Reduced Cholinergic Sinus Node Restraint in Hyperthyroidism

CARL W. WHITE M.D., AND THOMAS J. ZIMMERMAN, M.D.

SUMMARY The role of the cholinergic nervous system in the tachycardia of hyperthyroidism was investigated in this study of dogs made severely thyrotoxic by the administration of Na-L-thyroxine over a six to nine month period. Differences in heart rate between control and thyrotoxic unanesthetized dogs could be abolished by cumulative doses of intravenous atropine both before and after beta-adrenergic blockade with propranolol, and at submaximal as well as maximal heart rates. There were no differences in the heart rate response of control and thyrotoxic anesthetized dogs to vagal stimulation or to the selective injection of hypertonic saline or acetylcholine into the perfused sinus node artery. The results indicate that in addition to the direct effects of thyroid hormone on sinus node automaticity there is an abnormality in parasympathetic control of heart rate in hyperthyroidism. The data suggest that this abnormality is not due to a decreased responsiveness of the sinus node or an impaired release of the cholinergic neurotransmitter, but may reflect a reduction in cholinergic efferent activity in the thyrotoxic state.

INTERACTIONS between thyroid hormone and the autonomic nervous system have been a subject of interest to clinicians and basic scientists for the past half century. Because the symptoms and signs of thyrotoxicosis are similar to those of increased adrenergic stimulation, previous studies have focused primarily upon the role of the sympathetic division of the autonomic nervous system and have examined the hypothesis that the tachycardia of hyperthyroidism is the result of increased adrenergic activity or increased cardiac responsiveness. These investigations have generally shown, however, that plasma, urinary and myocardial catecholamine levels and turnover rates are normal in thyrotoxic states and that cardiac responsiveness to catecholamines is normal in the hyperthyroid dog, cat, rat, guinea pig, and human. Today the concept prevails that the tachycardia of hyperthyroidism is produced by a direct effect of thyroid hormone upon the automaticity of the sinus node, an effect which is not mediated by catecholamines.

An additional possibility is that the tachycardia of hyperthyroidism could result, at least in part, from decreased cholinergic inhibition of the sinus node. There is experimental evidence that thyroid hormone can affect the physiologic control of heart rate through a vagal mechanism. Studies in hyperthyroid animals and man have also suggested that the characteristic tachycardia of hyperthyroidism might result from an abnormality in parasympathetic control. Previous investigations have evaluated this possibility in three ways: by studying the chronotropic response to vagal stimulation and to atropine administration, and by infusion or systemic injection of cholinergic drugs. The results of these studies differ. These differences may be the result of at least three uncontrolled experimental variables: 1) the severity of the thyrotoxic state; 2) the concomitant adrenergic nervous system activity; and 3) differences in resting heart rate among various species.

In this study, the influence of cholinergic restraint on heart rate control was evaluated in severely and chronically thyrotoxic dogs. The effect of atropine was examined in unanesthetized animals in which changes in adrenergic activity were minimized by beta-adrenergic blockade. In addition, we evaluated the mechanism of the abnormality in parasympathetic control by studying the direct effect of the cholinergic neurotransmitter upon the automaticity of the sinus node using selective perfusion of the sinus node artery with acetylcholine. In previous studies, methylcholine was administered subcutaneously, so that changes in heart rate reflected reflex effects as well as direct effects on the sinus node.

Methods

Induction of Hyperthyroidism

Studies were conducted using 24 adult mongrel dogs of either sex weighing 22 to 25 kg: a control group of normal animals and a second group made thyrotoxic by the daily feeding of 30 mg of Na-L-thyroxine for 6–9 months. This regimen produced the classic hemodynamic and metabolic manifestations of chronic, severe hyperthyroidism as reflected by reductions of body weight, increases in heart rate, and an agitated appearance. Thyrotoxic dogs lost an average of 5 kg body weight by the time of study, even though they were given twice normal food intake.

