Hierarchy of Ventricular Pacemakers

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SUMMARY To characterize the pattern of pacemaker dominance in the ventricular specialized conduction system (VSCS), escape ventricular pacemakers were localized and quantified in vivo and in vitro, in normal hearts and in hearts 24 hours after myocardial infarction. Escape pacemaker foci were localized in vivo during vagally induced atrial arrhythmias by means of electrograms recorded from the His bundle and proximal bundle branches, and standard electrocardiographic limb leads. The VSCS was isolated using a modified Eliasson preparation or preparations of each bundle branch. Escape pacemakers were located by extra- and intracellular recordings. Escape pacemaker foci in vivo were always in the proximal conduction system, usually the left bundle branch. The rate was 43 ± 11 (mean ± SD) beats/min. After β-adrenergic blockade, the mean rate fell to 31 ± 10 beats/min, but there were no shifts in pacemaker location. In the infarcted hearts, pacemakers were located in the peripheral left bundle branch. The mean rate was 146 ± 20 beats/min. In isolated normal preparations, the dominant pacemakers usually were in the His bundle, firing at a mean rate of 43 ± 10 beats/min. The rates of pacemakers diminished with distal progression. In infarcted hearts, the pacemakers invariably were in the infarct zone. The mean firing rates were not influenced by β-adrenergic blockade. The results indicate that the dominant pacemakers are normally in the very proximal VSCS, but after myocardial infarction pacemaker dominance is shifted into the infarct. Distribution of pacemaker dominance is independent of sympathetic influence.

IT HAS BEEN stated that in the ventricles there is a hierarchy of pacemakers analogous to that in atria; the more proximal the locus in the specialized conduction system, the greater the intrinsic automaticity.1,2 However, data to substantiate this assertion are lacking. Recent attempts to localize ventricular escape pacemakers in the normal canine heart were interpreted to indicate that pacemaker activity is confined to the atrioventricular (AV) junction.3 There have been no systematic attempts to quantify and compare regional pacemaker activity within the ventricular specialized conduction system (VSCS).

In the later phase of ventricular arrhythmias after coronary occlusion4 there is an enhancement of the rate of firing of automatic foci.5,6 It has not been determined whether there is an acceleration of normally dominant pacemakers or whether there is a displacement of pacemaker dominance after coronary occlusion. This report describes the results of a study of the distribution of pacemaker dominance within the normal VSCS and its alteration after coronary occlusion. Since the rate of firing of cells of the VSCS is strongly dependent on catecholamine stimulation,7 we investigated the possibility that the normal distribution of pacemaker dominance might be related to regional differences in catecholamine influence. Correspondingly, we investigated the possibility that the accelerated firing of Purkinje fibers within an infarct zone might be due to excess catecholamine stimulation.

Materials and Methods

STUDIES IN VIVO

Thirteen normal dogs were anesthetized with pentobarbital (30 mg/kg, iv). Standard electrocardiographic leads (II, aVR, aVF) were recorded. Electrograms of the His bundle and the proximal right and left bundle branches were recorded by positioning electrode catheters at the aortic root and the right and left sides of the ventricular septum via appropriate peripheral arteries and veins.8,9 Electrograms were recorded with a frequency bandwidth of 40–200 Hz. Sinus arrest or complete AV block was induced by vagosympathetic trunk stimulation for 5–10 minutes with rectangular pulses of 1–10 V, 0.05 msec, and 20 Hz delivered through two silver wires (0.012-inch diameter) inserted in the nerve.10 The ventricular escape rhythms were characterized according to the sequence of activation of the His bundle and bundle branch potentials and the configurations of the QRS complexes. The ventricles were paced with various electrode catheters to simulate ventricular escape rhythms arising from the corresponding portions of the His-Purkinje system. Femoral arterial pressure was monitored with a Statham pressure transducer. All recordings were registered on a DR-8 Electronics for Medicine recorder at paper speeds of 100 and 200 mm/sec. Recordings were stored on magnetic tape (Honeywell 5600) and replayed so that sections could be copied on photographic paper for detailed analysis.

