Cardiac sympathetic nerve activity and ventricular fibrillation during acute myocardial infarction in a conscious sheep model

D. L. Jardine, C. J. Charles, C. M. Frampton, and A. M. Richards

Christchurch School of Medicine and Health Sciences, Christchurch Hospital, Christchurch, New Zealand

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Jardine DL, Charles CJ, Frampton CM, Richards AM. Cardiac sympathetic nerve activity and ventricular fibrillation during acute myocardial infarction (MI) has not been assessed in conscious animal models. During the first 60 min post-MI, mean blood pressure (MBP), heart rate (HR), and CSNA were recorded continuously in 20 conscious sheep. Resistant sheep (group A, n = 10) were compared with susceptible sheep (group B, n = 10) who developed fatal VF (n = 7) or sustained ventricular tachycardia (VT, n = 3). The mean time to VF/VT was 28.1 ± 3.3 min. In group B, MBP, HR, and CSNA were averaged at each consecutive minute from baseline at 14 min before the onset of VF/VT and compared with time-matched values in group A. When compared with those of group A, indexes of CSNA burst size increased before the onset of VF/VT: burst area/minute (F13,208 = 2.17, P = 0.01) and burst area/100 beats (F13,3208 = 1.86, P = 0.04). By contrast, burst frequency indexes were not significantly different: burst frequency (F13,208 = 1.6, P = 0.09) and burst incidence (F13,208 = 1.48, P = 0.13). In group A, CSNA burst area/min and burst area/100 beats did not change across this time period (F13,117 = 0.97, P = 0.5, F13,117 = 0.96, P = 0.7) but increased with time in group B (F13,91 = 2.3, P = 0.01; and F13,91 = 2.25, P = 0.01). Between-group comparisons demonstrated no differences in time of onset of ventricular ectopic beats: 18.5 (range 12–24) in group A versus 15.0 min (range 7–22) in group B (Mann-Whitney U-test, P = 0.09). Pre-MI baroreflex slopes were similar: R-R slopes were 11.8 ± 2 and 15.6 ± 1.1 ms/mmHg (t18 = −1.6, P = 0.14). CSNA slopes were −1.8 ± 0.3 and −2.3 ± 0.2%/mmHg (t18 = −1.4, P = 0.2). An early increase in CSNA burst size indexes (before 60 min post-MI), mediated by an excitatory sympathetic reflex, is important in the genesis of VF/VT.

Sudden cardiac death by definition occurs within the first hour of symptoms and is usually secondary to ventricular tachyarrhythmia (47). It remains extremely common in Western society and claims over 400,000 lives in the United States each year. In 80% of cases, coronary artery disease is the etiology (6, 43), and the association among myocardial ischemia, cardiac neural activity, and ventricular tachyarrhythmias is accepted although it has only been demonstrated in anesthetized animal models (13). In the setting of previous infarction and heart failure, decreased vagal tone may predispose to sudden cardiac death (23, 39). Sudden death is also common during acute myocardial infarction (MI), but over 50% of deaths occur during the first 60 min, usually before any form of monitoring can be undertaken (27). In these patients, ventricular fibrillation (VF) and polymorphic ventricular tachycardia (VT) are the common lethal arrhythmias and are often preceded by signs of sympathetic overactivity (34). In anesthetized animal models, single-fiber cardiac sympathetic nerve activity (CSNA) has been shown to increase during coronary occlusion. Brown (2) demonstrated that coronary occlusion caused an immediate increase in the firing of afferent nerves running in cardiac sympathetic nerves. Malliani et al. (29) subsequently recorded efferent cardiac sympathetic activity that increased usually within seconds of ischemia and proposed the existence of an excitatory sympathetic cardiac reflex (29). In vitro studies have shown that CSNA may facilitate tachyarrhythmia directly by changing action potential duration and indirectly by increasing heart rate (HR), transmembrane potassium leak, and infarct size (16). We therefore now require evidence that these neural mechanisms are operative in a conscious, neurally intact, large mammal. In particular, we need to know the exact temporal relationship between permanent coronary occlusion, increase in CSNA, and onset of tachyarrhythmias. Previous recordings on open-chest, anesthetized animals were inherently limited by anesthetic time and the effects of surgery and anesthesia on CSNA (30).

