The Role of Beta-1 Receptors in the Response to Myocardial Ischemia

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Abstract

Acute myocardial ischemia is commonly diagnosed by ST-segment deviations. These deviations, however, can show a paradoxical recovery even in the face of ongoing ischemic stress. A possible mechanism for this response may be the cardio-protective effects of the autonomic nervous system (ANS) via beta-1 receptors. We assessed the role of norepinephrine (NE), a beta-1 agonist, and esmolol (ES), a beta-1 antagonist, in the recovery of ST-segment deviations during myocardial ischemia. We used an experimental model of controlled myocardial ischemia in which we simultaneously recorded electrograms intramurally and on the epicardial surface. We measured ischemia as deviations in the potentials measured at 40% of the ST-segment duration. During control intervention, 27% of epicardial electrodes showed no ischemic ST-segment deviations, whereas during the interventions with NE and ES, 100% of epicardial electrodes showed no ischemic ST-segment deviations. Intramural electrodes revealed a different behavior with 71% of electrodes showing no ischemic ST-segment deviations during control ischemia, increasing to 79% and 82% for NE infusion and ES infusion interventions, respectively. These preliminary results suggest that recovery of intramural regions of the heart is delayed by the presence of both beta-1 agonists and antagonists even as epicardial potentials show almost complete recovery.

1. Introduction

Acute myocardial ischemia shows several characteristic electrocardiographic features, most commonly ST-segment deviations. Previously, the absence of ST-segment deviations was interpreted to mean an absence of ischemia; however, studies have shown the presence of electrocardiographically silent ischemia that is documented by deviations in intramural electrograms. [1, 2] The broad goal of our research is to understand the spatiotemporal evolution of acute myocardial ischemia through large-animal experiments.

Clinical and experimental studies from our group and others have shown initial increases in ST-segment deviations followed by reductions and resolutions of ST-segments even during ongoing ischemic stress. [3–5] Ischemic stress is known to stimulate the autonomic nervous system (ANS), which we hypothesize plays a role in this premature recovery of ST-segment deviations. [4, 6] The primary mechanism of action of the ANS on working myocardium is by means of beta-1 receptors located on the sarcolemma, [7]. However, the role of the beta-1 receptor has not been examined during acute ischemia, especially by means of three-dimensional mapping.

This study aimed to examine the role of beta-1 modulation on the recovery of ST-segment deviations during myocardial ischemia. We induced repeated episodes of acute ischemia, first under control conditions and then following local application of a beta-1 agonist (norepinephrine) and antagonist (esmolol). Throughout each experiment, we captured signals using intramurally placed needle electrodes together with an epicardial sock. Signals from these electrodes provided three-dimensional measurements of ST-segments, from which we could quantify deviations throughout 15-minute episodes of continuous and increasing stress induced by graded pacing of the heart following chronic reduction in coronary flow. Our results showed that both agonists and antagonists to beta-1 receptors altered the spatiotemporal response of the heart to ischemia, reducing the response quite forcefully.

2. Methods

Experimental protocol: Electrograms were acquired from an *in situ* porcine preparation as described previously. [8] Briefly, myocardial ischemia was induced by reducing perfusion through the left anterior descending coronary artery and increasing myocardial stress using controlled atrial pacing. Our experiment consisted of three interventions of controlled myocardial ischemia within the same subject. First, a control episode was induced with-

