LABORATORY INVESTIGATION
VENTRICULAR ARRHYTHMIA

Prevention of postischemic ventricular fibrillation late after right or left stellate ganglionectomy in dogs

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ABSTRACT To gain insight into the differences in antiarrhythmic potential of right vs left stellate ganglionectomy, 72 dogs were randomized to either unilateral stellectomy or second intercostal space thoracotomy and left circumflex coronary arteriovenous pedicle occlusion was performed, without vagotomy, a mean of 8 weeks later under anesthesia. The type and timing of ventricular ectopic beats, including both nonsustained and sustained ventricular tachycardia and ventricular fibrillation, were investigated. Several covariates, including postischemic electrocardiographic changes, were considered. Both right and left stellate ganglionectomy reduced the incidence of early (0 to 10 min) (p = .004 and p = .001, respectively) and total (0 to 60 min) (p = .009 and p = .008, respectively) ischemia-induced ventricular fibrillation, and improved outcome (p = .0013 and p = .0012, respectively). Early sustained ventricular tachycardia was similarly reduced (p = .02) in both stellectomized groups. By contrast, neither the type nor the time distribution of the other forms of ventricular arrhythmias differed significantly among the randomized groups. The multivariate Cox’s regression model showed that ST segment elevation at 3 min postocclusion, unilateral stellate ganglionectomy (either right or left), sex, and weight were significant independent predictors of the incidence of ventricular fibrillation during the occlusion period. Lower ST segment elevation and reduced incidence of sustained ventricular tachycardia in the early postischemic period might explain improved outcome in stellectomized dogs by Cox analysis. The side of intervention (either stellectomy or sham operation) did not influence survival; however, left-sided interventions were more effective than right-sided ones. These results confirm the previously reported antifibrillatory effect of left and indicate like effects of right stellate ganglionectomy in a randomized experimental study. Circulation 77, No. 4, 935–946, 1988.

IT IS generally believed that increased sympathetic tone at the onset of acute myocardial ischemia contributes to life-threatening arrhythmias in a variety of animal preparations, including anesthetized, morphine-sedated, and conscious ones.1,2 Whereas bilateral or unilateral left stellate ganglionectomy have shown antiarrhythmic effectiveness, the role of unilaterial right stellectomy is controversial.1–9 Antifibrillatory properties have been reported 2 to 3 weeks after left stellectomy in conscious dogs with previous myocardial infarction,3 an effect confirmed in the presence of the high sympathetic tone induced by exercise.4 An increased propensity to arrhythmias was observed after acute right stellectomy,4–7 although different but not opposite effects were reported in another study comparing acute ablations of either of the two stellate ganglia in the absence of ischemia.8 On the other hand, in a more recent investigation in anesthetized dogs no significant reduction in ischemia-induced arrhythmias was seen after acute left stellectomy, while acute ablation of the right stellate ganglion either increased the severity of arrhythmias or was without effect in most cases.9

No comparative investigation has been performed to elucidate the antiarrhythmic effects of right vs left stellate ganglionectomy on experimental ischemia-in-
duced ventricular arrhythmias. The present study was therefore undertaken, based on group comparisons in a large number of animals that were randomized to either unilateral stellatectomy or sham operation. By this method we hoped to eliminate factors of variability that were not controlled for in previous studies of the effects of unilateral \(^5\) \(^9\) and bilateral \(^10\) \(^{21}\) stellate ganglionectomy. Proximal \(^22\) \(^{24}\) one-stage \(^25\) occlusions of the left circumflex coronary arteriovenous pedicle were performed to prevent spontaneous variability as the consequence of a high incidence of postligation ventricular fibrillation. Anesthesia was necessary to permit high-quality standard electrocardiographic monitoring, \(^26\) which might contribute important predictive information on factors implicated in the development of life-threatening arrhythmias. \(^27\) Finally, multivariate analysis modeling the probability of survival as a function of several basal and postligation covariates was used in an effort to explain the mechanisms involved and to gain insight into the differences in antiarrhythmic potential of right vs left stellate ganglionectomy, a question that deserves addressing because of its clinical relevance. \(^3\) \(^4\) \(^8\)

**Methods**

Adult mongrel dogs of either sex (mean weight 19 ± 5 kg) were used. All the dogs were cared for in the laboratory by experienced technicians and were seen by a veterinary doctor before they were accepted as candidates for the study. No dogs with clinically evident infection or health disability were included. The study was approved by the appropriate institutional committee; the experimental procedures complied with the “Guiding Principles in the Use and Care of Animals” approved by the Council of the American Physiological Society as well as with state regulations.

