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Peer reviewed

# Mechanism of ventricular premature beats elicited by left stellate ganglion stimulation during acute ischaemia of the anterior left ventricle

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## Aims

Enhanced sympathetic activity during acute ischaemia is arrhythmogenic, but the underlying mechanism is unknown. During ischaemia, a diastolic current flows from the ischaemic to the non-ischaemic myocardium. This 'injury' current can cause ventricular premature beats (VPBs) originating in the non-ischaemic myocardium, especially during a deeply negative T wave in the ischaemic zone. We reasoned that shortening of repolarization in myocardium adjacent to ischaemic myocardium increases the 'injury' current and causes earlier deeply negative T waves in the ischaemic zone, and re-excitation of the normal myocardium. We tested this hypothesis by activation and repolarization mapping during stimulation of the left stellate ganglion (LSG) during left anterior descending coronary artery (LAD) occlusion.

## Methods and results

In nine pigs, five subsequent episodes of acute ischaemia, separated by 20 min of reperfusion, were produced by occlusion of the LAD and 121 epicardial local unipolar electrograms were recorded. During the third occlusion, left stellate ganglion stimulation (LSGS) was initiated after 3 min for a 30-s period, causing a shortening of repolarization in the normal myocardium by about 100 ms. This resulted in more negative T waves in the ischaemic zone and more VPBs than during the second, control, occlusion. Following the decentralization of the LSG (including removal of the right stellate ganglion and bilateral cervical vagotomy), fewer VPBs occurred during ischaemia without LSGS. During LSGS, the number of VPBs was similar to that recorded before decentralization.

## Conclusion

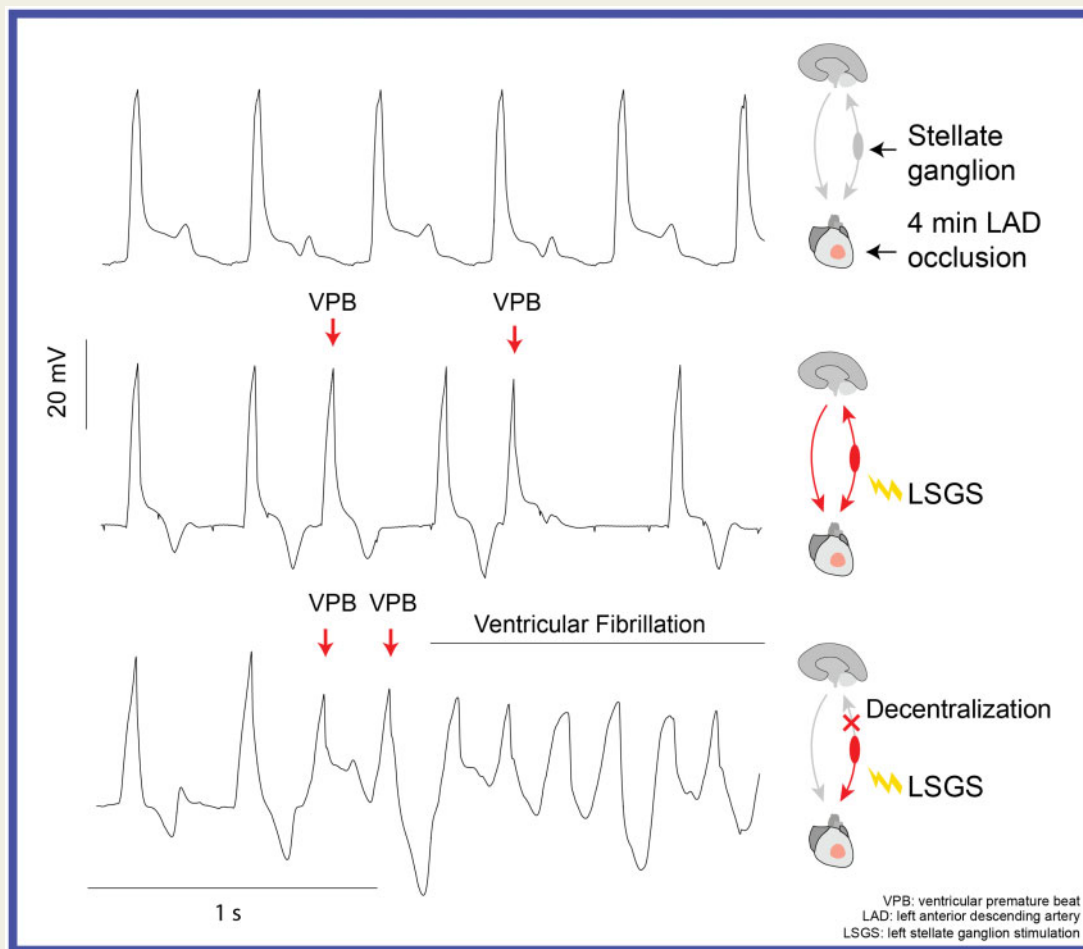
LSGS, by virtue of shortening of repolarization in the non-ischaemic myocardium by about 100 ms, causes deeply negative T waves in the ischaemic tissue and VPBs originating from the normal tissue adjacent to the ischaemic border.