We have recently demonstrated in our conscious sheep model of MI that a sustained increase in CSNA is present 60 min following anterior MI (16). However, this study did not include animals that died before this time, which, in sheep and humans, is the period of greatest risk for lethal arrhythmia (4, 26). For example, we reported a single animal that suffered fatal VF preceded by a bimodal increase in CSNA, 30 min after coronary occlusion (18). The question therefore remains as to whether there is an increase in CSNA preceding the onset of VF during the first 60 min of MI. We now report the CSNA response over this period, comparing those without to those with fatal or life-threatening ventricular tachyarrhythmias.

METHODS

All procedures were undertaken following the approval of the protocol by the Animal Ethics Committee of the Christchurch School of Medicine and Health Sciences. Coopworth ewes, between 2 and 4 yr old, were housed in cages in an air-conditioned room. A total of 20 sheep, previously instrumented via thoracotomy (see below), had CSNA, blood pressure (BP), and HR monitored following experimental MI. The sheep were divided retrospectively into “resistant” (group A, n = 10) and “susceptible” (group B, n = 10) based on the absence or presence of ventricular tachyarrhythmia within 60 min of acute MI. Group A included eight animals for which later (hours and days) data have previously been reported (17). Group B comprised three animals with sustained VT (with spontaneous reversion to sinus rhythm) and one animal with VF with spontaneous reversion to sinus rhythm. The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Address for reprint requests and other correspondence: D. L. Jardine, Dept. of General Medicine, Christchurch Hospital, Private Bag 4710, Christchurch, New Zealand (e-mail: david.jardine@cdhb.govt.nz).
sheep. Postectopic pauses are seen in the later recordings of both 14 min before onset of ventricular fibrillation (VF); and matched sequences are A B (HR) in a resistant ( ) and a susceptible ( ) at baseline, cardiac sympathetic nerve activity (CSNA), and heart rate ( ) faster than 200 beats/min. The methods for electrode manufacture, implantation, and coronary occlusion have been previously reported in detail (17, 19). Briefly, the animals underwent left thoracotomy under general anesthesia, using thiopentone induction (17 mg/kg), followed by halothane (2%) and nitrous oxide (50%) ventilation. Five stainless steel electrodes were pushed obliquely through the cardiothoracic nerves and fixed in place with cyanoacrylate glue (Selly’s supaglue). A nylon snare was placed around the second diagonal branch of the left anterior descending coronary artery and exteriorized with the chest drain. An arterial catheter was placed in the left common carotid, a central venous line in the left internal jugular vein, and a transdermal ECG electrode at each quarter using a safety pin.

CSNA recordings were made from pairs of electrodes via a pre-amplifier with an active probe (DAM-80, World Precision Instruments). The raw signal was amplified (×1000), filtered between 300 and 3,000 Hz, and integrated using a time constant of 100 ms. Initially, the raw and integrated signals were checked for background interference. The integrated signal was digitally converted using in-house software (sampling rate, 200 Hz), and postganglionic CSNA was identified by the following: bursts were synchronized to the diastolic phase of the arterial pulse, bursts were decreased during hexamethonium infusion (2 mg/kg over 2 h) on day 2 postthoracotomy, and there was an inverse relationship between diastolic BP and HR faster than 200 beats/min. The CSNA burst area/minute during baroreflex slopes performed each day. Only bursts with a signal-to-noise ratio of >2 were analyzed. The best signal from the 10 possible electrode combinations was selected. CSNA was quantified by 1) counting the number of bursts/minute (burst frequency); 2) counting the number of bursts/100 heart beats (burst incidence); and 3) measuring burst size, the area under the integrated signal/minute (burst area/min) and burst area/100 beats.

