Cryoblockade in Limbic Brain (Amygdala) Prevents or Delays Ventricular Fibrillation After Coronary Artery Occlusion in Psychologically Stressed Pigs

Clara Carpeggiani, Carole Landisman, Marie-Francois Montaron, and James E. Skinner

Neomammalian and paleomammalian (limbic) brain structures control different behaviors and the autonomic support specific to each. Both neural systems are involved in cardiovascular disorders. Our previous studies showed that bilateral cryoblockade of a neomammalian structure (the frontal lobes) reduces blood pressure elevations in experimental hypertension and prevents lethal arrhythmogenesis in experimental myocardial infarction. Other studies showed that bilateral lesions in a paleomammalian structure (amygdala) also reduce the blood pressure elevations. Thus, we hypothesized that cryoblockade of the amygdala would prevent lethal arrhythmogenesis. We found that cooling of cryoprobes implanted bilaterally in the amygdala prevented ventricular fibrillation in five of eight pigs during a 20-minute period of reversible myocardial ischemia, whereas cryoblockade in structures surrounding the amygdala (five pigs), unilateral cryoblockade in the amygdala (two pigs), or sham operations (three pigs) did not prevent ventricular fibrillation (p<0.003). In two of the five pigs with amygdaloid blockade, the cooling was reversed at 20 minutes while the coronary occlusion continued (24 hours), and still ventricular fibrillation did not occur. In all other cases, ischemia was reversed at 20 minutes so that the heart could recover; this enabled histochemical documentation that the heart was normal at the time(s) ischemia was induced, and it allowed within-subject control experiments. Amygdaloid cryoblockade produced a small but significant increase in heart rate (10 beats per minute) without a change in blood pressure. We conclude that the paleomammalian brain, like its neomammalian counterpart, mediates brain effects on fatal arrhythmogenesis. (Circulation Research 1992;70:600–606)

**Key Words** · ischemia · sudden cardiac death · neurocardiology

Novel stimuli produce markedly enhanced behavorial and hemodynamic reactions in rats inbred to have high blood pressure.1,2 Bilateral lesion of the amygdala reduces both the behavioral and hemodynamic responses and lowers the blood pressure elevations.3,4 Because some blood pressure elevation remains, another cerebral source must exist for maintaining this residual.5 Blockade in the frontal cortex reduces blood pressure elevation, whereas blockade of the output pathways from both frontal cortex and amygdala (i.e., as they travel from the forebrain to brainstem6) completely normalizes blood pressure.6,7

In humans, hypertension predicts enhanced risk of sudden cardiac death.8 Animal studies suggest that the same neural system, the frontal cortex, can both maintain raised blood pressure5,6 and control risk of lethal arrhythmogenesis.9 Therefore, the present experiments were carried out to investigate the role of the amygdala in arrhythmogenesis. Our present hypothesis is that bilateral blockade of the amygdala, like that in the frontal lobes, may prevent or significantly delay the onset of ventricular fibrillation (VF) in the acutely ischemic heart of the conscious psychologically stressed pig.

**Materials and Methods**

**Surgical Preparation of Pigs**

Two types of juvenile farm pigs were randomly assigned to experimental and control groups: 12 mixed-breed Hampshires obtained from a local prison farm and 12 mixed-breed Yorkshires obtained from a local research animal breeding facility. The pigs were anesthetized with pentobarbital (35 mg/kg i.v.), intubated, and supplemented with methoxyflurane anesthesia as needed. All pigs were intrathoracically operated on (sterile procedure) through a left thoracotomy. A hydraulically operated ligature occluder of the type previously described10 or a commonly manufactured balloon-cuff occluder was placed on the left anterior descending coronary artery 1 cm distal to its bifurcation with the circumflex artery. A pulsed-Doppler blood-velocity device for measuring coronary artery flow was placed 5 mm distal to the ligature. In all pigs a catheter was implanted in the mamillary or femoral artery for measurement of systolic/diastolic blood pressure. Permanently implanted, insulated, stainless-steel wire electrodes were placed on...
the myocardium or in the skin of the limbs for recording the electrocardiogram. A total of 18 pigs survived the surgery and had functioning cryoprobes, coronary constrictors, and blood velocity detectors.

