Cardiothoracic Anesthesia, Respiration and Airway

Epi and endomyocardial pH allows the detection of acute right ventricular ischemia in pigs: a new evaluation method

[La connaissance des pH épimyocardique et endomyocardique permet la détection d'ischémie aiguë du ventricule droit chez des porcs : une nouvelle méthode d'évaluation]

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Background: Techniques which identify acute right ventricular (RV) ischemia may help elucidate the pathophysiology of RV dysfunction. This study's goal was to validate an acute RV ischemia or infarction detection technique. Could RV endomyocardial and epimyocardial (interstitial) pH electrodes detect RV pH changes in an animal model of RV infarction produced by right coronary artery ligation?

Methods: In ten adult anesthetized pigs, RV interstitial (pH_{epi}) and transmural endomyocardial pH (pH_{endo}) were measured before and serially after right coronary occlusion.

Results: pH_{endo} and pH_{epi} fell significantly following coronary occlusion. The absolute and relative rates of change were greater for pH_{endo} (mean pH decreased from 7.36 to 7.04) compared to pH_{epi} (mean pH of 7.28 vs 7.08; $P < 0.002$). pH was unchanged in control experiments where the electrode was placed in the right atrial or ventricular chamber, and in sham-operated animals. These data suggest that coronary ligation induced RV ischemia produces RV myocardial pH changes, which can be recorded from an electrode placed against the RV wall via a central vein, or in the interstitium.

Conclusion: This newly described technique may be helpful in developing more discriminating tools to identify acute RV ischemia.

Objectif : Les techniques permettant de repérer une ischémie aiguë du ventricule droit (VD) peuvent aider à élucider la physiopathologie d'une dysfonction VD. L'objectif de la présente étude était de valider une technique de détection de l'ischémie aiguë ou d'un infarctus du VD. Des électrodes pour le pH endomyocardique et épimyocardique

VD (interstitiel) permettent-elles de détecter des modifications de pH chez un modèle animal d'infarctus du VD produit par la ligature de l'artère coronaire droite ?

Méthode : On a mesuré le pH VD interstitiel (pH_{épi}) et endomyocardique transmural (pH_{endo}) avant l'occlusion coronaire droite, et après en séquence.

Résultats : Les pH_{endo} et pH_{épi} ont chuté de façon significative après l'occlusion coronaire. Les taux de changement absolus et relatifs ont été plus grands pour le pH_{endo} (le pH moyen a baissé de 7,36 à 7,04) comparé au pH_{épi} (pH moyen de 7,28 vs 7,08 ; $P < 0,002$). Le pH est demeuré inchangé lors d'essais contrôlés où l'électrode était placée dans l'oreillette droite ou dans la cavité ventriculaire, et chez les animaux dont l'opération était fictive. Ces données laissent croire que l'ischémie VD induite par la ligature coronaire produit des changements de pH du myocarde VD, lesquels peuvent être enregistrés à partir d'une électrode placée sur la paroi VD en passant par la veine centrale, ou placée dans l'interstitium.

Conclusion : La nouvelle technique décrite pourrait favoriser la mise au point d'outils plus précis de détection de l'ischémie aiguë du VD.

MYOCARDIAL ischemia is a common problem among patients requiring intensive care.¹ Right ventricular (RV) ischemia is particularly challenging to identify, as reliable identifying measures are difficult to obtain. Standard electrocardiographic (ECG) tracings

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are not specific; right-sided ECG monitoring, although more reliable in detecting RV ischemia, is not used commonly. Two-dimensional echocardiographic measures of RV function and volume are limited by the asymmetrical and crescent shape of the ventricle and by difficulty in obtaining standardized views;² echocardiography does not distinguish mechanical from ischemic dysfunction. Nuclear imaging studies are limited by the ventricle's anatomy.³ Almost instantaneous measures of myocardial ischemia, and the ability to monitor the right ventricle's perfusion, would be clinically useful.