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## Graphical Abstract



## Keywords

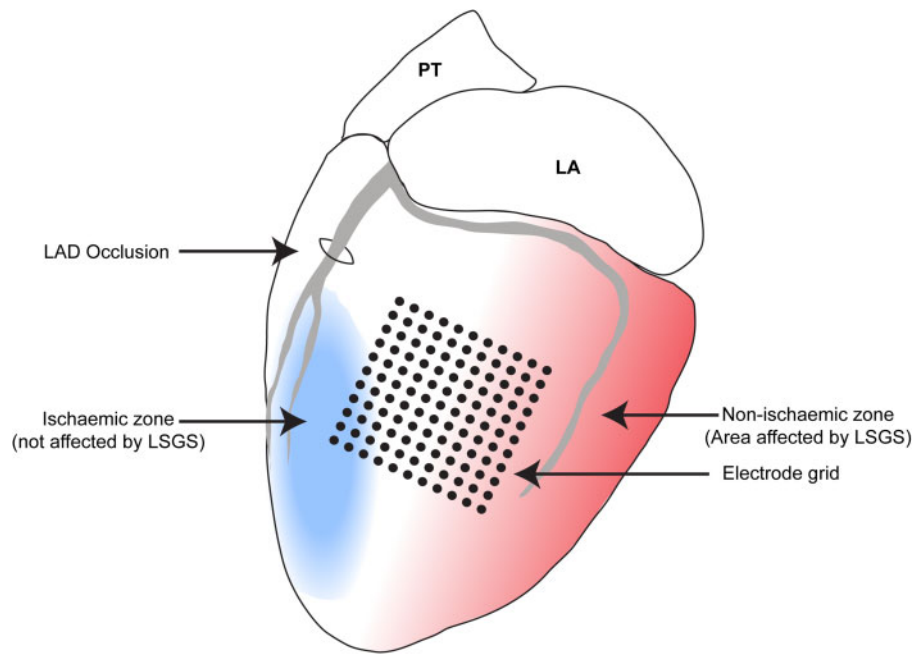
Ischaemia • Arrhythmias • Autonomic nervous system • Repolarization • Injury current

## 1. Introduction

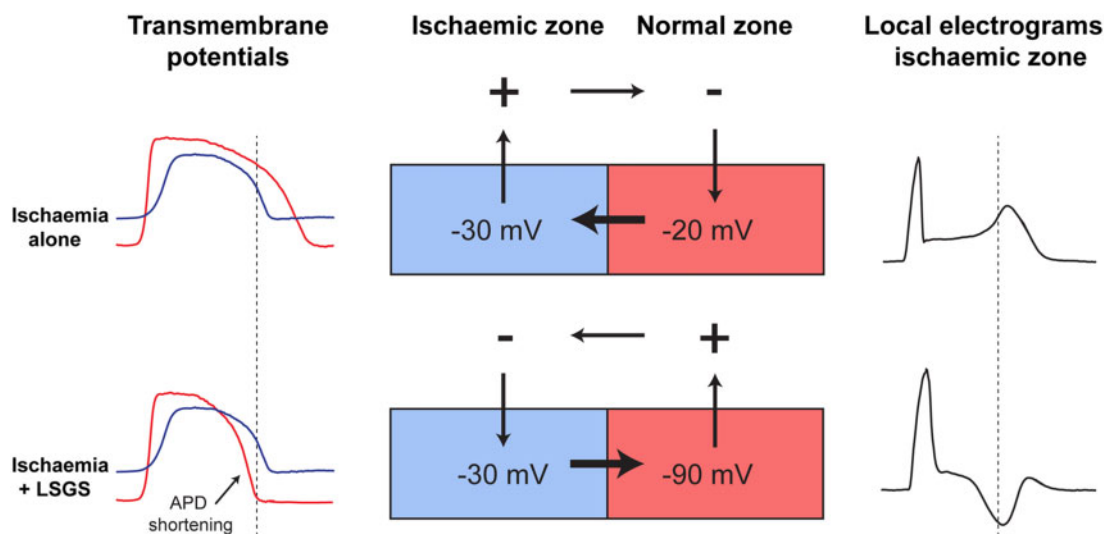
Enhanced sympathetic activity during acute myocardial ischaemia is arrhythmogenic<sup>1,2</sup>, and sympathetic denervation has been applied in the prevention of lethal arrhythmias.<sup>3–7</sup> Little is known about the electrophysiological effects of increased sympathetic activity in the presence of acute ischaemia. Conduction velocity in the ischaemic zone has been shown to increase during stellate ganglion stimulation, which would argue against the facilitation of reentry.<sup>7</sup> We have provided evidence that the ventricular premature beats that initiate reentrant arrhythmias during acute ischaemia originate in the normal myocardium close to the ischaemic border and probably are initiated by 'injury' currents flowing between ischaemic and non-ischaemic myocardium.<sup>8</sup> Characteristically, the ventricular premature beats would follow deep negative T waves in the ischaemic myocardium.<sup>8</sup>

Recently, we have shown that, in the healthy pig heart *in vivo*, left stellate ganglion stimulation (LSGS) modulates repolarization in the

lateral and posterior wall of the left ventricle, but not in the anterior wall.<sup>9</sup> Therefore, we hypothesized that occlusion of the left anterior descending coronary artery (LAD) combined with LSGS would lead to a condition where the anterior left ventricle is ischaemic, whereas the effects on repolarization would be confined to the non-ischaemic lateral and posterior left ventricle (Figure 1). Thus, when repolarization shortens in the non-ischaemic myocardium following LSGS, repolarization in the ischaemic myocardium occurs later compared to that in the non-ischaemic tissue, which promotes the genesis of negative T waves in local electrograms in the ischaemic area (Figure 2). This will extend the time window during which 'injury' currents will execute their pro-arrhythmic role and more ventricular premature beats (VPBs) are to be expected than during ischaemia without LSGS. The present experiments were undertaken to test the hypothesis that spontaneous VPBs would occur more often when brief periods of ischaemia were combined with 30 s of LSGS compared with ischaemia only, and would follow negative T waves in the ischaemic tissue.



**Figure 1** Schematic representation of the left ventricle with the multiple electrode covering both the ischaemic tissue (blue) and the non-ischaemic myocardium. The left stellate ganglion innervates primarily the area outside the ischaemic zone (red). LSGS, left stellate ganglion stimulation.



