

Vagal stimulation after acute coronary occlusion: The heart rate matters

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Abstract

Background: *There is a well documented causal link between autonomic imbalance and cardiac electrical instability. However, the mechanisms underlying the antiarrhythmic effect of vagal stimulation are poorly understood. The vagal antiarrhythmic effect might be modulated by a decrease in heart rate.*

Methods: *The proximal anterior interventricular artery was occluded in 16 pigs by clamping under general anaesthesia. Group 1: heart rates remained spontaneous (n = 6; 12 occlusions); Group 2: heart rates were fixed at 190 bpm with atrial electrical stimulation (n = 10; 20 occlusions). Each pig received two occlusions, 30 min apart, one without and one with vagal stimulation (10 Hz, 2 ms, 5–20 mA). The antiarrhythmic effect of vagal activation was defined as the time to the appearance of ventricular fibrillation (VF) after occlusion.*

Results: *In Group 1, vagal stimulation triggered a significant decrease in basal heart rate (132 ± 4 vs. 110 ± 17 bpm, p < 0.05), and delayed the time to VF after coronary occlusion (1102 ± 85 vs. 925 ± 41 s, p < 0.05). In Group 2, vagal stimulation did not modify the time to VF (103 ± 39 vs. 91 ± 20 s). Analyses revealed that heart rate and the time to VF were positively linearly related.*

Conclusions: *Maintaining a constant heart rate with atrial electrical stimulation in pigs prevented vagal stimulation from modifying the time to VF after acute coronary occlusion. (Cardiol J 2018; 25, 6: 709–713)*

Key words: vagal stimulation, myocardial ischemia, sudden death, myocardial infarction, ventricular fibrillation, heart rate

Introduction

Acute myocardial ischemia caused by coronary occlusion is at the root of malignant ventricular arrhythmias [1]. Several animal models have demonstrated that increasing vagal tone by electrically stimulating the vagal nerve reduced incidence of ventricular arrhythmias and delayed their appearance [2–5]. The mechanisms underlying the antiarrhythmic effect of vagal stimulation are poorly understood [6].

Apparently, the protective effect of vagal stimulation is greater when sympathetic tone is high, due to marked antagonism [7–9]. However, it is controversial as to whether vagal stimulation acts directly through its neuromediator, acetylcholine. During the subsidence of acute myocardial ischemia in the cat, both before and after vagotomy, tissue acetylcholine levels were increased in the ischemic zone. This elevation in acetylcholine was due to a modification in intracellular calcium movements [10]. Cholinergic activation diminished

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electric instability by reducing heterogeneity of refractory periods in ventricular myocytes. However, vagal activation could also maintain the density of Connexin-43 intracellular junction proteins [4], which favoured normal propagation of cardiac influx. These studies have provided a better understanding of the protective mechanism of vagal stimulation. Nevertheless, few data have confirmed that vagal stimulation has an antiarrhythmic effect independent of its negative chronotropic effect.

The aims of this study were: 1) to study the effect of vagal stimulation on the time to appearance of ventricular fibrillation (VF) after acute coronary occlusion; and 2) to determine, under acute ischaemic conditions, the role of the heart rate (HR) in the antiarrhythmic effect of vagal activation.

Methods

Domestic pigs ($n = 16$) of both genders, 2 to 3 months of age, that weighed between 20 and 25 kg were studied. After general anaesthesia, mechanical ventilation with a tracheostomy and a sternotomy was performed, this was followed by a pericardiectomy. After dissection, both right and left cervical vagal nerves were identified, then connected to a stimulator (S1 Hugo Sachs, Freiburg im Brisgau, Germany) with metal clips. An electrode probe was linked to another stimulator (S1 Hugo Sachs, Freiburg im Brisgau, Germany) and placed in the right atrium, via the jugular vein. Electrocardiogram (ECG), arterial blood pressure, and CO_2 concentration in exhaled expiratory gas were continuously recorded.

Each animal underwent two successive proximal interventricular artery occlusions by clamping. The two occlusions were separated by 30-min intervals. Vagal stimulation was associated with only one of the two occlusions. Therefore, each animal served as its own control. The animals were assigned to one of two treatment groups. Group 1 (6 animals) maintained a spontaneous HR. When the coronary occlusion was combined with vagal stimulation (10 Hz, 2 ms, 5–20 mA), the stimulation began 10 min before the occlusion, and was continued throughout the occlusion. Of 6 animals in this group, 3 received coronary occlusion with vagal stimulation, followed by occlusion without vagal stimulation; the other 3 animals received the reverse sequence.