**Cryoprobes**

For intracerebral cryoblockade, two stainless-steel cryoprobes were permanently implanted during surgery; each had a 1×2-mm cross section with a heater wire on the shaft, an exposed 4-mm tip, and thermocouples on the shaft and tip. We made a stereotaxic atlas of the pig brain to use as the implant guide; the coordinate planes were defined by the axis through the auditory meatus and infraorbital ridge; coronal planes were labeled, in millimeters, anterior (+) or posterior (−) to the junction of the frontal and parietal cranial sutures at the midline (i.e., bregma). The construction, operation, and results of use of the cryoprobes have been described in detail elsewhere. Each cryoprobe was sterilized, implanted, and then permanently secured to the cranium using stainless-steel screws and dental acrylic.

**Cerebral Targets**

The lateral and anterior borders of the central nucleus of the amygdala were the intended targets for the cryprobe tips. As controls, the structures surrounding the amygdala were targeted (globus pallidus, caudate nucleus/putamen, basis pedunculi, and ventrolateral thalamus). Additional controls had unilateral amygdaloid placements (i.e., with the other cryoprobe in a control structure), or they were sham-operated controls, in which cases the probes were lowered into a control target but not permanently implanted (i.e., they were immediately removed). The critical region of the central nucleus, between 13 and 15 mm lateral to the midline, was avoided to prevent surgical damage to this major output center of the amygdala.

**Behavioral Protocol for Pigs**

After 4 or 5 days of postoperative recovery, each pig was immobilized by taping its feet together and transported to the recording chamber. The recording cables and cryoprobe lines were attached. Methanol, cooled by dry ice, was circulated through the probes, and direct current from a 12-V battery was circulated through the shaft heater wires. The heater current was adjusted to keep the shaft at brain temperature while the tip was lowered to the desired temperature for cryoblockade; that is, the tip was lowered to a temperature of −5°C for maximum reversible cryoblockade, resulting in a gradient of 0–10°C extending radially from very near the tip surface to 3 mm out into the tissue. To allow sufficient time for each temperature gradient to stabilize, the desired tip temperature was maintained for at least 3 minutes before data collection. All pigs were unfamiliar with the laboratory and behaviorally reactive to it and the personnel. All pigs were awake and alert at the time the coronary artery was occluded. Complete obstruction of coronary blood flow was documented by the pulsed-Doppler device. If VF occurred, the constriction of the artery was reversed, and the heart was electroconverted with one or two extrathoracic 400-W/sec pulses. If the pig had not manifested VF by 20 minutes, the artery was disoccluded, and when reperfusion fibrillation occurred, the heart was electroconverted; cryoblockade was reversed only after a normal sinus rhythm had been established. It had been determined in previous pig studies that a safe interval for reversible myocardial ischemia was 20 minutes. Reversing the occlusion before the end of this period allowed 1) the histochemical confirmation that the recovered heart was normal (a finding that implies that the heart was also normal during the previous condition before ischemia was produced) and 2) the use of the pig in a second experiment as its own within-subject control. All data reported below are from experiments in which complete recovery from prior ischemia could be documented; that is, recovery was judged, as in previous studies, by the postmortem histochemical data, as well as in vivo hemodynamic and electrocardiographic observations.

**Histological Processing of Postmortem Tissue**

Each pig was anesthetized with sodium pentobarbital and intracerebrally perfused with formaldehyde (38%) through bilateral intracarotid arterial catheters. The heart was removed and fixed in 4% formaldehyde. Samples of myocardium were removed from the center of the field in the left ventricle perfused by the left anterior descending coronary artery. The coronary artery was opened and examined for signs of stenosis and arteritis. Later histological verification of the intracerebral location of each cryoprobe was made from photographic reconstructions of serial frozen sections of the brain. Histological assessment of the normal state of the myocardium was made by finding 1) no fibers in the field of ischemia that were stained positively with the hematoxylin–basic fuchsine–picric acid stain (HBFP), 2) no wavy fibers (hematoxylin and eosin stain), and 3) no infiltration by polymorphonuclear leukocytes. All pigs were humanely treated at all times according to the guidelines published by the American Physiological Society, and our research protocols were approved by the appropriate committee of Baylor College of Medicine.