**Figure 2** Diagram showing hypothetical transmembrane action potentials in normal (red) and ischaemic tissue (blue) (left), and local extracellular electrograms from the ischaemic myocardium (right). In the middle, diagrams showing intra- and extracellular current flow at the moments indicated by the dotted lines drawn through the action potentials at the left and the local electrograms at the right.<sup>8,10</sup> Before LSGS (upper panels), this current causes a current source in the extracellular space in the ischaemic tissue leading to a positive T wave. During LSGS (lower panels), the action potential in the non-ischaemic zone shortens, and the current now causes a current sink and a negative T wave in the ischaemic tissue.

## 2. Methods

Animal handling and care followed the recommendations of the National Institutes of Health Guide for the Care and Use of Laboratory

Animals and the University of California, Los Angeles, Institutional Animal Care and Use Committees. Animal protocols were approved by the Chancellor's Animal Research Committee, University of California, Los Angeles.

## 2.1 Animal preparation

Female Yorkshire pigs ( $n=9$ , weighing 45–64 kg) were premedicated with intramuscular telazol (8–10 mg/kg), intubated, and ventilated. General anaesthesia during surgical procedures was maintained with isoflurane (2–3%, inh) and with intermittent boluses of fentanyl (20–30  $\mu\text{g}/\text{kg}$ , iv) to maintain analgesia. Animals underwent a medial sternotomy to expose the anterior surface of the heart and the sympathetic nerves in the posterior thorax. Following completion of all surgical procedures, anaesthesia was switched to solely alpha chloralose (20–30 mg/kg/h) for the remainder of the experimental protocols. Continuous intravenous saline was infused throughout the procedure, and anaesthesia and haemodynamics were monitored closely during the experimental protocols by using a surface electrocardiogram and an arterial line via femoral artery access.

The left stellate ganglion was electrically stimulated by using a bipolar platinum electrode connected to a Grass stimulator (S88, Grass Technologies, West Warwick, RI, USA) connected to a SIU6 constant current stimulus (4 Hz) isolation unit as published previously.<sup>9</sup> Aortic pressure was monitored by using a 5-Fr pigtail pressure catheter connected to a MPVS Ultra processor (Millar Instruments, Inc, Houston, TX, USA) inserted via the carotid artery. For LSGS, an increase in pulse pressure by 30% was targeted.

The LAD was prepared free just above the first diagonal branch, and a ligature was passed underneath the artery. The threads of the ligature were passed through a rubber tube, and temporary coronary artery occlusion was performed by pulling the ligatures and clamping the tube. Occlusions lasted 5 min and were separated by a 20 min reperfusion interval. The electrophysiological changes during a first occlusion are different from those during a second occlusion, whereas the changes in the second occlusion and any subsequent occlusion are reproducible.<sup>11–13</sup> We therefore used the second coronary occlusion as the control occlusion. During a short occlusion of 15 s, the ischaemic zone was identified and the electrode grid was positioned to cover the ischaemic zone (approximately 30% of electrodes) and the normal tissue.

Animals were euthanized by intravenous administration of a lethal dose of potassium chloride and sodium pentobarbital (100 mg/kg).

## 2.2 Electrophysiologic recordings

Recordings were made from 121 epicardial sites via a 11 by 11 surface electrode (interelectrode distance 5 mm) which covered both the ischaemic and non-ischaemic area (see Figure 1). The reference electrode was positioned subcutaneously at the thoracic incision site. A bipolar stimulus electrode was attached to the right atrium. The right atrium was stimulated at a cycle length of 450 ms. Unipolar electrograms were recorded via a multichannel data acquisition system [24 bit dynamic range, 122.07 nV LSB, total noise 0.5  $\mu\text{V}$  (BioSemi)]. Signals were recorded at a sampling frequency of 2048 Hz [bandwidth (-3dB) DC–400 Hz]. Body surface electrocardiograms (leads I, II, and III) were recorded for monitoring heart condition during the experiment. In each experiment, recordings were made throughout four successive ischaemic episodes (5 min duration each, separated by 20 min following reperfusion): the control (2nd) occlusion, the 3rd occlusion during which LSGS for 30 s was initiated after 3 min of ischaemia, the 4th occlusion following decentralization of the left stellate ganglion (by cutting the caudal extension of the ganglion), removal of the right stellate ganglion and cutting both vagal nerves, and finally the fifth occlusion with 30 s of LSGS after 3 min of ischaemia. Electrical signal analysis was performed offline using custom-made data analysis software based on MATLAB 2016a

(Mathworks Inc., Natick, MA, USA) as published previously.<sup>14</sup> The levels of ST-segment and T-wave potential elevation were determined based on the average of four neighbouring electrodes that were located the furthest away from the border zone (a 1 cm band of tissue separating myocardium with ST-elevation from myocardium with ST-depression). Electrodes in the border region were excluded from this analysis. Repolarization times were measured as the interval between the reference time (beginning of the q wave in the electrocardiogram) and the time of maximum positive slope of the T wave in the local electrograms.

## 2.3 Data analysis and statistics

In one pig, the ischaemic zone was considerably larger than in the other eight animals, resulting in early ventricular fibrillation in all occlusions even before LSGS was started. This animal was excluded from analysis.

Continuous variables were presented as mean  $\pm$  SEM. A linear mixed model for repeated measurements was used to test the effects of LSGS on repolarization.