In Group 2 (10 animals), the ventricular contraction rate was controlled by atrial electrical stimulation. Electrical stimulation was set at a fixed frequency of 190 bpm; it began 10 min before oc-

clusion, and it continued throughout the occlusion. Again, each animal received two occlusions, one without vagal stimulation, and the other combined with vagal stimulation (10 Hz, 2 ms, 5–20 mA). Vagal stimulation had begun 10 min before and continued throughout the occlusion. Of the 10 animals in this group, 5 received a coronary occlusion with vagal stimulation, followed by occlusion without vagal stimulation; the other 5 animals received the reverse sequence.

The time to the appearance of spontaneous ventricular fibrillation (TaVF) after ischemia was noted during each experiment. As soon as VF was triggered, the occlusion was stopped, and external electric shock was administered to restore sinus rhythm.

Statistical analysis

Mean values were compared between groups with the Student t-test. The Pearson coefficient was used to evaluate correlations. Values are expressed as the mean \pm standard deviation. A value of $p < 0.05$ was considered significant.

Results

In Group 1, vagal stimulation triggered a significant increase in the interval between the P and R waves on the ECG (PR-interval; 100 ± 5 vs. 136 ± 12 ms, $p < 0.05$) and a decrease in sinus rhythm (132 ± 4 vs. 110 ± 17 bpm, $p < 0.05$). After 10 min of stimulation, prolongation of the PR-interval was less marked, but remained significant. After vagal stimulation, the mean arterial pressure remained unchanged (93 ± 16 vs. 83 ± 18 mmHg). After coronary occlusion, TaVF was not significantly different between occlusions and without vagal stimulation. In Group 1, after arterial occlusion, TaVF was longer for occlusions combined with vagal stimulation than for occlusions without vagal stimulation (1102 ± 85 vs. 925 ± 41 s, $p < 0.05$).

In Group 2, with a fixed rate of 190 bpm, vagal stimulation provoked a significant prolongation of time between atrial stimulation artefact and QRS wave on the ECG (127 ± 5 vs. 103 ± 6 ms, $p < 0.05$). Additionally, the mean arterial pressure tended to be higher during vagal stimulation (87 ± 19 vs. 68 ± 17 mmHg), but this difference was not significant (NS). However, after coronary occlusion, TaVFs were not significantly different between occlusions with or without vagal stimulation (90 ± 21 vs. 103 ± 39 s, NS; Fig. 1).

The pigs in Group 1 had lower HRs (121 ± 19 vs. 191 ± 3 bpm, $p < 0.05$) and displayed longer

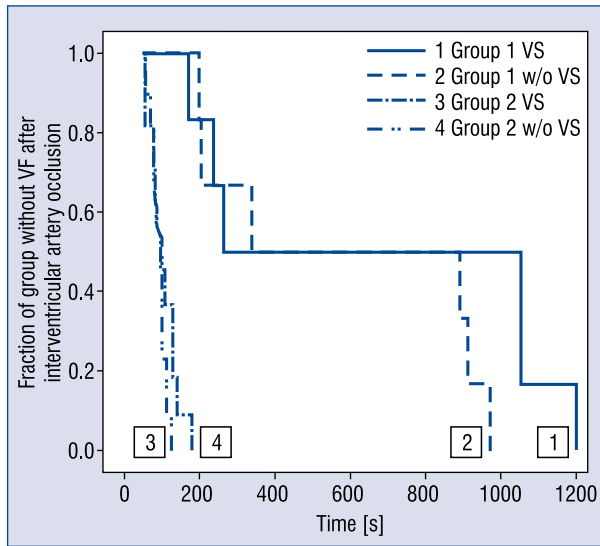


Figure 1. Survival curves according to the Kaplan-Meier estimation show the fraction of each group of pigs that remained without ventricular fibrillation (VF) at different time points after a coronary occlusion (VS — vagal stimulation; w/o VS — without vagal stimulation).

