). A Ducor #4

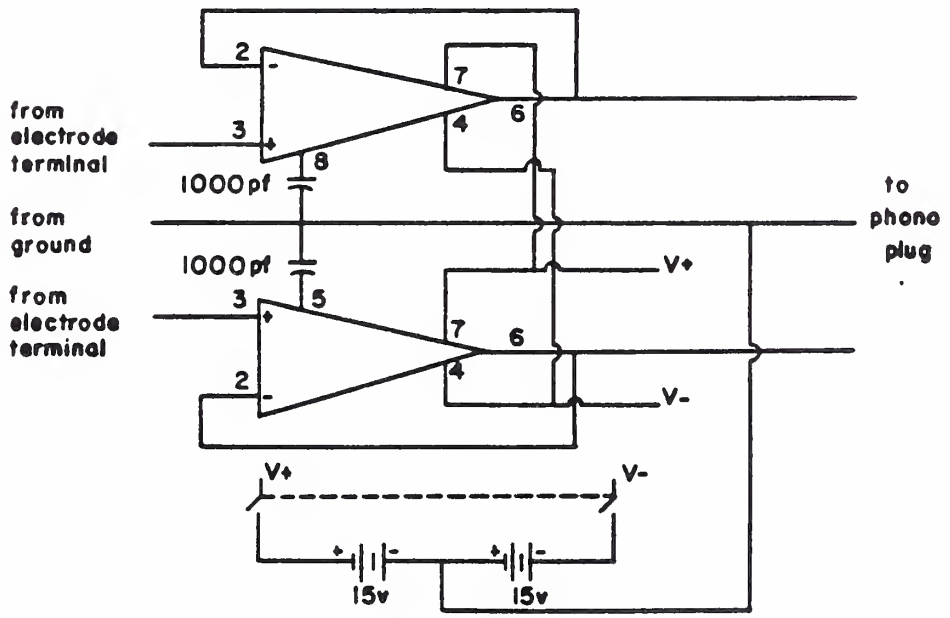
femoral-right coronary catheter was introduced into the left common carotid artery and advanced to the aortic root for intracoronary injections.

The animal was then turned to the right lateral decubitus position. A thoracotomy in the left fifth intercostal space was performed, the heart was exposed and the pericardium fashioned into a cradle. Care was taken to make the cradle as stable as possible in order to minimize intrathoracic changes in position of the heart. No special attempt was made to retain the original position of the heart or to alter it in any predetermined way. After the cradle was secured, a 10 lead-point needle electrode of design (see Figure 1) similar to that described by Durrer, et al. [59], was introduced into the free wall of the left ventricle and fastened to the epicardial surface with fast-setting methyl cyanoacrylate adhesive (Loc-Tite 404). The positions of the needle electrodes in different experiments are shown in Figure 2.

Recordings: The LBE, HBE, standard leads III and aVR, needle electrode intramyocardial electrogram (IME) and the subendocardial electrogram (SEE) were simultaneously recorded in varying combinations. The SEE was recorded from the most distal lead-point pair of the needle electrode which resided in a region in which 2 or more lead-point pairs were depolarized simultaneously [49,60].



MULTIPOLAR ELECTRODE NEEDLE



BUFFER AMPLIFIER CIRCUIT

FIGURE 1

POSITIONS OF ELECTRODE NEEDLES

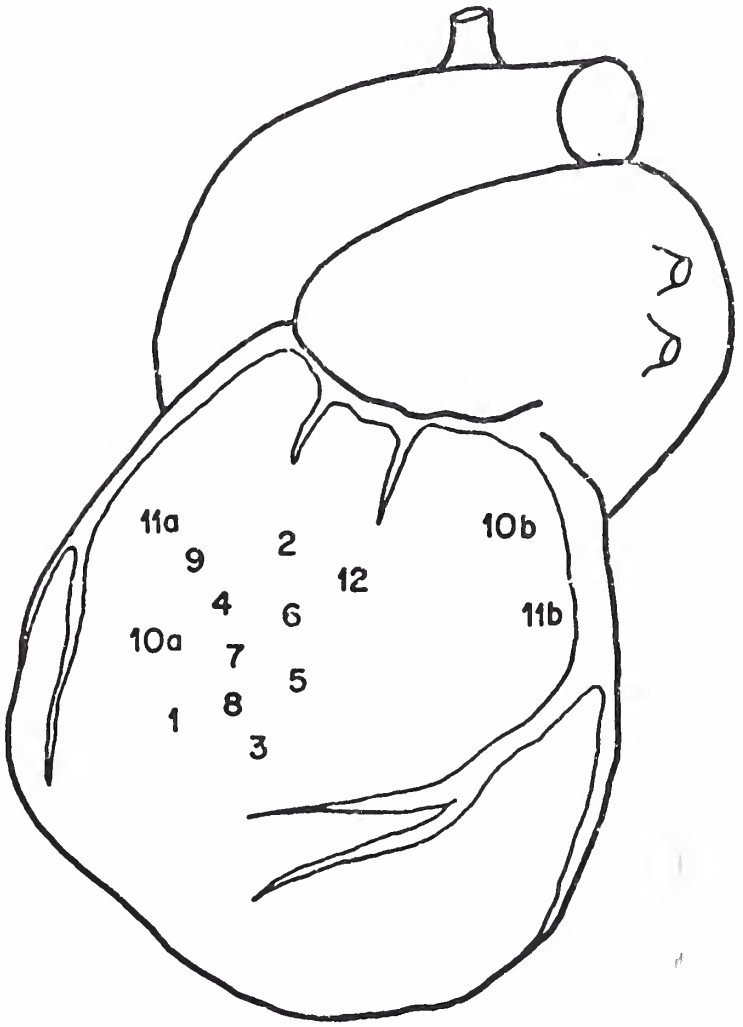


FIGURE 2

The IME was recorded from the lead-point pair nearest the epicardium. Clip leads were attached to the electrode catheter terminals and the terminal box of the needle electrode, and led into a unity-gain buffer amplifier with an input impedance of 1.5×10^{11} ohm and a frequency response of 1×10^{-1} hz to 6×10^{3} hz (kindly supplied by the Yellow Springs Instrument Company, Yellow Springs, Ohio). The buffer amplifier output was led into an Elema-Schonander Mingograf 34 ink-writing recorder equipped with 4 electrocardiographic amplifiers and a 2-channel oscilloscope. The input impedance and frequency response of this unit are 1×10^{8} ohm and 0 hz to 4.5×10^{3} hz. Standard 25 to 400 hz filters were available for the LBE and HBE or one of the needle electrode electrograms. Standard leads III and aVR were recorded for trigonometric computation of the QRS axis [53]. Care was taken to maintain identical foreleg [54] and hindleg positioning during all recordings. Constant positioning of the electrode catheter in the ventricular cavity was assured by control recordings before each intervention and by fluoroscopy.

It was apparent that as much of the ventricular conduction system as possible must be studied. However, compromises due to equipment limitations were necessary. In dogs 1 and 3, 2 groups of simultaneous 4-channel recordings were obtained as controls and during left coronary arteriography with hand-injected Renografin 76.

One group included the LBE, leads III and aVR, and the IME. The second group comprised the LBE, 2 SEEs, and the IME. In dogs 2 and 4, only this group was recorded. In dog 5, the first group was as before, and the second group differed by the substitution of standard lead III for one of the SEEs. These permutation made it possible to compare the chronology of the electrophysiologic changes in the limb leads (QRS axis) with those in the cavity electrogram (duration of activation), LBE, IME, and SEE within the limitations of the available equipment. Such a temporal correlation is essential if one is to ascribe a causal relationship between any of the individual components of the system. The data from dog 5 rendered it apparent that the QRS axis in the 2 groups of recordings could not be correlated with assurance since the lead III deflection changed in opposite directions in each set of recordings. Hence, in dogs 6-10, the recording pattern was changed and the QRS axis data of previous experiments discarded. In these experiments, the LBE, and an IME and SEE were recorded continuously on the Mingograf 34, while the fourth channel registered lead III, with brief switches to lead aVR during control and during post-injection periods of peak electrocardiographic effect. Thus, a fairly good computation of axis could be obtained with use of only 1 channel. In experiments 10 and 11, SEEs from 2 different needle electrodes were also simultaneously recorded, in order

to make some investigation of the 2-dimensional relationships of the conduction delay. In experiment 12, the HBE, the LBE, an SEE from an electrode needle and standard lead III were continuously recorded.

Selective left coronary artery (LCA) and right coronary artery (RCA) injections of Renografin 76 (R76), Renografin 60 (R60) and normal saline (SAL) in each experiment were performed as shown in Table 1. Several injections were performed in each experiment.

The parameters analyzed were defined as follows. The R-R interval was the time between the peaks of the R waves of 2 successive sinus beats. The QRS axis in degrees was trigonometrically computed [53] from the net positive area under the QRS complex in leads III and aVR. The cavity potential (V) duration was measured from the initial to the terminal deflection of cavity depolarization detected by the left ventricular cavity electrode catheter. The bundle of His depolarization (H) was the fast deflection occurring between the atrial (A) and ventricular (V) complexes detected by the right heart electrode catheter (experiment 12). The H-V interval was measured between the initial deflection of the H potential and the initial deflection of the V potential, and considered to represent to conduction time from the bundle of His to the initial depolarization of the interventricular septum. The left bundle-branch potential (LB) and conduction time from it to the earliest septal

TABLE 1

SOLUTIONS USED IN INTRACORONARY INJECTIONS

Experiment	R76(LCA)	R60(LCA)	SAL(LCA)	R76(RCA)
1	10 cc			
2	10 cc			
3	10 cc			
4	15 cc			
5	10 cc	10 cc		
6	10 cc			7 cc
7	10 cc		10 cc	7 cc
8	10 cc	10 cc	10 cc	5 cc
9	10 cc	10 cc	10 cc	5 cc
10[1]	10 cc		10 cc	8 cc
10[2]	10 cc			
11[3]	10 cc	10 cc	10 cc	7 cc
12	7 cc		7 cc	

[1] Experiment 10, using 1 needle electrode.

[2] Experiment 10, using 2 needle electrodes.

[3] In experiment 11, 2 needle electrodes were used during all injections.

depolarization (LB-V interval) were obtained in exactly the same way from the recordings from the left heart electrode catheter. The H-LB interval was measured from the initial H deflection to the initial LB deflection and considered to define the conduction time from a portion of the bundle of His to a portion of the left bundle-branch. The H-SEE, LB-SEE and V-SEE intervals were thought to define the conduction time from the bundle of His (precise anatomic level unspecified), the main left bundle-branch (precise anatomic level unspecified, but above its division; see Discussion), and the approximate point of division of the left bundle-branch (see Discussion) to the subendocardial region of the ventricular free wall (as defined above by simultaneous depolarization), specifically to the needle electrode lead-point pair closest to the ventricular cavity. Measurements were made from the initial H, LB or V deflection to the intrinsic deflection of the depolarization potential recorded on the SEE (if it was monophasic) or the isoelectric point of the SEE depolarization potential (if it was diphasic). Potentials which were monophasic or diphasic during control remained so during intracoronary injections. The conduction time from the proximal (nearest the cavity) SEE (PSEE) to the distal (nearest to epicardium) SEE (DSEE) was the PSEE-DSEE interval, measured from the depolarization potentials recorded from the appropriate lead-points of the electrode needle, as described above. The SEE-IME interval,

or conduction time from the PSEE to the IME nearest the epicardium, was measured from the appropriate recordings as described above. The SEE and IME potential durations were measured (from recordings of the PSEE and the IME nearest the epicardium) from the initial fast upstroke to the terminal rapid downstroke.

Intervals were measured independently by 2 observers. The resulting means agreed to within 1 msecond or less. The estimated uncertainty in measurement is 1 msecond.

ANATOMIC STUDIES

Within an hour after the animal's death, the heart (dogs 7-10) was removed and placed in a warm saline bath. The coronary arteries were cannulated and colored barium-gelatin masses prepared by the method of Hales and Carrington [55] were injected under a pressure of 160 mm Hg for 10 minutes. Anteroposterior, lateral and apicobasal contact radiographs were made using Kodak single-emulsion film (type SR-54). The entire ventricular septum, from the level of the aortic valve down to and including the bases of both papillary muscles was then removed. Thus, wide dispersions of the conduction system could be studied. The septum was cut into blocks, each of which was sectioned at 6 microns. Each 100th section was retained and stained with the Goldner trichrome stain [56]. The sections were examined microscopic-

ally for evidence of colored gelatin from the right coronary injection in proximity to the left-sided conduction system and the distribution of blood vessels (to the level of arterioles, reference 74) containing colored material was carefully noted.

The Goldner method stains myocardium red, connective tissue green, and the specialized conduction tissue a purplish gray. The conduction tissue was identified by several criteria: the differential staining reaction; slightly larger cell size and relative opacity of perinuclear myofibrils when compared with ordinary myocardial cells; the presence of numerous fairly uniform, rounded nuclei; a constant relation to connective tissue; and (at the level of the bundle-branch and peripheral to it) a sub-endocardial location.

Identification of vessels perfused by the left and right coronary arteries is simple: the barium-gelatin injection masses retain their colors through histologic processing, so a vessel containing blue pigment is marked as a right coronary artery tributary and a vessel containing pink pigment is fed from the left coronary artery. Identification of intercoronary anastomoses presents a more difficult problem. These are almost always detected in quite small vessels (although blue pigment was found in a large proximal branch of the anterior septal artery in dog 9), and in these both pigments appear darker. The

injection masses mix poorly in anastomotic channels, producing a layered or patchwork appearance. There are several sources of artifacts, however. Anastomotic vessels in the dog are very small, and poorly penetrated by viscid solutions such as the injectate used in this study [48,57]. The color changes in small vessels at times make individual colors difficult to evaluate, especially since the barium occasionally separates from the pigment dispersion. Most troublesome is the frequent overlay of fragments of perivascular connective tissue upon vessel lumens due to the trauma of sectioning. The green connective tissue superimposed upon the pink injectate from the left coronary artery produces a grayish blue color the hue of which is impossible to distinguish in small vessels from the blue mass injected into the right coronary artery. Thus, criteria had to be established for identification of intercoronary anastomoses. Blue coloration in a vessel lumen was considered artifactual if it was continuous with an identifiable segment of perivascular connective tissue; if the connective tissue sheath was not continuous, rendering it possible that an apparently absent portion of the sheath was present in the lumen; and if the blue coloration did not have relatively smooth borders. If there was any doubt, the putative anastomosis was considered factitious. Hence, it is probable that we obtained a conservative estimate of the distribution of anastomoses. Reconstruction to 3 dimensions was accomplished

by plotting the drawings made of individual sections on diagrams of the original blocks; these were then redrawn upon diagrammatic drawings of an idealized septum.

