Use of Myocardial Electrical Impedance to Assess the Efficacy of Preconditioning

CL del Río[†,‡], R Dzwonczyk[†], B Clymer[‡], T McSweeney[†], H Awad[†], P Czerwinski[†], MB Howie[†]

[†]Anesthesiology and [‡]Electrical Engineering, The Ohio State University, Columbus, USA

Abstract

Myocardial electrical impedance (MEI) has been found to correlate with ischemia and ischemic preconditioning (PC).

In this study, the short-term effects of adenosine preconditioning on the MEI were studied in a swine model of beating heart coronary revascularization. Juvenile farm pigs were assigned to have either no PC (CTRL) or adenosine PC (ADO), receiving subsequently two ischemia/reperfusion (IR) insults.

In both groups, MEI increased immediately with induced ischemia. However, its progression to ischemic plateau after reaching a maximum rate of change took significantly longer for ADO animals (7.13 ± 1.03 min) than for the CTRL (4.56 ± 0.16 min) (P<0.05). Such period of time was defined as a time constant.

MEI was able to distinguish between study groups by evaluating the time required to reach ischemic plateau and from its rate of change (first derivate).

1. Introduction

Myocardial electrical impedance (MEI), a passive electrical property of the heart muscle, has been studied for more than a century and found to reflect various diseased states of the myocardium. It has been shown to change predictably with myocardial ischemia [1,2,3] and rejection [4], being sensitive not only to perfusion disturbances, but to metabolic and ultra-structural changes such as ATP depletion, lactate accumulation, edema and electrical cellular uncoupling. At this laboratory, it has been demonstrated (1) to increase immediately with occlusion of the left anterior descending coronary artery (LAD) reaching a plateau subsequently [3], and (2) to differentiate between drug-induced metabolic states. MEI, therefore, has potential value as an intra-operative monitoring and predictive tool, especially in beating heart myocardial revascularization procedures, where during the grafting process the heart muscle is forced to work in ischemic conditions and traditional ischemia monitoring techniques are ineffective.

In this setting, several preconditioning (PC) techniques attempt to protect the myocardium from an ischemic insult by raising its intrinsic anti-ischemic shields. Preconditioning, by brief periods of ischemia/reperfusion, referred as "ischemic preconditioning", has been found to increase myocardial tolerance, limit ATP wastage, attenuate myocardial acidosis and to reduce the rate of anaerobic glycolysis during prolonged ischemia (for review see [5]). On the other hand, these techniques have also been found to fail, and since there is no on-line, reliable and clinically feasible method to assess their efficacy, in practice, they are performed "blindly".

There is significant evidence that suggests MEI is a possible monitoring tool during preconditioning [6-7], given its ability to detect cellular uncoupling [8]. However, in such investigations, the early behaviour of MEI during ischemia (with or without PC), specifically before the onset of cellular uncoupling and cellular damage, has been neglected. Thus, the purpose of this study was to further investigate the value of MEI as a measure of preconditioning success.

2. Materials and methods

The short-term effects of adenosine preconditioning on MEI were studied in a swine model of beating heart coronary artery revascularization. Adenosine infusion before acute ischemia has been shown to mimic the protective effects of ischemic preconditioning [9-10]. However, studies correlating this technique with MEI data are lacking.

2.1. Animal preparation

With institutional approval, unconditioned juvenile farm pigs (25 - 30kg) of either sex were anesthetized with Telazol (6mg/kg) and Xylazine (2.2mg/kg), placed on a respirator and instrumented with arterial and pulmonary artery (PA) catheters. Blood gases were sampled periodically and maintained within normal limits. Continuous monitoring included: Trans-esophageal echocardiogram (TEE), electrocardiogram (ECG), ST-segment, heart rate, pulse oximetry, temperature, cardiac output, arterial and PA pressures.