**Surgical preparation.** Anesthesia was induced \(^22\) in each dog by the same anesthesiologist (J. C. G.) using levomepromazine (0.5 mg/kg im) followed 30 min later by sodium pento-barbital (10 mg/kg iv). After endotracheal intubation, ventilation was maintained (with 1:1 oxygen and nitrous oxide) with a Logics 5 respirator with a respiratory rate of 20 strokes/min and a tidal volume of 20 ml/kg. Pancuronium bromide (0.1 mg/kg) and atropine sulfate (0.01 mg/kg) were administered intravenously immediately after intubation. The animals were covered with surgical blankets and central temperature was monitored. The same cardiovascular surgeon (F. L.) performed a left thoracotomy in each animal at the level of the fourth intercostal space \(^29\) within 15 min of the injection of sodium pento-barbital. The pericardium was incised parallel to the phrenic nerve and arranged to form a cradle in which the heart was suspended. A catheter (20 g) was introduced in the ascending aorta and connected to an Elema-Schoenander transducer (0 to 300 mm Hg) with a Vygon bolt extensor (tested at 40 kg/cm) for aortic pressure determinations and blood sampling. Arterial gases and pH were measured after thoracotomy and several times thereafter and remained within the physiologic range (90 < PaO\(_2\) < 160 mm Hg, 25 < PaCO\(_2\) < 35 mm Hg, 7.38 < pH < 7.44). \(^30\) \(^32\) The left circumflex coronary arteriovenous pedicle was occluded 15 min after thoracotomy. \(^22\) Occlusion was obtained in one stage \(^25\) with a braided thread (Teflene 2.0) mounted on a half

round-curve needle (Archimed 2.0) positioned at a site distant (1 to 5 mm) from the left main division. \(^23\) \(^24\) The occlusion period lasted until ventricular fibrillation had ensued or 60 min had elapsed.

**Monitoring and measurements.** The animals were restrained in a fixed standardized position \(^26\); needle-limb electrodes were inserted and a standard six-lead frontal electrocardiogram \(^27\) was recorded (P. E. P. and R. J.) on a jet-ink electrocardiograph (Elema-Schoenander, Mingograf 81) that allowed paper speeds from 2.5 to 1000 mm/sec (10 mm = 1 mV). Continuous electrocardiographic (ECG) recording of standard leads D\(_1\), D\(_2\), and D\(_3\) was performed thereafter to document the occurrence of both early (0 to 10 min) and late (10 to 60 min) postocclusion arrhythmias. \(^23\) In addition, a couourograph display of lead D\(_2\) was obtained. \(^34\) This was aimed at providing a synoptic view \(^22\) \(^27\) \(^24\) of ECG changes, including arrhythmias.

All the ECG measurements were obtained by the same observer (P. E. P.) with the aid of a caliper and a magnifying device with a grid (Minnesota lens). R wave amplitude was measured in millivolts from the isoelectric line to the zenith of R wave. \(^27\) Absolute ST segment changes were also measured in millivolts perpendicular to the isoelectric line and 60 msec after the beginning of R wave or the nadir of Q wave, when present. \(^27\) These measurements were performed at 100 mm/sec paper speed every 60 sec throughout the experiments starting 1 min before ligation, but for the purpose of the present investigation they are reported only before occlusion and at 3 min after occlusion, a time when no ventricular fibrillation had occurred. Each data point represents a mean of 5 to 10 consecutive beats to avoid respiratory influences. \(^27\) Both R wave amplitude and ST segment displacements were measured in all recorded leads. However, to facilitate clinical correlations, \(^27\) data are reported only from leads D\(_2\) and D\(_3\) (mean data). Finally, heart rate and mean aortic pressure as calculated at the same time intervals as for standard ECG records were measured.

**Stellate ganglionectomy.** The animals were anesthetized and monitored electrocardiographically as described above. By a sterile procedure, either the right or the left stellate ganglia were exposed through the omolateral second intercostal space by the same surgeon (F. L.) in all cases. Care was taken to identify all the branches running to and out the ganglia, including the rami communicantes to the seventh and eighth (when present) cervical nerves, the mixed rami to the first, second, third, and fourth thoracic nerves, and both the ventral (often connected directly to the right stellate ganglion) and dorsal limbs of the ansae subclaviae. \(^36\) After isolation, all the above-mentioned branches were cut in a point 5 to 15 mm distal from the ganglia and always distal to the origin of the stellate cardiac nerves. \(^36\) \(^37\) Finally, the ganglion itself was removed, the thorax was closed in layers, air was evacuated from the chest, and the animals were allowed to recover from the operation while receiving only intramuscular streptomyacin (25 mg/kg) for 5 days.

**Experimental protocol.** The study comprised 72 dogs randomly assigned over 12 consecutive months to undergo either right (n = 18) or left (n = 18) stellate ganglionectomy or to undergo a sham operation of either right (n = 18) or left (n = 18) second intercostal space thoracotomy. The number of randomizable animals (sample size) was calculated with standard formulas for comparison of two proportions based on the following arguments: (1) the probability (p) of dying of ventricular fibrillation during 60 min after left circumflex coronary arteriovenous occlusion is .60 (.50 < p < .70) in controls, \(^22\) \(^38\) (2) it is desirable to detect an absolute difference probability of .40 or more in stellactomized as compared with sham-operated dogs, \(^3\) (3) 5% alpha and 33% beta errors might be acceptable. Availability of cages and laboratory schedule were also con-
considered in determining the number of operable animals. Randomization was done immediately before the animals arrived at the laboratory by the drawing of a procedure identification code number from a sealed envelope prepared previously by one of us (R. J.). A mean of 8 (range 7 to 9) weeks after randomization the dogs underwent proximal one-stage left circumflex coronary arteriovenous pedicle occlusion as described above.

Data analysis. Variables measured (mean ± SD) in all randomized animals before and immediately after left circumflex coronary arteriovenous pedicle occlusion were tested for significant differences by one-way analysis of variance with the addition of all possible comparisons between pairs. The following variables were scored: sex, month of occlusion, ventricular arrhythmias 0 to 10 min after occlusion, and treatment assignment. A paired t test was used to analyze the significance of ECG and hemodynamic changes 3 min after occlusion.