TaVFs (625 ± 415 vs. 98 ± 31 s, $p < 0.05$) than the animals in Group 2 (Table 1). When the animals in Groups 1 and 2 were combined, a negative correlation was found between the HR, measured within a 3-min period prior to ventricular fibrillation (VF), and TaVF. This correlation was strongest, when only the first occlusion periods were included in linear regression analysis (Fig. 2).

Discussion

The present findings suggest that, when rapid HR was fixed with atrial electrical stimulation, vagal stimulation did not modify the time to appearance of VF after occlusion of a coronary artery. The model herein indicated that HR was the major determining factor for electrical stability during an acute event that caused myocardial ischemia. This result was consistent with other studies which showed that medications that slowed HR, like beta-blockers [11], calcium channel inhibitors [12], or ivabradine [13], had favourable, antiarrhythmic effects.

In contrast to previous studies [2–4, 6, 7], a protective effect following rapid fixed frequency vagal stimulation by atrial stimulation was not found. However, the stimulation parameters applied in the present model were similar to those used in other studies [2–4, 6, 7]. Consistent with previous studies, a significant reduction in the

basal HR and an increase in the atrioventricular conduction time was observed. One explanation for differences between studies could be that interspecies variations in coronary anatomy played a role in the effects measured. For example, in animals with a developed collateral circulation, vagal stimulation could have a protective effect, because it causes vasodilation [14, 15]. This anatomy could account for an effect independent of HR in dogs, which was not found in pigs [3]. In addition, the present coronary occlusions were quite proximal, near the ostia of the artery in our model, and the location was different in other studies. Finally, it has been suggested that vagal nerve stimulation exerts anti-arrhythmogenic effects by preventing the loss of phosphorylated Connexin-43 during an acute myocardial infarction [4]. Indeed, in aged rats, loss of antiarrhythmic effect of vagal nerve stimulation was associated with reduced expression of Connexin-43 protein.

Surprisingly, previous studies that suggested that vagal stimulation effect was independent of HR did not directly compare experiments with a fixed HR to experiments with a variable HR. Ando et al. [4] described a model, where vagal stimulation was applied before ischemia was produced. That method provided results similar to the results obtained herein when vagal stimulation was performed during myocardial ischemia. Those data also suggested that establishing a low HR prior to triggering myocardial ischemia provided a protective effect. However, their study did not include a group of animals that received a fixed frequency stimulation to maintain a constant HR. Rosentrauckh et al. [6] studied cats that experienced total blockage of vagal activation with the administration of pertussis toxin and atropine. The harmful effect of vagal tone suppression was noted, independent of the frequency, but the authors did not demonstrate that vagal stimulation at a fixed frequency had a protective effect. Nevertheless, interpretation of results from the present study was reinforced by their results, because they indicated that animals that experienced VF had higher HRs than animals that did not experience VF. Kent et al. [2] studied VF threshold in dogs after vagal stimulation, without myocardial ischemia. They noted that the antiarrhythmic effect of vagal stimulation persisted at a fixed HR.

Some studies that used pharmacologic methods for vagal stimulation did not report an antiarrhythmic effect. In the study of Meesmann et al. [16], a cholinergic agonist injected retrogradely into the coronary sinus or administered systemi-

Table 1. Time to the appearance of ventricular fibrillation (VF) after coronary occlusion (TaVF) for groups with (wVS) or without vagal stimulation (w/o VS)

	Mean HR 3 min before VF [bpm]	Mean TaVF [s]
Group 1 VS (n = 6)	110 ± 17	664 ± 484
Group 1 w/o VS (n = 6)	132 ± 14	586 ± 375
Group 1 total (n = 12)	121 ± 19	625 ± 415
Group 2 VS (n = 10)	192 ± 4	91 ± 20
Group 2 w/o VS (n = 10)	190	103 ± 39
Group 2 total (n = 20)	191 ± 3	98 ± 31