In 12 additional dogs the anterior descending coronary artery was occluded with a ligature in two stages, according to the method of Harris,4 and the chest was closed. Twenty-four hours later the dogs again were anesthetized with sodium pentobarbital and the procedures described above were performed.

The effects on ventricular escape rhythms of stimulation and blockade of β-adrenergic receptors were studied in eight of the normal dogs and seven dogs which had been subjected to ligation of the left anterior descending artery 24 hours previously. In both these groups ventricular rhythms were characterized by the methods described above. The response to β stimulation was assessed by the rate response to the intravenous administration of a bolus...
of epinephrine, 0.5 μg/kg or 1 μg/kg. β blockade was accomplished by the intravenous administration of practo-
lor, 1 mg/kg, and verified by a lack of rate response to
epinephrine.

STUDIES IN VITRO

Hearts of normal dogs anesthetized with pentobarbital
(30 mg/kg) were excised. A modified Elizari prepara-
tion11,15 was dissected to include most of the endocardial
surface of both ventricles.15 Also, preparations were dis-
sected to include the left or right endocardial surface of
the ventricular septum and the adjoining free wall. All of
the proximal left or right bundle branches and most of their
Purkinje networks were included in the preparations.

Sketches of representative preparations are shown in Fig-
ure 1. Preparations were superfused with a solution equili-
brated with 95% O₂ and 5% CO₂ at 37°C of the following
millimolar composition: Na⁺, 151.1; K⁺, 4.0; Ca²⁺, 1.4;
Mg²⁺, 0.5; Cl⁻, 131.3; HCO₃⁻, 24.0; HPO₄²⁻, 1.8; and
dextrose, 5.5. An hour was allowed after dissection before
data were collected for analysis. The spontaneous rates
stabilized within 30 minutes after dissection in normal
preparations. Close bipolar electrograms and transmem-
brane potentials were recorded by standard techniques.13

During spontaneous rhythm, the earliest activity was lo-
calized by means of three mobile bipolar electrodes which
were placed to form the apices of equilateral triangles. The
triangles were made successively smaller by holding the
point of earliest activation constant while the other two
points were moved closer. The pacemaker site was local-
ized within a few millimeters, then intracellular recording
was used to pinpoint the location of pacemaker potentials.

In some experiments, the bundle branch systems were
divided into separate zones with transecting incisions. The
rate of spontaneous firing of each of the isolated zones was
measured. The approximate locations of the incisions are
depicted in Figure 1. The same procedures for studying
the bundle branches were followed in hearts excised from
dogs in which the anterior descending coronary artery had
been ligated 24 hours before.

In the isolated preparations, β stimulation was accom-
plished by adding epinephrine to the superfusate in a
concentration of 0.2 μg/ml. β blockade was accomplished
by adding propranolol in a concentration of 1.0 μg/ml. The
effectiveness of β blockade was tested by adding epineph-
rine to the superfusate (0.2 μg/ml) containing propranolol
after 10–20 minutes of exposure to the propranolol. The
pacemaker locus during β blockade was compared to the
locus in the same preparation before β blockade.