Arrhythmias. To analyze univariately the incidence of ventricular ectopic beats, including ventricular fibrillation, in all animals, independently of the score system, an arbitrary classification was made into categories of increasing severity: (1) no arrhythmias, (2) ventricular ectopic beats whether single, in couples, or triplets, (3) nonsustained ventricular tachycardia (4 to 50 successive impulses at a rate > 250 beats/min), (4) sustained (but spontaneously ceasing) ventricular tachycardia (more than 50 successive impulses at a rate > 250 beats/min), and (5) ventricular fibrillation. The definition of ventricular tachycardia as greater than 250 beats/min eliminates the spontaneous multiform accelerated idioventricular rhythm from consideration as ventricular tachycardia. On the other hand, the criterion of spontaneous ceasing for sustained ventricular tachycardia prevents consideration in this category of immediate pre fibrillatory rhythms. Arrhythmic phases, as previously reported, were taken into account. All categories of arrhythmias as described above were considered either present or absent in each animal for each of the two arrhythmic phases, 0 to 10 and 10 to 60 min after occlusion. Thus, the number of animals with any given category of arrhythmia rather than the number or the categories of arrhythmias were considered in this analysis. Since some animals presented with more than one category of arrhythmias, the numerators vary accordingly in each group. However, arrhythmias were counted only in survivors and therefore the denominators reflect the survival status at later phases. The Fisher’s exact test (one tail) was used to test the significance of the differences among groups.

Survival and the Cox regression model. To analyze the data on survival among the study groups the cumulative proportions surviving were first calculated by life table methods (BMDP 1L) with use of the generalized Wilcoxon test as proposed by Breslow. In addition, since several studies have shown that measured covariates such as weight, sex, and month of occlusion, latencies from anesthesia to occlusion and from occlusion to thoracotomy, heart rate, R wave amplitude and ST segment changes, mean aortic pressure, and the occurrence of various forms of ventricular arrhythmias during the early postocclusion phase might all influence survival after coronary occlusion, survival has been tested (BMDP 2L) by the Cox regression model. Variables significant by univariate analysis were jointly analyzed by Cox regression, which models the probability of survival S(t) at time t by:

\[ S(t) = (S_0(t))^\exp(\sum_\beta \text{x}_i) \]

where \( x \) is the vector of variable included in the model. The beta coefficients of Cox’s model allow the computation of a relative risk (supposed constant over time, proportional-hazards model) for the occurrence of the analyzed event. The proportional-hazards regression model was also used to test the significance of treatment effects while simultaneously accounting for baseline and immediate postocclusion characteristics. A partial likelihood approach was used for calculations. Models were compared with a likelihood ratio test. The analyses were repeated for prediction of ventricular fibrillation during 60 min after occlusion in a stepwise mode with: (1) all variables except those related to treatment assignment, (2) all variables plus the treatment assignment ranked (1 to 4) in accordance with the increasing incidence of postligation ventricular fibrillation observed empirically in the study groups, and (3) all variables plus two variables defining the presence or absence of treatment and the side (right or left) of the intervention.

Correlations and other survival prediction models. After choosing the combination of variables that provided the best solution for the Cox regression model, a linear correlation matrix among all those variables was built. Moreover, a multiple linear regression (BMDP 1R) and a stepwise logistic regression (BMDP LR) were computed on all such variables in an attempt at systematic comparison among survival prediction models. Since the number of cases read in this investigation was the same for Cox, linear, and logistic models of survival prediction, a direct comparison of t values calculated from the same covariates was in fact possible.

In all the analyses performed as described above significant differences were those with \( p < .05 \).

Results

No postoperative death occurred after stellate ganglionectomy or second intercostal space thoracotomy. All the animals undergoing stellate ganglionectomy developed omolateral persisting Bernard-Horner’s syndrome. This syndrome was not observed in sham-operated dogs. Therefore, a mean of 8 weeks later all 72 initially randomized dogs were subjected to left circumflex coronary arteriovenous pedicle occlusion. By the time of coronary occlusion these animals were significantly heavier than at the time of randomization (21 ± 5 vs 19 ± 5 kg, \( p < .01 \)). Dogs in the right stellate ganglionectomy group were the heaviest (table 1). The mean values of \( \text{Pao}_2 \), \( \text{Paco}_2 \), and pH measured immediately before ligature averaged 124 ± 22 and 29 ± 3 mm Hg and 7.41 ± 0.02 units, respectively (n = 72); no statistically significant difference was detected among the study groups. There was no difference among groups in sex distribution, latency from thoracotomy to occlusion, and either basal ST segment elevation or R wave amplitude (table 1). Dogs in the right stellate ganglionectomy group were occluded later during the year than those in the left stelllectomy group, and the latter later than their respective sham-operated controls (table 1). Latency from anesthesia to thoracotomy was longer in both the right and left stellate ganglionectomy groups than in sham-operated animals (table 1). The dogs in the left stelllectomy group had longer mean latency from anesthesia to thoracotomy and higher mean aortic pressure than their respective controls (table 1).
### TABLE 1
Basal characteristics and immediate changes after left circumflex coronary arteriovenous occlusion in all 72 randomized animals