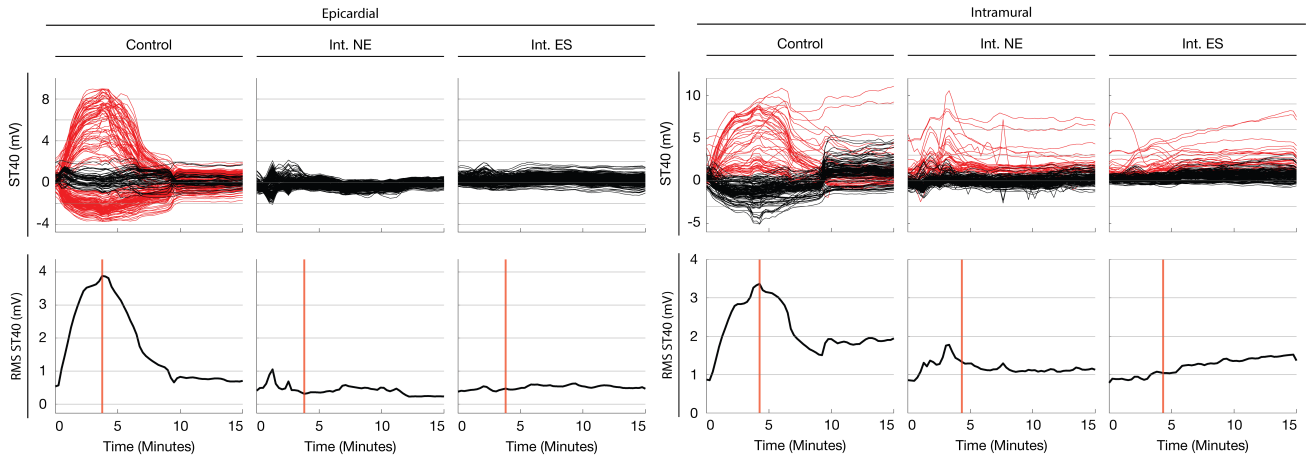

Figure 1. Run-metric plots of ST40% potential changes throughout an ischemic episode. The left panel shows ST40% values from the epicardial surface recordings and the right panel shows the intramural values. For both panels, the columns represent the control intervention (left), the intervention with NE (middle), and the intervention with ES (right). The top row shows the ST40% potentials, where each line represents the electrical activity of one electrode. A red line corresponds to an ischemic electrode, and a black line corresponds to a nonischemic electrode. The bottom row shows the RMS time course of the ST40% potentials with the time of peak response during the control intervention marked with a vertical red line.

out the presence of any beta-1 modulators. The second ischemic episode was accompanied by the infusion of norepinephrine (NE) at a constant rate of 13.5 μg/kg*hour to simulate physiological NE concentrations during graded exercise. [9] The third ischemic episode was accompanied by the infusion of esmolol (ES) at a constant rate of 300 μg/kg*min to replicate clinical dosing. [10] Throughout the interventions, electrograms were recorded from a 247-electrode epicardial sock and 23 intramural plunge needles, each with 10 unipolar electrodes. Electrograms were sampled at 1 kHz [11] and signals were filtered, baseline corrected, and fiducialized using the open-source software PFEIFER. [12] All experiments were approved by the Institutional Animal Care and Use Committee of the University of Utah, protocol number 20-11001.

Evaluation metrics: ST-segment deviations were used as indicators of myocardial ischemia. From each beat, we extracted the average potential values in an 11 ms window 40% of the way between the end of the QRS and the peak of the T wave. Representative ST40% potentials were extracted every 15 s from continuously acquired electrograms throughout the intervention. To compare the ST40% potentials at equivalent times during subsequent interventions, we determined the time point of peak ischemic stress during the control intervention from the root mean square (RMS) of the ST40% potentials. We refer to this time point as 'peak control ischemic stress'.

For intramural recordings, ST40% potentials above 1 mV were considered ischemic. For epicardial recordings, ST40% potentials above 2 mV or below -1 mV were considered ischemic. These thresholds were used to determine the percentage of electrodes considered 'clinically detectable' as these thresholds mimic those used in evaluating ST-segments deviations in patients.[5]

3. Results

Figure 1 shows the ST40% potentials from each electrode (both epicardial and intramural) throughout each intervention. The baseline ischemic intervention had initial ST-segment deviations followed by a notable recovery of ST-segment deviations that we have documented previously. [5] However, we also observed for both NE (beta-1 agonist) and ES (beta-1 antagonist) that the ischemic response was greatly reduced in comparison to that measured during the control intervention. Table 1 contains the average, standard deviation, minimum, maximum, and range of the ST40% potentials at 4 minutes into each intervention (corresponding to the peak control ischemic stress), as well as the percent of nonischemic electrodes. Overall, the baseline ischemic intervention had a more notable ischemic response in comparison to the interventions with NE and ES.

Epicardial response to ischemia: The range of ST40% potentials was approximately eight times larger for the control intervention when compared to the interventions with NE and ES. Furthermore, the percent of nonischemic electrodes was 27% for the control intervention and 100% for the interventions with NE and ES. Lastly, Figure 2 shows the distribution of the ST40% potentials for each

Table 1. ST40% statistics: Mean $\pm$ one standard deviation (mV), minimum (mV), maximum (mV), range (mV), and percent of nonischemic electrodes. Statistics are shown for both the epicardial surface (Epi.) and intramural recordings (Intra.) at the time point corresponding to peak control ischemic stress, as described above.

		Mean $\pm$ STD (mV)	Min / Max (mV)	Range (mV)	Nonischemic Electrodes (%)
Epi.	Int. 1	0.7 ± 3.8	-3.7 / 9.0	12.7	27
	Int. 2 (NE)	-0.1 ± 0.3	-0.7 / 0.9	1.6	100
	Int. 3 (ES)	0.3 ± 0.4	-0.7 / 1.2	1.9	100
Intra.	Int. 1	0.4 ± 3.4	-5.1 / 9.7	14.8	71
	Int. 2 (NE)	0.5 ± 1.3	-1.0 / 7.2	8.2	79
	Int. 3 (ES)	0.6 ± 0.9	-0.7 / 4.7	5.4	82

intervention. For epicardial recordings, the baseline intervention had a large density of electrodes showing ST-segment depression. The interventions with NE and ES, however, showed ST-segment depressions and elevations, respectively, that were considerably lower than the ischemic thresholds.

Intramural response to ischemia: The peak values of ST40% potentials were reduced by approximately half for the intervention with NE and one-third for the intervention with ES when compared to the control intervention. Furthermore, the percent of nonischemic electrodes climbed from 71% for the control intervention to 79% and 82% for the interventions with NE and ES, respectively. The distributions of the ST40% potentials also differed by interventions, as shown in Figure 2. For intramural recordings, the baseline intervention had a large density of electrodes showing ST-segment depressions, the intervention with NE, by contrast, produced a large density of electrodes showing no ST-segment deviations, and the intervention with ES produced only slight (< 1 mV) ST-segment elevations. However, none of the deviations during application of the beta-1 modulators reached the ischemic threshold.