On day 5 postthoracotomy, MI was induced under sedation. After up to three boluses of pethidine (50 mg) and diazepam (10 mg), given over a 30-min period, the sheep became drowsy and sat down. If the CSNA burst size was decreased, the animal was rested for 10 min until levels returned to baseline. Once a stable level of sedation was achieved without perturbation of CSNA, MI was induced by an application of continuous tension to the coronary suture. Acute changes were seen in the ECG (for example, ST elevation or depression) within 1 min of occlusion (Fig. 1). The suture was then clamped inside the sheath (to maintain the occlusion) for a period of 24 h. Time to onset of ventricular ectopics (VEs) and ectopic frequency was measured for both groups. Mean BP, HR, CSNA, and VE counts were averaged each minute in both groups. In group B, the mean time to VF/VF was calculated (28.1 ± 3.3 min) and 14 1-min time packets preceding this time point were analyzed. This time frame represents the maximum period for which data could be obtained from the sheep in group B. Data were compared with time-matched values in group A, that is, between 15 and 28 min post-MI. We took care not to include any CSNA occurring after the onset of VF/VF, because there was always a baroreflex-modulated surge in CSNA at this time secondary to hypotension. Baroreflex slopes for R-R interval versus systolic BP, and normalized CSNA burst area versus mean (MBP), were calculated on 3 separate days between thoracotomy and MI and averaged. Nitroprusside (150 µg) followed by phenylephrine (100 µg) intravenous boluses were given to achieve a total change in BP of 30 mmHg or greater, and only those correlation slopes with correlations >0.8 were used. Phenylephrine always caused total inhibition of CSNA.

Results are expressed as means ± SE. Repeated-measures ANOVA with time as a repeated measures factor was used to determine differences over time between the two groups, and when significant differences (time × group interactions) were identified, independent t-tests were used to compare individual time points between the two groups. Repeated-measures ANOVA was used to demonstrate time effects within each group. The comparison of the time to onset of VEs was compared between groups using the Mann-Whitney U-test.

RESULTS

Ten animals suffered significant ventricular tachyarrhythmias during the first hour of MI (group B). The mean time to arrhythmia was 28.1 ± 3.3 min. In seven out of ten animals, the initial arrhythmia was VF resulting in death. The remaining three animals had sustained VT (rates, 200, 360, and 400 beats/min; MBP, 63, 54, and 37 mmHg; and duration, 65, 115, and 155 s, respectively) but spontaneously reverted to sinus rhythm and survived to subsequent euthanasia on day 7. In eight animals the ECG demonstrated “R on T” immediately preceding the tachyarrhythmia. Sample recordings from one resistant (group A) and one susceptible sheep (group B) are shown in Fig. 1. In both groups, MBP and HR remained constant over the 14-min time period. CSNA also remained constant in group A but increased in group B. At baseline in

Fig. 1. Effects of myocardial infarction (MI) on blood pressure (BP), cardiac sympathetic nerve activity (CSNA), and heart rate (HR) in a resistant (A) and a susceptible (B) sheep. Time-matched sequences are 1) at baseline, 15 min postocclusion or 14 min before onset of ventricular fibrillation (VF); and 2) 2 min before the onset of VF. Large CSNA bursts during postectopic pauses are seen in the later recordings of both sheep.

A

B

CSNA

ECG

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CSNA AND VF

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Fig. 3. CSNA burst incidence (top), burst area/minute (middle), and burst area/100 beats (bottom) from 10 resistant sheep (○, group A) and 10 susceptible sheep who developed VF/VT post-MI (●, group B). Results are time matched from the time of VF/VT (-14 to -1 min) and expressed as means ± SE. CSNA burst area/minute (F13,208 = 2.17, P = 0.01 by 2-way ANOVA) and burst area/100 beats (F13,208 = 1.86, P = 0.04) both increase before VF/VT. Significant differences between groups (independent t-tests) are indicated as follows: *P < 0.05; †P < 0.01.