**Statistical Tests**

All parametric statistics used are Student’s t test (between-subject comparisons) or paired t test (within-subject comparisons), both of which presume continuous scales, random sampling, and homogeneity of variance. Homogeneity of variance was tested using Hartley’s Fmax statistic. When the presumptions of the parametric statistics could not be strictly met, the binomial distribution was used for determining nonparametric statistical significance.

**Results**

Table 1 shows all of the data for all of the subjects. Of the total of 18 pigs, four Hampshire (H1, H2, H3, and H4) and four Yorkshire (Y1, Y2, Y3, and Y4) pigs had bilateral placement of cryoprobes in the amygdala, as indicated by the dotted probe surfaces on the cerebral reconstructions shown in Figure 1. The other pigs had the following placements: pigs Y14 and Y17 had placements that were unilateral for the amygdala, pigs H5–H8 and Y5 had placements in structures adjacent to the amygdala (some of which were outside the coronal planes shown in Figure 1), and pigs Y6–Y8 were sham operated. Of the six pigs having multiple experiments,
**TABLE 1. Hemodynamics in Conscious Unadapted Hampshire and Yorkshire Juvenile Farm Pigs Before, During, and 10 Minutes After Bilateral Cryoblockade; the Cryoblockade Effect on Ventricular Fibrillation Latency After Left Anterior Descending Coronary Artery Occlusion; and Histological Staining of Myocardial Tissue After Recovery From Ischemia**

<table>
<thead>
<tr>
<th>Pig No.</th>
<th>Cryoprobes locations</th>
<th>Coronal coordinates from atlas (mm)</th>
<th>Hemodynamics at rest</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR (bpm)</td>
<td>BP (mm Hg)</td>
</tr>
<tr>
<td>H1*</td>
<td>AM O</td>
<td>+15.0</td>
<td>165</td>
</tr>
<tr>
<td>H2†</td>
<td>AM L</td>
<td>+16.2</td>
<td>121</td>
</tr>
<tr>
<td>H3†</td>
<td>AM M</td>
<td>+16.2</td>
<td>133</td>
</tr>
<tr>
<td>H4*</td>
<td>AM B</td>
<td>+16.2</td>
<td>102</td>
</tr>
<tr>
<td>Y1*</td>
<td>AM O</td>
<td>+15.0</td>
<td>144</td>
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<tr>
<td>Y2*</td>
<td>AM B</td>
<td>+16.2</td>
<td>145</td>
</tr>
<tr>
<td>Y3</td>
<td>AM B</td>
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<tr>
<td>Y4</td>
<td>AM L</td>
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</tr>
<tr>
<td>Mean</td>
<td></td>
<td>136§</td>
<td>114</td>
</tr>
<tr>
<td>Y14</td>
<td>AM L + GP</td>
<td>+16.2</td>
<td>179</td>
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<tr>
<td>Y17</td>
<td>GP + AM L</td>
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</tr>
<tr>
<td>Y5*</td>
<td>DOR AM</td>
<td>+17.5</td>
<td>120</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>134</td>
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</thead>
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<tr>
<td>Y6†</td>
<td>No CP</td>
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<td>132</td>
</tr>
<tr>
<td>Y7†</td>
<td>No CP</td>
<td>...</td>
<td>131</td>
</tr>
<tr>
<td>Y8†</td>
<td>No CP</td>
<td>...</td>
<td>143</td>
</tr>
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Pre, before cryoblockade; Cool, during cryoblockade; Post, 10 minutes after cryoblockade; VFL, ventricular fibrillation latency; HBFP, positive (+) or negative (−) hematooxylin–basic fuchsin–picric acid stain; HR, heart rate, averaged over a quiescent control period of ~3–5-minute duration (values from similar pigs in a separate hemodynamic study from our laboratory) are n=52, HR=134±17 beats per minute [bpm]); BP, systolic/diastolic blood pressure, averaged over the same quiescent control period described above (values from similar pigs in a separate study from our laboratory are systolic BP=105±6 mm Hg); PHR, peak HR, the highest value recorded during each condition; H, Hampshire pigs; Y, Yorkshire pigs; AM, amygdaloid nucleus; O, corticalis; L, lateralis; M, medialis; B, basalis; GP, globus pallidus; CAUD, caudate nucleus; PUT, putamen; TH, thalami; VL, ventralis lateralis; DOR AM, just dorsal to the amygdala; No CP, no cooling period. All cryoprobe locations were histologically verified to be bilateral, except those for Y14 and Y17, which were unilateral. The coronal coordinate column gives the coronal plane in our stereotactic atlas, in millimeters anterior to the bregma (i.e., the midline joint of the frontal and parietal cranial sutures). VFL was determined during cryoblockade to the nearest 0.1 minute; values >20 minutes indicate that ventricular fibrillation did not occur within the 20-minute period of reversible ischemia (H1, H2, and Y1) or the 24-hour period of maximum observation (H3 and H4). Because the mean coronary blood velocity dropped to zero, occlusion was complete. Oclusions maintained for >20 minutes produced positive HBFP stains in the myocardial tissue from the middle of the field of ischemia.