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<tr>
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<th>Right SG</th>
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<tr>
<td></td>
<td>SG</td>
<td>Sham</td>
<td>SG</td>
<td>Sham</td>
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<tr>
<td>Basal characteristics before occlusion</td>
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<tr>
<td>Weight (kg)</td>
<td>24 ± 4&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>21 ± 5</td>
<td>20 ± 5</td>
<td>20 ± 4</td>
</tr>
<tr>
<td>Sex&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.22 ± 0.43</td>
<td>1.39 ± 0.50</td>
<td>1.50 ± 0.51</td>
<td>1.39 ± 0.50</td>
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<td>Month of occlusion&lt;sup&gt;e&lt;/sup&gt;</td>
<td>7.46 ± 2.12&lt;sup&gt;d&lt;/sup&gt;</td>
<td>6.61 ± 4.35</td>
<td>6.89 ± 2.59&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.67 ± 1.09</td>
</tr>
<tr>
<td>Latency period (min)</td>
<td></td>
<td></td>
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<tr>
<td>Anesthesia to thoracotomy</td>
<td>13 ± 2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>11 ± 4</td>
<td>14 ± 2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10 ± 2</td>
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<tr>
<td>Thoracotomy to ligation</td>
<td>15 ± 2</td>
<td>14 ± 4</td>
<td>15 ± 2</td>
<td>14 ± 2</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>128 ± 19&lt;sup&gt;a,d&lt;/sup&gt;</td>
<td>151 ± 22</td>
<td>158 ± 22</td>
<td>160 ± 20</td>
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<tr>
<td>ST segment elevation (mV)</td>
<td>1.84 ± 0.61</td>
<td>1.97 ± 0.80</td>
<td>2.21 ± 0.55</td>
<td>1.98 ± 0.76</td>
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<tr>
<td>R wave amplitude (mV)</td>
<td>104 ± 5</td>
<td>101 ± 5</td>
<td>104 ± 3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>100 ± 4</td>
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<td>MAP (mm Hg)</td>
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<tr>
<td>Immediate (3 min) postocclusion changes</td>
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<tr>
<td>Heart rate (beats/min)</td>
<td>130 ± 19</td>
<td>144 ± 37</td>
<td>140 ± 21&lt;sup&gt;f&lt;/sup&gt;</td>
<td>151 ± 28&lt;sup&gt;f&lt;/sup&gt;</td>
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<tr>
<td>ST segment elevation (mV)</td>
<td>0.86 ± 0.58&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.52 ± 0.83</td>
<td>1.25 ± 0.93</td>
<td>1.51 ± 0.95</td>
</tr>
<tr>
<td>R wave amplitude (mV)</td>
<td>2.37 ± 0.57&lt;sup&gt;c,f&lt;/sup&gt;</td>
<td>2.76 ± 0.91&lt;sup&gt;f&lt;/sup&gt;</td>
<td>2.97 ± 1.12&lt;sup&gt;f&lt;/sup&gt;</td>
<td>2.71 ± 0.69&lt;sup&gt;f&lt;/sup&gt;</td>
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<tr>
<td>MAP (mm Hg)</td>
<td>94 ± 9&lt;sup&gt;f&lt;/sup&gt;</td>
<td>93 ± 4&lt;sup&gt;f&lt;/sup&gt;</td>
<td>95 ± 3&lt;sup&gt;a,f&lt;/sup&gt;</td>
<td>91 ± 3&lt;sup&gt;f&lt;/sup&gt;</td>
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SG = stellate ganglionectomy; MAP = mean aortic pressure.

<sup>a</sup>p < .05 vs sham; <sup>b</sup>p < .01 vs sham; <sup>c</sup>p < .05 vs left SG; <sup>d</sup>p < .01 vs left SG (one way analysis of variance); <sup>e</sup>p < .06 vs before occlusion; <sup>f</sup>p < .01 vs before occlusion (paired t test).

<sup>g</sup>Scored 1 when male and 2 when female. No significant differences when analyzed by one-tail Fisher’s exact test of frequencies.

<sup>h</sup>Scored from 1 (January) to 12 (December).