Sternotomy was performed, the heart exposed and suspended in a pericardial cradle. A portion of the LAD, distal to the first diagonal branch was isolated and a Robinson's vessel tie was loosely placed around the isolated portion of the artery. Two monopolar standard temporary pacing electrodes were placed in the region known to be rendered ischemic by the LAD occlusion, stitched 1cm apart parallel to each other, and oriented perpendicular to the muscle fibers.

MEI was measured every second throughout the experiment in a fashion previously described [11] and demonstrated [3]. In short, through the temporary pacing leads, a computer controlled analog circuit impresses onto the myocardium a zero mean bipolar current, consisting of two alternating rectangular pulses (±5μA, 100μs wide) generated 10ms apart. The (positive) current stimulus and the respective voltage response of the myocardium are band-pass filtered (0.27 – 5.90 kHz), digitized (@ 22.0 kHz) and transformed into the frequency domain by a radix-2 Fast Fourier Transformation (FFT). In this domain, the complex MEI spectrum is calculated as the voltage to current ratio at each frequency component. MEI is reported as the ensemble average (10 measurements) of the mean MEI modulus in the range 0.5 kHz to 5.0 kHz.

2.2. Experimental protocol

After instrumentation and 10 minutes of baseline recordings, the animals were randomly assigned to have either no preconditioning (CTRL, n=5) or adenosine preconditioning (ADO, n=5), receiving respectively, a 10 min infusion of placebo (0.9% normal saline) or adenosine (20 mg/kg) through the PA catheter distal port. Supportive Levophed (1μg/kg) was co-infused with adenosine (ADO group) in order to maintain hemodynamic stability.

In both groups, infusion was followed by a washout period of 5 min, and an initial ischemia/reperfusion (IR) test period (10 min zero-flow ischemia/30 min reperfusion) performed. Upon completion of this insult, the animals were subjected to a second IR test of 30 min (each phase), mimicking a worse than average setting for coronary revascularization on the beating heart. In all cases, ischemia was induced by LAD occlusion, securing the Robinson's tie. A marker was placed in the MEI data after the LAD occlusion procedure was completed.

2.3. Analysis

Myocardial electrical impedance recordings were assumed to be contaminated with zero mean white Gaussian noise. In order to mitigate its effects, the MEI signal was filtered using a moving average filter of length $N = 120$ samples (2 min),

$$z_N[n] = \sum_{i=0}^{N} h_N[i] \cdot z[n-i]$$

The weighting function was chosen to be rectangular, i.e.

$$h_K[n] = \begin{cases} \dfrac{1}{K+1} & 0 \le n \le K \\ 0 & otherwise \end{cases}$$

From the filtered MEI signal, a smooth approximation to the myocardial electrical impedance rate of change (first derivate) was computed using two linear filtering stages:

- A two-point finite difference filter, i.e.,

$$\Delta z_N[n] = \sum_{i=0}^{1} h_\Delta[i] \cdot z_N[n-i] = z_N[n] - z_N[n-1]$$

- A moving average filter of length $M = 60$ (1 min) with weighting function $h_M[n]$ (as defined above),

$$\Delta z_{N,M}[n] = \sum_{i=0}^{M} h_M[i] \cdot \Delta z_N[n-i]$$

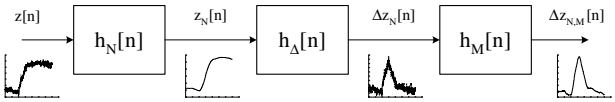

Fig. 1. Cascade of linear filters used to generate smooth signals representing the myocardial electrical impedance ($z_N[n]$) and its first derivate ($\Delta z_{N,M}[n]$).