## 3. Results

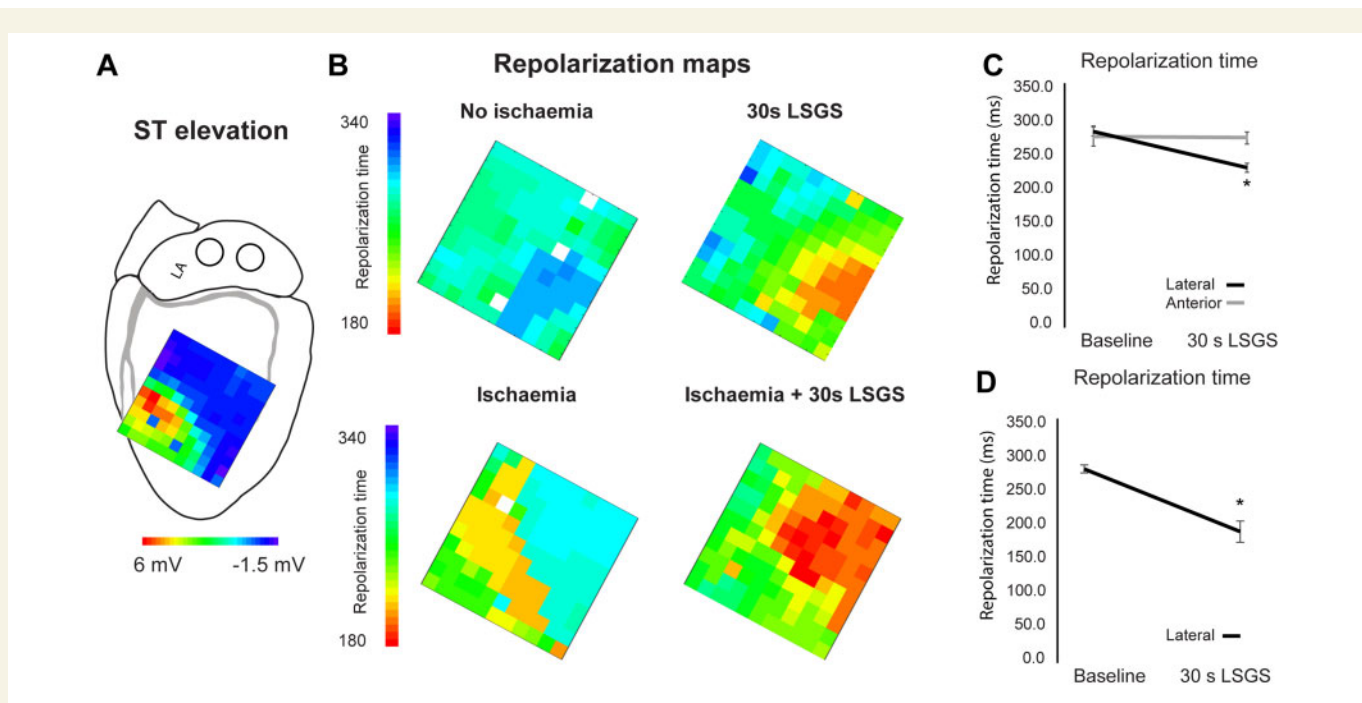
We confirmed that the development of ischaemia in the successive 2–5 episodes of ischaemia following the first occlusion were similar. Average ST-segment elevation was measured in all of these occlusions, 3 min after the beginning of ischaemia. For the control (2nd) occlusion, this was  $6.8 \pm 0.7$  mV, for the 3rd occlusion  $5.9 \pm 0.5$  mV, for the 4th occlusion  $4.5 \pm 0.7$  mV, and for the 5th occlusion  $5.3 \pm 0.8$  mV (average and SEM). The differences were not statistically significant ( $P=0.54$ ).

Figure 3 shows ST elevation in the ischaemic area at the anterior wall and ST-depression in the adjacent non-ischaemic zone. Repolarization maps in Figure 3B show that repolarization shortened upon LSGS in the lateral but not the anterior wall (ms:  $280 \pm 6.6$  to  $228 \pm 6.0$   $P=0.002$  vs.  $273 \pm 13.6$  to  $270 \pm 9.2$   $P=0.732$ , respectively). This can also be seen in the panels during ischaemia and LSGS where repolarization shortened on average from  $271 \pm 8.0$ – $206 \pm 8.9$  ms ( $P=0.003$ ) in non-ischaemic area. Upon ischaemia, repolarization also shortened slightly in the anterior wall (Figure 3B). However, the relation between the local moment of repolarization and the local T wave in the presence of elevated ST-segments is unreliable.