### TABLE 2
Incidence and distribution of ventricular arrhythmias in the study groups

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<td></td>
<td>SG</td>
<td>Sham</td>
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<tr>
<td>No ventricular ectopic beats (n)</td>
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<tr>
<td>Total</td>
<td>2/18</td>
<td>2/18</td>
<td>1/18</td>
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<tr>
<td>0–10 min after occlusion</td>
<td>2/18</td>
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<td>1/18</td>
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<tr>
<td>10–60 min after occlusion&lt;sup&gt;f&lt;/sup&gt;</td>
<td>2/17</td>
<td>2/9</td>
<td>1/18</td>
<td>1/10</td>
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<tr>
<td>Ventricular ectopic beats (n)</td>
<td></td>
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<tr>
<td>Total</td>
<td>16/18</td>
<td>16/18</td>
<td>17/18</td>
<td>17/18</td>
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<td>0–10 min after occlusion</td>
<td>9/18</td>
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<tr>
<td>10–60 min after occlusion&lt;sup&gt;f&lt;/sup&gt;</td>
<td>14/17</td>
<td>7/9</td>
<td>15/18</td>
<td>9/10</td>
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<tr>
<td>Nonsustained ventricular tachycardia (n)</td>
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<td></td>
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<tr>
<td>Total</td>
<td>12/18</td>
<td>9/18</td>
<td>12/18</td>
<td>11/18</td>
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<tr>
<td>0–10 min after occlusion</td>
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<tr>
<td>10–60 min after occlusion&lt;sup&gt;f&lt;/sup&gt;</td>
<td>11/17</td>
<td>3/9</td>
<td>7/18</td>
<td>5/10</td>
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<tr>
<td>Sustained ventricular tachycardia (n)</td>
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<tr>
<td>Total</td>
<td>1/18</td>
<td>5/18</td>
<td>1/18</td>
<td>5/18</td>
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<tr>
<td>0–10 min after occlusion</td>
<td>0/18&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5/18</td>
<td>0/18&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5/18</td>
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<tr>
<td>10–60 min after occlusion&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1/17</td>
<td>1/9</td>
<td>1/18</td>
<td>1/10</td>
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<tr>
<td>Ventricular fibrillation (n)</td>
<td></td>
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<tr>
<td>Total</td>
<td>4/18&lt;sup&gt;e&lt;/sup&gt;</td>
<td>12/18</td>
<td>3/18&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>0–10 min after occlusion</td>
<td>1/18&lt;sup&gt;e&lt;/sup&gt;</td>
<td>9/18</td>
<td>0/18&lt;sup&gt;e&lt;/sup&gt;</td>
<td>8/18</td>
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<tr>
<td>10–60 min after occlusion&lt;sup&gt;f&lt;/sup&gt;</td>
<td>3/17</td>
<td>3/9</td>
<td>3/18</td>
<td>3/10</td>
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SG = stellate ganglionectomy.

<sup>a</sup>p = .02; <sup>b</sup>p = .009; <sup>c</sup>p = .008; <sup>d</sup>p = .004; <sup>e</sup>p = .001, All vs sham-operated dogs (one-tail Fisher’s exact test).

<sup>f</sup>Incidence calculated in animals alive by 10 min after occlusion.
Hemodynamic and ECG changes. Mean heart rates at the time of randomization were similar in all groups (154 ± 18, 152 ± 17, 151 ± 22, and 154 ± 18 beats/min, respectively in the right stellate ganglionectomy group and its control and in the left stellate ganglionectomy group and its control, respectively, NS). In the right stellate ganglionectomy group a significant reduction in mean heart rate was observed an average of 8 weeks after surgery (154 ± 18 vs 128 ± 19 beats/min, p < .01). By this time (i.e., before occlusion) this latter group presented a slower mean heart rate as compared with both sham-operated animals and those undergoing left stellate ganglionectomy (154 ± 18 + 152 ± 17 beats/min, respectively, p < .01). Basal R wave amplitude did not differ among groups, nor was there basal ST segment elevation in any dog. Table 1 also lists immediate (3 min) postocclusion changes: dogs in the right stellate ganglionectomy group presented lower mean R wave amplitude as compared with left stellate-pectomized dogs and lower mean ST segment elevation as compared with control dogs. Immediately after occlusion mean heart rate was unchanged in the right stellate ganglionectomy group and decreased in the other groups of animals (156 ± 21 vs 149 ± 32 beats/min, NS, in sham-operated dogs) but was only significantly decreased in the left stellate ganglionectomy group (158 ± 22 vs 140 ± 21 beats/min, p < .01). On the other hand, mean R wave amplitude was increased significantly in the presence of decreasing mean aortic pressure in all groups; the slightly higher mean aortic pressure observed in left stellate-pectomized animals reflected their higher basal levels.

Arrhythmias. Thirty of the 72 animals randomized to stellate ganglionectomy or second intercostal space thoracotomy (table 2) had ischemia-induced ventricular fibrillation. Whereas four cases were seen in the right stellate ganglionectomy group, 12 occurred in the right sham-operated group (p = .009). Furthermore, three dogs in the left stellate ganglionectomy group developed ischemia-induced ventricular fibrillation, whereas 11 cases were observed in the left sham-operated group (p = .008). In both sham-operated groups the incidence of ventricular fibrillation was higher early (0 to 10 min) after occlusion, whereas only one dog in the right stellate ganglionectomy group developed this arrhythmia (p = .004), and no case occurred in the left stellate ganglionectomy group (p = .001). In contrast, during the late (10 to 60 min) postocclusion period the incidence of ischemia-induced ventricular fibrillation was not statistically different among groups. The incidence of sustained ventricular tachycardia was not significantly lower (p = .09) in either the right or left stellate-pectomized group compared with its respective control group when data from the entire postocclusion period were analyzed. However, a significant difference

![Diagram](attachment:image.png)

**FIGURE 1.** The cumulative proportions surviving after left circumflex coronary arteriovenous pedicle occlusion are shown for right stellate ganglionectomy and right sham-operated groups (right) and for left stellate ganglionectomy and left sham-operated groups (left). Numbers of animals are also illustrated. X axis is time to ventricular fibrillation (in min) since all deaths were due to this arrhythmia. p values, as calculated with the Fisher's exact test, at 10 and 60 min after occlusion are indicated. The survival rates are calculated for the total 60 min postocclusion period with the modified Wilcoxon test. SG = stellate ganglionectomy.
(p = .02) was noted when data from the early (0 to 10 min) postocclusion phase were analyzed. On the other hand, neither the incidence nor the time distribution of nonsustained ventricular tachycardia or ventricular ectopic beats after occlusion differed statistically among the randomized groups (table 2).