Unanesthetized Animals

To evaluate differences in basal parasympathetic activity between control and toxic animals, experiments were conducted observing heart rate responses to intravenous administration of atropine. Dogs were studied in a quiet room, awake, and without premedication. Control heart rate values reflect one full minute’s count. Atropine sulfate, 0.04 mg/ml, was injected intravenously in incremental doses until a total of 0.8 mg was given. In three of the normal animals with disproportionately low heart rates following 0.8 mg atropine, an additional 1.6 mg atropine was given. The incremental doses were administered every three minutes and the heart rate was recorded at the end of each three-minute period. Atropine was given to all 24 dogs. In seven control and seven toxic dogs, racemic propranolol hydrochloride, 0.6 mg/kg, was injected intravenously prior to atropine administration. This dose had been previously shown in our laboratories to block the increase in heart rate produced by the intravenous infusion of isoproterenol 0.5...
μg/kg/min over 3–5 minutes. It has been subsequently shown to block the heart rate response to a 1 μg bolus injection of isoproterenol in similarly thyrotoxic dogs (unpublished data).

A possible nonspecific effect resulting only from differences in basal heart rate was examined in supplemental studies performed in five additional normal animals. Intravenous atropine was administered as described above. Four days later isoproterenol was infused into the same unanesthetized animals in doses sufficient to produce a control heart rate approximating that seen at rest in the thyrotoxic dogs. While keeping the isoproterenol infusion constant, incremental atropine was again administered in the same fashion. Total atropine dosage in these five animals was 4 mg.

Anesthetized Animals

To evaluate mechanisms underlying abnormalities observed in thyrotoxic unanesthetized animals, studies were performed with dogs anesthetized with intravenous alphachloralose, 50 mg/kg, and urethane, 500 mg/kg. Animals were ventilated with room air and supplemental oxygen through an endotracheal tube using a volume respirator adjusted to maintain normal PO2 and pH. A right thoracotomy was performed and the heart suspended in a pericardial cradle. The right coronary artery and the distal right atrial branch supplying the region of the sinus node (hereafter referred to as the “sinus node artery”) were identified. One dog in which the sinus node artery arose from the left coronary artery was excluded from the study.

Both vagal trunks were isolated and transected. The distal end of the right vagus nerve was stimulated using a platinum electrode and a Grass stimulator. Square wave pulses of supramaximal voltage and 3 msec duration were used to stimulate the vagus nerve at 0.1, 0.3, 1, 3, 10, and 15 Hz for 15 seconds. The maximal heart rate slowing which persisted at least 3 seconds was recorded as the response.

The sinus node artery was selectively perfused using a modification of techniques developed by James and Nadeau. Animals were anticoagulated with sodium heparin, and polyethylene tubing (1.0 to 1.3 mm outer diameter) was introduced directly into the sinus node artery immediately distal to its origin from the right coronary artery. The sinus node artery was perfused at constant flow with autologous blood obtained via a femoral artery cannula and routed through a Holter pulsatile infusion pump, model RL175. Perfusion pressure was monitored using a strain gauge joined with a T-connector placed between the pump and the right coronary artery cannula. Equal flow rates (2.5 ml/min) were used in both groups.

Injections into the perfusion system of the sinus node artery were made upstream from the infusion pump to avoid artifactual increases in pressure at the sinus node. Sinus node perfusion was not interrupted during injections. Acetylcholine injections were made at varying concentrations with a constant injectate volume of 0.1 ml. As an internal control, bradycardia was produced by injections of 0.6 ml saline solutions of varying osmolarity (1.8%, 841 mOsm; 3.6%, 1600 mOsm; 7.2%, 2320 mOsm).

A direct writing multichannel recorder was run at 2.5 mm/sec to transcribe aortic pressure, sinus node artery perfusion pressure, the surface electrocardiogram, an atrial electrocardiogram, the tachogram and the precise moment of drug injection. Parameters were recorded on magnetic tape and replayed later at a paper speed of 25 mm/sec. The electrocardiogram was also monitored on a rapid-sweep oscilloscope to detect changes in cardiac rhythm. Only beats in which the sinoatrial node remained the dominant pacemaker were analyzed. Transient atrial fibrillation was sometimes seen with high doses of acetylcholine injection. In such instances the sinus rate of the first beats following the spontaneous cessation of this arrhythmia was analyzed. Statistical analyses were performed using unpaired t-test, split plot design analysis of variance, and orthogonal comparison of treatment means. Values with a probability level greater than 5% (P > 0.05) were not considered significant.