STATISTICAL METHODS

Means and standard deviations were computed by usual methods for each parameter of interest, pooling the raw data resulting from control recordings and recordings during injections of each test solution into the LCA or RCA in each experiment (see Tables 2-7, 9 and 10). Statistical significance of the changes from control observed during intracoronary injections was analyzed by the paired-sample two-tailed "t" test as described by Colton [58]. A value for P of more than 0.05 was considered not statistically significant (N.S.). The resultant means for these parameters were then averaged over all experiments.

RESULTS

SURFACE ELECTRODARDIOGRAM

QRS Morphology: In all experiments, the QRS complex became broader and of greater amplitude in both leads following injection of R76 or R60 into the LCA (see Figure 3); slight changes occurred during RCA opacification. Onset of QRS changes occurred between 5 and 16 seconds after the beginning of the injection, and the perturbation lasted for 10 to 20 seconds after onset. No change in QRS morphology resulted from injection of normal saline into either coronary artery. This result is comparable to those described above (see Review of Previous Work).

R-R Interval: The behavior of the R-R interval during intracoronary injections is shown in Table 2. Marked changes in individual experiments occurred rarely (e.g., Experiment 5). There were no significant changes from control in R-R interval during injections of opaque solutions into either coronary artery, but there was a significant difference between saline injections and both opaque solutions and the control.

TABLE 2

MEAN R-R INTERVAL (MILLISECONDS) ± STANDARD DEVIATION

Experiment	Control	R76(LCA)	R60(LCA)	SAL(LCA)	R76(RCA)
1	430 ± 3	405 ± 14			
2	430 ± 1	448 ± 14			
3	424 ± 4	415 ± 5			
4	502 ± 2	500 ± 5			
5	606 ± 2	713 ± 3	709 ± 4		
6	467 ± 1	440 ± 3			451 ± 3
7	353 ± 3	358 ± 4		366 ± 4	336 ± 2
8	361 ± 3	335 ± 10	324 ± 4	385 ± 4	378 ± 7
9	379 ± 3	400 ± 2	395 ± 1	399 ± 2	404 ± 3
10[1]	462 ± 4	435 ± 4		473 ± 5	472 ± 8
10[2]	470 ± 4	487 ± 2			
11	387 ± 6	377 ± 2	389 ± 4	399 ± 4	401 ± 2
12	547 ± 8	520 ± 2		545 ± 1	
Grand Mean	448 ± 74	449 ± 96	454 ± 173	428 ± 68	407 ± 49
Δ R-R[3]		+8 ± 40	+26 ± 56	+13 ± 9	+6 ± 18
% Δ R-R[4]		+2 ± 8	+4 ± 9	+2 ± 4	+1 ± 5
P Values	<—— N.S. ——>				
	<—— N.S. ——————>				
	<—— P < 0.010 ——————>				
	<—— N.S. ——————>				
		<—— N.S. ——>			
		<—— P < 0.025 ——>			
		<—— N.S. ——————>			

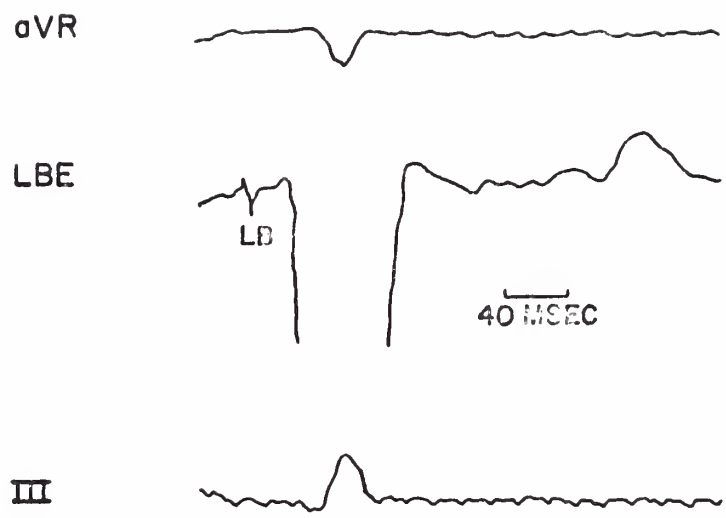
1 Experiment 10, using 1 needle electrode.

2 Experiment 10, using 2 needle electrodes.

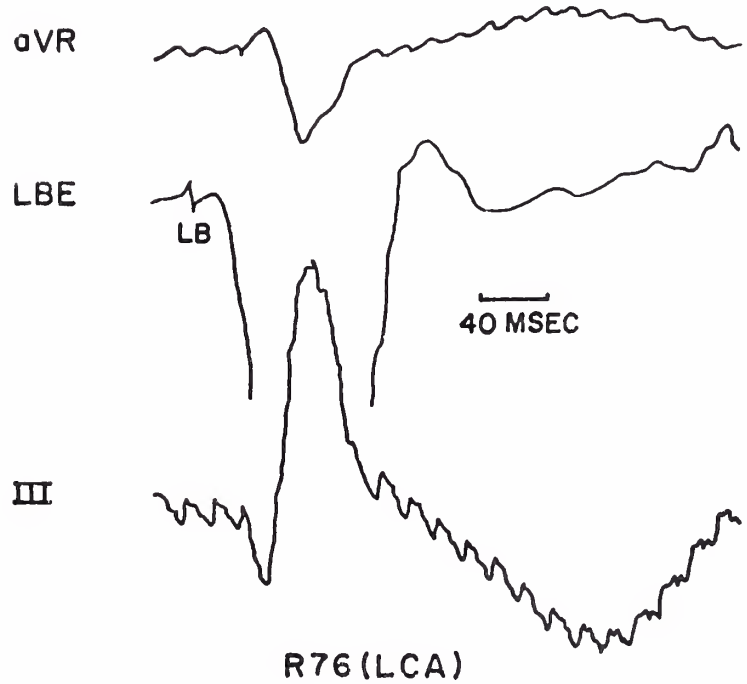
3 Mean change relative to matched controls (milliseconds) ± S.D.

4 Mean percent change relative to matched controls ± S.D.

EXPERIMENT 3



CONTROL



R76 (LCA)

FIGURE 3

QRS Axis: The QRS axis during control and injection periods is shown in Table 3. No marked changes occurred during intracoronary injections. It is somewhat surprising that LCA injections resulted in rightward axis shifts more often than leftward axis shifts, although the changes in individual experiments were not often significant.

CAVITY, BUNDLE OF HIS, AND LEFT-BUNDLE BRANCH ELECTROGRAMS

Cavity Electrogram: In all experiments, the cavity potential became broader and the terminal deflection became slurred or fragmented (see Figures 3-6). The changes in duration are detailed in Table 4. These changes were simultaneous with changes in the needle electrode recordings and the surface electrocardiogram (see Figures 4 and 6).

Bundle of His Electrogram: As in previous reports, no change in H-V time occurred during LCA injections of R76 or normal saline (see Figure 4 and Table 5). There was no change in H-LB time or H-SEE time during injections of saline in the LCA. R76 injections into the LCA produced a prolongation of H-SEE time without change of the H-LB time.

TABLE 3

MEAN QRS AXIS (DEGREES) ± STANDARD DEVIATION

Experiment	Control	R76(LCA)	R60(LCA)	SAL(LCA)	R76(RCA)
1	--	--	--	--	--
2	--	--	--	--	--
3	--	--	--	--	--
4	--	--	--	--	--
5	--	--	--	--	--
6	+85 ± 8	+79 ± 6	--	--	+86 ± 8
7	+76 ± 7	+79 ± 1	--	+76 ± 2	+83 ± 2
8	+82 ± 3	+79 ± 2	+80 ± 1	+80 ± 2	+81 ± 1
9	+67 ± 6	+74 ± 2	+74 ± 3	+66 ± 6	+60 ± 12
10[1]	+85 ± 4	+87 ± 2	--	+87 ± 3	+88 ± 3
10[2]	+86 ± 2	+93 ± 4	--	--	--
11	+70 ± 8	+67 ± 11	+71 ± 7	+69 ± 9	indeterminate
12	--	--	--	--	--
Grand Mean	79 ± 8	79 ± 9	75 ± 5	76 ± 8	80 ± 11
Δ QRS[1]		-3 ± 3	-1 ± 5	-2 ± 3	-1 ± 5
% Δ QRS[4]		-4 ± 5	-2 ± 7	-2 ± 5	-0.5 ± 7
P Values	<—— N.S. ——>				
	<—— N.S. ——————>				
	<—— N.S. ——————————>				
	<—— N.S. ——————————————>				
		<—— N.S. ——>			
		<—— N.S. ——————>			
		<—— N.S. ——————————>			

1 Experiment 10, using 1 needle electrode.

2 Experiment 10, using 2 needle electrodes.

3 Mean change relative to matched controls (milliseconds) ± S.D.

4 Mean percent change relative to matched controls ± S.D.

TABLE 4

MEAN CAVITY POTENTIAL DURATION (MILLISECONDS) ± STANDARD DEVIATION

Experiment	Control	R76(LCA)	R60(LCA)	SAL(LCA)	R76(RCA)
1	77 ± 2	112 ± 4			
2	83 ± 4	110 ± 5			
3	75 ± 1	123 ± 4			
4	94 ± 2	124 ± 9			
5	92 ± 7	111 ± 5	118 ± 5		
6	95 ± 5	101 ± 5			99 ± 5
7	65 ± 6	74 ± 5		67 ± 6	75 ± 4
8	95 ± 4	107 ± 6	108 ± 3	94 ± 6	95 ± 4
9	85 ± 2	111 ± 5	131 ± 6	90 ± 3	90 ± 3
10[1]	128 ± 5	145 ± 8		126 ± 6	111 ± 5
10[2]	105 ± 5	143 ± 13			
11	90 ± 2	107 ± 2	111 ± 3	93 ± 3	93 ± 2
12	81 ± 4	88 ± 4		81 ± 5	
Grand Mean	90 ± 16	112 ± 19	117 ± 10	92 ± 20	94 ± 12
Δ DUR[3]		+22 ± 13	+26 ± 14	+1 ± 3	+1 ± 9
% Δ DUR[4]		+26 ± 17	+30 ± 17	+2 ± 3	+3 ± 9
P Values	<—— P < 0.005 —>				
	<—— P < 0.005 ————>				
	<—— N.S. ————————>				
	<—— N.S. ————————>				
	<—— N.S. ——>				
	<—— P < 0.005 ——>				
	<—— P < 0.025 ————>				

[1] Experiment 10, using 1 needle electrode.

[2] Experiment 10, using 2 needle electrodes.

[3] Mean change relative to matched controls (milliseconds) ± S.D.

[4] Mean percent change relative to matched controls ± S.D.

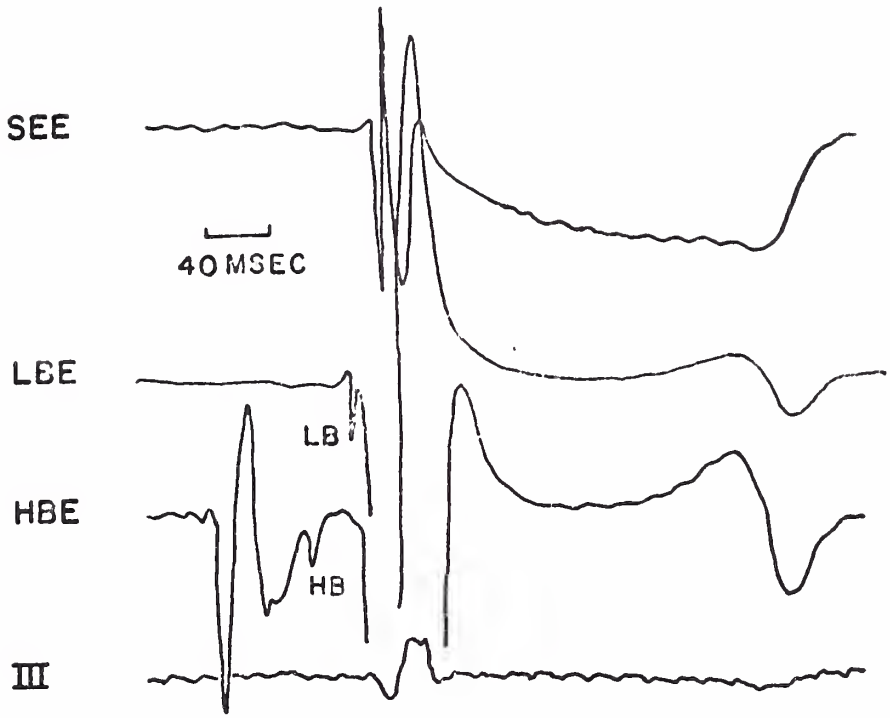
TABLE 5

MEAN HBE PARAMETERS (MILLISECONDS) ± STANDARD DEVIATION

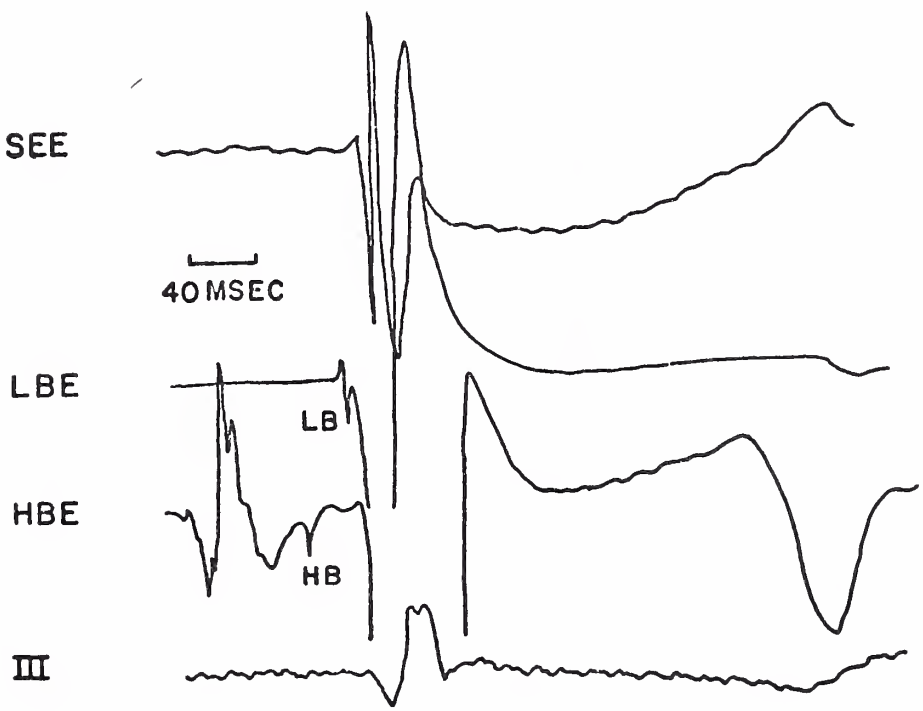
EXPERIMENT 12

Parameter	Control	R76(LCA)	SAL(LCA)
H-V Interval	35 ± 1	35 ± 1	35 ± 1
H-LB Interval	21 ± 1	21 ± 1	22 ± 1
H-SEE Interval	61 ± 1	63 ± 1	61 ± 1
LB-SEE Interval	40 ± 1	42 ± 1	39 ± 1

EXPERIMENT 12



CONTROL



R76 (LCA)

FIGURE 4

LB-V Interval: In one experiment, there was a decrease of greater than 2 msecond (twice the usual standard deviation for the measured values of this parameter) in LB-V time upon LCA injections of R76 (see Figure 3 and Table 6), as reported by Nakhjavan [26]. Other permutations of artery and injectate produced no change, and no significant change was noted in other experiments following LCA injections of R76 (see Figures 4,5 and 6, and Table 6). In no case did the LB potential gradually disappear during injection, contrary to Nakhjavan's experience [26]. In 2 experiments abrupt disappearance occurred due to catheter movement (fluoroscopically documented); this data was not included in the analysis.