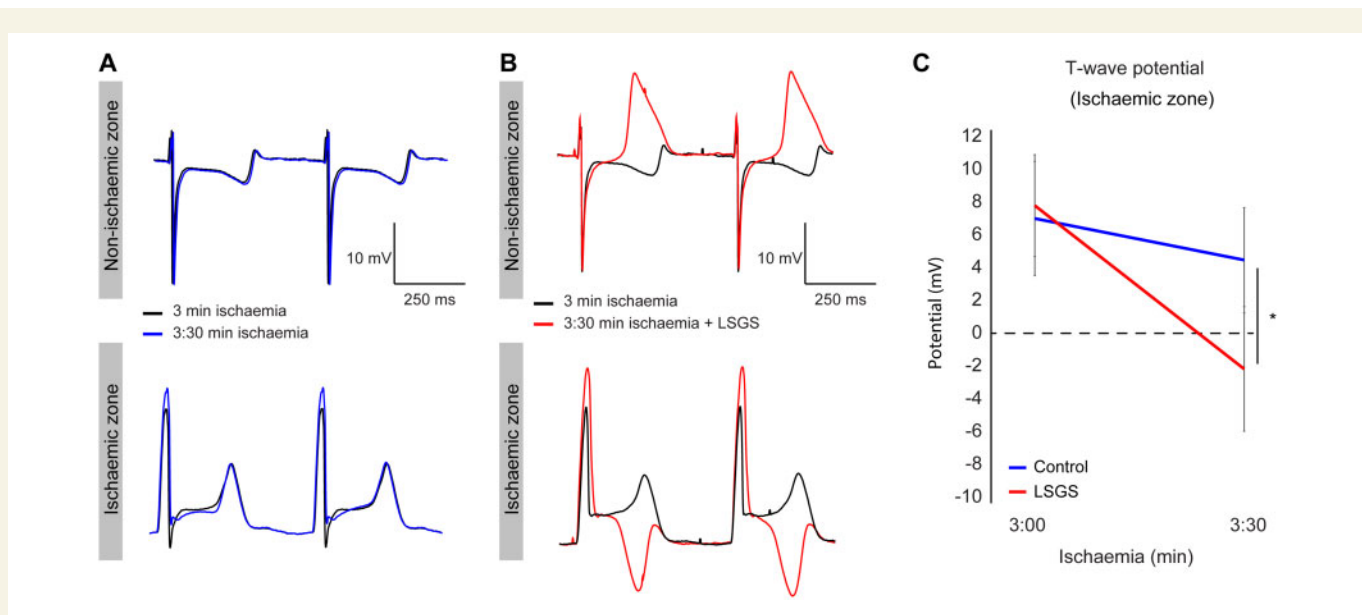
In Figure 4, superimposed local electrograms from the ischaemic zone and non-ischaemic zone are shown during ischaemia alone (Figure 4A) and after 3 min of ischaemia before LSGS and after 30 sec of LSGS (Figure 4B). Note that after 30 s of LSGS, deeply negative T waves were recorded from the ischaemic tissue at the moment when repolarization shortened (positive T wave) in the non-ischaemic zone (red tracing). On average the T wave amplitude in the ischaemic zone changed from  $7.9 \pm 3.0$  to  $1.7 \pm 3.6$  mV ( $P=0.006$ ) during LSGS.

In Figure 5, electrograms of the ischaemic zone are depicted after 3 min of ischaemia without (upper trace) and with LSGS (lower trace). Note the development of deep negative T waves in the lower electrograms after 3 min 20 s of LSGS that are followed by VPBs. In the upper trace, no negative T waves developed and noVPBs occurred.

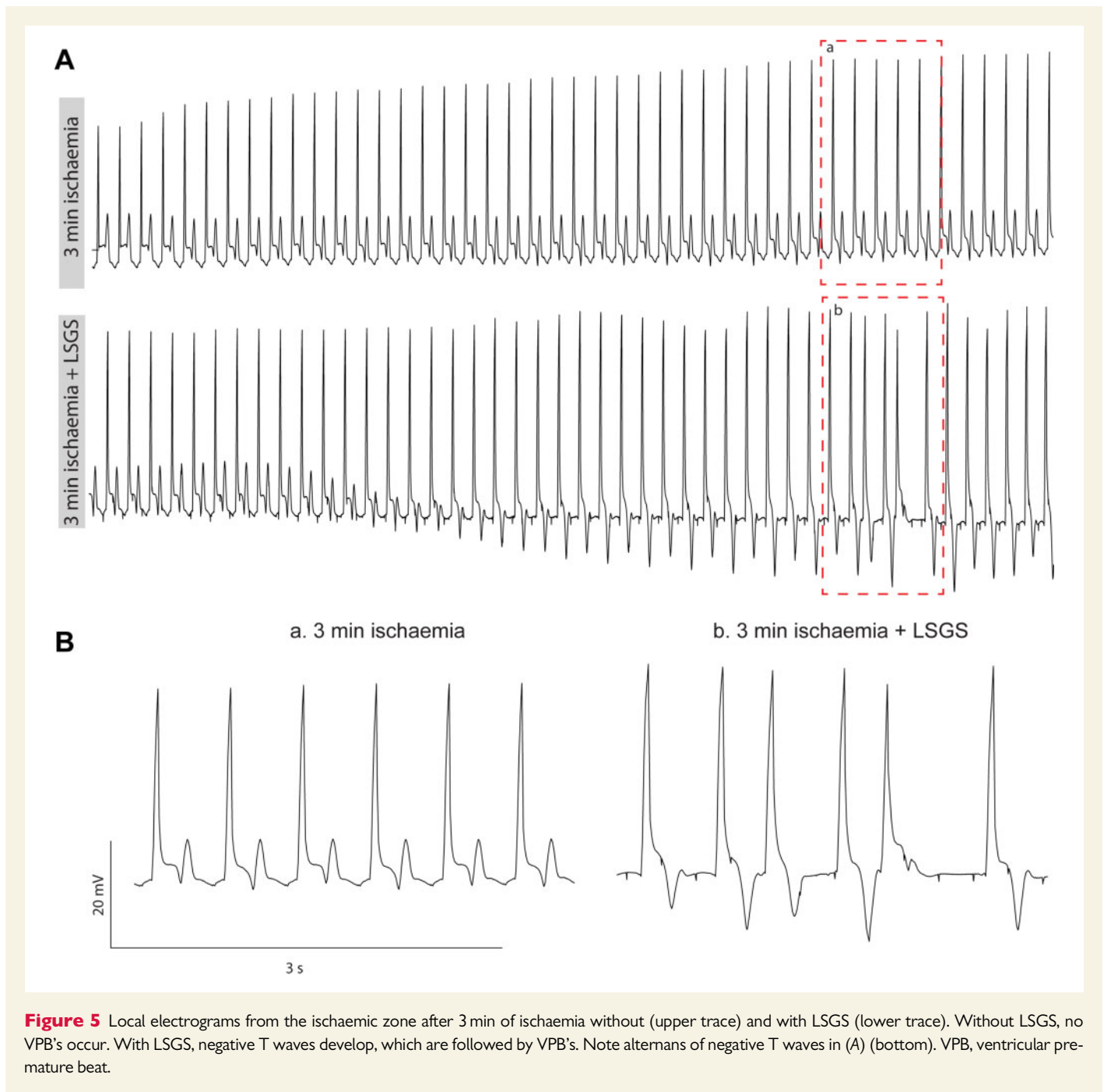
Figure 6 shows the activation map and electrograms of the initial VPB that initiated ventricular tachycardia and fibrillation. The earliest activation of the first VPB occurred in the non-ischaemic myocardium close to the ischaemic border (a). It closely followed the deep negative T wave recorded from the ischaemic zone (b). Single VPBs, or the first PB initiating a tachycardia or fibrillation, had their origin in the non-ischaemic myocardium in 82% of cases; the other 28% originated in remote non-