Fig. 2. Serial mean blood pressure (MBP; top), HR (middle), and CSNA bursts/minute (bottom) from 10 resistant sheep (○, group A) and 10 susceptible sheep who developed VF/VT post-MI (●, group B). Results are time matched from the time of VF/VT (-14 to -1 min) and expressed as means ± SE, bpm, Beats/min.

group A (at 15 min postocclusion) and group B (at 14 min pretachyarrhythmia), hemodynamic indexes were similar: MBP, 91 ± 3 versus 89 ± 6 mmHg (t16 = 0.02, P = 0.98); and HR, 129 ± 6 versus 125 ± 7 beats/min (t16 = 0.46, P = 0.65), respectively (fig. 2), whereas CSNA indexes of burst size were lower in group B: burst area/minute, 6.0 ± 4 units versus 4.6 ± 0.3 U/min (t16 = 2.75, P = 0.01); and burst area/100 beats, 4.7 ± 0.4 versus 3.7 ± 0.3 U/100 beats (t16 = 1.7, P = 0.05) (Fig. 3). Baseline CSNA burst frequency and burst incidence tended to be lower in group B compared with group A, but these differences did not achieve statistical significance: 64 ± 4 versus 53 ± 7 bursts/min (t16 = 2.0, P = 0.07) for burst frequency and 54 ± 3 versus 43 ± 6 bursts/100 beats (t16 = 1.7, P = 0.12) for burst incidence. A comparison of hemodynamic and CSNA indexes presedation/MIs showed that they were similar between groups: MBP, 86 ± 3 versus 87 ± 6 mmHg (t18 = −0.37, P = 0.72); and HR, 109 ± 4 versus 106 ± 8 beats/min (t18 = 0.25, P = 0.81). However, three out of four CSNA indexes were lower in group B: burst frequency, 70 ± 4 versus 56 ± 5 bursts/min (t18 = 2.2, P = 0.04); burst area/minute, 6.8 ± 0.5 units versus 5.1 ± 0.4 U/min (t18 = 2.8, P = 0.01); and burst area/100 beats, 6.3 ± 0.5 versus 5.0 ± 0.4 U/100 beats (t18 = 2.1, P = 0.05). Presedation/MI baseline differences in burst incidence between groups did not achieve statistical difference: 65 ± 4 versus 55 ± 3 bursts/100 beats (t18 = 1.7, P = 0.1).

Between-group comparisons showed that MBP and HR remained stable and similar over the 14-min period of prearrhythmia (Fig. 2). By contrast, CSNA indexes of burst size, which remained relatively stable in group A, increased in group B: burst area/minute (F13,208 = 2.17, P = 0.01) and burst area/100 beats (F13,208 = 1.86, P = 0.04) (Fig. 3). However, indexes of burst frequency were not significantly different between the groups: burst frequency (F13,208 = 1.6, P = 0.09) and burst incidence (F13,208 = 1.48, P = 0.13) (Fig. 3). Further assessment of change over time within individual groups revealed that CSNA burst area/minute and burst area/100 beats did not change across this time period in group A (F13,117 = 0.97, P = 0.5; and F13,117 = 0.96, P = 0.7) but increased with the time in group B (F13,91 = 2.3, P = 0.01; and F13,91 = 2.25, P = 0.01). Given the significant differences at baseline for most CSNA indexes, these data were also analyzed as change from baseline. Thus comparison of normalized data for CSNA confirmed that, whereas CSNA remained stable in group A, there were significant increases in all indexes in group B before arrhythmia: burst frequency (F13,208 = 2.07, P = 0.02), burst incidence (F13,208 = 2.2, P = 0.01), burst area/minute (F13,208 = 2.18, P = 0.01), and burst area/100 beats (F13,208 = 2.15, P = 0.01) (Fig. 4).