Survival rate and prediction. A significant difference in the survival rate was noted in both the right (p = .0013) and left (p = .0012) stellate ganglionectomy groups vs their respective control groups (figure 1). The results of multiple stepwise Cox’s regression analysis are displayed in tables 3 and 4. Of univariate predictors of ventricular fibrillation considered in this study, sex (p = .011), ST segment elevation at 3 min after occlusion (p = .000), and treatment assignment (p = .000) remained significant predictors after multivariate analysis by all three solutions listed in Methods. Mean aortic pressure at 3 min postocclusion (p = .003) and occurrence of sustained ventricular tachycardia during 0 to 10 min after occlusion (p = .000) remained significant multivariate predictors only by solutions 1 and 2. Neither basal mean aortic pressure, R wave amplitude at 3 min postocclusion, ventricular ectopic beats, nor nonsustained ventricular tachycardia during 0 to 10 min after occlusion, which were all univariate predictors (p = .049, p = .017, p = .003, and p = .004, respectively), predicted multivariately the occurrence of ventricular fibrillation. On the other hand, weight entered in the multivariate prediction of ventricular fibrillation only with solutions 2 and 3 (p = .024 and p = .014, respectively). Comparing the global chi squares of the three solutions adopted for the multivariate Cox prediction model, a significantly (p < .000) better prediction was obtained with solution 3.

The correlation matrix among all measured variables (all possible pairs) for all 72 randomized animals is presented in table 5. Significant correlations (p < .01) were observed, in particular, between ECG changes.

### TABLE 3
Univariate and independent predictors of ventricular fibrillation during the 60 min after occlusion in all 72 randomized animals (Cox regression analyses)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
<th>Univariate p value</th>
<th>Multivariate p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>p value</td>
<td>1</td>
</tr>
<tr>
<td>Basal characteristics before occlusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>21 ± 5</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Sexa</td>
<td>1.37 ± 0.49</td>
<td>.011</td>
<td>.003</td>
</tr>
<tr>
<td>Month of occlusion</td>
<td>6.43 ± 2.94</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Latency period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anesthesia to thoracotomy</td>
<td>12 ± 3</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Thoracotomy to occlusion</td>
<td>15 ± 2</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>149 ± 24</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>R wave amplitude (mV)</td>
<td>1.99 ± 0.69</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>103 ± 5</td>
<td>.049</td>
<td>NS</td>
</tr>
<tr>
<td>Immediate (3 min) postocclusion changes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>142 ± 28</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>ST segment elevation (mV)</td>
<td>1.28 ± 0.86</td>
<td>.000</td>
<td>.000</td>
</tr>
<tr>
<td>R wave amplitude (mV)</td>
<td>2.70 ± 0.86</td>
<td>.017</td>
<td>NS</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>93 ± 4</td>
<td>.003</td>
<td>.012</td>
</tr>
<tr>
<td>Ventricular arrhythmias during 0–10 min after occlusionb</td>
<td>0.65 ± 0.48</td>
<td>.003</td>
<td>NS</td>
</tr>
<tr>
<td>Ventricular ectopic beats</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsustained ventricular tachycardia</td>
<td>0.35 ± 0.48</td>
<td>.004</td>
<td>NS</td>
</tr>
<tr>
<td>Sustained ventricular tachycardia</td>
<td>0.15 ± 0.36</td>
<td>.000</td>
<td>.002</td>
</tr>
<tr>
<td>Treatment assignmentc</td>
<td>0.5 ± 0.5</td>
<td>.000</td>
<td>.000</td>
</tr>
<tr>
<td>Stellate ganglionectomyd</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side of interventione</td>
<td>0.5 ± 0.5</td>
<td>.000</td>
<td>.000</td>
</tr>
</tbody>
</table>

1, 2, and 3 refer to the three solutions of the Cox’s model.
MAP = mean aortic pressure.

aScored 1 when male and 2 when female.
bScored from 1 (January) to 12 (December).
cScored 1 when present and 0 when absent.
dRank 1 to 4 based on the incidence of ventricular fibrillation (from the lowest to the highest) observed empirically in the randomized groups (table 2).
eScored 0 when present and 1 when absent.
fScored 0 when right and 1 when left.

(p = .02) was noted when data from the early (0 to 10 min) postocclusion phase were analyzed. On the other hand, neither the incidence nor the time distribution of nonsustained ventricular tachycardia or ventricular ectopic beats after occlusion differed statistically among the randomized groups (table 2).