4. Discussion

The goal of this study was to evaluate a possible mechanism by which the autonomic beta-1 receptor could mediate the recovery of ST-segment deviations during myocardial ischemia. [4, 6] We implemented experimental models of acute myocardial ischemia and incorporated NE, a beta-1 agonist, and ES, a beta-1 antagonist, while recording electrograms from the epicardial surface and intramurally. The results of this unique, three-dimensional mapping showed a notable blunting of ST-segment deviations on the epicardial surface and within the myocardium in response to both NE and ES.

The fact that both NE and ES blunted the ST-segment responses to ischemia was not expected since the two drugs are known to have opposite effects on beta-1 receptors. [13, 14] Other mechanisms contribute to the overall response, and our preparation could not isolate them. One possible mechanism to describe the reduced ST-segment response with NE is a reduction in extracellular potassium concentration, which is a known and rapid contributor to the elevation in myocardial resting potentials. [5] According to this hypothesis, NE stimulates the sodium-potassium pump, whose activity is limited during ischemia [4, 13]. In the face of ES, a different mechanism is possible in which there is a decrease in contractility leading to a reduction in the oxygen demand of the myocardium. The decrease in oxygen demand could result in a rebalancing of the supply/demand mismatch that arises during partial-flow ischemia. [10, 14] Thus, both NE and ES, through different beta-1 pathways, could help resolve the ischemic stress.

Our examination of the changes in the ST40% potentials throughout a region of the myocardium allowed us to compare responses across the ventricular wall. We found a complete recovery of ST-segment deviations on the epicardial surface, but persistent ischemic zones intramurally for both NE and ES (Table 1). On the epicardial surface, 100% of electrodes showed healthy ST potentials for both NE and ES, suggesting that the underlying tissue was adequately perfused. A consequence of this epicardial recovery masks the underlying intramural ischemic tissue, resulting in a false negative marker for the presence of ischemia, electrocardiographically silent ischemia. Previous studies have shown that significant damage can still occur within the masked ischemic tissue despite an absence of the electrical indication on the body surface [4]. Further studies must pursue different markers of ischemia that can detect intramurally localized perfusion deficits and guide suitable interventions.

This study was limited to one biological sample (N=1). We also were unable to measure the specific concentrations of both NE and ES within the experimental preparation, limiting evaluation of quantitative relationships. Furthermore, the natural autonomic response that leads to neurotransmitter interactions could have been altered by the deep anesthesia during the experiments. Overall, we observed that NE and ES both result in the disappearance of ischemic signals despite ongoing ischemic stress.

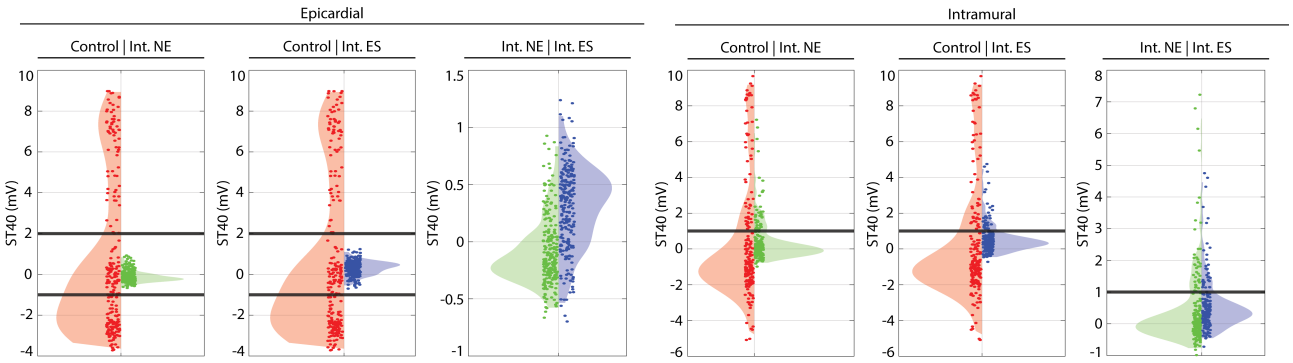

Figure 2. Frequency distribution of ST40% potentials at the time point corresponding to the peak control ischemic stress. The left set of panels shows the epicardial surface recordings, and the right set of panels shows the intramural recordings. The three interventions are represented as follows: red corresponds to the control intervention, blue corresponds to the intervention with NE, and green corresponds to the intervention with ES. The black horizontal lines represent the ischemic threshold bounds. The thresholds are not present in the epicardial histogram comparison between the interventions with NE and ES because no ST-segment deviations were detected.

Acknowledgments

Support for this research came from the NIH / NIGMS Center for Integrative Biomedical Computing (www.sci.utah.edu/cibc), NIH NIGMS grant R24 GM136986, the NSF GRFP, and the Nora Eccles Treadwell Foundation for Cardiovascular Research.

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