Results

NORMAL HEARTS IN VIVO

The heart rates during normal sinus rhythm and ventric-
ular escape rhythms are listed in Table 1. Ventricular
escape rhythms invariably originated in sites in the prox-
imal SVCS, as evidenced by the observation that the elec-
 trograms recorded from these sites always preceded the
onset of the QRS during the escape rhythms. In normal
dogs the left bundle branch was the pacemaker site in 15,
the right bundle branch in seven, and the His bundle in
three. During normal sinus rhythm the interval between
the His bundle deflection and ventricular activation (H-V
interval) ranged from 28 to 38 msec. The interval between
the right bundle branch electrogram and ventricular acti-
vation (RB-V interval) ranged from 19 to 23 msec; and from
the left bundle branch electrogram to ventricular acti-
vation (LB-V interval), from 15 to 22 msec. These
values indicate that the bundle branch electrograms were
recorded from sites in the proximal 1 or 2 cm of the bundle
branches. In every instance the morphology of the QRS
complex was in keeping with the pacemaker locus indi-
cated by the earliest electrogram. When the His bundle
electrogram was earliest, the QRS was identical to that
observed during sinus rhythm. When the left bundle
branch or right bundle electrograms were earliest, the
QRS presented the pattern of right or left bundle branch
block, respectively. Examples of escape rhythms originat-
ing in the His bundle and in the left bundle branch are
shown in Figure 2. The QRS morphology in three stand-
ard electrocardiographic leads and the sequence of activa-
tion of His bundle, right bundle, and left bundle electro-
grams during sinus rhythms are shown in Figure 2A. In
Figure 2B, vagally induced atrial arrest unmasked under-
lying ventricular escape rhythms. In the first set of com-
plexes, the configuration of the QRS and the sequence and
timing of the various electrograms were essentially the
same as during sinus rhythm. These findings characterized
this escape rhythm as originating within the His bundle.
The His bundle pacemaker was occasionally superseded
by another proximal focus (second complex in panel B). In
this rhythm, the left bundle branch electrogram was first,
followed in sequence by the His bundle and right bundle
branch electrograms and the QRS with a configuration of
right bundle branch block. The locus of origin of this
rhythm was placed in the proximal left bundle branch.

The effects of β-adrenergic stimulation and blockade on
the sinus and the normal ventricular escape pacemakers
are shown in Table 1. Epinephrine increased the rate of
ventricular pacemakers. However, with a dose of 0.5 μg/
kg, the effect on ventricular pacemakers was inconstant,
six of eight dogs showing no significant increase. With a
dose of 1 μg/kg, there was consistent speeding of ventricular pacemakers. Practolol significantly slowed both the sinus and ventricular pacemakers.

INFARCTED HEARTS IN VIVO

When the anterior descending coronary artery was ligated 1 day before, the dogs usually showed normal sinus rhythm with multiple ectopic ventricular beats. In some cases, vagally induced atrial arrest was required to unmask the underlying ventricular rhythm. During sinus rhythm, the sequence of activation of the VCS and the configuration of the QRS in the limb leads was similar to that in normal hearts. Recordings from a representative experiment are illustrated in Figure 3. The recording site in the left bundle branch was somewhat more distal than in the experiment illustrated in Figure 2. The left bundle branch electrogram occurred 20 msec after the His bundle electrogram and 10 msec before ventricular activation.

During vagally induced atrial arrest, a rapid ventricular rhythm was unmasked. In Figure 3B, 2 beats are shown. Note that ventricular myocardial activation (electrocardiogram leads) preceded activation of specialized conducting tissue, although the left bundle branch potential was still the first of the deflections to be seen. In Figure 3C, pacing from the infarct zone closely reproduced the QRS of the spontaneous ventricular rhythm in all leads. These findings suggested the peripheral origin of the ventricular rhythm within the infarct zone. In 19 such experiments the results were similar, indicating dominant ventricular pacemakers within the infarct zone. The mean rates of ventricular pacemakers of infarcted hearts and the mean sinus rates are shown in Table 1. The effects of β-adrenergic stimulation and blockade on sinus rhythm in infarcted hearts resembled the effects in normal hearts. The accelerated ventricular rhythms of myocardial infarction were consistently responsive to epinephrine in the dose of 0.5 μg/kg; there was an increase in rate in all hearts. The mean rates are shown in Table 1. β-Adrenergic blockade produced minimal slowing which was not statistically significant.

THE NORMAL HEART IN VITRO

In the Elizari preparations containing most of the ventricular conduction system, the pacemakers were in the His bundle in eight of 10 experiments. The loci of pacemakers in the 10 Elizari preparations are shown in Figure 4. The mean rate of His bundle pacemakers was 43 ± 10 beats/min (Table 2). There was no shift in pacemaker loci with β-adrenergic blockade and the mean rate was unchanged.