Data are shown as mean ± standard deviation; HR — heart rate

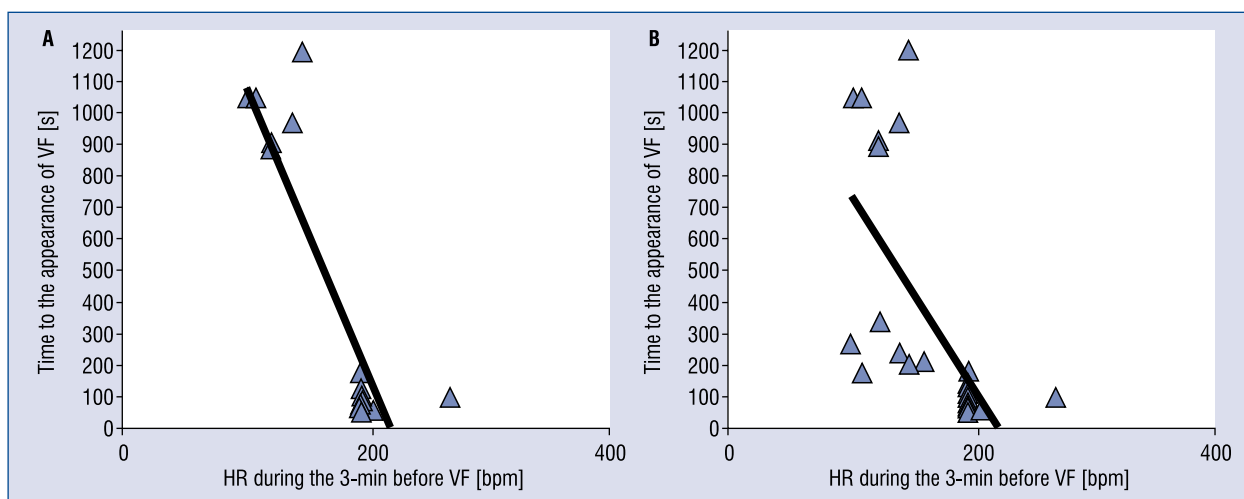


Figure 2. Correlation between the time to the appearance of ventricular fibrillation (VF) after occlusion and the mean heart rate (HR), measured within 3 min prior to VF, for all animals (Groups 1 and 2). **A.** Correlation without taking the first occlusion into account (correlation coefficient: 0.89); **B.** Correlation that included both occlusions for each animal (correlation coefficient: 0.67).

cally did not modify the incidence of ventricular tachycardia in dogs.

The study by Inagaki et al. [17] stressed the importance of bradycardia in the antiarrhythmic action of vagal stimulation. A vagal nerve stimulation technique via an intravascular approach in dogs was used. They reported a reduction in spontaneous ventricular arrhythmia incidents after acute myocardial ischemia. However, that protective effect disappeared when the atrium was stimulated at a fixed frequency of 170 bpm.

Limitations of the study

There were three major limitations in this study. First, the appropriateness of the present experimental model could be debated. It was chosen to approximate human clinical conditions. Compared to a mouse or rat, pig physiology is closer

to human physiology. For example, pigs resemble humans in HR (100 to 150 bpm at rest in pigs and man vs. 500 bpm in mouse) and coronary anatomy (epicardial-like in pigs and man vs. endocardial-like in rats) [18]. In animals with developed collateral vessels, mean blood flow can be maintained in the ischemic zone. Dogs maintain an equivalent of 15% of flow observed before coronary occlusion. This value is 6% in rats, but in pigs it is less than 1% [18]. Moreover, the use of an animal model made it possible to take the complexity of the autonomic nervous system into account [19]. The second limitation was that there was no measurement of the link between HR and coronary arterial vasomotion. The vasodilatation of vagal arteries could explain the vagal antiarrhythmic effect. It has been shown that vagal action in the presence of muscarinic and beta-adrenergic blockade significantly reduced the

resistance of coronary arteries, due to facilitation of the release of vasoactive intestinal peptide [20]. The third limitation was that the time to the appearance of VF after coronary occlusion was not the best criterion for cardiac electrical instability. However, this measurement was considered to be closer to criterion used in human clinical scenarios rather than artificially obtained criteria, such as the fibrillation threshold.

Conclusions

This study showed that, when HR was maintained at a constant rate with atrial electrical stimulation in pigs, vagal stimulation did not modify the time to appearance of VF. The negative correlation between HR and the time to appearance of VF suggests that HR played a determining role in cardiac electrical stability after arterial occlusion. These results reinforce the need to prescribe bradycardia-inducing medications in the acute phase of myocardial infarction. Finally, these findings call for future studies on mechanisms that underlie antiarrhythmic actions of medicinal substances. Moreover, non-pharmacological approaches for vagal stimulation are rapidly developing, and validation of these approaches should include antiarrhythmic measurements.

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