Results

Responses to Atropine in Unanesthetized Dogs

The control heart rate averaged 142 ± 7 (SEM) beats/min in the thyrotoxic dogs and 70 ± 10 in normal dogs (P < 0.001). After receiving a cumulative dose of 0.18 mg atropine, the difference in heart rate at rest between the two groups of animals was no longer statistically significant (fig. 1). With increasing cholinergic blockade the two curves tended to approximate one another. Following 0.8 mg atropine, the heart rate was 240 ± 11 beats/min in the control group and 248 ± 11 in the thyrotoxic group. Differences in heart rate between the two groups were abolished not only at the maximal heart rate achieved, but also at submaximal levels (about 190 beats/min).

To minimize the possibility that changes in resting sympathetic nervous system activity might influence these

![Figure 1. Effect of cumulative intravenous administration of atropine on the heart rate of unanesthetized dogs. Triangles represent thyrotoxic dogs; circles represent control dogs. Bars indicate 1 SEM. Heart rate in the two groups at rest and after 0.18 mg atropine are statistically different at the P < 0.01 level. With increasing doses of atropine, significant differences between the two groups are abolished. Note that significant differences in heart rate are eliminated at submaximal heart rate values.](http://circ.ahajournals.org/doi/10.1161/01.CIR.89.4.891)
A heart rate response to cumulative intravenous atropine administration following beta-adrenergic blockade in unanesthetized dogs. Following beta-adrenergic blockade with propranolol, the significant (P < 0.01) differences between the two groups remain. After 0.24 mg atropine, no significant differences in heart rate remain between the toxic and control groups.

**Table 1. Heart Rate during Cholinergic Blockade**

<table>
<thead>
<tr>
<th>Control</th>
<th>Propranolol (0.6 mg/kg)</th>
<th>Atropine cumulative dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>.04</td>
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<td>Normal animals</td>
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<tr>
<td>90</td>
<td>73</td>
<td>70</td>
</tr>
<tr>
<td>Mean ± sEM</td>
<td>80</td>
<td>75</td>
</tr>
</tbody>
</table>

*P < 0.01 normal vs toxic at each dosage level (t-test).

**Figure 2.** Heart rate responses to cumulative intravenous atropine administration following beta-adrenergic blockade in unanesthetized dogs. Following beta-adrenergic blockade with propranolol, the significant (P < 0.01) differences between the two groups remain. After 0.24 mg atropine, no significant differences in heart rate remain between the toxic and control groups.

Prompranolol, the beta-adrenergic blockade curves, increasing and 12 (table separate) indicated a two groups to statistical method, the difference of the control and remain.

Orthogonal comparison of heart rate levels. After a plot. Atropine, Blockade, and toxic groups still

Mean ± sEM was 175 ± 11 whereas the maximum heart rate was 249 ± 8 (P < 0.01).

**Table 2. Change in Heart Rate with Vagal Nerve Stimulation in Anesthetized Dogs**

<table>
<thead>
<tr>
<th>Dog #</th>
<th>0.1</th>
<th>0.3</th>
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<th>3</th>
<th>10</th>
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<td>Normal animals</td>
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<td>71</td>
<td>76</td>
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<td>4</td>
<td>32</td>
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<td>56</td>
<td>104</td>
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<td>8</td>
<td>32</td>
<td>56</td>
<td>104</td>
<td>135</td>
<td></td>
</tr>
<tr>
<td>Mean ± sEM</td>
<td>26 ± 6</td>
<td>36 ± 3</td>
<td>49 ± 9</td>
<td>78 ± 10</td>
<td>114 ± 12</td>
</tr>
</tbody>
</table>

**Thyrotoxic animals**

<table>
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<tr>
<th>Dog #</th>
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<th>0.3</th>
<th>1</th>
<th>3</th>
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<td>32</td>
<td>56</td>
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<td>135</td>
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</tr>
<tr>
<td>Mean ± sEM</td>
<td>27 ± 5</td>
<td>35 ± 6</td>
<td>58 ± 6</td>
<td>88 ± 7</td>
<td>132 ± 5</td>
</tr>
</tbody>
</table>

Responses to Acetylcholine, Hypertonic Saline, and Vagal Nerve Stimulation in Anesthetized Dogs

These studies were done to determine the mechanism of the reduction in resting parasympathetic activity seen in the thyrotoxic dogs. We tested the hypothesis that this reduction having both linear and quadratic components. The results of these statistical comparisons are listed in table 2 and confirm the abolition of the differences between the groups at submaximal heart rates. Both before and after propranolol administration, the significant differences in heart rate present at rest were abolished at submaximal heart rates with low doses of atropine.