**Figure 3** (A) ST elevation in the ischaemic zone and ST depression in the non-ischaemic tissue. (B) Repolarization maps before (top left panel) and after 30 s of LSGS (top right panel) without ischaemia. The bottom left panel shows the repolarization map after 3 min of ischaemia. The bottom right panels show the repolarization maps after 30 s of LSGS during continued ischaemia. Note shortening of repolarization time in the non-ischaemic zone in the order of 100 ms. The bar graphs show repolarization times in the anterior and lateral wall during LSGS without (C) and during ischaemia (D). Data are shown as mean  $\pm$  SEM ( $n = 8$ ). It was not possible to determine repolarization times in the anterior wall during ischaemia because of ST-segment elevation. (C)  $*P = 0.014$  interaction effect LSGS\*location (two-way ANOVA, LSGS = repeated factor, location = repeated factor) followed by a Bonferroni-corrected  $t$ -test ( $P = 0.0018$ ). (D)  $*P = 0.0031$  Bonferroni-corrected  $t$ -test. LSGS, left stellate ganglion stimulation.



**Figure 4** (A) Superimposed local electrograms from normal and ischaemic tissue after 3 min and 3'30'' of ischaemia. Note the development of a negative T wave in the ischaemic zone when repolarization outside the ischaemic zone is markedly shortened by LSGS (B). (C) T-wave amplitude of local electrograms recorded from the ischaemic zone on after 3 min and 3'30'' of ischaemia, with (red) and without (blue) LSGS. Data are shown as mean  $\pm$  SEM ( $n = 8$ ).  $*P = 0.021$  interaction effect LSGS\*location (two-way ANOVA, LSGS = repeated factor, location = repeated factor) followed by a Bonferroni-corrected  $t$ -test ( $P = 0.006$ ).