Survival rate and prediction. A significant difference in the survival rate was noted in both the right (p = .0013) and left (p = .0012) stellate ganglionectomy groups vs their respective control groups (figure 1). The results of multiple stepwise Cox’s regression analysis are displayed in tables 3 and 4. Of univariate predictors of ventricular fibrillation considered in this study, sex (p = .011), ST segment elevation at 3 min after occlusion (p = .000), and treatment assignment (p = .000) remained significant predictors after multivariate analysis by all three solutions listed in Methods. Mean aortic pressure at 3 min postocclusion (p = .003) and occurrence of sustained ventricular tachycardia during 0 to 10 min after occlusion (p = .000) remained significant multivariate predictors only by solutions 1 and 2. Neither basal mean aortic pressure, R wave amplitude at 3 min postocclusion, ventricular ectopic beats, nor nonsustained ventricular tachycardia during 0 to 10 min after occlusion, which were all univariate predictors (p = .049, p = .017, p = .003, and p = .004, respectively), predicted multivariately the occurrence of ventricular fibrillation. On the other hand, weight entered in the multivariate prediction of ventricular fibrillation only with solutions 2 and 3 (p = .024 and p = .014, respectively). Comparing the global chi squares of the three solutions adopted for the multivariate Cox prediction model, a significantly (p < .000) better prediction was obtained with solution 3.

The correlation matrix among all measured variables (all possible pairs) for all 72 randomized animals is presented in table 5. Significant correlations (p < .01) were observed, in particular, between ECG changes.
and arrhythmias and between arrhythmias and the occurrence of ventricular fibrillation during the observation period. This analysis also showed that the only significant correlation between the side of intervention and any of these variables was that between left side and higher basal heart rates (p < .01).

Higher t values were found with the Cox model (table 4, solution 3) than with the linear or the logistic regression models (table 6) for each of the significant covariates related to survival (ST segment elevation at 3 min postocclusion, presence of stellate ganglionectomy, and weight), with the exception of sex. Thus, the Cox model provided a better fit to the data and indeed was more appropriate for prediction of survival in this investigation. It might therefore be of interest to point out that during the stepwise calculations, the Cox model indicated that although not statistically significant in terms of survival prediction, the contribution of left-sided interventions (either stellectomy or sham operation) was more favorable than that of interventions on the right side (table 4).

Discussion

This is the first investigation to have explored the antiarrhythmic effects of right as compared with left stellate ganglionectomy in a large series of randomized dogs1-21 according to the intention-to-treat plan.51 In addition, the multivariate Cox regression model,46-48 including several covariates that might explain differences in survival after coronary occlusion,27, 33, 35, 41-45 was used for the first time31, 52-55 in the experimental setting.

After 8-week-old right or left stellate ganglionectomy the incidence of ischemia-induced ventricular fibrillation was significantly reduced (figure 1). Late after unilateral stellectomy the predictable potency of the Cox regression model was improved significantly (table 4). These effects were associated with reduced ST segment elevation at 3 min after occlusion. A reduced incidence of sustained ventricular tachycardia during the early postocclusion period might also be implicated. The side of intervention did not influence survival significantly; however, left-sided interventions were more effective than right-sided ones.

Limitations. Anesthesia22 might have interfered with sympathetic cardiovascular excitatory reflexes.56-58 However, the significant differences in basal mean heart rate in right stellctomized animals as compared with sham-operated and left stellctomized dogs and the changes observed after occlusion indicate that neurovegetative adaptation1, 2, 58-62 was not overshadowed in this study. Moreover, significantly lower mean heart rate at 3 min after occlusion in left stellctomized dogs might have followed to reduce sympathovagal inhibi-
tion as compared with that in both groups of sham-operated animals, still suggesting that neurovegetative adaptation was not impaired in this study.

Presence or absence of collaterals in hearts subjected to acute myocardial ischemia can affect outcome. In fact, the incidence of ventricular fibrillation after high ligation of the left circumflex coronary artery in anesthetized dogs with preexisting collaterals was 3.7% (one of 27), whereas that of dogs without collaterals was 100% (19 of 19). This gives an overall incidence of 43.5% (20 of 46), with a 99% confidence interval of 19.4% to 67.5%, which is in keeping with results obtained in our laboratory. On the other hand, occlusion of the left circumflex coronary arteriovenous pedicle was performed, which might be less than ideal since such occlusion is unlikely to occur in the clinical situation. However, the 60 min incidence of ventricular fibrillation after such a procedure has been observed to be 60.71% in a group of 28 control dogs. The 999/1000 confidence interval for a group of 18 dogs ranges from 22.8% to 99.6%. It thus follows from statistical analysis that the results of the present investigation are not slanted at a probability of 1/100 or less.

**Cox regression analysis and survival.** The Cox model was chosen over linear or logistic regression, since the observation period was short, the incidence of death was high, and the time to death was known and believed to be important. Indeed a systematic comparison of these three methods disclosed a better fit to data with the Cox model (tables 4 and 6).

Male sex, greater weight, and lower mean blood pressure increased the risk of ventricular fibrillation, which confirms and extends the results of previous univariate studies. Latency periods from thoracotomy to occlusion, or season of the year, contrary to previous reports, were not predictors. Finally, ventricular ectopic beats and nonsustained ventricular tachycardia were predictors of ventricular fibrillation, but significantly so only by univariate analysis.