To exclude the possibility that the differences seen in these two groups might represent only a nonspecific effect resulting from differences in basal heart rate of any cause, supplemental studies were performed in normal animals before and during isoproterenol infusion. In these studies resting heart rate averaged 88 ± 5 beats/min control, and 137 ± 4 (P < 0.01) during isoproterenol infusion. After 0.8 mg atropine heart rates were 149 ± 9 before and 237 ± 9 (P < 0.01) during constant isoproterenol infusion. The maximum heart rate achievable in the control animals following atropine was 175 ± 11 whereas during isoproterenol infusion the maximum heart rate was 249 ± 8 (P < 0.01).
in parasympathetic tone might result from an impaired responsiveness of the sinoatrial node.

Initial heart rates were 181 ± 13 in the control group and 192 ± 8 in the thyrotoxic group (NS). Acetylcholine injected into the sinus node artery produced dose-related bradycardia. However, there were no significant differences between the heart rate responses of normal and thyrotoxic dogs at each dose level (fig. 3). Transient atrial fibrillation (10 sec–2 min) was seen in five control and four thyrotoxic animals when large doses (300 µg) of acetylcholine were administered. Atrial fibrillation was not observed with 30 µg acetylcholine and in only one control animal at the 100 µg dose. If data points in which transient atrial fibrillation occurred are eliminated from the calculations, the mean values are similar and there remain no significant differences between the groups.

Perfusion of the sinus node artery with hypertonic saline yielded increasing bradycardia as the osmolarity of the perfusate was increased. Thyrotoxic dogs, however, showed no significant differences in cardiac slowing produced by this noncholinergic, negative chronotropic agent when compared to the control group (fig. 4).

Since the tachycardia of thyrotoxicosis did not appear to be secondary to a decreased responsiveness of the sinus node, either cholinergic or non-specific, we tested the postulate that the increased heart rate might be secondary to a defect in the neural release of acetylcholine. To investigate this possibility, the bradycrotic response to graded vagal nerve stimulation was tested. There were no significant differences between the control and thyrotoxic groups in the response to vagal nerve stimulation, using frequencies from 0.5–15 Hz (table 2).

Discussion

The purpose of these studies was to determine if there is an abnormality of parasympathetic control of heart rate in severely thyrotoxic animals, and if so, to evaluate the mechanism of the abnormality. Our results indicate that the tachycardia of hyperthyroidism results in part from a defect in parasympathetic control. The data suggest that the defect does not reside in the efferent limb of the baroreflex and thus is probably located in the central or afferent components.

Atropine abolished the differences in heart rate between control and severely thyrotoxic unanaesthetized dogs. This finding contrasts with studies of Cairoli and Crout18 in which no differences were seen when the change in heart rate produced by atropine after beta-adrenergic blockade was compared in hyperthyroid and euthyroid rats. Our work, however, is consistent with the observation of Helmbach and Crout18 that the increase in heart rate after atropine was less in hyperthyroid patients than in normals. In the latter study, however, adrenergic receptors in the heart were intact. The differing results of these studies may also reflect dissimilarities in basic electrophysiologic mechanisms between species with markedly disparate control resting heart rates (350–400 beats/min in the unanaesthetized rat vs 70–100 in the dog and man).