In the preparations of the right bundle branch, the pacemaker was usually localized in the upper half of the main right bundle branch. The loci of pacemakers in 13 preparations are depicted on the sketch of the right bundle branch in Figure 5a. The dominance of pacemakers located in the proximal bundle branch was related to a more rapid rate of diastolic depolarization of proximal cells compared to distal cells. Transmembrane potentials recorded from a cell located 2 mm from the origin of the right bundle branch and a cell located 2 cm distal to the origin, near the anterior papillary muscle, are compared in Figure 6. When the cells were driven (Fig. 6A), the proximal cell had an action potential of similar amplitude but

![Image](http://circres.ahajournals.org/)

**Figure 2** Localization of the site of origin of ventricular escape rhythms in the normal heart in vivo. The recordings in panel A during sinus rhythm show the QRS in standard electrocardiographic limb leads (L-I), aVR, and aVF; and electrograms recorded from the His bundle (H), proximal right bundle branch (Rb), and proximal left bundle branch (Lb). In panel B are shown the QRS and electrograms recorded from the same electrodes during ventricular escape rhythms emerging because of atrial arrest induced by vagal stimulation. See text for discussion.

![Image](http://circres.ahajournals.org/)

**Figure 3** Localization of the site of origin of accelerated ventricular rhythm in an infarcted heart. The recordings of standard electrocardiographic limb leads and the various electrograms, as described in Figure 2, were made during sinus rhythm (panel A), vagally induced atrial arrest (panel B), and while pacing an endocardial site within the infarct zone (IZ). The pacer impulse (Pi) appears in the Lb electrogram. See text for discussion.

| Table 1 Mean Rates of Sinus and Ventricular Pacemakers in Vivo |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Pacemaker site  | Control         | Epinephrine     | Practolol       | Epinephrine     |
| Normal Sinus    | 130 ± 24        | 184 ± 32*       | 109 ± 18        | 120 ± 22        |
| Normal Ventricular | 43 ± 11        | 67 ± 57*       | 31 ± 10*        | 34 ± 11         |
| Infarct Sinus   | 153 ± 32        | 195 ± 42*       | 132 ± 15        | 132 ± 14        |
| Infarct Ventricular | 146 ± 20       | 203 ± 45*       | 132 ± 10*       | 141 ± 12        |

Values are means ± so.
* Significantly different from control (P < 0.01, Student's t-test).
shorter duration. The rate of diastolic depolarization in the proximal cell was greater and it became the pacemaker during spontaneous rhythm (Fig. 6B).

The mean rate of pacemakers in the left and right bundle branches were shown in Table 2. The mean rates of the proximal portions approximated those of the rates of normal preparations. There were no shifts in the proximal bundles of the left and right bundle branches. There was a predilection for the posterior fibers of the proximal bundle.

When the bundle branches were divided by incisions roughly into proximal, middle, and distal portions (Fig. 1), the rates of the proximal portions approximated those of the intact preparations (left bundle, 35; right bundle, 40), whereas the middle portions were slightly slower (left bundle, 32; right bundle, 29). The distal portions had rates less than 10 beats/min. Many preparations were quiescent.

**INFARCTED HEARTS IN VITRO**

The mean rate of the left bundle branches of infarcted hearts was significantly higher than the normal as shown in Table 2. The right bundle branches were slower, averaging 22 beats/min. In contrast to the normal preparations, the pacemakers in the infarcted hearts were invariably located within the portions of the specialized conduction system which were contained in the infarct zone. The infarct zone was predominantly in the distal portion of the left bundle branch in section III of Figure 1. Pacemakers in vitro responded to epinephrine with an increase in rate. However, there was no significant slowing of the control rate after β blockade. Although the firing rate during β-adrenergic block was slower than the initial control in the infarcted preparations (Table 2, LB), it was faster than the final control. There was a progressive slowing of the rate with time in the infarcted preparations independent of the β blockade. However, within the time span of these experiments (about 2 hours), the rates of firing of pacemakers in the infarct zone remained substantially higher than the rates of normal preparations.