*Bad arterial catheter (no reflux, no valid pressures).
†Unreliable diastolic pressure not shown (i.e., diastolic values changed after flushing catheter with saline; systolic values did not).
‡Data not available; pig broke arterial catheter or cryoprobe line after cooling period (broken cryoprobe line squirted alcohol on pig and disrupted experiment).
§Mean HR increased by cryoblockade, within-subject comparisons (paired t=2.01, df=7, p<0.05).
||Not significant (paired t=1.11, df=3, p>0.05).
¶Mean PHR increased by cryoblockade, within-subject comparisons (paired t=2.48, df=7, p<0.05).
##Frequency of no ventricular fibrillation significantly different for group with cryoprobes inside amygdala vs. group with cryoprobes outside amygdala (p<0.003, binomial probability ratio).

three had cryoprobes in the amygdaloid nuclei and three had cryoprobes in surrounding structures. Of the 12 pigs having single experiments, five had cryoprobes in the amygdaloid nuclei and seven had placements that were either unilateral, in surrounding structures, or sham. Heart rate and blood pressure were observed just before the cryoprobes were operated, 3–10 minutes after stable cryoblockade had been established, and 10 minutes after the cessation of cryoprobe cooling. All hemodynamic data were observed at rest after a 3–5-minute period of behavioral quiescence.

Figure 2 shows the effects of bilateral cooling of the amygdala on the VF latency after occlusion of the left anterior descending coronary artery in comparison with the results from the controls. Those pigs not manifesting VF by 20 minutes (no VF) had both their acute myocardial ischemia and cryoblockade reversed after 20 minutes of ischemia; pigs H3 and H4 had only
The activity in these descending coronary artery or delayed had fibrillation occurred external capsule; external with the to stria terminalis and medial to the nucleus lateralis; S (arrow), stria terminalis; L, lateralis, the lateral extent of which is the external capsule (dashed lines); M, medialis, containing the uncus; O, corticalis, superficial, lateral to M, ventral and medial to external capsule; B, basalis, dorsal to O and M and ventral to C and L. Pigs are represented as follows: stippling (left to right): Y3, H2, H4/Y2, H3, Y1, H1, and Y4; stripes (left to right): Y5, H7, H6, and H5, where Y indicates mixed-breed Yorkshire pigs and H indicates mixed-breed Hampshire pigs.