In both groups, a phase of VEs occurred following coronary occlusion. The median time to onset from coronary occlusion was 18.5 (range 12–24) min in group A and 15.0 (range 7–22) min in group B (Mann-Whitney U-test, P = 0.09). Throughout the 14-min period during which the groups were compared, there was no time × group interaction (F13,208 = 0.58, P = 0.87). Preinfarction baroreflex slopes for the HR period (R-R interval) versus systolic BP and CSNA (normalized nerve area) versus MBP, respectively, were similar. R-R slopes were 11.8 ± 2 and 15.6 ± 1.1 ms/mmHg in groups A and B.
the onset of VF/VT (14 to 0.3 and 2.2, P = 0.02, 2-way ANOVA), burst incidence (2nd panel; F_{13,208} = 2.2, P = 0.01), burst area/min (3rd panel; F_{13,208} = 2.18, P = 0.01), and burst area/100 beats (bottom; F_{13,208} = 2.15, P = 0.01). Significant differences between groups (independent t-tests) are indicated as follows: *P < 0.05; †P < 0.01.

respectively (t_{18} = -1.6, P = 0.14). CSNA slopes were 1.8 ± 0.3 and -2.3 ± 0.2%/mmHg (t_{18} = -1.4, P = 0.2).

**DISCUSSION**

Whereas the relationship between CSNA and VF is well established in anesthetized animals, there is no direct evidence in conscious animal models. Therefore, we have reported for the first time in a conscious animal model the CSNA response during the first 60 min of anterior MI leading to fatal VF or near-fatal VT in susceptible sheep. Whereas all CSNA indexes remained stable in resistant animals, there was a significant and progressive increase in indexes of CSNA burst size in susceptible animals before arrhythmia. When analyzed as percent changes from baseline, these differences were also apparent for CSNA indexes of burst frequency. We have therefore demonstrated, in a large conscious mammal, temporal association among MI, early increase in CSNA, and lethal arrhythmia. These results support previous data from human and animal studies and the hypothesis that CSNA may be a major factor in the triggering of VF/VT following acute MI (23, 40, 41). Furthermore, this early increase in CSNA that we have demonstrated in susceptible animals during the first 30 min of MI appeared to be less than that which occurred later (and persisted) in resistant animals, namely, a 30–40% increase, occurring from 1- to 2-h post-MI onward, as previously reported in this sheep model (17). Therefore, it is probably the timing, rather than the magnitude of the increase in CSNA, that determines survival. This illustrates that the time course of CSNA post-MI and its relationship to arrhythmia are complex. Thus recordings from conscious, neurally intact animals, as in this study, may give us novel information on the sequence of events leading to sudden cardiac death in humans.

Although MBP and HR levels were similar at baseline and before MI, the susceptible animals had lower levels of CSNA at baseline (particularly those relating to burst size), which increased toward the stable CSNA levels of the resistant animals during the 14 min preceding arrhythmia. That baseline levels of CSNA were lower in the susceptible group (selected retrospectively) is a potential limitation of the study. However, we think that the difference in baseline levels was a chance effect and that, in this situation, a change in CSNA was more important than absolute levels. Of note, differences in CSNA indexes between groups were also apparent before sedation/MI. Between individuals, direct recordings (from humans and animals) have demonstrated that there is a major variation in sympathetic burst frequency and incidence, regardless of which nerves are used (7, 19, 30, 45). The reasons for this variation are poorly understood, but variations in burst size are highly dependent on needle position, and, therefore, between-group comparisons of absolute indexes such as burst size/minute or burst size/100 beats may be invalid. To allow for this, we and other investigators have analyzed the change in activity over time and compared normalized data (45). Although it is possible that a low level of CSNA before MI may somehow predispose to arrhythmia, it is unlikely because lower levels of CSNA have been shown to be protective in a variety of models (10, 13, 16, 26). One could postulate that as the resistant sheep started with higher CSNA, this may have limited the response if CSNA was already near maximal levels. However, it is important to note that we have previously reported that these resistant (surviving) animals are able to mount a significant increase in CSNA later (1- to 2-h post-MI) than the time interval being reported in the present study (17).