**Discussion**

The idea that within the VSCS there is a gradation of intensity of automaticity diminishing from proximal to distal has insinuated itself into the literature without experimental substantiation, perhaps by analogy with the distribution of pacemaker activity within the atria. The data of this study support this idea in its general form. Both in vivo and in vitro, the dominant escape pacemakers were located in the proximal 1 or 2 cm of the bundle branches or in the His bundle itself. The distal Purkinje network had weak automatic properties. However, the rule of proximal dominance appeared to have an exception: His bundle pacemakers did not consistently supersede pacemakers in the bundle branches in vivo. Only three of 25 escape ventricular pacemakers were located in the His bundle. Clinical observations of patients with heart block and escape His bundle pacemakers also have suggested that the natural rates of His bundle pacemakers do not exceed pacemakers in the bundle branches.14-16 In our experiments the left bundle branch dominated most frequently in vivo but the mean rates of

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<th>Table 2 Mean Rates of Pacemakers in Vitro</th>
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Values are means ± sd. HB = His bundle; LB = left bundle branch; RB = right bundle branch.

* Significantly different from control (P < 0.01, Student's t-test).
The findings in vitro were somewhat different. Most often, the dominant pacemakers in vitro was in the His bundle; the mean rate of firing of pacemakers in the His bundle slightly exceeded the rates of pacemakers in the left and right bundle branches. The basis for this discordance may lie somewhere in the various sources of experimental error. The His bundle in vitro was subjected to trauma of dissection which may enhance automaticity.17,18 On the other hand, the method of inducing heart block in vivo (stimulation of the vagosympathetic trunks) may have affected the automaticity of the ventricular conduction system. The long-standing debate concerning the extent of vagal influence on automaticity of the ventricular specialized conducting cells has not been resolved.19 If vagal influence can affect the automaticity of ventricular specialized conducting cells, the natural distribution of pacemaker dominance might have been altered by the experimental procedure. Specifically, His bundle pacemakers may have been slowed by vagal influence. The rates of His bundle and idioventricular pacemakers during heart block induced by injection of formalin into the AV node10 are quite similar to the rates of His bundle pacemakers in vitro effectively dispelled that possibility. In vivo, there was a modest slowing of the rate of escape pacemakers but they remained proximal in their location. In vitro, the pacemaker loci rarely shifted when β receptors were blocked. The use of β-adrenergic blockade disclosed another slight discordance between the data obtained in vivo and in vitro. During β blockade in vivo there was a small but significant decrease in the rate of ventricular escape pacemakers, indicating a partial dependence on sympathetic stimulation by circulating catecholamines or catecholamines released from nerve endings in the tissue. In vitro, there was no such evidence of dependence on catecholamines. Therefore, the “intrinsic” (independent of catecholamines) rates were somewhat slower in vivo than in vitro. However, the disparity of the data is not great. It does not negate the assumption that the contrived environment in vitro is a reasonable replica of the milieu in vivo in relation to the property of automaticity.

The automaticity of the peripheral Purkinje network in vitro was poor. In many of these fibers, diastolic depolarization reached a plateau without attaining threshold; spontaneous firing did not occur. Further diastolic depolarization and spontaneous firing could be induced by β-adrenergic stimulation. These findings agree in part with conclusions of other studies showing poorly developed automaticity in peripheral Purkinje fibers.2 The poor automaticity of peripheral fibers may have clinical implications. Painstaking pathological examinations indicate that in most cases of acquired heart block, the proximal ven-

![Figure 5](https://example.com/figure5.jpg)

**Figure 5** Dominant pacemaker loci in preparations of the right and left bundle branches in vitro. Each locus designated by x was derived from a separate preparation. The dashed lines denote shifts in loci in the same preparation. The upper sketches (a and b) represent the preparations of the right bundle branch; the lower (c and d), the preparations of the left bundle branch. The distribution of loci during standard superfusion (panels a and c) is compared with the distribution after β blockade (panels b and d). AV = aortic valve; APM = anterior papillary muscle; MB = moderator band; PPM = posterior papillary muscle; TV = tricuspid valve.