NEEDLE ELECTRODE ELECTROGRAMS

LB-SEE Interval: The LB-SEE interval was prolonged in all experiments by R76 or R60 injections into the LCA (range, 2 msecond to 10 msecond); LCA injections of saline and RCA injections of contrast did not affect this parameter (see Table 7). There was a difference between the changes produced by the 2 contrast agents (R60 producing more delay), but it was not statistically significant. The LB potential was used as a marker for timing of interval in addition to the usual convention of cavity potential. The absolute

TABLE 6

MEAN LB-V INTERVAL (MILLISECONDS) ± STANDARD DEVIATION

Experiment	Control	R76(LCA)	R60(LCA)	SAL(LCA)	R76(RCA)
1	20 ± 1	20 ± 1			
2	20 ± 0	20 ± 0			
3	25 ± 1	19 ± 2			
4	13 ± 1	13 ± 1			
5	16 ± 1	17 ± 1	17 ± 2		
6	14 ± 2	14 ± 2			16 ± 1
7	18 ± 2	16 ± 1		17 ± 1	16 ± 1
8	20 ± 2	19 ± 1	18 ± 2	20 ± 1	19 ± 1
9	16 ± 1	16 ± 0	16 ± 0	16 ± 1	16 ± 1
10[1]	11 ± 1	11 ± 1		11 ± 1	12 ± 1
10[2]	10 ± 1	11 ± 1			
11	15 ± 1	15 ± 1	14 ± 1	15 ± 1	14 ± 1
12	11 ± 1	11 ± 1		11 ± 1	
Grand Mean	16 ± 4	15 ± 4	16 ± 2	15 ± 3	16 ± 2
Δ LB-V[3]		-0.5 ± 2	-0.5 ± 1	-0.1 ± 0.5	0.0 ± 1
% Δ LB-V[4]		-2 ± 8	-3 ± 7	-1 ± 3	+1 ± 9
P Values	<—— N.S. ——>				
	<—— N.S. ——————>				
	<—— N.S. ——————————>				
	<—— N.S. ——————————————>				
		<—— N.S. ——>			
		<—— N.S. ——————>			
		<—— N.S. ——————————>			

1 Experiment 10, using 1 needle electrode.

2 Experiment 10, using 2 needle electrodes.

3 Mean change relative to matched controls (milliseconds) ± S.D.

4 Mean percent change relative to matched controls ± S.D.

TABLE 7

MEAN LB-SEE INTERVAL (MILLISECONDS) ± STANDARD DEVIATION

Experiment	Control	R76 (LCA)	R60 (LCA)	SAL (LCA)	R76 (RCA)
1	40 ± 1	43 ± 1			
2	41 ± 1	46 ± 2			
3	53 ± 1	60 ± 1			
4	33 ± 1	38 ± 1			
5	39 ± 1	44 ± 1	44 ± 2		
6	33 ± 1	37 ± 1			35 ± 1
7	29 ± 1	36 ± 1		29 ± 1	30 ± 1
8	39 ± 2	44 ± 2	46 ± 4	37 ± 1	38 ± 1
9	41 ± 1	49 ± 1	50 ± 1	42 ± 1	43 ± 1
10[1]	28 ± 1[a]	38 ± 1[a]		28 ± 1[a]	29 ± 1[a]
10[2]	27 ± 1[a]	31 ± 1[a]			
	33 ± 1[b]	38 ± 1[b]			
11	40 ± 1[a]	43 ± 1[a]	43 ± 1[a]	40 ± 1[a]	40 ± 1[a]
	42 ± 1[b]	47 ± 1[b]	51 ± 1[b]	42 ± 1[b]	42 ± 1[b]
12	40 ± 1	42 ± 1		39 ± 1	
Grand Mean	37 ± 7	42 ± 7	47 ± 4	38 ± 6	37 ± 6
Δ LB-SEE[3]		+5.3 ± 2	+6.6 ± 3	-0.3 ± 1	+0.7 ± 1
% Δ LB-SEE		+15 ± 7	+17 ± 7	-0.7 ± 2	+2.2 ± 3
P Values	<—— P < 0.0005 —>				
	<—— P < 0.005 ——————>				
	<—— N.S. ——————————>				
	<—— N.S. ——————————————>				
		<—— N.S. ——————>			
		<—— P < 0.0005 ——————>			
		<—— P < 0.0005 ——————————>			

1 Experiment 10, using 1 needle electrode.

2 Experiment 10, using 2 needle electrodes.

3 Mean change relative to mateched controls (milliseconds) ± S.D.

4 Mean percent change relative to matched controls ± S.D.

a Needle 10[a] or 11[a] in Figure 2.

b Needle 10[b] or 11[b] in Figure 2.

changes in LB-SEE and V-SEE intervals were similar, although the change expressed as percent of control was, of course, different (Table 8).

PSEE-DSEE Interval: The PSEE-DSEE interval was measured in three experiments (see Table 9). No conduction delay was elicited by left coronary opacification. Indeed, in Experiment 1, the more distal electrode pair was excited before the more proximal during the intracoronary injections (Figure 5). In the other 2 experiments, there was no significant difference between control and injection. The midpoints of the distal (DSEE) and proximal (PSEE) electrode pairs were separated by 4 mm.

SEE-IME Interval: No significant prolongation of the SEE-IME interval was observed with injections of any of the test solutions into either coronary artery (see Table 10). The midpoints of the proximal (SEE) and distal (IME) electrode pairs were separated by 6 to 12 mm depending upon the thickness of the ventricular wall.

SEE and IME Potential Durations: The SEE and IME potential durations were uniformly increased by R76 and R60 injections into the LCA. R60 produced more widening of the complexes in SEE and R76 in the IME, but the differences were not statistically significant. R76 opacification of

TABLE 8

COMPARISON OF CHANGES (MILLISECONDS AND PERCENT) IN LB-SEE AND V-SEE INTERVALS RELATIVE TO MATCHED CONTROLS

MEAN ± STANDARD DEVIATION

Parameter	Control	R76 (LCA)	R60 (LCA)	SAL (LCA)	R76 (RCA)
Grand Mean LB-SEE	37 ± 7	42 ± 7	47 ± 7	38 ± 6	37 ± 6
Δ LB-SEE		+5.3 ± 2	+6.7 ± 3	-0.3 ± 1	+0.7 ± 1
% Δ LB-SEE		+15 ± 7	+17 ± 7	-0.7 ± 2	+2.2 ± 3
P Values		See Table 7			
Grand Mean V-SEE	20 ± 4	26 ± 6	29 ± 3	20 ± 6	21 ± 4
Δ V-SEE		+6.1 ± 2	+8.7 ± 2	0.0 ± 2	+1.1 ± 1
% Δ V-SEE		+31 ± 6	+44 ± 3	0.0 ± 2	+5.5 ± 2
P Values	<—— P < 0.0005 –>				
	<—— P < 0.0005 ——————>				
	<—— N.S. ——————————>				
	<—— N.S. ——————————————>				
		<—— N.S. ————>			
		<—— P < 0.0005 ————>			
		<—— P < 0.005 ——————————>			

TABLE 9

MEAN PROXIMAL SEE-DISTAL SEE INTERVAL (MILLISECONDS) ± STANDARD DEVIATION

Experiment	Control	R76(LCA)
1	-1 ± 1	+3 ± 2
2	0 ± 1	+1 ± 2
3	-1 ± 1	0 ± 2
Grand Mean	-1 ± 1	+1 ± 2
Δ PSEE-DSEE[1]		+2 ± 2
P Values	<—— N.S. ——>	

[1] Mean change relative to matched controls ± standard deviation

TABLE 10

MEAN SEE-IME INTERVAL (MILLISECONDS) ± STANDARD DEVIATION

Experiment	Control	R76(LCA)	R60(LCA)	SAL(LCA)	R76RCA)
1	27 ± 1	28 ± 1			
2	6 ± 1	8 ± 2			
3	6 ± 1	4 ± 1			
4	11 ± 1	11 ± 1			
5	4 ± 1	5 ± 2	4 ± 2		
6	15 ± 1	15 ± 1			13 ± 2
7	7 ± 1	8 ± 1		7 ± 1	6 ± 1
8	11 ± 2	12 ± 2	12 ± 4	12 ± 1	11 ± 1
9	7 ± 1	7 ± 1	6 ± 1	6 ± 1	6 ± 1
10[1]	17 ± 1	14 ± 2		17 ± 1	18 ± 1
10[2a]	--	--	--	--	--
11[a]	--	--	--	--	--
12[a]	--	--	--	--	--
Grand Mean	11 ± 7	11 ± 7	7 ± 4	11 ± 5	11 ± 5
Δ SEE-IME[3]		+0.1 ± 2	0.0 ± 1	0.0 ± 1	-0.6 ± 1
% Δ SEE-IME[4]		+3 ± 19	-2 ± 12	-1 ± 10	-7 ± 10
P Values	<—— N.S. ——>				
	<—— N.S. ——————>				
	<—— N.S. ——————————>				
	<—— N.S. ——————————————>				
		<—— N.S. ——>			
		<—— N.S. ——————>			
		<—— N.S. ——————————>			

1 Experiment 10, using 1 needle electrode.

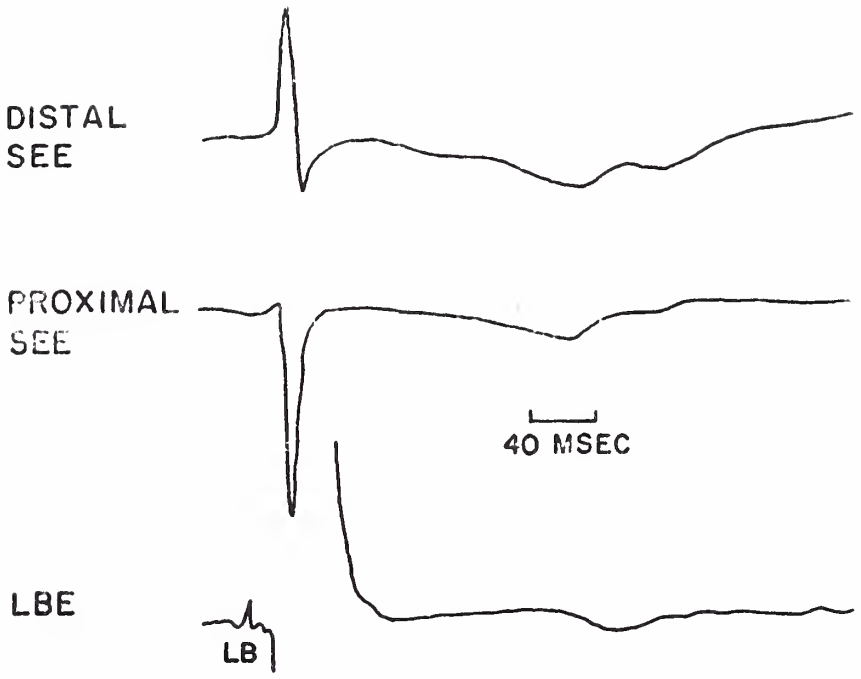
2 Experiment 10, using 2 needle electrodes.

3 Mean change relative to matched controls (milliseconds) ± S.D.

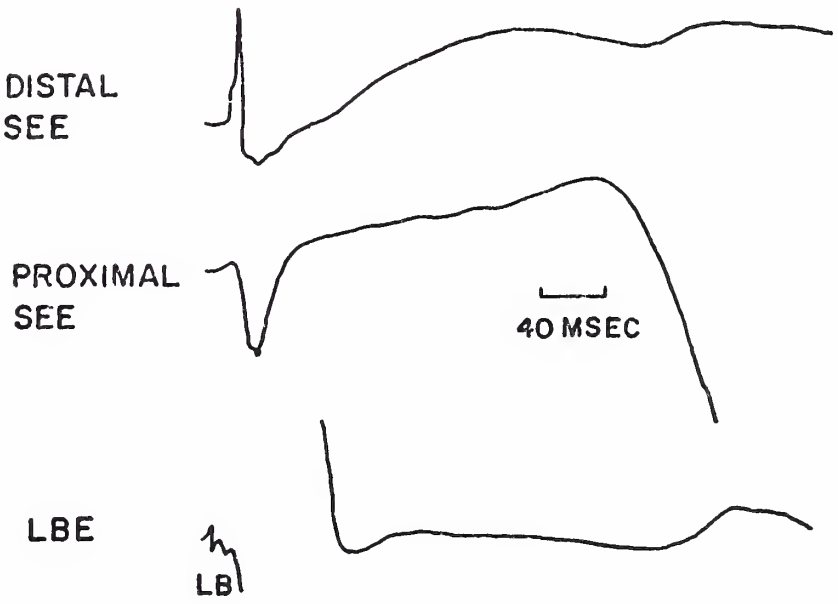
4 Mean percent change relative to matched controls ± S.D.

a IMEs were not recorded in these experiments.

EXPERIMENT 1



CONTROL



R76 (LCA)

FIGURE 5

the RCA resulted in no change (Tables 11 and 12). The complexes in both leads exhibited a similar degree of broadening. The durations of the SEE and IME potentials were similar in the control state.

TEMPORAL RELATIONSHIP OF ELECTROPHYSIOLOGIC EVENTS

As illustrated in Figure 6, there is a close coincidence in onset, peak, and disappearance of effect between the above-described parameters. In the experiments in which a significant axis shift occurred, the change in axis was simultaneous with the conduction delays.

ANATOMIC STUDIES

No direct supply (defined morphologically, as a vessel in proximity to or surrounded by the conduction tissue) to the divisions of the left bundle-branch from the RCA or from anastomotic channels was demonstrated, although numerous small vessels supplying the conduction system were identified in all septa studied.