Fig. 1 (above) summarizes and exemplifies the three filtering procedures described before. After filtering, the point of occlusion (n_{occ}) was selected as the sample (in a close neighborhood of the occlusion marker) where the smoothed MEI first derivate reached a local minimum (i.e., an MEI inflection point). In order to account for any differences in electrode spacing and placement, the filtered MEI data were normalized by the value at this time (baseline), i.e.

$$\zeta[n] = \frac{z_N[n] - z_N[n_{occ}]}{z_N[n_{occ}]}$$

Similarly, the sample where the smoothed MEI rate of change peaked ($n_{\Delta peak}$) was detected and used to normalize the filtered signal representing its first derivate, i.e.,

$$\Delta\zeta[n] = \frac{\Delta z_{N,M}[n]}{\Delta z_{N,M}[n_{\Delta peak}]}$$

For simplicity, in the remaining of the paper when referring to the normalized versions of the smoothed MEI and its derivate, the adjectives (normalized, smoothed, filtered, etc.) will be generally dropped, e.g., $\zeta[n]$ will be referred simply as MEI.

Two parameters commonly used in the literature to correlate myocardial electrical impedance with ischemia were extracted from the MEI data: "peak" change from baseline (i.e., MEI ischemic plateau value, ζ_{peak}) [1-3], and cellular uncoupling time (UT, t_u). Electrical cellular uncoupling is usually associated with a 10% MEI change from baseline [4,7,8].

Additionally, considering that MEI's ischemic plateau may hold important information regarding physiological processes occurring during the early stages of ischemia, and that the initial fast rise in MEI may be due simply to vasculature compression after coronary flow elimination [7], a *new* third parameter was defined: *time constant* (TC, τ). A TC was used to represent the time required by MEI to reach its ischemic plateau value (ζ_{peak}) after its maximal rate of change was observed:

$$\tau = T \cdot \left(n_{peak} - n_{\Delta peak}\right),$$

where $T = 1\,\text{s}$ is the MEI's sampling period, and n_{peak} is the point (sample) where the MEI's rate of change ($\Delta\zeta[n]$) decreases below 3% of its peak value (observed at $n_{\Delta peak}$), in other words,

$$\Delta\zeta[n_{peak}] \le 0.03, \text{ and } n_{peak} > n_{\Delta peak}$$

Results are reported as means with standard deviations (mean ± std. dev.) and parameter differences between groups were compared using two-sample student's t-test assuming unequal variances ($\alpha = 0.05$).

3. Results

Changes in the MEI signaled coronary perfusion disturbances produced by LAD occlusion. MEI increased immediately with induced ischemia, remaining elevated from its baseline value until reperfusion (Fig. 2), as expected.

However, the rate of change in MEI varied between groups and significant differences were observed. During ischemia, adenosine-treated animals (ADO) had a longer progression to ischemic MEI plateau, reaching such value in 9.49±1.29 min. While for animals in the control group (CRTL), stable MEI was observed in 7.02 ± 0.33 min, i.e., 26% faster (P<0.05) as highlighted by Fig. 2.

As previously defined, a time constant (TC, τ) represents the time required by MEI to reach ischemic plateau after its maximal rate of change has been observed. Thus, it was calculated that $\tau_{ADO} = 7.13 \pm 1.03\,\text{min}$ in adenosine-treated animals, while $\tau_{CTRL} = 4.56 \pm 0.16\,\text{min}$ in non-treated animals (P<0.05).

As it can be seen in Table I, MEI's time constant (τ) performed better than the MEI ischemic plateau value (ζ_{peak}) and the cellular uncoupling time (t_u), since it is the only parameter of the three where significant differences were observed. For example, Fig. 3 compares the performance of MEI's time constant (τ) against peak MEI percentage of change from baseline (ζ_{peak}).

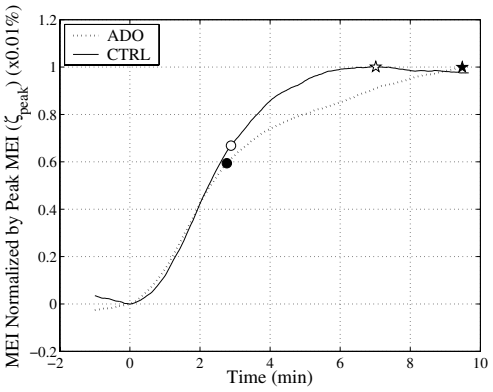

Fig. 2. Ensemble average of MEI ($\zeta[n]$) normalized by the ischemic plateau value (ζ_{peak}, 5-point stars) for control (CTRL, n=5) and adenosine-treated (ADO, n=5) groups. Time zero ($t = 0\,\text{min}$) corresponds with the point of occlusion (n_{occ}), while circles mark cellular electrical uncoupling (t_u).