FIGURE 1. Reconstruction of cooling surfaces on coronal brain sections from our stereotaxic atlas of the pig brain. All pigs shown had bilateral cryoprobe in the amygdala or nearby surrounding structures. Those cooling surfaces indicated by stippling prevented or delayed (i.e., beyond 20 minutes to 24 hours) the initiation of ventricular fibrillation after occlusion of the left anterior descending coronary artery in the conscious unadapted pig (prevents VF); those surfaces indicated by stripes show ineffective sites at these levels, with others being at other levels (no effect). The surface with the number 2 represents congruent reconstructions from two pigs. The plus sign beneath each plane indicates its distance (in millimeters) anterior to the bregma cranial suture (i.e., with the horizontal plane defined by the top of the infraorbital ridge and the center of the auditory meatus). C, centralis, lateral to the stria terminalis and medial to the nucleus lateralis; S (arrow), stria terminalis; L, lateralis, the lateral extent of which is the external capsule (dashed lines); M, medialis, containing the uncus; O, corticalis, superficial, lateral to M, ventral and medial to external capsule; B, basalis, dorsal to O and M and ventral to C and L. Pigs are represented as follows: stippling (left to right): Y3, H2, H4/Y2, H3, Y1, H1, and Y4; stripes (left to right): Y5, H7, H6, and H5, where Y indicates mixed-breed Yorkshire pigs and H indicates mixed-breed Hampshire pigs.
in pain. Additional control values were observed in our laboratory in a separate hemodynamic study in the pig\(^1\) and are shown in Table 1 in the footnotes.

The effect of amygdaloid cryoblockade on mean resting heart rate is demonstrated in Table 1. A small but significant increase occurred that is 10 beats per minute higher for grouped within-subject comparisons (paired \(t = 2.01, df = 7, p < 0.04\)). Mean systolic blood pressure is not significantly altered during this cryoblockade. Peak heart rate was also increased during amygdaloid cryoblockade (paired \(t = 2.48, df = 7, p < 0.03\)).

Figure 4 demonstrates the sensitivity of the HBFP stain to the local ischemic injury created by coronary artery occlusion for 35 minutes (HBFP-POS in the figure); this positive HBFP seen in the center of the field of ischemia is contrasted with a negative stain observed in one of the present experimental animals in which the occlusion lasted only 20 minutes (HBFP-NEG in the figure). In each case, reperfusion VF occurred, the heart was electroconverted, and the tissue sample was taken after 24 hours of recovery. The tissue containing the tie-down suture for the coronary constrictor invariable showed a small amount of positive HBFP staining, but this occurred in all pigs and could not account for any of the results. The tabulation for positive HBFP staining in the previously ischemic field of the left ventricle is shown for all pigs in Table 1. Six Hampshire and 10 Yorkshire pigs showed complete histochemical and hemodynamic recovery of the myocardium after severe ischemia had been induced for a maximum of 20 minutes; two Hampshire pigs (H3 and H4) had their coronary artery constriction maintained for 24 hours, and at autopsy their hearts showed positive HBFP stains and severely ischemic left ventricles.

**Discussion**

Our results show that temporary cryoblockade of the amygdala in the unadapted (i.e., psychologically stressed) pig has a salutary effect on susceptibility of the acutely ischemic heart to lethal arrhythmogenesis. Our previous studies have shown that if a pig does not manifest VF within 14 minutes after acute occlusion of the left anterior descending coronary artery, then it is not likely to occur within the next 24 hours\(^9,10\); this is the case, even though the salutary effects of cryoblockade may have been reversed at an earlier time.\(^9\) These prior findings are supported in the present study by two observations (in pigs H3 and H4) in which VF did not occur even though the cryoblockade was reversed at 20 minutes. Thus, delayed VF (i.e., VF occurring after 20 minutes) is interpreted to indicate no VF.

The gradient of cryoblockade produced by a cryoprobe tip temperature of \(-5^\circ\)C is \(-3\) mm in radius.\(^11,12,14\) Thus, all gradients produced in the amygdala should have completely inactivated all synaptic and axonal transmissions within this limbic structure. Similar gradients of cryoblockade in structures surrounding the amygdala (including the contiguous tissue at the dorsal border) had no influence on VF latency. Also, cryoblockade of one amygdala appears to have no
effect. Thus, the observed salutary effects on arrhythmogenesis are attributed to complete inactivation of the amygdala.

The bilateral cryoblockade of the amygdala is associated with an increase in both resting and peak heart rate, while arterial blood pressure remains unchanged. These data are in agreement with results obtained in rodents and felines, in which it is interpreted that the frontal lobes are relatively more responsible for evoked heart rate changes and that the amygdaloid nuclei mediate blood pressure alterations. 15,16 Although tonic blood pressure does not seem to change during amygdaloid cryoblockade, transient alterations can still occur (Figure 3).