These studies of atropine in hyperthyroid dogs extend the observations of Helmbach and Crout18 in hyperthyroid patients in two areas: first, study of the dose-response relationships with atropine; and second, study of the effects of atropine after beta blockade. Incremental administration of atropine abolished significant differences in heart rate between normal and thyrotoxic animals both before and after propranolol. Furthermore, the differences in heart rate between the groups were normalized by atropine at heart rates which were submaximal. Thus, the effects of atropine in abolishing the difference in heart rates were not merely a reflection of the highest heart rates achievable in the dog. These findings suggest that basal parasympathetic activity is reduced in hyperthyroidism. It is of interest that differences in heart rate, though statistically insignificant, remained after cholinergic blockade. This probably reflects the contribution of the direct effect of thyroid hormone on sinus node automaticity.

These results do not merely reflect nonspecific differences produced by differing basal rates. The heart rates produced by atropine given to animals whose resting sinus rate was increased by isoproterenol infusion remained significantly different from the control rates at all submaximal as well as the maximal heart rates achieved. Such findings were not seen in the thyrotoxic animals.

It is possible that the doses of propranolol used in these
studies to achieve adrenergic blockade may have, in addition, produced direct membrane effects in both the normal and thyrotoxic groups.26 The response to atropine administration, however, within each group was similar with or without propranolol (figs. 1 and 2). This would appear to indicate that any direct membrane effects of propranolol were not responsible for the major differences in the heart rate changes seen with atropine.

To evaluate the mechanism of the parasympathetic abnormality in hyperthyroid dogs, we studied two components of the efferent limb of the baroreflex: the efferent nerve and the sinus node. Vagal nerve stimulation in these thyrotoxic animals produced equivalent bradycardia when compared to euthyroid controls (table 2), and thus gave no evidence that the defect in parasympathetic control involved release of the cholinergic neurotransmitter.

Previous workers studying vagal nerve stimulation in hyperthyroidism have found conflicting results. Moran and Van der Shout15 reported in an abstract that vagal nerve stimulation in dogs produced equivalent bradycardia in the euthyroid and hyperthyroid state, but Frazer and Hess,16 studying hyperthyroid rats, noted decreased responsiveness to vagal nerve stimulation. Bilder and Hess suggested that the differences in these studies might be related to a difference in the severity of the hyperthyroid state.17 Our studies, therefore, were performed in dogs chronically and severely thyrotoxic and in which a defect in parasympathetic control of heart rate had been demonstrated. Despite this, there was no evidence for a defect in the release of the cholinergic neurotransmitter in this experimental model of hyperthyroidism. Thus, it is difficult to explain the differences in the studies on hyperthyroid rats vs dogs and humans on the basis of the severity of the hyperthyroid state. We suggest, therefore, that the contrasting results may be the result of a species difference in resting heart rates and differing electrophysiologic mechanisms of heart rate control.

To test whether a diminution in the sensitivity of the sinus node might be responsible for the abnormalities in parasympathetic control of heart rate in hyperthyroidism, we selectively perfused the sinus node artery. This technique provides a means by which the direct effect of drugs on heart rate can be studied without producing the reflex effects which occur with systemic administration. Acetylcholine selectively injected into the sinus node artery produced equivalent bradycardia in both hyperthyroid and normal animals. Similar results were obtained with selective perfusion of the sinus node with hypertonic saline, a non-cholinergic negative chronotropic agent. These studies indicate that the reduction in resting cholinergic activity does not reflect either a specific or a nonspecific impairment of responsiveness of the sinus node to a negative chronotropic stimulus.

These findings suggest that the parasympathetic abnormality observed in hyperthyroidism is not the result of a defect in the release of the cholinergic neurotransmitter or a decrease in the sensitivity of the sinus node. It should be noted, however, that the defect in parasympathetic control was demonstrated in conscious animals and the studies regarding the mechanism performed in anesthetized animals. It is clear that alterations in the balance of cholinergic and adrenergic tone occur as a result of anesthesia. Heart rate during chloralose-urethane anesthesia is increased, an effect generally attributed to increased sympathetic activity.26 However, some evidence exists that this increase in heart rate may also reflect partial inhibition of parasympathetic activity.28 These changes account for the equalization of heart rates under anesthesia between the normal and thyrotoxic groups and they permit the response to cholinergic interventions to be studied at comparable control heart rates. According to the concept of "accentuated antagonism,"29 the response to vagal stimulation or acetylcholine is greater when basal heart rate is increased by sympathetic activity or norepinephrine. Increases in sympathetic activity which might occur as the result of anesthesia would therefore be expected to magnify, not obscure, differences in response to parasympathetic interventions.