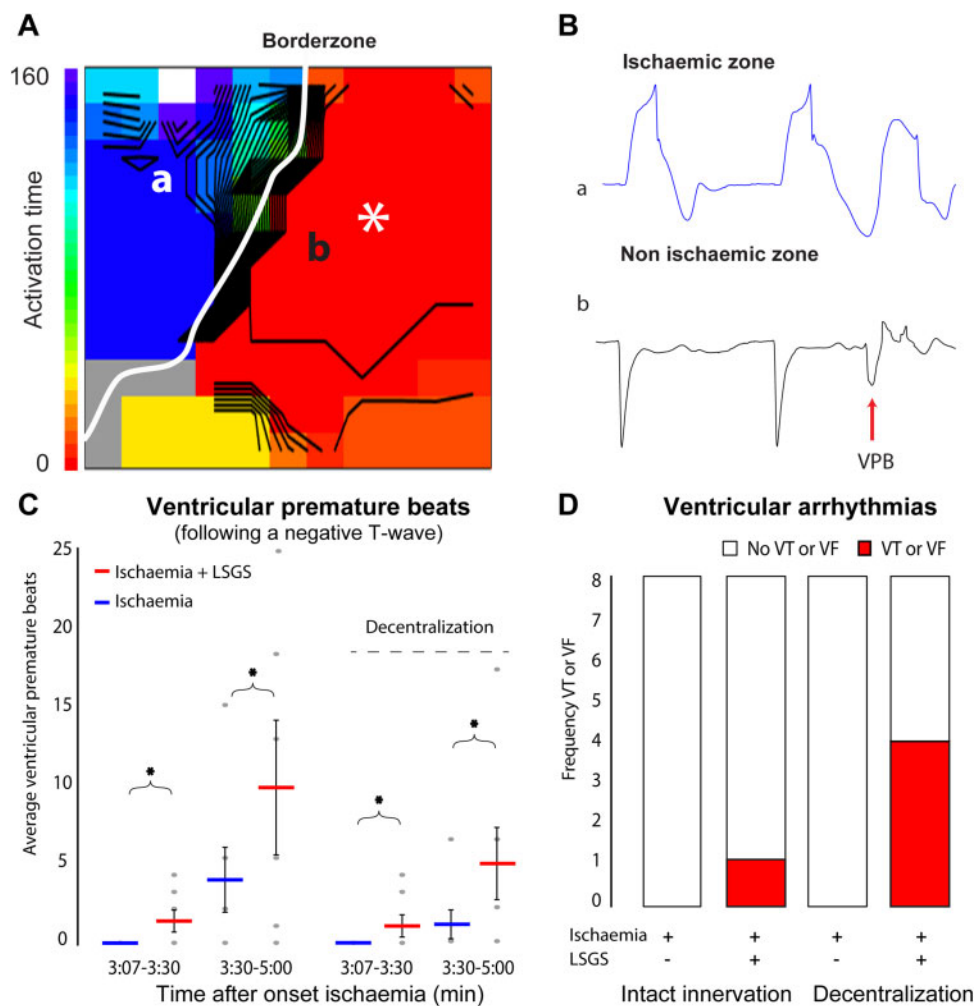


ischaemic myocardium. In *Figure 6C*, the average number of VPBs in seven pigs are shown (in the experiment of *Figure 7*, the control occlusion showed bigeminy and ventricular fibrillation after LSGS; this experiment is not represented in *Figure 6*). Data are shown with intact innervation and after decentralization of the left stellate ganglion (LSG), removal of the RSG, and bilateral vagotomy. In *Figure 6D*, the incidence of ventricular tachycardia or fibrillation is depicted. These arrhythmias only occurred after LSGS. LSGS was initiated after 3 min of ischaemia. During the initial 7 s, when repolarization in the normal tissue temporarily prolonged, no VPBs occurred. In the periods between 3:07–3:30 and 3:30–5:00, when repolarization in the non-ischaemic myocardium was shortened, the number of VPBs was significantly larger after LSGS than

during ischaemia alone both before and after decentralization (2nd and 4th occlusion,  $P = 0.019$ ).

*Figure 7A* shows electrograms exhibiting bigeminy during the control occlusion and ventricular fibrillation during ischaemia plus LSGS. Note that all VPBs follow deeply negative T waves. In *Figure 7B*, an activation map of the first VPB that initiated ventricular fibrillation is shown, and activation maps of beats II and III during fibrillation. Note the focal origin of the first VPB and reentrant activity in the later beats.

To exclude the possibility that VPBs during LSGS were caused by an increase in left ventricular pressure, we determined the LSGS-induced change in aortic pressure at 3 min of ischaemia. The maximal systolic pressure increased by  $7.7 \pm 3.6$  mmHg (12.3%) during ischaemia +



**Figure 6** Local electrograms and activation map of a single VPB (A and B). The VPB originated in the non-ischaemic myocardium close to the ischaemic border (a) and followed a deeply negative T wave in the ischaemic zone (b). (C) The average number ( $\pm$ SEM) of VPBs in seven pigs, after various times of ischaemia with LSGS (red bars) and without LSGS (blue). Data are shown both with an intact denervation and following decentralization of the LSG, removal of the RSG, and bilateral vagotomy. \* $P = 0.019$  main effect of LSGS on the occurrence of VPBs (three-way Analysis of Variance, decentralization = repeated factor, LSGS = repeated factor, time = repeated factor). The effect of LSGS on VPBs was significant before and after correcting (log transformation) for possible skewedness of the data. (D) Incidence of ventricular tachycardia (VT) or ventricular fibrillation (VF) in eight pigs. These arrhythmias only occurred after LSGS ( $P = 0.015$ , chi-square 5.9). LSGS, left stellate ganglion stimulation; RSG, right stellate ganglion; VPB, ventricular premature beat.

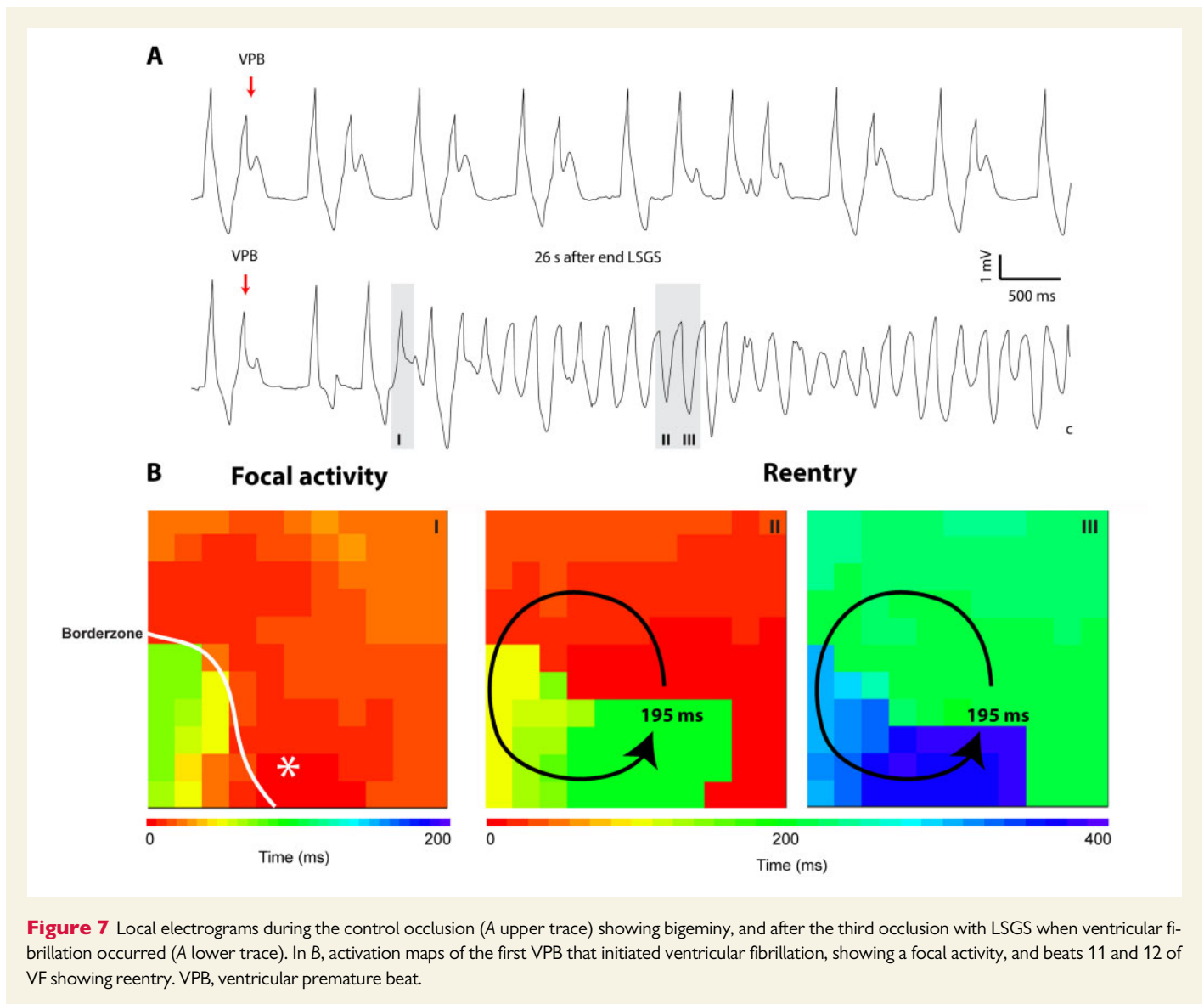
LSGS. There was no correlation between the number of VPBs and maximal systolic pressure (Supplementary material online, Figure S1).