Critical tissue hypoperfusion is accompanied by decreases in tissue pH.⁴ A decrease in RV perfusion should result in reduced myocardial pH. The objectives of this study were to validate the application of a diagnostic method known to reflect ischemia in the left ventricle⁵ to the right ventricle, in anesthetized pigs, and to attempt to monitor ischemic changes with the least invasive technique possible: by measuring transmural pH changes. The domestic pig model was chosen because its coronary circulation,⁶ conduction system,⁷ and epicardial blood supply,⁸ more closely resemble that of the human than any other non-primate animal species.

Materials and methods

Animal preparation

The experiments were performed on 14 Yucatan pigs of either sex weighing 35 to 45 kg. Sedation was initiated with 10 to 20 mg·kg⁻¹ of *im* ketamine. An *iv* catheter was inserted in either ear. The pig was then anesthetized with a bolus of *iv* fentanyl, at 100–200 µg·kg⁻¹, and *iv* propofol, at 1–2 mg·kg⁻¹, followed by fentanyl (100–200 µg·hr⁻¹) and propofol (20 to 80 mg·hr⁻¹) infusions.⁹ The animal was intubated, and mechanical ventilation was initiated with a mixture of air and 50% oxygen. Antiarrhythmics (bretylium, 5–10 mg·kg⁻¹) and magnesium sulfate (2 g) were administered as needed.

A sternal thoracotomy was performed, and the pericardium was opened. The right coronary artery was identified and circled with a silk suture. The heart was covered with warm compresses to minimize heat loss. The dissected jugular vein was cannulated with a 10-F catheter.

A pH electrode was placed under direct vision in the RV interstitial myocardium (epicardial electrode) and sutured in place (Figure 1). A second pH electrode was inserted via the 10 F catheter in the jugular vein; advanced with the electrode wire (which is quite similar to a pacemaker wire in stiffness and manipulation potential); and positioned against the RV wall

FIGURE 1 A graphic representation of the experimental model. The right ventricle (RV) is depicted, with the epimyocardial pH probe imbedded in the myocardium. The endomyocardial pH probe, introduced via a central vein, is leaning against the endomyocardial wall. Both glass-tipped pH probes are identical; the wire for the endomyocardial probe was custom-made (to ensure insertion ability via a central venous catheter) by Vascular Technology Inc. for the purposes of this experiment.

(endomyocardial electrode, Figure 1). Initially, prior to each study, its position was confirmed by palpation; repeat palpation and direct visual verification were carried out at the end of the experiment. The reference electrode was placed behind the lung parenchyma. The glass-tipped endomyocardial and epimyocardial pH electrodes, from Vascular Technology Inc., were identical in each experiment. All the measurements were recorded simultaneously every 20 sec. The pH readings were analyzed from a computer using software developed by Vascular Technology Inc.¹⁰ ECG tracings were recorded by attaching an ECG lead onto the pericardium.

The animals died of ventricular fibrillation under general anesthesia. All procedures followed were in accordance with the guidelines of the Canadian Council of Animal Care, and were approved by the local Animal Care Committee.

Experimental protocols

Following a recovery period from surgery, baseline measurements of epicardial and endomyocardial pH were obtained for five minutes.

The right coronary artery was then ligated with the silk suture described above. The endo- and epi- myocardial pH readings were recorded every 20 sec (this frequency was limited by our equipment) until the inevitable ventricular fibrillation of the pig. When feasible, four to six additional measurements were recorded.

Technical considerations

PH was calculated from the voltage (in mV) generated from the glass-tipped pH probe as follows: $pH = (1/\text{slope})(mV) + pH_0$, where slope (T) = $-59.2 \text{ TK}/298.15$ and $pH_0 = -0.00705 \text{ T (C)} + 7.174$ between 25 and 40°C (76 and 103°F). In our experiments, the tissue temperature ranged from 30°C to 35°C (86 to 93.5°F), as measured by a temperature probe.