All the septa had vessels supplied from the RCA, and anastomotic vessels were identified in all septa. The extent of distribution was quite different in different specimens (see Figures 7-10). Anastomotic vessels were rarely identified. Most putative anastomoses failed to meet the criteria

TABLE 11

MEAN SEE POTENTIAL DURATION (MILLISECONDS) ± STANDARD DEVIATION

Experiment	Control	R76(LCA)	R60(LCA)	SAL(LCA)	R76(RCA)
1	39 ± 1	53 ± 2			
2	35 ± 2	43 ± 2			
3	44 ± 2	73 ± 3			
4	41 ± 1	53 ± 2			
5	56 ± 4	67 ± 3	70 ± 4		
6	46 ± 2	54 ± 2			47 ± 3
7	37 ± 2	39 ± 2		37 ± 1	39 ± 2
8	48 ± 2	59 ± 4	60 ± 5	47 ± 2	48 ± 1
9	45 ± 2	59 ± 3	60 ± 2	47 ± 2	46 ± 3
10[1]	59 ± 2[a]	71 ± 3[a]		61 ± 3[a]	59 ± 2[a]
10[2]	58 ± 2[a]	67 ± 5[a]			
	47 ± 2[b]	60 ± 5[b]			
11	46 ± 2[a]	52 ± 2[a]	54 ± 1[a]	45 ± 2[a]	46 ± 1[a]
	46 ± 2[b]	54 ± 2[b]	52 ± 2[b]	46 ± 2[b]	46 ± 1[b]
12	46 ± 2	53 ± 1			
Grand Mean	46 ± 7	57 ± 10	63 ± 5	47 ± 8	47 ± 6
Δ SEE[3]		+11 ± 6	+11 ± 4	+0.3 ± 1	+0.6 ± 1
% Δ SEE[4]		+24 ± 14	+23 ± 8	+0.6 ± 3	+1 ± 2
P Values	<—— P < 0.0005 —>				
	<—— P < 0.0005 ——————>				
	<—— N.S. ——————————————>				
	<—— N.S. ——————————————————>				
		<—— N.S. ———>			
		<—— P < 0.005 ——————>			
		<—— P < 0.005 ——————————>			

1 Experiment 10, using 1 needle electrode.

2 Experiment 10, using 2 needle electrodes.

3 Mean change relative to matched controls (milliseconds) ± S.D.

4 Mean percent change relative to metched controls ± S.D.

a Needle 10a or 11a in Figure 2.

b Needle 10b or 11b in Figure 2.

TABLE 12

MEAN IME POTENTIAL DURATION (MILLISECONDS) ± STANDARD DEVIATION

Experiment	Control	R76(LCA)	R60(LCA)	SAL(LCA)	R76(RCA)
1	103 ± 2	109 ± 2			
2	40 ± 1	49 ± 2			
3	68 ± 4	100 ± 5			
4	41 ± 1	55 ± 3			
5	53 ± 2	65 ± 2	72 ± 3		
6	47 ± 1	54 ± 4			49 ± 2
7	37 ± 2	41 ± 2		39 ± 1	39 ± 2
8	48 ± 2	59 ± 4	62 ± 5	48 ± 2	48 ± 1
9	40 ± 2	56 ± 4	56 ± 3	40 ± 2	42 ± 2
10[1]	60 ± 3	75 ± 4		61 ± 3	59 ± 2
10[2a]	--	--	--	--	--
11[a]	--	--	--	--	--
12[a]	--	--	--	--	--
Grand Mean	54 ± 20	66 ± 22	63 ± 8	47 ± 10	47 ± 8
Δ IME[3]		+12 ± 2	+14 ± 2	+1 ± 1	+1 ± 2
% Δ IME[4]		+23 ± 13	+30 ± 9	+2 ± 2	+2 ± 4
P Values	<—— P < 0.0005 —>				
	<—— P < 0.025 ——————>				
	<—— N.S. ——————————————>				
	<—— N.S. ——————————————————>				
		<—— N.S. ——————>			
		<—— P < 0.025 ——————>			
		<—— P < 0.025 ——————————>			

1 Experiment 10, using 1 needle electrode.

2 Experiment 10, using 2 needle electrodes.

3 Mean change relative to matched controls (milliseconds) ± S.D.

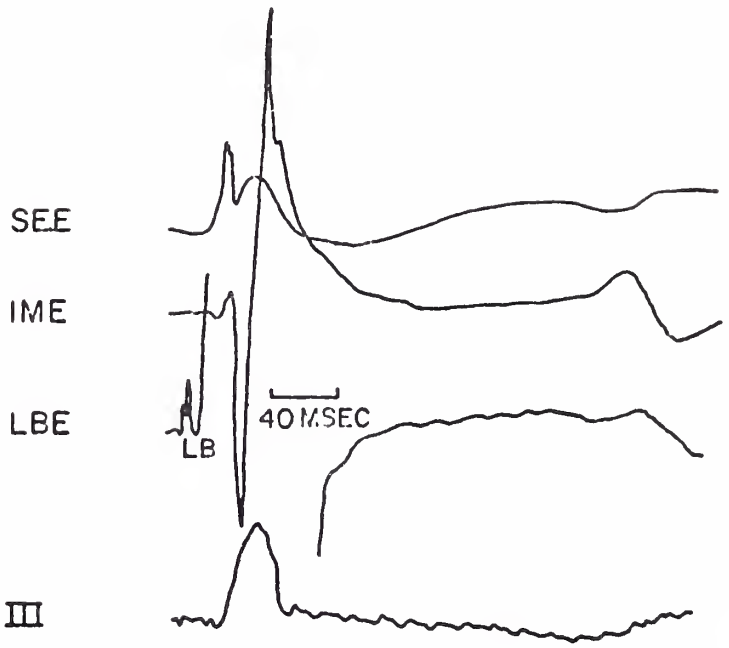
4 Mean percent change relative to matched controls ± S.D.

a IMEs were not recorded in these experiments.

intended to exclude artifacts. About 3 or 4 anastomotic vessels which met these criteria were present in each specimen; hence, the distributions of these depicted in Figures 7-10 are necessarily more approximate than those of the right coronary artery tributaries. It is likely that this paucity of identifiable anastomotic vessels is due to their small size and the high viscosity of the barium-gelatin injectate [48].

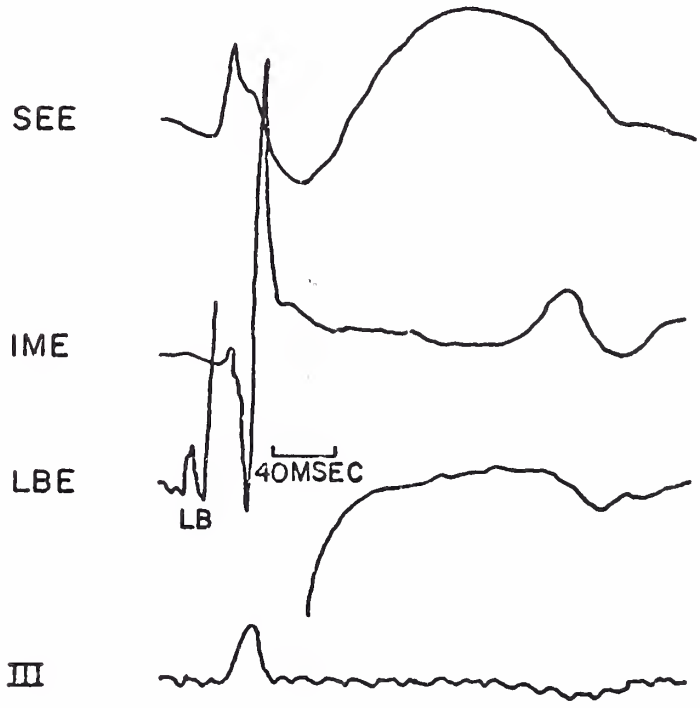
The contact radiographs of the intact specimens are shown in Figures 11-14. In all of these illustrations one can appreciate a vessel or vessels coursing from the RCA to the upper portion of the ventricular septum.

EXPERIMENT 4



16.5 SECONDS AFTER START OF INJECTION

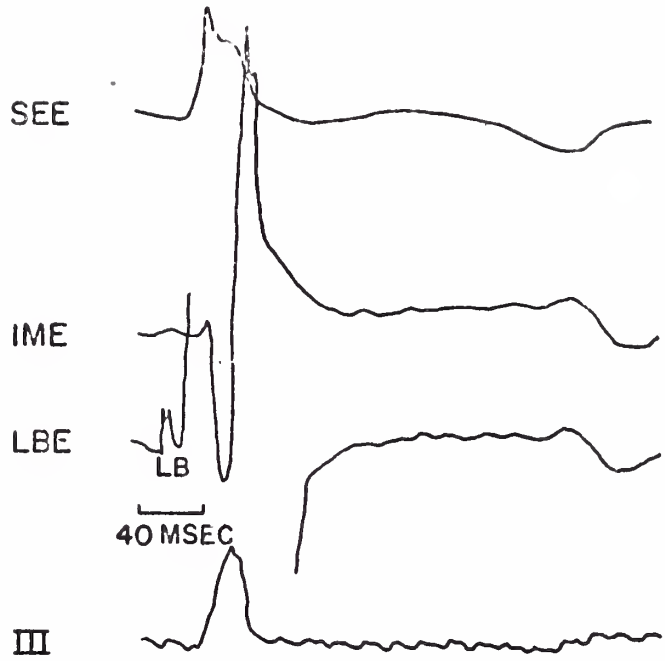
FIGURE 6a



25 SECONDS AFTER START OF INJECTION

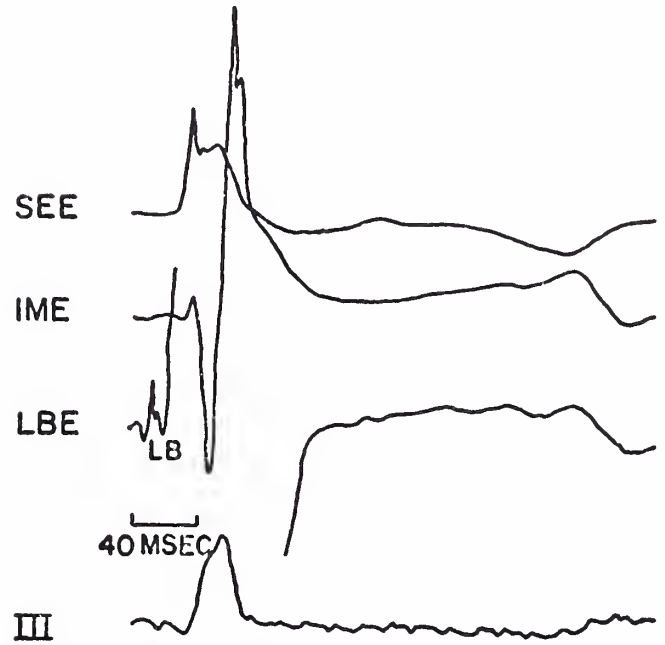
FIGURE 6b

EXPERIMENT 4



8 SECONDS AFTER START OF INJECTION

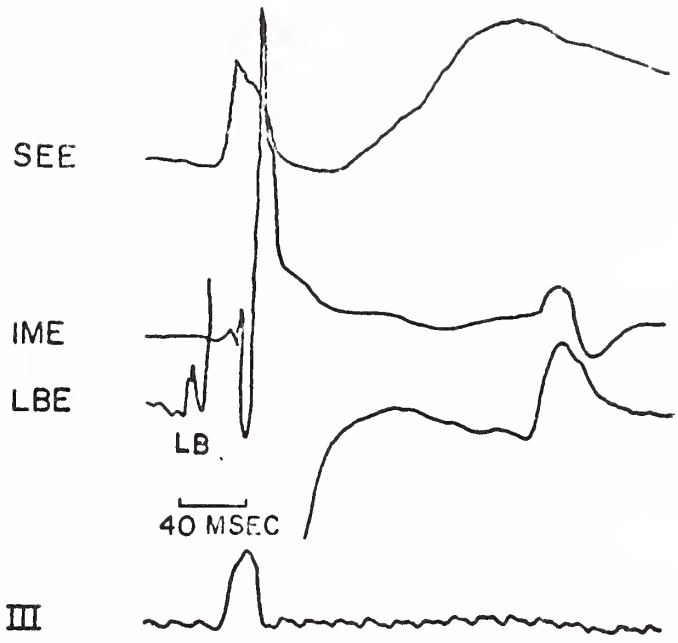
FIGURE 6c



10 SECONDS AFTER START OF INJECTION

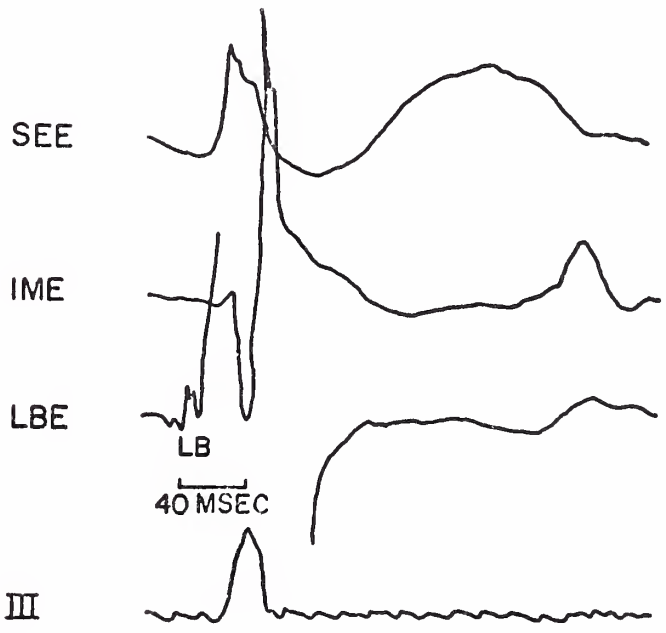
FIGURE 6d

EXPERIMENT 4



CONTROL

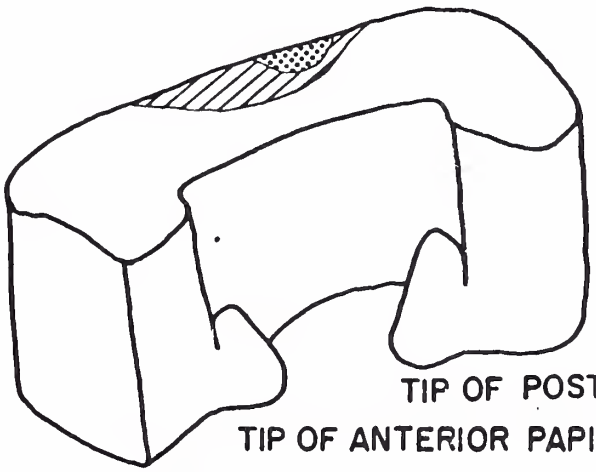
FIGURE 6e



5 SECONDS AFTER START OF INJECTION

FIGURE 6f

ARTERIAL SUPPLY TO SEPTUM OF DOG 7

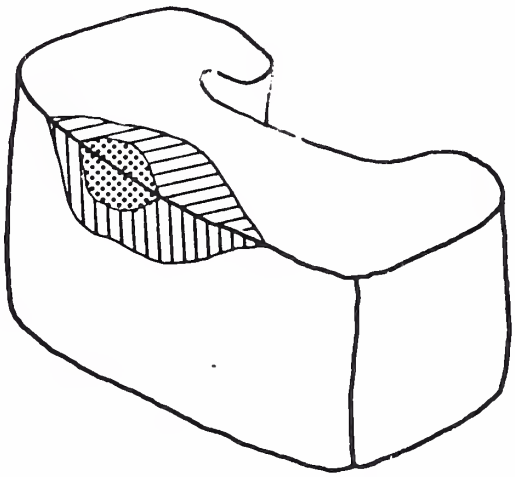


SEPTUM, LEFT ENDOCARDIAL SURFACE

RIGHT CORONARY ARTERY PERFUSION

INTERCORONARY ANASTOMOSES AND LEFT CORONARY ARTERY PERFUSION

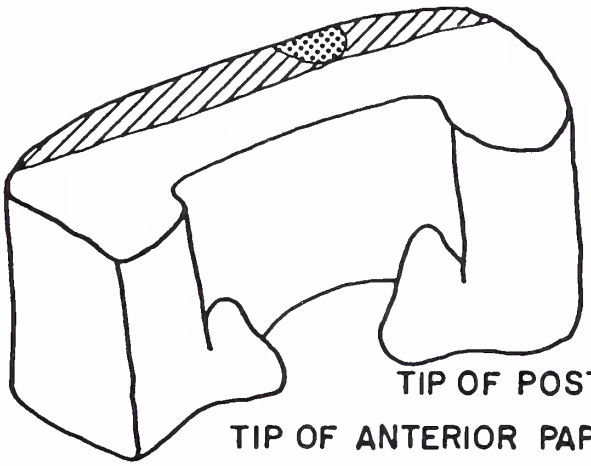
LEFT CORONARY ARTERY PERFUSION



SEPTUM, RIGHT SURFACE ENDOCARDIUM (DISSECTED)