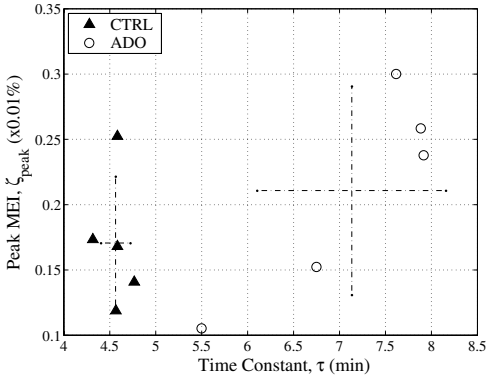

Fig. 3. Relation between the ischemic plateau value (ζ_{peak}, ordinates) and the time constant (τ, abscissas) for control (CTRL, filled triangles) and adenosine-treated (ADO, empty circles) groups. Notice inter-group distance in the abscissa.

Additionally, all animals in the CTRL group developed ventricular fibrillation and died. Conversely, all of the adenosine-treated pigs (ADO group) survived and completed the experiment.

Table I. Set of MEI parameters extracted from in-vivo measurements. ($^{(*)}$ indicates P<0.05)

MEI Parameter	*ADO (n=5)*	*CTRL (n=5)*
Peak MEI (ζ_{peak} , %)	21.08 ± 7.98	17.06 ± 5.01
UT (t_u , min)	2.76 ± 1.65	2.89 ± 0.95
TC (τ , min) $^{(*)}$	7.13 ± 1.03	4.56 ± 0.16

4. Discussion

MEI, an electrical property of the heart muscle, was able to distinguish between control (CTRL) and adenosine-preconditioned (ADO) study animals. Such differentiation was achieved by studying the time required for MEI to reach a certain value relative to its ischemic plateau and to its maximal rate of change (i.e., a time constant, τ).

In this study, a longer time constant was correlated with preconditioning success. Although further research is needed in order to correlate MEI with other properties of the preconditioning phenomenon, a meaningful definition of outcome-related MEI time constants might allow a quantitative early assessment not only of preconditioning success, but of several myocardial diseases.

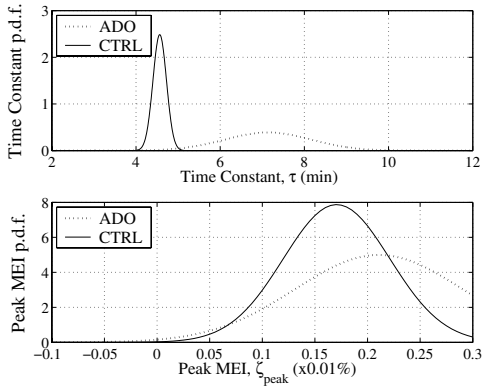

Fig. 4. Estimated normal distributions of peak MEI (ζ_{peak}) and the time constant (τ) for control (CTRL, n=5) and adenosine-treated (ADO, n=5) groups.

Also, it should be mentioned that for the experimental conditions and sample size here presented, adenosine-treated animals displayed larger inter-subject variability in all the derived MEI parameters (see Table I). This is further shown, by Fig. 4 where estimated normal distributions for peak MEI (ischemic plateau value, ζ_{peak}) and MEI time constant were generated. A possible cause for this wider distribution is the short half-life of adenosine in plasma [9].

Acknowledgements

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Address for correspondence:

Carlos L. del Rio
Dept. of Anesthesiology / The Ohio State University
410 West 10th Avenue
Columbus, OH 43210

del-rio.4@osu.edu