Statistical analysis

Data obtained from each pH probe (epicardial and endomyocardial) were subjected to comparison over time to determine differences from baseline values. The baseline values were obtained by averaging all pre-ligation values. The pre-fibrillation pH was calculated as the average of all observed values prior to fibrillation.

All comparisons were done by the Wilcoxon signed rank test.¹⁰ A $P < 0.05$ was considered significant for each test.

Results

We completed the experiment with endomyocardium-adjacent probes and epicardial probes in ten animals. Following right coronary artery ligation, endomyocardial pH declined from 7.36 to 7.048 (Figure 2). A statistically significant decrease in endomyocardial pH could be detected at three minutes post ligation. Readings from the epimyocardial electrode decreased from 7.28 to 7.08. Significant changes occurred at 3.3 minutes. In eight out of ten animals, fibrillation occurred after five minutes of ligation.

As the duration of the experiment (from ligation to ventricular fibrillation) was different for each pig, pre-fibrillation endomyocardial and epimyocardial pH measurement timing varied from animal to animal. The decreases in endomyocardial pH were greater than epimyocardial pH ($P < 0.002$).

ECG tracings were obtained from surface electrodes placed on the pericardium. ST segment elevation denoting current of injury began at three seconds following ligation of the right coronary artery. Maximal ST segment elevation occurred between ten

FIGURE 2 Changes in endo and epimyocardial pH following ligation of the right coronary artery. Time 0 refers to the right coronary artery ligation. Values are measured in ten animals. Asterisks reflect statistically significant changes ($P < 0.05$). Standard deviation (not exceeding 10% of the mean) has been omitted for the sake of clarity.

and 15 sec following the ligation, and ranged from 5 to 11 mm (mean, 7 mm).

Additional pH readings were obtained from a group of four animals in which the endomyocardial electrode was left free-floating in the right ventricle or inferior vena cava, or placed against the septal (supplied by the left coronary artery) or atrial wall (Figure 3). There was no significant change over time in these probe readings, in contrast to endomyocardial measurements recorded simultaneously. Direct pH measurement was confirmed by blood gas analysis of right atrial blood. The floating pH electrode accurately reflected blood pH values, and did not change over time (data not shown).

Sham-ligated control experiments were performed to test the variability of pH measurements over periods of 20 to 30 min. Neither epicardial or endomyocardial pH measurements changed over time.

Discussion

We describe a novel technique which detects RV ischemia-induced pH changes and simply requires the

FIGURE 3 Comparison of epimyocardial pH values to pH values obtained by a floating electrode (i.e., where the pH electrode floated free in the right ventricle or the right atrium). Note the decrease in epimyocardial pH following right coronary artery ligation (time 0), whereas the floating electrode measured pH did not change. Values are measured in four animals. Standard deviation (not exceeding 10% of the mean) has been omitted for the sake of clarity.

introduction of a pacemaker-like pH probe into the right ventricle via a central vein.

In the extensively studied left ventricle model, myocardial intracellular hydrogen $[H^+]$ ion concentrations rise in subperfusion arrest and in coronary occlusion/myocardial ischemia.⁴ Interstitial myocardial pH can also be assessed by implanting a small pH electrode in tissue, or by attaching a vacuum-filled Teflon catheter to a mass spectrometer to measure PCO_2 , which correlates with pH.¹²⁻¹⁵ Interstitial myocardial measurements correspond to intracellular myocardial measurements. Brief coronary occlusion reduces interstitial myocardial pH.¹⁶⁻²¹ ST segment elevation accompanies this pH reduction. Attenuated decreases in pH are followed by a plateau, if the occlusions are repeated at fixed intervals.¹⁷ Endomyocardial pH falls more rapidly than the epicardial pH for any given regional vascular occlusion.¹⁶

Glass-tipped pH electrodes are used in the experimental setting and in clinical practice to determine the degree of myocardial ischemia during various cross-clamping times and to assess warm or cold cardioplegia times.²¹⁻²⁴ The trans-mural evaluation of tissue pH has been studied extensively in the setting of gastric and intestinal pH measurements.²⁵ However, measurements of myocardial tissue pH to assess ischemia require direct visualization of the myocardium, either *in vitro* or by thoracotomy, for electrode or catheter placement. The only non-invasive method known to correspond to interstitial pH measurements is 31 -phosphorus magnetic resonance spectroscopy.²⁶ The equipment required for obtaining this information is not readily available, and the method has not been validated for the human heart.