FIGURE 7

ARTERIAL SUPPLY TO SEPTUM OF DOG 8

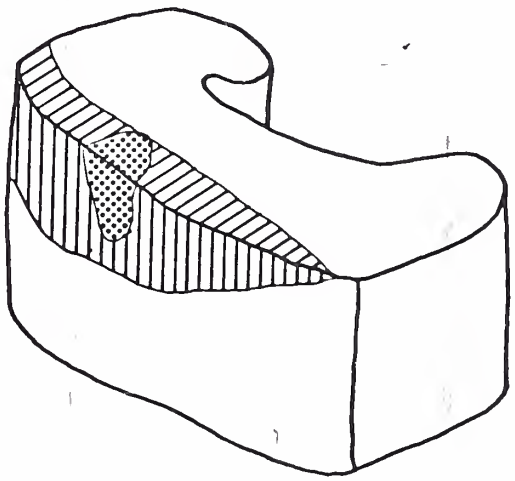


SEPTUM, LEFT ENDOCARDIAL SURFACE

RIGHT CORONARY ARTERY PERFUSION

INTERCORONARY ANASTOMOSES AND LEFT CORONARY ARTERY PERFUSION

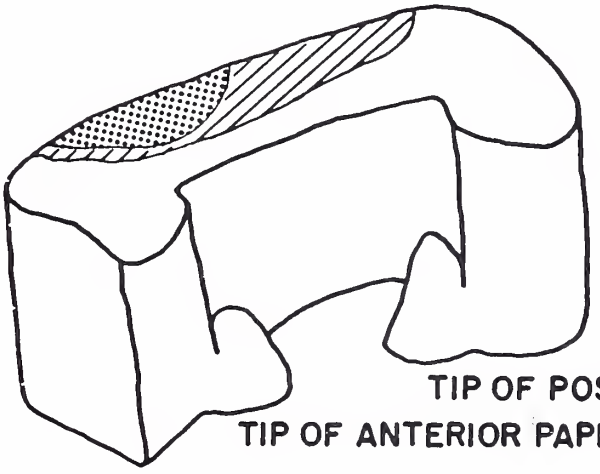
LEFT CORONARY ARTERY PERFUSION



SEPTUM, RIGHT SURFACE (ENDOCARDIUM DISSECTED)

FIGURE 8

ARTERIAL SUPPLY TO SEPTUM OF DOG 9

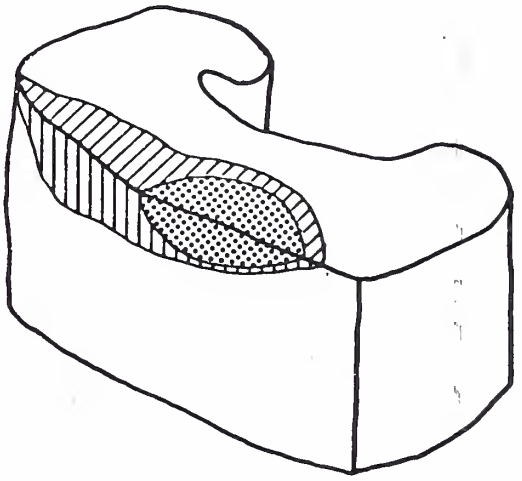


SEPTUM, LEFT ENDOCARDIAL SURFACE

RIGHT CORONARY ARTERY PERFUSION

INTERCORONARY ANASTOMOSES AND LEFT CORONARY ARTERY PERFUSION

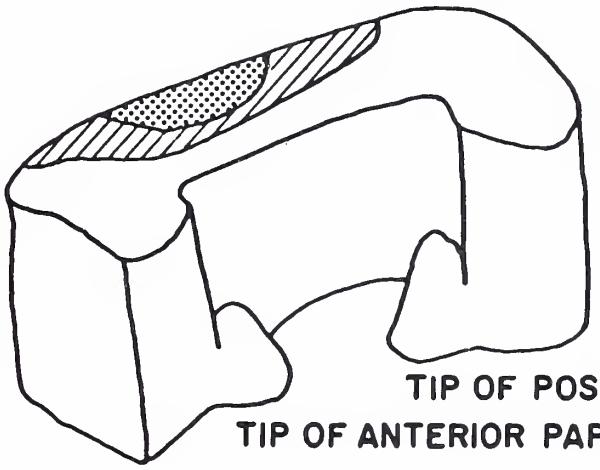
LEFT CORONARY ARTERY PERFUSION



SEPTUM, RIGHT SURFACE (ENDOCARDIUM DISSECTED)

FIGURE 9

ARTERIAL SUPPLY TO SEPTUM OF DOG 10

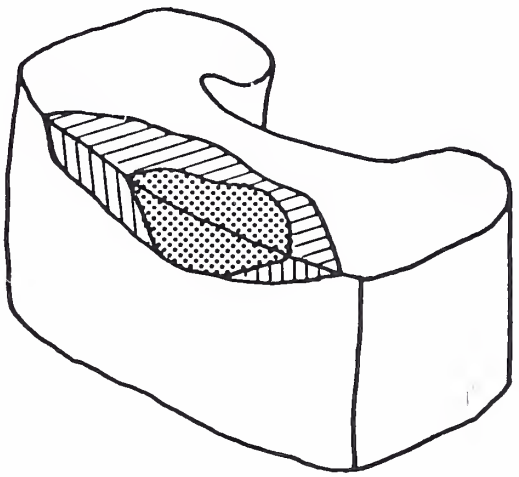


SEPTUM, LEFT ENDOCARDIAL SURFACE

RIGHT CORONARY ARTERY PERFUSION

INTERCORONARY ANASTOMOSES AND LEFT CORONARY ARTERY PERFUSION

LEFT CORONARY ARTERY PERFUSION



SEPTUM, RIGHT SURFACE (ENDOCARDIUM DISSECTED)

FIGURE 10

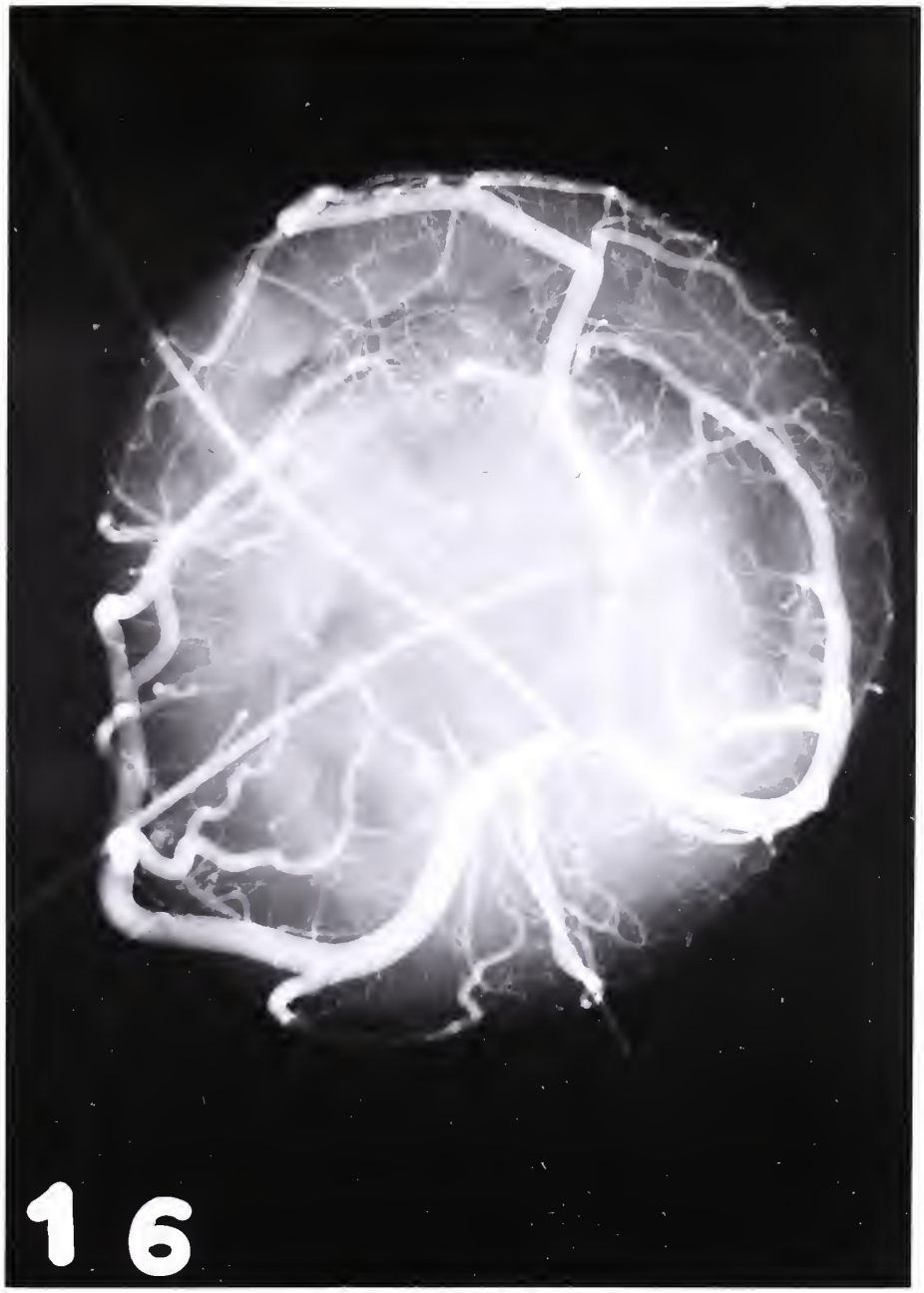


FIGURE 11

Postmortem radiograph of excised, injected heart of dog 7. A hypodermic needle of the same size as the electrode needle marks the position of the latter.

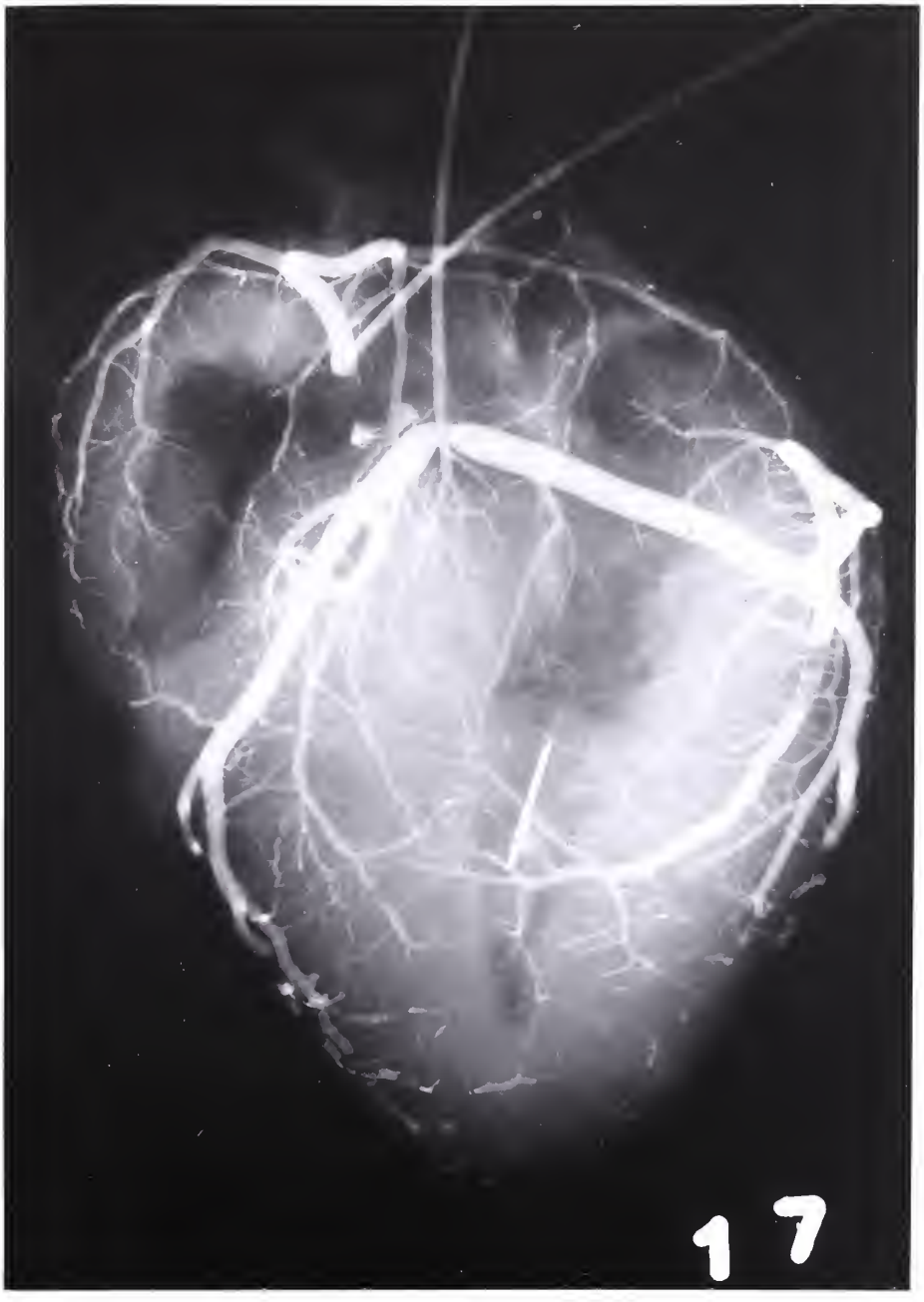


FIGURE 12

Postmortem radiograph of excised, injected heart of dog 8. A hypodermic needle of the same size as the electrode needle marks the position of the latter.