The gradual increase in CSNA that we measured between 15- and 30-min post-MI, using multifiber recordings, would appear to be much later than what has been previously recorded from single fibers in anesthetized cats and dogs (13, 24, 29, 31). Single-fiber recordings demonstrated a rapid increase in efferent CSNA (within seconds) following coronary occlusion, which persisted while occlusion was maintained. We suspect that this difference relates to methodology in that the multifiber technique produces an integrated signal which may require recruitment, as well as central drive, to increase (15). Thus multifiber recordings allow us to measure change in burst size (as well as frequency). As such, multifiber recordings may be physiologically more relevant than single-fiber recordings. Of
note in the present study, an analysis of the raw data showed significant increases in the two indexes of burst size but not burst frequency. Differences in burst frequency indexes were only statistically significant when data were normalized and analyzed as change from baseline. It may be, with regard to the generation of VF, that the recruitment of multiple fibers is more important than individual-fiber firing frequencies. We know that multifiber activity (and therefore recruitment) is inhibited by general anesthesia (including chloralose, halothane, and phenobarbitone), whereas single-fiber activity is not (8, 30). Therefore, it will be difficult to demonstrate the time lag between multi- and single-fiber recordings following MI. Taken together, it is clear that all the previous work on the cardiac sympathetic reflex and its relationship to VF needed to be reassessed in conscious animals, as in the present study. A rapid increase in multifiber CSNA has been demonstrated during the first minute of coronary artery occlusion in conscious cats, but these studies were of very short duration (100 s) (30), and, furthermore, we have found the nerve signal very difficult to discern from movement artefact in response to pain and stress and so have not analyzed this time period.

The time frame for the onset of VEs and VF/VT post-MI fits with the later sustained increase in CSNA that we have observed from ~15 min postocclusion. This pattern has also been demonstrated in other animal models (10) and fits with the time frame for sudden cardiac death in humans post-MI (27). We suggest that the magnitude of the increase is less than what we previously recorded in resistant sheep [at a later stage in the infarction process 2 h post-MI (17)], because VF (and death) intervene before CSNA reaches equivalent levels. During early infarction, other mechanisms, besides an increase in CSNA, are likely to contribute to the risk of VF/VT. As CSNA increases, poorly perfused myocardium may initially be protected by an inhibition of catecholamine release and an increased catecholamine reuptake at the nerve terminals, but after a few minutes, these mechanisms fail, resulting in major stimulation of adrenergic receptors (37). Consequently, in humans, early β-adrenoreceptor blockade significantly decreases the incidence of VF during MI (5).

The concept of an increase in CSNA during the first minutes of acute MI is not new but has not been proven in humans. Observational studies in coronary care units found an association between anterior MI and sympathetic effects, for example, tachycardia, hypertension, and VF, particularly in the first hour of infarction (33, 34, 46). Tachycardia and hypertension have also been documented during relatively brief (5 min) episodes of anterior ischemia in patients with coronary spasm (36). Indirect measurement of CSNA, using spectral analysis during 2-min angioplasty balloon inflation, has produced conflicting results. For example, different authors have shown increases in both low- and high-frequency HR variability during anterior wall ischemia (1,20). HR variability and sequential venous catecholamine levels have been measured during acute MI, but studies include very few patients during the first hour of symptoms (21, 25). Furthermore, frequent VEs may impair an analysis of HR variability when the time is limited, and venous plasma levels underestimate myocardial catecholamine concentration (9, 43a). Coronary catecholamine spillover studies are too invasive to undertake, and, to date, the earliest muscle sympathetic nerve recordings have been only undertaken 2–4 days post-MI (14).