The functioning of the frontocortical and amygdaloid systems may not be independent of one another. For example, electric stimulation of the central nucleus of the amygdala was initially thought to produce hemodynamic responses similar to those elicited naturally by fear,17 but it was later discovered that the direction of each autonomic response (i.e., whether it increases or decreases) is dependent on the particular sleep/waking state that exists at the moment of stimulation.18-20 The frontal lobes have an important role in regulating sleep/waking states,21 so they must be able to control the direction of any responses that can be evoked by amygdaloid stimulation. Regulation of the amygdala by the frontal lobes is supported by anatomical studies that show a substantial projection from each frontal lobe to its corresponding amygdala.22 Also supporting this arrangement is the observation that electric stimulation of a frontal lobe can completely inhibit the cardiovascular reaction that normally follows a stimulus to the central nucleus of the amygdala.23 In summary, the frontal lobes can regulate and even completely inhibit amygdaloid cardiovascular functions. This is precisely the hierarchical arrangement hypothesized by MacLean24 between the neomammalian and paleomammalian cerebral systems.

The descending cerebral regulation of the cardiovascular system may operate indirectly, as well as directly, through the modulation of three autonomic reflexes (i.e., via respiration, low-level blood pressure regulation, and body temperature change).25 These peripheral autonomic reflexes appear to be inhibited at the level of the brainstem by descending projections from the frontal cortex or amygdala.27 Thus, the convergence of descending central and ascending peripheral information at the brainstem centers determines the beat-to-beat intervals and their corresponding blood pressure pulses.

The mechanism by which the frontal lobes and the amygdala, either singly or jointly, regulate the vulnerability of the heart to lethal arrhythmogenesis may be related to their net contributions in the control of the heartbeat intervals. In patients with a recent myocardial infarction, several physiological measures have been shown to be prospective predictors of lethal arrhythmogenesis. Kleiger et al28 showed that a reduced standard deviation of the RR intervals was a statistically significant prospective predictor, and La Rovere and colleagues29,30 demonstrated that a reduced change in the mean of the RR intervals in response to high levels of

FIGURE 4. Photomicrographs showing histological evidence for the reversibility of temporary myocardial ischemia. The lower left panel shows a negative hematoxylin–basic fuchsin–picric acid stain (HBFP-NEG) in recovered porcine left ventricular tissue that was taken from the middle of the area of ischemia caused by a prior 20-minute period of complete occlusion of the left anterior descending coronary artery. In another pig, the binding of fuchsin to the extracellular mucopolysaccharides that have not recovered from temporary ischemia are indicated as dark spots (HBFP-POS, lower right panel); in this latter case, the coronary occlusion was maintained for 35 minutes before flow was reestablished. Reperfusion fibrillation occurred in both of the cases shown, and successful electroconversion was achieved after the second extrathoracic discharge (400 J each); normal coronary flow was reestablished in both cases. The HBFP-POS stains were associated with the presence of wavy fibers and polymorphonuclear leukocytes seen in adjacent sections stained with hematoxylin and eosin (H&E, top panels).
blood pressure (i.e., a reduced baroreflex sensitivity) also predicts increased risk. Following the suggestion that normal heartbeats manifest a pattern characterized by mathematical chaos,31,32 our laboratory used a chaos descriptor (the point correlation dimension) to investigate risk in a pig model of experimental myocardial infarction. We found that the correlation dimension declines proportionally as the heart becomes more vulnerable to lethal arrhythmogenesis.33

We conclude that the amygdala, through its descending control of cardiovascular dynamics, has an important role in determining the vulnerability of the acutely ischemic heart to lethal arrhythmogenesis. The mechanism by which this role is expressed is not yet known. Because the amygdala is a component of a higher cognitive structure (i.e., the limbic system or paleomammalian brain) and has both direct and indirect control over autonomic effectors, it seems likely that the mechanism, when it becomes known, will be extraordinarily complex. One way around this “complexity barrier” may be through the use of descriptors of the low-dimensional chaos inherent in heartbeat dynamics.

References
Cryoblockade in limbic brain (amygdala) prevents or delays ventricular fibrillation after coronary artery occlusion in psychologically stressed pigs.
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