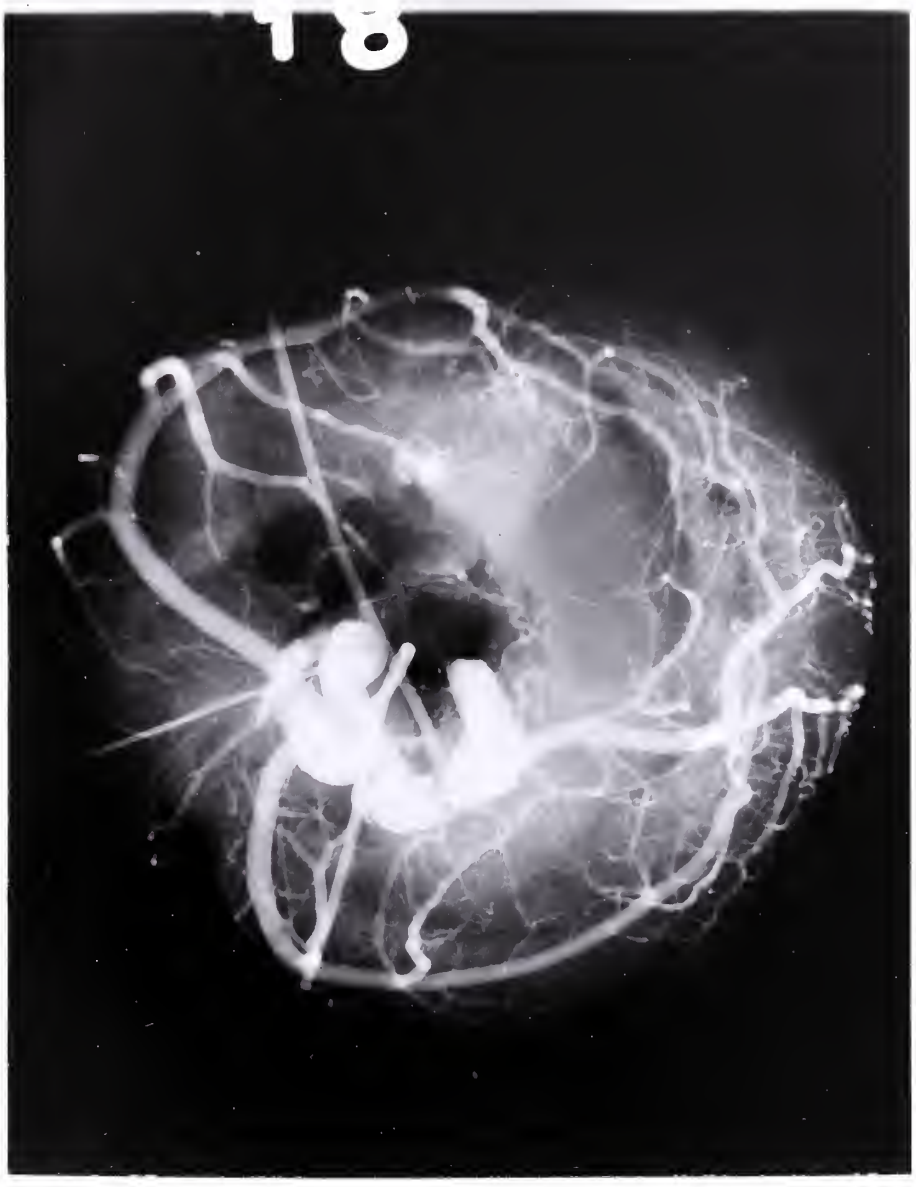


FIGURE 13

Postmortem radiograph of excised, injected heart of dog 9. A hypodermic needle of the same size as the electrode needle marks the position of the latter.

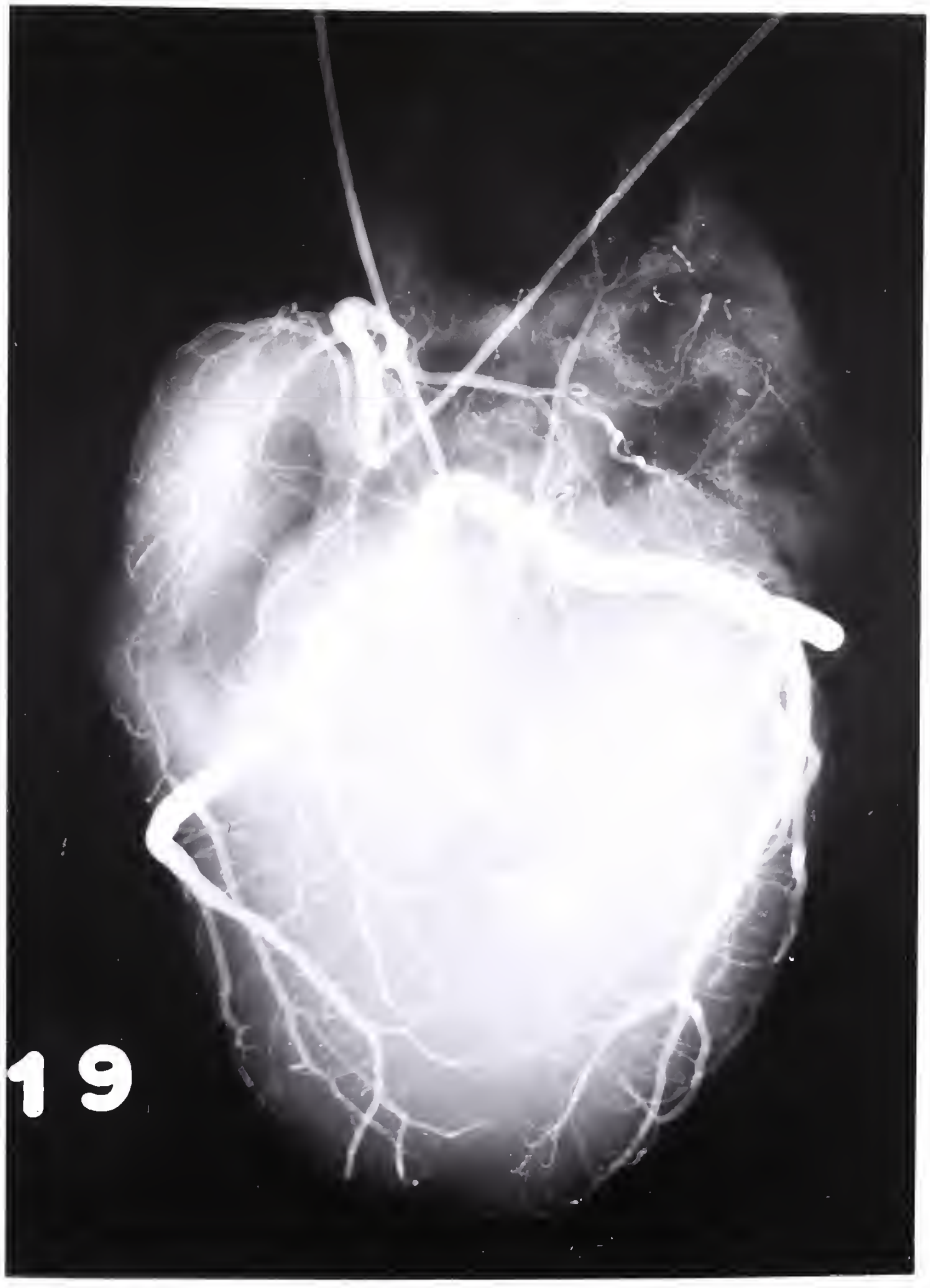


FIGURE 14

Postmortem radiograph of excised, injected heart of dog 10. Hypodermic needles of the same size as the electrode needle mark the position of the latter.

DISCUSSION

DISCUSSION OF METHOD

The reliability of the needle-electrode technique has been demonstrated by the good agreement achieved on most points by several groups studying the normal and abnormal human and canine heart [49,59-70]. Our control data is in good agreement with previous work on the normal canine heart [49,59,61,63-65,68,69] with regard to the times of subendocardial and epicardial activation, as well as corroborating once again the existence of a substantial simultaneously depolarized inner layer of the ventricular wall in the dog.

Considering the path of the depolarization impulse, one may separate the excitation of the left ventricle into conceptual compartments comprising, in the order of activation, the bundle of His, the main left bundle-branch, the anterior, posterior and septal [36,71-73] divisions of the left bundle-branch, their arborizations, the subendocardial Purkinje system, and the myocardium. Ideally, events in each compartment should be directly assessed for a detailed analysis of left ventricular depolarization. Since previous data is unanimous concerning the lack of change in the main

bundle of HIs [26-29] in both human and dog, we chose to record the bundle of His electrogram in only 1 dog. This experiment confirmed the experience of previous workers. Direct recording from the divisions of the left bundle-branch [74] is not a well-understood or accepted technique, and involves great technical difficulties; we chose to ignore this method as well. We are aware that this renders any statements regarding this "compartment" of ventricular depolarization inferential, but feel that the inference may be made with confidence. Our electrode positions allow direct recording from the left bundle-branch, the subendocardial Purkinje zone [49,60-62,75,76], and the myocardium. It is theoretically acceptable to assume that with this arrangement one may differentiate "parietal" block from fascicular or "arborization" block, although one cannot distinguish between the latter two.

Although the effect of the sodium content of the angiographic dye on repolariztion has been well studied [22], no data on its role in depolarization has been gathered by other than standard electrocardiography. One vectorcardiographic study [12] demonstrated that sodium-free solutions (not containing iodinated organic acids) were without effect on cardiac depolariztion, but no low-sodium contrast agents were studied. The injections of Renografin 60 were intended to investigate this issue.

The right coronary opacification and left coronary saline infusions were included as controls for rate-dependent conduction anomalies [77], Bezold-Jarisch reflexes [50] and possible coronary distension reflexes.

SUITABILITY OF THE DOG AS AN EXPERIMENTAL ANIMAL

The experimental methodology described above is unsuitable for application to humans. The principal scientific argument supporting use of the dog as an alternate experimental subject is the comparatively rich supply of data concerning experimental hemiblock [33-37,75,76,78,79], focal block [80,81] and electrophysiologic correlates of coronary arteriography [13-18,22,26,28] in the dog. In no other non-human species is there work in all of these areas, hence in no other species a suitable background of correlative knowledge.

The effect of significant differences between the primate and canine hearts must be considered. These include disparities between the results of experimental hemiblock in the dog and those of experimental hemiblock in the primate and clinical hemiblocks in man, and the different anatomy of the human and canine coronary arteries.

Experimental Hemiblock in the Dog and Primate: Watt and Pruitt [34], while studying arborization block produced by the ligature technique in 42 mongrel dogs, noted that small but definite differences in changes in QRS axis discriminated interruption of anterior and posterior fibers of the left bundle-branch. Anterior septal lesions resulted in appearance or deepening of a Q wave in lead I, deepening of the S waves in leads III and aVF, and increased amplitude of the terminal R wave in lead aVL. Posterior septal lesions were characterized by decrease or disappearance of S waves in leads III and aVF and of the terminal R wave in lead aVL. Accepted clinical criteria for significant axis deviation in the human were never met. Even with interruption of anterior and septal divisional fibers axes beyond +30° were not observed. Complete transection of all left bundle-branch fibers at proximal or mid-septal levels resulted in left bundle-branch block.

However, rather marked changes were noted in depolarization complexes recorded from direct epicardial leads from regions of the ventricular wall, conduction to which had been perturbed by the septal lesions. A lesion dividing either division of the left bundle-branch system caused a maximal delay in occurrence of the intrinsic deflection of approximately 20 msecond. Increase in R/S ratio and appearance of a new, or widening and/or deepening of an existing Q wave were consistently observed.

The minimal axis shifts attending even subtotal interruptions of the ramifications of the left bundle-branch prompted these investigators to include as part of their continuing work on this topic an investigation of species differences in electrocardiographic consequences of such lesions between canine and primate hearts.

In a subsequent publication, Watt, et al. [82], described the electrocardiographic effects of lesions similar to the maximally effective canine lesion in 8 baboons. In the 6 animals in whom satisfactory lesions were produced, the lesion resulted in an axis shift to beyond -30°, varying from -40° to -70°. The records of direct epicardial leads, however, displayed a remarkable correspondance to those noted in the dog in changes in intrinsic deflection, R/S ratio, and behavior of Q waves.

From analysis of the QRS deflections in the limb leads, the authors argued that the Wilson "electrocardiographic position of the heart" was essentially similar in both species in the control state and hence that the difference in axis deviation could not be ascribed to this factor. They mentioned, nevertheless, that anatomic rotation of the heart could markedly alter the control QRS axis; however, they made no statement regarding the relative anatomic positions of the heart in the two species.

Since no gross differences in thickness of the ventricular myocardium were observed, the authors ascribed no etiologic

significance to this parameter.

Two possible contributing factors were advanced in explanation of the species differences. First, over most of the epicardial surface, the R/S ratio of direct leads is less in the baboon heart than in the dog heart. This may be taken to imply, in Durrer's [62] hypothesis, a greater thickness of the electrical endocardium in the baboon, with correspondingly greater tangential forces generated during depolarization. This supposition has since been disproven in the human heart [49]. Second, the origin and course of the divisional fibers was said to envelop, in the primate heart, a wider area of the free ventricular wall. The authors proposed that, by virtue of this difference, "these tangential forces ... envelop the left ventricular wall from its septal attachments anteriorly and posteriorly and converge toward the lateral margin of that free wall" in the control state; after septal laceration "these tangential forces spread from the posterioseptal into the apicolateral left ventricualar wall, and thence into that portion of the basal anterolateral wall to which the rami of the left branch have been severed." The analogous schema in the dog was left implicit; presumably the narrower angle of dispersion proposed for canine conduction system, if one assumes a similar anatomic position of the heart, results in a lesser diagonal traversed by the abberant path of excitation, with concomitantly less axis

deviation (reference 82, Figure 8). The proposed role of the greater tangentiality of the electrical forces in the primate heart was not discussed. The postulated anatomic differences were, however, based only on gross inspection of the iodine-stained endocardial surface and as such are hardly detailed.