On the other hand, the evidence from anesthetized animal studies for an excitatory sympathetic reflex during the first minutes of cardiac ischemia is strong (29). The sympathetic excitatory reflex initially demonstrated in cats by Brown (2) and Malliani et al. (29) has also been studied in dogs (12). Myocardial ischemia activates cardiac sympathetic nerve endings and the afferents, primarily thinly myelinated Aδ-fibers and unmyelinated C-fibers have been traced to the dorsal horn of the upper thoracic spinal cord via the stellate ganglia and sympathetic chain (22). Consequently, during myocardial ischemia, the dorsal root section from C8-T5 decreased VE frequency (38), whereas increased CSNA was associated with decreased VF threshold (26). The excitatory reflex may be inhibited by vagal afferents and pathways from the higher centers (11, 12). Thus increased vagal activity during the first minutes of MI has been associated with decreased incidence of VF (3, 44). Our study is important because it has demonstrated the dominance of the excitatory sympathetic reflex during early MI in the conscious animal, with all of the inhibitory mechanisms intact. The same may not apply in anesthetized animals and is reflected in the practice of routinely sectioning vagal afferents to assess the excitatory CSNA reflex (10–12, 31).

We remain uncertain as to why CSNA increased relatively early in the arrhythmia group. We need to be sure that the rapid CSNA response was not secondary to other factors, which may also have predisposed to arrhythmia post-MI. For example, CSNA may be increased by acute left ventricular failure. There was no clinical or hemodynamic evidence of failure in the VF/VT group. We did not measure infarct size in the animals who died but ensured that the occluded artery was always the same. Sheep, like humans, have limited collateral coronary vessels, and we have achieved consistent infarct size previously using this method (4, 17). We have also observed that using this artery, the position of the infarct (in the anterior free wall of the left ventricle) is consistent and therefore unlikely to contribute to variations in CSNA response. Furthermore, only left-sided cardiothoracic nerves were used. Analysis of other variables revealed no clear differences between groups: these included the transient inhibitory effect of pethidine on CSNA, including the dose and timing of boluses (data not shown); the baroreflex control of CSNA and HR preinfarction; and the time of onset and frequency of VE activity postinfarction. Ectopic activity is of interest because the transient increase in CSNA following a postectopic pause has been proposed as a mechanism for VF (32). In the absence of any other obvious difference that might explain the early increase in CSNA and VF/VT post-MI, it is probable that the excitatory sympathetic reflex is important, but we are unable to speculate further on the exact mechanisms controlling the magnitude and timing of the CSNA response. We did not section the cardiothoracic nerves distal to where we recorded from, and so it is possible that afferent neurons, activated by myocardial ischemia, contributed to the increase in the nerve activity we measured. Similarly, we cannot be sure that all the efferent activity we recorded is sympathetic. The increase in CSNA was not associated with an acceleration of HR before arrhythmia. We suspect this relates to the lateralization of sympathetic cardiac innervation. All of our recordings have been from the left cardiothoracic nerves, which affect ventricular contractility and excitability more than sinus rate, as documented in anesthetized (35) and conscious animals (42).
In summary, our results, from conscious sheep recordings, advance earlier work on anesthetized models by giving further information on the exact temporal relationship between myocardial ischemia, the onset of increased CSNA, and malignant tachyarrhythmias. Whereas CSNA remained stable during the early post-MI period in resistant animals, there was a significant and progressive rise in CSNA indexes observed in susceptible animals during the 14 min immediately preceding arrhythmia. In sheep, as is the case with humans, sudden death is relatively common during the first hour of infarction, and it may be that the timing of the increase in CSNA, rather than the magnitude, is the critical deciding factor for survival immediately after MI.

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