### 3. Discussion

The main findings of this study were the following: (i) LSGS caused more VPBs during ischaemia induced by occlusion of the LAD than during ischaemia alone; (ii) the majority of VPBs followed negative T waves recorded from the ischaemic myocardium; (iii) LSGS caused a prolongation of repolarization in the non-ischaemic zone of about 10 ms during the initial 7 s and a shortening of about 100 ms after 30 s. It did not change the time course of development of ischaemia. The VPBs only occurred during the period of repolarization shortening, and their earliest activity occurred in the non-ischaemic myocardium adjacent to the

ischaemic border, where the repolarization time had been shortened by about 100 ms by LSGS. The most likely mechanism for the VPBs is re-excitation of non-ischaemic myocardium—e.g. conduction system tissue—after the end of their refractory period by an increased ‘injury’ current flowing intracellularly from ischaemic to normal myocardium during the negative T wave.<sup>8,15</sup> Indeed, the flow of ‘injury’ current is associated with increased excitability of tissue in the non-ischaemic tissue close to the border.<sup>16</sup> It is likely that other factors, such as the geometry of the cellular network or changes in intracellular  $Ca^{2+}$  cycling set favourable conditions for the injury current to elicit premature excitations. (iv) Following decentralization of the left stellate ganglion, removal of the right stellate ganglion and cutting both vagal nerves, the number of VPBs during LSGS was not significantly altered ( $P = 0.165$ ) but during ischaemia without LSGS fewer VPBs occurred compared to the 2nd (control) occlusion. This points to involvement of the stellate ganglia in





arrhythmogenesis also during control ischaemia and explains the antiarrhythmic effect of beta-blockade and decreasing sympathetic activity.<sup>5,6</sup> During ischaemia and LSGS, the number of VPBs was similar before and after decentralization. We speculate that the LSGS maximally activates the LSG and therefore leads to a similar number of VPBs following LSGS with or without decentralization. Ventricular fibrillation only occurred during LSGS, both in the 3rd and in the 5th occlusion.

In agreement with earlier findings in the pig,<sup>9</sup> LSGS has no effect on repolarization of the anterior wall of the left ventricle, but does change repolarization on the lateral and posterior wall of the left ventricle. In the present study, we generated ischaemia in the anterior wall which means that the arrhythmogenic effects of LSGS are due to changes in non-ischaemic tissue. A previous study has shown that sympathetic stimulation of ischaemic tissue leads to increased conduction velocity.<sup>7</sup> This is potentially antiarrhythmic. Our present study gives a plausible explanation why LSG excision may be antiarrhythmic by decreasing the autonomic influence on the non-ischaemic myocardium.

VPBs without preceding negative T waves were also observed. Whereas it is possible that no recordings were available from sites that did show negative T waves, it is also possible that VPBs were due to reentry within the ischaemic zone. Although we found no evidence for this in the present experiments, reentry as a cause for VPBs has been described before.<sup>15</sup>

## 4. Conclusion

LSGS exerts an arrhythmogenic effect on remote ischaemic myocardium by shortening repolarization in non-ischaemic tissue, thereby increasing an excitatory current of 'injury'.

## Data availability

The data are available at <https://github.com/bjboukens/Data-CVR-2019-1316R2>.

## Supplementary material

Supplementary material is available at *Cardiovascular Research* online.

## Authors' contributions

Acquisition of data: B.J.B., M.D., V.M.F.M., M.J.J., J.H., P.H., M.A.S., T.O., R.C.; Analysis or interpretation of data: B.J.B., M.D., V.M.F.M., M.J.J., T.O., J.A., K.S., R.C.; Drafting the manuscript: B.J.B., M.J.J.; Critically editing the manuscript: V.M.F.M., T.O., J. L.A., K.S., R.C.

**Conflict of interest:** none declared.

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## Translational perspective

Cardiac sympathetic denervation is a promising therapy for reducing arrhythmias during acute ischaemia. Currently, it is not clear which patients with ischaemic heart disease would benefit from cardiac sympathetic denervation and for which patients it is unlikely to have an effect. This is important because cardiac sympathetic denervation by removing the stellate ganglia often results in severe side effects and morbidity. Our results indicate that left stellate ganglion activity is pro-arrhythmic and suggest that left stellectomy is beneficial for the prevention of arrhythmias during anterior wall ischaemia. When the ischaemic zone is in the lateral and posterior wall, the effects of left stellate ganglion stimulation will be different because it will directly modulate the ischaemic myocardium, and might even be antiarrhythmic. Thus, the effect of left stellate stimulation can be pro or antiarrhythmic, depending on the location of myocardial ischaemia.