In a review of this work, Pruitt and Murao [71] proposed that, "If the electrical endocardium of the baboon heart is slightly thicker than that of the canine heart ... boundaries set up by tangential spread of excitation might be of greater magnitude in the baboon than in the dog." One may observe that this hypothesis is not supported by the epicardial activation data presented by Watt and Pruitt [35], Watt, et al. [76], and Watt, et al. [82], which demonstrate virtually identical distribution and magnitude of epicardial activation delays in both species, as well as by the work of Durrer, et al. [49], whose intramural and epicardial studies showed a close similarity in excitation of human and canine hearts.

Watt and Pruitt later subscribed to this interpretation of their results [83], and stated that, "Species differences have appeared primarily in remote leads which reflect electrical behavior of the heart as a single dipole .... Simple awareness of these demonstrated species differences should permit circumspect application of results derived from experiments on dogs to interpretation of changes encountered

in tracings recorded in man."

Further, Rosenbaum, et al. [36], have demonstrated that the relatively minor QRS axis changes resulting from experimental hemiblock in the dog are due to the anatomic position of the heart within the thorax. Both the initial and main QRS vectors after experimental hemiblock were significantly altered by tipping the apex of the heart and suturing it to the chest wall, thus altering its position to an approximation of that of the human heart. It is important to note that this maneuver of "horizontalization" does not induce significant changes in the normal canine EKG (contrary to the effect of rotation). Comparative experiments in monkeys revealed changes virtually identical to those in the human, closely similar to those in the "horizontalized" dog heart, but far more conspicuous than those in the normally positioned canine heart.

On the basis of the above evidence, one may conclude that: first, close activation data obtained during coronary angiography in dogs can, from the standpoint of the conduction system, be reliably extrapolated to primates including man; second, changes in the QRS axis are unlikely to be as marked as in the primate. As a consequence of the former point, the latter does not represent a serious objection to the validity of a study performed on dogs. A difficulty in interpretation of axis data arises as a consequence of

the necessity for the chest to remain open during our experiments.

This may bear upon the predominance of rightward axis shifts with left coronary contrast injections in our experiments. In humans, as mentioned above (see Review of Previous Work), left axis shifts are usually observed with left coronary injections. In Nakhjavan's series [26], only 1 of 5 dogs evidenced a rightward axis shift. In humans, the greater right-sided perfusion of the posterior fascicle relative to the anterior might exert a protective effect. In addition, baseline disease of the anterior fascicle is by far more common in humans than posterior fascicular disease; the posterior fascicle is the least vulnerable part of the intraventricular conducting system [84]. This would predispose to left axis shifts if both fascicles were equally exposed to the superimposed toxin; in our dogs, pathological alterations of the conduction system were not observed histologcally. With respect to the difference between Nakhjavan's results and ours, a possible difference in axis computation may be responsible (vide infra). The difference in anatomic position of the animals, and the effect of the sling and thoracotomy used in our experiments with the resultant possible displacement of the position of the heart may be invoked; unknown factors may, of course, be responsible.

Another surprising result is that the same volume of the same contrast agent injected into the same artery of the same dog resulted in 1 case in oppositely directed axis shifts, with other parameters not changing significantly in relation to one another. A reasonable explanation for this phenomenon is that it is due to spontaneous temporal variation in regional myocardial blood flow [85], with consequent variation in regional delivery of the contrast agent. Perturbations due to previous experimental interventions may also be responsible. It is doubtful that this represents a rate-related change in fascicular conduction, since the variation in rates between injections in this experiment (dog 5) is probably not sufficient to support such an explanation. The same factors may be responsible for the different number of dogs experiencing axis shifts during left coronary artery injections of R76 and R60 (see Table 3).

Comparison of Electrophysiologic Effects of Contrast Media in Dogs and Humans: No significant electrophysiologic difference between humans and dogs during coronary arteriography has been reported [11-14, 16-29]. Only 1 communication [26] has been addressed to the QRS axis in dogs during coronary injections. In this report only 5 dogs were studied, but the range of axis shifts was roughly comparable to that observed in humans. In light of the preceding discussion

of experimental hemiblock in the dog, this is perhaps surprising. In our study, the QRS axis changed little with significant conduction delays. This is more compatible with previous work [34,35,82]. Possible explanations for this discrepancy are, first, that the axes reported by Nakhjavan were incorrectly derived (the author gives no information concerning his method), or, second, that the animals' hearts were, in effect, "horizontalized" (p. 63) since they were in the left lateral position during the experiment.

Coronary Circulation of the Dog: Objections have been raised to use of the dog in experiments involving the coronary arteries [57]. One can hardly improve upon James' lapidary description of the anatomy, based upon the vinylite injection-corrosion method:

> In the dog, the left coronary artery regularly supplies the entire left ventricle, the entire interventricular septum, virtually all the left atrium, and a small portion of the right ventricle adjacent to the anterior and posterior interventricular sulci. This degree of predominance by the left coronary artery is observed in less than 5% of humans, principally in males. The anterior descending and left circumflex arteries are similar in dogs and humans, except that in dogs the left circumflex artery regularly terminates as the posterior descending artery. In the dog there is a large constant artery penetrating the interventricular septum, with smaller penetrating arteries entering the septum from the anterior and posterior descending arteries to join it. The canine septal artery originates near the bifurcation of the left coronary artery and enters the septum diagonally in an anterior-to-posterior and apical direction. In human

> subjects the blood supply to the interventricular septum is principally provided by 4-6 equally large branches of the left anterior descending artery; a single predominant septal artery was not observed in the 106 human hearts studied.
>
> The canine right coronary artery supplies most of the right atrium and right ventricle, except the portion directly adjacent to the interventricular sulci. It does not cross the crux of the heart, whereas the human right coronary artery crosses the crux in approximately 90 percent of cases. [48]

A further significant difference observed by James between the human and canine coronary circulations is that intercoronary anastomoses are smaller in canine hearts and are far more difficult to penetrate with a viscid solution such as vinylite.

From this it seems obvious, and other workers [44-47,85] affirm the conclusion, that the left coronary artery is the sole source of perfusion of the conduction system of the left ventricle (and part of the right ventricle) in the dog. Nevertheless, newer techniques had not been applied to this question. For example, until the recent work of Frink and James [32], who described blood supply to the left anterior fascicle from both right and left coronary arteries, it was thought that this structure had in humans only a single vascular supply. Since humans have been studied more intensively than dogs it was not surprising that prevailing theories were incorrect in this instance also, even considering the less "balanced" circulation of the dog. The right axis deviation during left coronary arteriography in 1 of Nakhjavan's dogs [26] could be explained

by a posterior "hemiblock"; Betriu, et al. [25], described a left axis shift during right coronary opacification (albeit in humans); hence, the detailed coronary artery anatomy has been important in some past cases. Our early results indicated that right axis shifts could occur during opacification of the right coronary circulation in the dog, so we decided to prepare the hearts of our animals in the manner used by Frink and James for the human, in the hope of demonstrating right-sided perfusion of the appropriate fascicle of the left bundle-branch. The results of these studies may indicate why axis shifts during RCA opacification occurred in 2 experiments. If the mechanism indicated by our other results is to be credited, the dye must in some way have affected the posterior fascicle or its tributaries with only minimal effects on the anterior (since RCA injections did not cause statistically significant delays in the anterolateral left ventricle).

A pathway by which the dye can directly perfuse the septum after injection into the RCA is clearly established by our radiographic and histologic studies. This is in conflict with almost all previous work [44,45,47,48,87]. In only 1 previous report is any blood supply to the ventricular septum from the right coronary artery acknowledged [46]. This study mentioned the "occasional" anastomosis of the conus artery with a branch of the anterior descending coronary artery. Although our sample size (4 hearts) was

samll, the uniform occurrence of RCA supply to the septum in our series does suggest that older studies on this subject must be considered inapplicable to our results. In any event, our anatomic studies complement and support our electrophysiologic results. The volume of distribution of the contrast medium in the myocardium during arteriography is undoubtedly much greater than that of the barium-gelatin mass during post-mortem injection for 2 important reasons. First, the dye is much less viscous than the barium-gelatin suspension, and so will pass through small anastomotic channels more easily [48,55]. Second, during arteriography the perfusion pressure of the vessel being studied is greater than that of the vessel perfused by aortic pressure; this should increase undirectional flow through anastomoses. In the post-mortem injection, both vessels are perfused by the same head of pressure, and this mechanism cannot operate.

AXIS SHIFTS

The extent and location of RCA tributaries and anastomotic channels does not correlate well with the axis shifts observed upon RCA opacification. In the hearts we studied, reliable axis data was available (experiments 7-10). In the 2 specimens with the greatest right coronary tributary

system there were, respectively, no axis shift (experiment 8) and a significant right axis shift (experiment 10). In the 2 specimens with relatively little RCA supply, there were, respectively, a significant right axis shift (experiment 7) and a left axis shift associated with subendocardial activation delay in the anterolateral left ventricular free wall (neither of which achieved statistical significance -- $0.05 < P < 0.10$ -- experiment 9). Reasons for this poor correlation may include the difficulty of identifying inter-coronary anastomoses (vide supra) and the conditions of injection during arteriography, for example, positioning of the catheter in such a way that a jet effect may have caused relatively less dye to enter the septal branch of the RCA.

The lack of significant LB-SEE delay with right axis shifts induced by RCA injections is consistent with involvement of the posterior fascicle or its tributaries selectively, since we studied only the distribution of the anterior fascicle with needle electrodes. Similarly, the absence of significant prolongation of the cavity potential probably indicates little involvement of the septal bridging network. The occurrence of LB-SEE delay with right axis shifts during LCA injections probably indicates depression of conduction in both fascicles, greater in the posterior fascicle. Absence of an axis shift is probably due to a balanced conduction delay (vide infra).

CONDUCTION DELAY

Two interesting papers have been published which report studies of fascicular conduction blocks using the intramural needle electrode technique.

The first, by Watt, Freud, et al. [76], is part of the series of reports by Watt and Pruitt concerning ventricular activation after various experimental lesions of the conduction system. It describes for the most part epicardial activation data, but the results of a few needle electrode insertions were discussed. No delays in intramural activation occurred after left anterior arborization block, produced by the ligature technique, when the needle was placed in the posterior left ventricle or in the right ventricle. When the needle was placed in the anterolateral left ventricle, along the left side of the anterior descending coronary artery, the spread of excitation was reversed from that obtaining in the control after arborization block was produced. The excitation of the epicardial lead points was unchanged after arborization block, but the spread of excitation now proceeded from epicardium to endocardium, with a considerable delay in activation of the endocardial lead points. Superimposed right bundle-branch block reversed the order of activation to normal, with a substantial delay at all lead points.

A more recent and more extensive communication from Gallagher, et al. [75] concerned the effects of surgical

left anterior divisional block in 25 dogs. The authors made numerous needle electrode insertions in the lateral wall of the left ventricle. In the control, the 2 electrically distinct zones described by others were noted, and activation proceeded from within outward. The times of local activation these authors report in the control are closely similar to those we obtained for comparable leadpoints in the same region of the ventricular wall. After surgical section of the left anterior fascicle, delays of 6-20 msecond (mean 12.8 $\pm$ 4.8 msecond) in subendocardial activation occurred, with concomitant delays of 3-25 msecond (mean 12.4 $\pm$ 5.6 msecond) in muscle excitation. Spread of excitation continued to proceed from endocardium to epicardium, as in the control. The mean QRS axis was essentially unchanged, with a 5-15 msecond (mean 9.7 $\pm$ 2.7 msecond) prolongation of the QRS complex. Small S waves typically developed in leads II, III and aVF. If section of the left anterior fascicle was combined with section of the septal fibers, leaving only the posterior division intact, the alterations in the QRS duration were more striking, and pronounced leftward axis shift developed. The delays in mural activation were qualitatively the same but of greater magnitude (up to 30 msecond). Left anterior divisional block combined with lateral myocardial infarction resulted in a combined pre-mural and parietal conduction delay in contrast to the purely pre-mural delay

observed with divisional block alone. No reversals of the order of activation, as reported by Watt, et al., were observed.

In the pre-mural delay (LB-SEE) observed in our experiments, reversal of that type also did not occur.

A reasonable explanation for this disparity can be derived from the electrode positions used by Watt and his co-workers. The electrode needles were placed so close to the right ventricle that it is most likely, expecially considering the rather extensive septal lesions produced by the ligature technique [34], that this region of the near left ventricle was depolarized from the right ventricle by tangential spread of excitation [69]. After production of right bundle-branch block, activation necessarily occurred through the Purkinje system of the left ventricle and therefore in the normal endocardial to epicardial direction. The electrode positions used by Wallace, et al., and by us, were so situated that this anomalous and undoubtedly localized situation was not observed.

A reversal phenomenon which we did encounter is obvious in Table 9. The more distal SEE in experiment 1, which was depolarized simultaneously with the more proximal SEE during control, was depolarized earlier than the proximal SEE during LCA opacification. Reversals of this type, which are sometimes observed in the normal canine heart [49,60,68], may be related to intramural Purkinje penetra-

tion, as Durrer has proposed [49,60]. Whether or not this is so, one may suppose that a latent reversal may be made overt if the effect of the dye caused a greater conduction delay in one population of conducting fibers than in the other, thus leading to the disparity in activation times. This hypothesis must be considered unproven, although a theoretical and experimental basis has been established by many researchers [88].

Several groups have reported values for conduction delays in experimental hemiblock. For left anterior hemiblock, or arborization block, Watt, et al. [76], reported endocardial delays in dogs of 10-30 msecond; Pruitt, et al. [71], described delays in epicardial activation of 0-8 msecond in dogs and 0-17 msecond in baboons; Watt and Pruitt [83] reported activation at various epicardial points in dogs ranging from 6 msecond earlier than control to 24 msecond later; Watt, et al. [82], reported epicardial delays in baboons ranging from -5 to +30 msecond. Watt and Pruitt [35] recorded epicardial delays after left posterior hemiblock of approximately +20 msecond in dogs and consistently greater delays in baboons. The endocardial delays noted by Wallace, et al., are detailed above. Medrano, et al. [78,79], found 10-20 msecond delays in dogs after left anterior hemiblock.

In vitro studies by Myerburg, et al. [89,90], demonstrated 0-10 msecond delays in activation of tissues distal

to experimental lesions of the conduction system. Similar studies by Scherlag, et al. [73], revealed 7-33 msecond delays, the magnitude of which was related to the transverse extent of the lesion; an earlier study by Lazzara, et al. [72], on a similar preparation had shown 2-8 msecond delays.