ST segment elevation at 3 min after occlusion was an independent predictor of ventricular fibrillation (table 3), overshadowing the predictive contribution of R wave changes due to the high correlation between the two (tables 3 and 5). This is in keeping with previous clinical and experimental reports. Basal heart rate and ST segment elevation at 3 min after...
occlusion did not correlate (table 5), suggesting that a reduced incidence of arrhythmias might result from interventions that reduce ischemia\textsuperscript{31} independently of an effect on heart rate.\textsuperscript{43} In the right stellatectomy group, the lower ST segment elevation reached in the immediate postocclusion phase might follow subtle improvement in collateral function\textsuperscript{64} resulting from reduced sympathetic tone at the level of the anterior wall of the left ventricle.\textsuperscript{58, 71–73} It is more difficult to explain the antifibrillatory effect of left stellate ganglionectomy.\textsuperscript{3, 4, 9, 58} Since left sympathetic nerves distribute predominantly to the inferoposterior wall of the left ventricle,\textsuperscript{71} a reduction in locally released catecholamines\textsuperscript{17, 69, 74} and/or local changes in electrophysiological properties\textsuperscript{75, 76} after inferoposterior wall ischemia might be implicated. Clearly, a more precise definition of the mechanisms involved in the antifibrillatory effects late after both types of unilateral stellate ganglionectomy is needed.

The incidence of sustained ventricular tachycardia during the early postocclusion period was an independent predictor of ventricular fibrillation only with the first two solutions of the Cox model (table 4). Since right and left stellate ganglionectomy reduced the incidence of early-phase sustained ventricular tachycardia (table 2), this effect might be considered, as was the case after nadolol in chronic canine myocardial infarction,\textsuperscript{39} as contributory to the prevention of ventricular fibrillation. However, neither type of stellatectomy reduced the other forms of arrhythmias. This is in keeping, early after occlusion, with data obtained in immunosympathectomized dogs.\textsuperscript{77}


c| Ve1 | VT1 | Sust VT1 | MO | Treat |
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<tbody>
<tr>
<td>.5319</td>
<td>.3097</td>
<td>.2579</td>
<td>.1074</td>
<td>.0875</td>
</tr>
<tr>
<td>.0875</td>
<td>.0292</td>
<td>.3474</td>
<td>-.2707</td>
<td>-.2232</td>
</tr>
</tbody>
</table>

Abbreviations are as in table 5. t values above | 1.96 | are significant, with p < .05 or less. Multiple linear regression (BMDP 1R) has VFO as the regression dependent variable; multiple $r = .7676$ and multiple $r$ square = .5892 ($p < .0000$). Logistic regression (BMDP LR) was performed with the asymptotic covariation estimation method; all variables are in at step 0 and one movement is permitted (remove limit: $p > .15$). At the end of the stepwise procedure the Hosmer's goodness-of-fit test provided a $p$ value = .651, thus indicating a good fit of the predicted values to the data.

Higher basal heart rates were present in sham-operated dogs; these latter animals developed earlier posts ischemic ventricular fibrillation (table 5). However, neither basal nor immediate postocclusion heart rate contributed significantly to the prediction of outcome (table 3). These findings do not indicate that heart rate will not affect outcome when varied over wider ranges or that the lower basal heart rate in right stellactomized animals did not contribute to the lessening of ischemia after occlusion and to improved outcome. The analysis does suggest, however, that heart rate did not, in our study, substantially alter the relationship observed between outcome and the other significant covariates. On the other hand, it is possible to conclude that the significant effects of left stellatectomy were rate independent.\textsuperscript{3, 4, 76}

Effects of stellate ganglionectomy on arrhythmias and survival. In the context of acute myocardial ischemia neither the arrhythmogenic effect of right\textsuperscript{5, 6, 9} nor the antiarrhythmic effect of left stellate ganglionectomy\textsuperscript{3–7, 9} had been indisputably proven independent
of vagotomy, presence, type, and amounts of anesthesia, and of whether it was late or early after unilateral stellpectomy. In a randomized study in conscious dogs with anterior myocardial infarction Schwartz and Stone reported that 2- to 3-week-old left stellpectomy exerts a major protective effect in reducing the incidence of acute posts ischemic ventricular fibrillation (five of 15 or 33% vs 11 of 17 or 65%). Schwartz et al. confirmed that left stellpectomy reduced to 0 the incidence of ventricular fibrillation in 14 dogs of a group of 35 with anterior myocardial infarction and subjected to repeated exercise-induced ischemia plus left circumflex coronary artery occlusion-reperfusion. The effect of right stellpectomy on the incidence of ventricular arrhythmias was less clearly established and largely different protocols were used, often in limited groups of animals.

The data from the present investigation, obtained in all the 72 initially randomized animals, show that late after left stellate ganglionectomy, despite anesthesia, significant antibrillatory effects are seen, but also indicate that similar effects are obtained late after right stellate ganglionectomy. Both interventions improved survival in this preparation as judged from either a univariate or multivariate approach (figure 1; tables 3 and 4). These results therefore confirm previous reports on the antibrillatory effects of left 1, 4 and indicate like effects of right stellate ganglionectomy in a canine preparation of sudden death.

This article is a tribute to the memory of Jean Torresani, M.D., Professor of Cardiology, University of Aix-Marseille II, Marseille, who supported this investigation and gave his talented advice during all phases of the study. His sudden and unexpected demise on January 14, 1986, prevented his formal approval of the final draft. It would not have been possible to refine the analysis of the data without the expert counsel of Alessandro Menotti, M.D., Professor of Epidemiology and Biostatistics, Istituto Superiore di Sanità, Rome, whose courtesy and fine judgment are deeply appreciated. Our gratitude is also extended to Peter J. Schwartz, M.D., Associate Professor of Medicine, University of Milan, Milan, who kindly reviewed this manuscript and made suggestions.

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