In this study endomyocardial pH decreased three minutes following right coronary artery ligation. The endomyocardium shows ischemia earlier than the epimyocardium in left ventricular ischemia models because of vascular anatomy. Our findings confirm that the same is true for the right ventricle: absolute epicardial pH decreased less than endomyocardial pH in all experiments. A technical factor may have influenced these findings: the right ventricle of the pig is very thin (at approximately 1 mm, it is thinner than an equivalent-sized dog's right ventricle). We inserted a 1-mm thick, 4-mm long pH electrode into the RV wall at an angle to ensure that the electrode was at all times surrounded by tissue, and attempted to ensure the tip was not protruding into the RV lumen. Tissue distortion with impaired blood flow to the region, caused by the probe itself, may have contributed to the measurement differences.

The probes not positioned against the RV endomyocardium did not register any change in pH. Had the RV blood or systemic pH influenced the endomyocardial pH, a change in these unpositioned probe readings would have been detected. The pH would therefore drop only if the probe is leaning against the endomyocardial wall supplied by the coronary that has just been ligated. Correct positioning, verified manually in our experiment, could also be ensured in any potential non-thoracotomy model, since the metal wire in the probe is radio-opaque.

The pH changes described varied in parallel (with a delay) with ECG abnormalities. The decrease of one unit of pH over minutes reflects a ten-fold increase in hydrogen ion concentration within the cell. This dramatic change suggests that perhaps milder, non-infarction-inducing ischemia could also be detected.

The obvious limitation to the study is the use of complete coronary occlusion rather than graded coro-

nary flow limitation. Several reasons justify this choice. The pig resembles the human in myocardial anatomy, vascularization and receptors. The pig is notoriously prone to lethal arrhythmias, even with minimal manipulations such as passing a suture around a coronary artery. The loss of several animals in the "pilot" experiments (not described here) because of arrhythmias during sub-clinically significant graded occlusions was disturbing. Moreover, graded flow occlusion techniques are described with a C-shaped magnetic flow-measuring instrument against the coronary artery at a perfect 90 position; this measurement is always sub-optimal in the beating heart. We therefore induced lethal ischemia. This animal model does not clarify whether pH changes would be detected if the induced ischemia had been moderate, or address whether chronic forms of RV dysfunction are associated with detectable myocardial pH changes. The degree to which coronary flow impairment may cause pH changes may also vary with RV strain caused by mechanical variables (i.e., increasing pulmonary flow occlusion, or mechanical ventilation setting changes).^{28,29} Once more, the propensity to arrhythmias, which characterizes the porcine heart, prevented us from pursuing these possibilities, as well as from assessing pH changes during the reperfusion period. Further experiments are required to elucidate these points.

Conclusion

We do not currently possess a convenient, inexpensive tool that would allow for a rapid and coronary- distribution specific method for assessing acute RV ischemia. The present study suggests that RV endomyocardial pH can be measured by leaning a transvenously introduced pH electrode against the endomyocardial wall. The endomyocardial pH changes measured reflect RV ischemia caused by right coronary artery occlusion.

We describe a novel technique for assessment of RV ischemia. This experimental model represents an initial feasibility study for this technique. Additional studies are required to explore the potential validation of this technique in reversible ischemia models and in settings where RV anatomy is strained or distorted. Further work may elucidate physiologic elements applicable to the intensive care unit patient, in whom RV dysfunction is a clinically common but difficult to detect and poorly understood phenomenon.

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