We conclude that differences in resting heart rates between normal and thyrotoxic animals appear to represent not only a direct effect of thyroid hormone, but also a reduction in the cholinergic restraint upon the sinus node. This is not due to a decreased responsiveness of the end-organ or an impaired release of the cholinergic neurotransmitter. We speculate that these differences reflect a reduction in efferent cholinergic discharge in the thyrotoxic state, which may result from an abnormality in central or afferent mechanisms.

Acknowledgment

We gratefully acknowledge the technical assistance of Warren Block, and the secretarial assistance of Ms. Joanne Pusack, Ms. Jeannie Coffin, and Ms. Dian Knappen.

References

14. Bilder GE, Hess ME: Studies on the negative chronotopic response to...
Angiographic Findings and Prognostic Indicators in Patients Resuscitated from Sudden Cardiac Death

W. Douglas Weaver, M.D., Gerald S. Lorch, M.D., Hernan A. Alvarez, M.D., and Leonard A. Cobb, M.D.

SUMMARY Sixty-four patients with coronary artery disease (CAD) who had been resuscitated from out-of-hospital ventricular fibrillation (VF) underwent cardiac catheterization and angiography. The majority (72%) had a previous history of cardiovascular disease; in the remaining 28%, VF was the first manifestation of CAD. Advanced coronary arteriosclerosis was a common finding; 94% of the patients had severe stenoses (70% or greater diameter narrowing) in one or more of the major coronary arteries, and most (70%) had ventricular wall contraction abnormalities. In over half of the patients, coronary anatomy was potentially suitable for complete revascularization.

During an average follow-up period of 20.4 months, fourteen of the 64 patients developed a second episode of VF and/or died suddenly (VF/SD). In an attempt to identify characteristics which might be of prognostic value, the clinical, hemodynamic, and angiographic characteristics of this group were compared to those patients who had a single episode of VF and survived during follow-up. Patients who developed recurrent VF/SD had more triple vessel CAD (P < 0.01), lower ejection fractions (P < 0.05), and far more severe abnormalities of left ventricular contraction (P < 0.001). These results indicate that angiographic findings can identify individuals at high risk for recurrent VF and also suggest that myocardial scarring may be an important factor in the initiation of ventricular fibrillation and in its recurrence.

SUDDEN CARDIAC DEATH is a common manifestation of ischemic heart disease and accounts for a large proportion of deaths from coronary arteriosclerosis. In recent years, recognition of this fact has stimulated the development of mobile coronary care units and rapid response emergency care systems1-3 which have demonstrated that many victims of out-of-hospital ventricular fibrillation (VF) can be resuscitated. In the first four years of operation, the Seattle emergency medical care system resuscitated 234 patients who ultimately returned home as functional individuals.4 In these patients, clinical evidence indicated that the majority of episodes of VF were "primary" dysrhythmic events and not secondary to acute myocardial infarction.5 During an average follow-up of 14 months (range 1–50 months), 26% of these 234 patients developed a second episode of VF and/or died suddenly.6

Since VF might be prevented by prophylactic therapy, it is important to identify indicators predictive of this lethal dysrhythmia. Autopsy studies have demonstrated that the majority of victims of sudden cardiac death had severe coronary stenoses.7-8 Hypertension, electrocardiographic evidence of left ventricular hypertrophy, and frequent premature ventricular beats are among the clinical findings which may help identify patients with ischemic heart disease who are at greater risk to develop sudden cardiac death.9-13 However, these factors are nonspecific in a given patient.

In order to understand the underlying pathophysiologic mechanisms leading to the development of VF, we have examined the coronary anatomy and left ventricular characteristics of 64 patients successfully resuscitated from out-of-hospital VF. In addition, to identify further those angiographic and hemodynamic findings associated with VF, we have compared these observations to a subgroup of 14 patients who developed recurrent ventricular fibrillation or sudden death (VF/SD) during follow-up.
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Circulation. 1976;54:890-895
doi: 10.1161/01.CIR.54.6.890

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1976 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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