Despite these potential sources of error, the disparity between the results in vivo and in vitro is rather minimal. Mean rates of pacemakers in the His bundle and bundle branches differed only by a few beats per minute both in vivo and in vitro. Thus, with both experimental approaches, the data warrant the conclusion that the pacemakers in the His bundle were not substantially faster than those in the proximal bundle branches. The dominance of the pacemaker site may be determined not only by its intrinsic firing rate, but also by its susceptibility to overdrive suppression.31-33

We considered the possibility that the gradation of intensity of automatic activity might be related in part to the density of distribution of sympathetic nerve endings. The findings during β-adrenergic blockade both in vivo and in vitro effectively dispelled that possibility. In vivo, there was a modest slowing of the rate of escape pacemakers but they remained proximal in their location. In vitro, the pacemaker loci rarely shifted when β receptors were blocked. The use of β-adrenergic blockade disclosed another slight discordance between the data obtained in vivo and in vitro. During β blockade in vivo there was a small but significant decrease in the rate of ventricular escape pacemakers, indicating a partial dependence on sympathetic stimulation by circulating catecholamines or catecholamines released from nerve endings in the tissue. In vitro, there was no such evidence of dependence on catecholamines. Therefore, the “intrinsic” (independent of catecholamines) rates were somewhat slower in vivo than in vitro. However, the disparity of the data is not great. It does not negate the assumption that the contrived environment in vitro is a reasonable replica of the milieu in vivo in relation to the property of automaticity.

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![Figure 6](https://example.com/figure6.jpg)

**Figure 6** Comparison of transmembrane potentials of a cell in the proximal pacemaker locus (P) of the right bundle branch and a more distal cell (D). The proximal pacemaker cell was 2 mm distal to the origin of the bundle branch and the other cell was located 2 cm distal. The action potentials of driven (panel A) and spontaneous (panel B) beats are compared. In the driven beats, the stimulating electrodes were located distally so that activation of the bundle branch was retrograde.
tricular conduction system is extensively involved with sclerosis and degeneration. When continuity of conduction is completely interrupted, distal escape pacemakers emerge. If the lesions are widespread within the proximal bundle branches, not only conduction but automaticity will be impaired because of the loss of the more automatic proximal cells. The resultant slow and erratic firing of distal pacemakers may be an important factor in Stokes-Adams attacks and sudden death.

Twenty-four hours after occlusion of the anterior descending coronary artery, there was an acceleration of ventricular pacemakers within the infarct zone. The peripheral Purkinje network within the infarct, normally weakly automatic, showed accelerated firing. The mean ventricular rates during vagally induced atrial arrest in vivo were about twice as fast as the rates of the infarcted preparation in vitro. It is likely that the ventricular rates in vivo resulted from reentrant as well as automatic beats. In vitro, direct recording from pacemaker cells indicated that the basic firing rates were comprised almost entirely of automatic beats. Also, there was a slowing of abnormal automatic foci with time during superfusion. This phenomenon has been attributed to washout of a factor promoting automaticity. The washout probably began during dissection and pinning, resulting in slower rates by the time of the initial control period. The reduced firing rates of preparations of the right bundle branch from infarcted hearts suggest that augmented firing of cells within the infarct zone was associated with suppression of automaticity in normal cells. This long-lasting effect was not the usual form of overdrive suppression which has a duration of seconds or minutes.

The enhanced automaticity of Purkinje fibers in the infarct zone could not be ascribed to local release of catecholamines. Effective blockade of the β-adrenergic receptors failed to restore the automaticity to normal. Moreover, there was no evidence of altered sensitivity to the catecholamines. The factor enhancing automaticity of Purkinje fibers within infarcts remains unidentified.

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