Our results for LB-SEE delays (mean post-injection delays ranged from 2-10 msecond) are comparable to the lesser delays reported by previous workers. When one considers that surgical lesions produce a constant degree of delay, while the toxic delays produced by the contrast media in our studies waxed and waned, it is apparent that the peak effect of the contrast for a few beats during each injection was larger than the mean indicates. However, we never observed a delay as great as 20 msecond even during peak effect of the contrast. Thus, it is apparent that the dye produced an incomplete block when compared to surgically induced complete block investigated with techniques comparable to ours [75,76]; however, some groups mentioned above [71,89,90] obtained lower values in complete block. This probably depends upon the extent of the lesion [75] and the type of preparation.

The use of the LB potential as a timing marker tends to decrease the relative magnitude of the delay we observed. However, septal activation (which almost certainly represents the initial negative deflection of the cavity potential (V), with the catheter electrode in the position we used) may occur

from the right in the dog during even a slight delay in left bundle-branch conduction [49] as may occur during coronary arteriography [26, present communication], so it is possible that the area of the septum which is first depolarized is different in control and injection states; this would render it obviously unsuitable as a marker for measurement of intervals. In addition, although a left bundle-branch conduction delay was rarely documented in our study, removing the left bundle-branch from the computations might have led to a falsely decreased figure for delay distal to the left bundle-branch. However, the figures for LB-SEE interval and V-SEE interval are comparable (see Table 8), so neither of these criticisms were valid in practice. Another argument for reporting the data as LB-SEE interval is that it may provide a more realistic estimate of the importance of the delay to the genesis of the axis shift. However, the opposite conclusion is probably more correct; the portion of the conduction system contributing to the QRS axis is that distal to the division of the left bundle-branch. It is impossible to say without more precise anatomic correlations than could be obtained in this study from exactly what levels of the bundle-branch the LB potential and the V potential arise. It is probably accurate to state that the LB-SEE mode of analysis (showing a 15 percent increase in conduction time) underestimates the percent increase in "axis-active" conduction time, more

than the V-SEE mode (showing a 30 percent increase) overestimates it [49,65,69]. The work of Scher, et al. [64], in particular supports the conclusion that the V-SEE time more accurately reflects the "axis-active" conduction time. In over 1000 needle insertions into the interventricular septums of 25 dogs, 3 monkeys and 1 goat, these workers found the earliest septal activation to occur on the left septal surface at the level of the division of the main left bundle-branch. For completeness, both sets of data were reported here.

The correlation of conduction delay with QRS widening and axis shift is imprecise but qualitatively well established. In the study by Watt and Pruitt [34], as the septal lesion was extended transversely across the conduction system, the axis deviated farther to the left and the QRS duration increased. Similar results were presented in the vectocardiographic study of Uhley and Rivkin [33]; larger incisions, particularly of the interior septal bridging network, increased the QRS duration, while lesions of the border fibers had greater effects on QRS axis with some increase in duration. In a later report by Watt and Pruitt [35], left posterior fascicular block alone increased QRS duration very slightly while leading to marked but circumscribed epicardial activation delays and some rotation of mean QRS axis. The results of Gallagher, et al. [75], are reminiscent of the first-mentioned experiments of Watt and Pruitt [34], but their

techniques are more sophisticated and the correlations more detailed. As previously described, the endocardial activation delay, the shift in QRS axis and the QRS duration all increased concurrently between control and different lesions of the conduction system. This is, of course, the conventional picture of fascicular blocks. As Rosenbaum [36] and Lazzara [72] have emphasized, the unimpressive QRS widening observed with pure LAHB and LPHB is related to the widespread interconnections offered in the septal bridging fibers. In all reports of experimental block, the most profound changes in QRS axis and duration have been observed in preparations which leave one segment of the conduction system completely unaffected while conduction through the balance of it is completely abrogated [34,75]. We observed relatively little change in QRS axis while substantial endocardial delays and increased ventricular activation time (30 percent and 24 percent, respectively) occurred. Apart from the rather unexpressive behavior of the frontal plane axis in the dog, the most likely reason for this phenomenon is that delays occurred more or less equally throughout the conduction system; without marked disparity of conduction time between the components of the system the dyssynchrony necessary for an axis shift is limited. The effect of the thoracotomy and pericardial sling cannot be assessed well from our data and poses difficulties in interpretation, but is probably

minimal; this was the experience of Watt, et al. [82]. In the hearts of humans undergoing coronary arteriography, this necessary dyssynchrony can be supplied from 3 sources which do not exist in the normal dog. First, the distribution of the coronary arteries is generally such that some parts of the conduction system receive a supply of blood containing none or less of the toxic contrast agent. Second, occlusive disease of the coronary system may in certain cases accentuate this tendency. Third, minimal or silent disease of parts of the conduction system may render these more susceptible to the effects of the dye; such silent disease was recently described in all of a small group of normal elderly subjects studied by quantitative stereologic techniques [91]. There can be little doubt that the delay we observed is the mechanism of the QRS changes on the basis of concordance with established theory, temporal correlation of the effects, and absence of any other process which might produce them.

The data presented in Table 2 demonstrates that the conduction delays are not rate-related, since they are associated with only minor changes in rate and since, during RCA injections of R76 or LCA injections of SAL, changes in rate are not accompanied by conduction delays.

We observed no delay in radial transmural conduction through subendocardial or subepicardial regions, indicating that the parietal block postulated by previous authors [23,24]

does not occur in the dog.

SITE AND MECHANISM OF THE CONDUCTION DELAY

Several other questions remain. Of most interest is at what level of the portion of the conduction system which was not studied the delay is maximal. Our data cannot, of course, resolve this question, but some informed speculation can be made. If one considers the previous work on this subject, it is at once clear that there is a progression of susceptibility to the effects of the dye along the length of the conduction system. No effect on the bundle of His has ever been observed [26-29, this monograph]. The left bundle-branch is sometimes affected in varying degrees [26, this monograph]. Although fascicular conduction delay has only rarely been observed [25], this is probably the results of the paucity of techniques for direct study of this segment of the left bundle-branch and the necessary rigidity of criteria based on indirect methods. Consequently, there is no way of assessing conduction delay which is not sufficient to cause functional "block" [30]. From our data, it is apparent that the mechanistically important delay characteristically occurs between the bifurcation of the left bundle-branch and the insertion of its ramifications into the left ventricular free wall. In light of this central-to-peripheral progres-

sion of increasing sensitivity, one searches for other properties of the conduction system which show a similar distribution. The action potential durations observed by microelectrode techniques show such a progression. There are "marked variations in conduction velocity and refractory period as the fibers course from the common bundle to the periphery" [89]. As Myerburg and co-workers [92] observed, there is an area of maximum action potential duration along a group of conducting fibers a few millimeters before the termination of the fiber group in ventricular muscle. Local refractory periods, of course, followed the same pattern as the action potentials. This area was the site of block of premature impulses, behaving as a limiting segment or "gate" for both antegrade and retrograde conduction. As illustrated by their Figure 2 [92]; the action potential durations at a particular level also exhibited a certain variability. This might relate to the reversal phenomenon we observed in experiment 1 (Table 9) in that some fiber groups might be more affected than others. Numerous agents which increase the cellular action potential have been described, including contrast agents of high sodium content [22], which prolong phases 2 and 3. It is possible that other components of the contrast media may affect other parts of the action potential, for instance resting potential, or phases 0 or 1, and affect the velocity of the impulse in that way. A study by Mendez and others [93] described a progressive gradation of shortening of action

potential durations from the most distal Purkinje fibers, to transitional cells, to muscle. Viewed as part of the "gate" formulation of our results, this agrees with our finding that no delay occurs in the ventricular wall; that is, any delay that will occur has already been manifest in the conduction system proximal to the gates and no delay will occur distal to them. Myerburg, Gelband and Hoffman [84] found that conduction delay or block may occur anywhere between the bundle-branch and the distal gates, depending upon the degree of prematurity of a premature impulse. If the action potential duration were pathologically increased, one might expect an early impulse to be delayed more proximally in the bundle-branch. Whether such an increase in duration could result in block of a normally timed impulse is unknown, but it is a theoretically possible mechanism for the delay we observed. In any event, for any mechanism of delay considered within the framework of the gate theory, the larger the increase in action potential duration, the more proximally the block must begin.

Another mechanism for delay in conduction of a normally timed impulse due to increased action potential duration was established by Myerburg, et al. [84]. When an impulse occurs before cells at an area of maximum action potential have repolarized to -75 or -80 mV, delayed conduction may occur. This is more common in depressed than in healthy tissue, but a human with minimal or manifest heart disease

or a dog under general anesthesia might fit such a description; in any event, it has been documented in healthy, rapidly conducting tissue as well [94]. It is also possible that different sites in the His-Purkinje system are differentially sensitive to the toxic effect; this has been suggested for other drugs [95,96].

One might also consider decremental conduction as an etiology for the delay; this is perhaps least likely in the Purkinje system, and so might not be related to the gating mechanism, but may occur therein under conditions which cause defects in amplitude or rate of rise of the action potential [97-99]. These are discussed further in the next section.

A mechanism for delay involving the gate hypothesis is theoretically attractive, but we have no experimental data to support it. Indeed, although several reports have indicated that a gating mechanism operates in in situ canine [100-102] and human [103,104] hearts, a recent communication suggests that, in vivo, retrograde functional block occurs proximal to the gates [105]. It is interesting to extend the gate-related speculation further, however, to explain the lack of change in initial forces associated with the axis shift. As previously noted, this was a major argument of those who postulated a parietal block as the genesis of the QRS changes. Since the delay we observed could be included under a loose definition of

hemiblock, it might be profitable also to consider the circumstances under which a "hemiblock" could occur without change in the initial QRS vector. Rosenbaum and co-workers [36,37,106] have related the initial vector shift to change in path of the impulse before the fascicles reach their respective papillary muscles. It is obvious that block due to the gates would occur no sooner than at the point the fascicles pass the bases of the papillary muscles and possibly after it [90,94]; hence, the initial forces would be unchanged.

EFFECTS OF SOLUTIONS OF HIGH AND LOW SODIUM CONCENTRATION

There were no significant differences between R76 (240 meq/l Na^+) and R60 (40 meq/l Na^+) with regard to any parameter studied. Normal saline injections gave results which were not different from control recordings and which were significantly different from records obtained during injections of contrast in all cases in which the latter differed from control. Interestingly, the only significant changes in R-R interval occurred following LCA saline injections (Table 2). This might be explained by a faster rate of infusion of the less viscous saline solution, leading to local distension of a sinus node artery. As Halpern [86] has emphasized, the canine sinus node receives significant perfusion from the left coronary artery. The local

distension reflex, as described by Adams and Paulin [42], James and Nadeau [51], and Books, et al. [52], is not affected by atropinization. Consequently, it seems the most likely explanation for the changes noted with saline injections.

It is significant that no differences between R76 and R60 were noted. This supports the finding that the myocardium itself is not involved in the aberrations of conduction, since the action potential of the myocardium is quite differently affected by altering the sodium content of the perfusate [22]. Thus, another component of the pathway of ventricular excitation or another component of the contrast solution must be responsible for the effects we observed. This could most profitably be investigated by microelectrode studies of the endocardial surface of the isolated ventricle.

The concordance between the results obtained with R76 and R60 may militate against involvement of the gating mechanism in the angiographically-induced conduction delay. Since delay or block related to the gates is principally dependent upon phases 2 and 3 of the action potential, it is less attractive to entertain an effect which does not operate principally by increasing the duration of these phases. Such an effect is probably unlikely in our system, since the effect on duration of phases 2 and 3 has been shown in vivo to vary with the sodium concentration of the

contrast medium [22]; we found the degree of delay to be independent of sodium concentration. However, although the resting membrane potential of cardiac muscle is independent of extracellular sodium concentration in a range of approximately 10 meq/l to 210 meq/l, both increases and decreases in sodium concentration affect phases 0 and 1 [89]. These effects are probably not sufficient to account for the delay we observed. A theoretical framework within which decay of the action potential upstroke may lead to very slow conduction has been recently reviewed by Cranefield [89]. One might postulate that the anionic moiety of the dye has a weak blocking effect on the "fast" sodium channel; this has been observed with procaineamide [107], a compound which is structurally similar to diatrizoate. This would certainly produce a delay sufficient to account for our data; and if, as some workers propose [88], the relative density of fast and slow channels varies between different cell types in the heart, a theoretical basis for a differential effect on depolarization of Purkinje tissue and myocardial muscle is established. It might or might not operate through the gating mechanism. This is, of course, entirely speculative. Here again, microelectrode studies or superimposed pharmacologic interventions are required for further analysis.

SUMMARY AND CONCLUSIONS

The effect of coronary arteriography on intraventricular conduction was studied in 12 atropinized, open chest dogs. Left bundle-branch (LB) and cavitary (V) bipolar potentials were recorded using a bipolar electrode catheter positioned against the interventricular septum below the aortic valve. Subendocardial (SE) and subepicardial (IM) bipolar potentials were obtained through distal and proximal poles of multipolar electrode needles inserted into the myocardium. Constant proximity of the needles relative to the cavity catheter was assured by fluoroscopy. Simultaneous intracardiac tracings were recorded together with a surface electrocardiogram at 250 mm/sec on a multichannel recorder. Conduction time from LB to V, LB to SE and SE to IM were obtained during Renografin 76 (R76), Renografin 60 (R60) and normal saline (SAL) injections into right (RCA) and left coronary artery (LCA). Each intervention was preceded by a control recording.

R76 to LCA produced a statistically significant delay of 5 msecond (15 percent) in conduction from LB to SE and a 6 msecond (30 percent) delay from V to SE. No delays occurred from LB to V or in transmural conduction (SE-IM). R76 to RCA or SAL to LCA or RCA did not affect conduction time.

Injection of arteriographic dye into the left coronary artery of the dog results in a characteristic delay in conduction between the division of the left bundle-branch and the subendocardium of the left ventricular free wall. This delay is associated with, and is the genesis of, increase in QRS duration and shifts in mean frontal plane QRS axis. The QRS widening without axis shift is not due to proximal left bundle-branch block. There is no evidence for a more distal delay.

RCA injections sometimes result in axis shifts which may occur because the dye can reach the left ventricle through RCA branches to the interventricular septum and intercoronary anastomoses therein. This degree of right sided perfusion of the septum is greater than that previously reported in the dog, and suggests that careful studies of a larger sample using our technique might lead to a revision of previous concepts.

The effect of the dye is not dependent upon sodium concentration within the range studied, upon hypoxia, or upon distension of the coronary arteries. The effects of the iodinated anion should be studied further.

The principal flaw in experimental equipment design was inability to study the posterior surface of the heart. The significance of this flaw is vitiated by a substantial body of previous work concerning experimental axis deviation [33-37,75,76,82,83]. Rightward axis shifts occurred more often than expected after LCA injections.

Microelectrode mapping and iontophoresis studies of the endocardial surface of the opened, perfused left ventricle, or studies of the type described herein conducted on dogs on whom additional pharmacologic interventions have been imposed, would extend this work.

The methodology described herein is suitable for investigating the effects of other drugs on intraventricular conduction *in vivo*.

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