Mathematical modeling from ion channel to ECG

an Introduction

Mark Potse
Why a model?

\[ v = \frac{1}{2} g t^2 \]
• A model is a theoretical construct that allows to translate theory into predictions

• Daily life: weather forecast
• Engineering: design of constructions
• Science: verifying theories!
The first mathematical heart model

reality

model
Multiple dipoles

WT Miller and DB Geselowitz, *Circ Res* 1978
Hodgkin-Huxley membrane model

\[ g_{Na} = m^3 h \tilde{g}_{Na}, \]
\[ \frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m, \]
\[ \frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h, \]

AL Hodgkin and AF Huxley, J. Physiol 117:500-544, 1952
Contemporary membrane model

\[ I_{Kr} = G_{Kr} \sqrt{\frac{K_o}{5.4}} w(V_m - E_K) \]

\[ \frac{dv(t)}{dt} = \frac{v_\infty - v(t)}{\tau_v} \]

\[ \frac{dw(t)}{dt} = \frac{w_\infty - w(t)}{\tau_w} \]

\[ v_\infty = \frac{1}{1 + e^{(-26-V_m)/7}} \]

\[ w_\infty = \frac{1}{1 + e^{(V_m+88)/24}} \]

\[ \tau_v = \frac{450}{1 + e^{(-45-V_m)/10}} \cdot \frac{6}{1 + e^{(V_m+30)/11.5}} \]

\[ \tau_w = \frac{3}{1 + e^{(-60-V_m)/20}} \cdot \frac{1.12}{1 + e^{(V_m-60)/20}} \]

\[ \frac{dV_m}{dt} = -\frac{I_{ion}}{C_m} \]
Reaction-diffusion model

\[ \frac{dV_m}{dt} = - \frac{I_{\text{ion}} + I_{\text{dif}}}{C_m} \]
Regional differences
Anisotropy
Whole ventricles: 12M elements
Is reaction-diffusion necessary?
$V_m$ (mV)

RD

fixed-AP

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“Bidomain” models and their application
“Bidomain” models and their application
Computation of electrograms

\[ \nabla \cdot \left( (G_i + G_e) \nabla \varphi_e \right) = -\nabla \cdot (G_i \nabla V_m) \]
Membrane potentials and electrograms

\[ V_m (\text{mV}) \]

\[ \phi_e (\text{mV}) \]

\[ \text{time (ms)} \]
Activation-Recovery Intervals

Wyatt

ARI

alternative
Repolarisation

\[ T_{\text{up}} (\text{negative T waves}) \]
\[ T_{\text{up}} = 0.991 \cdot T_H + 4 \]
residual \( \sigma = 1.334 \)

\[ T_{\text{up}} (\text{positive T waves}) \]
\[ T_{\text{up}} = 0.985 \cdot T_H + 11 \]
residual \( \sigma = 2.619 \)

\[ T_{\text{down}} (\text{positive T waves}) \]
\[ T_{\text{down}} = 0.652 \cdot T_H + 136 \]
residual \( \sigma = 6.679 \)
Electrode in the cavity

\[ T_{up} \text{ (endocardium = 0 mm)} \]
\[ T_{up} = 0.935 \cdot T_h + 19 \]
residual \( \eta = 5.304 \)

\[ T_{up} \text{ (2 mm)} \]
\[ T_{up} = 0.579 \cdot T_h + 121 \]
residual \( \eta = 10.479 \)

\[ T_{up} \text{ (5 mm)} \]
\[ T_{up} = 0.003 \cdot T_h + 290 \]
residual \( \eta = 5.832 \)
positive T waves

negative T waves

$T_R$ (ms)
Understanding ST depression in the stress-test ECG

Mark Potse, Alain Vinet, A.-Robert LeBlanc, Jean G. Diodati, Réginald Nadeau
Occlusion and ST depression

Local subendocardial ischemia

Primary ST depression

No ST changes

Presentation

Working Dx

Ischemic discomfort

Acute coronary syndrome

ECG

Blochem marker

Final Dx

No ST elevation

NSTEMI

ST elevation

Myocardial infarction

Qw MI

Braunwald 2005
Problem 1: animal models of ST↓ need rapid pacing

Progressive epicardial coronary blood flow reduction fails to produce ST-segment depression at normal heart rates

Marilyn de Chantal,1,4 Jean G. Diodati,1,2,4 James B. Nasmith,1,2,4 Robert Amyot,1,2,4 A. Robert LeBlanc,1,4 Erick Schampaert,1,2,4 and Chantal Pharand1,3,5

1Research Center, 2Division of Cardiology and 3Pharmacy Department, Hôpital du Sacré-Cœur de Montréal, Montréal, Québec, Canada; and Faculties of 4Medicine and 5Pharmacy, Université de Montréal, Montréal, Québec, Canada
Problem 2: relation between area and ST↓ is complicated

**Figure 10** Polarity and relative magnitude of TQ-ST segment deflections computed at epicardial intramyocardial, endocardial, and intracavitary locations and various shapes of ischemic involvement. + (−)TQ-ST segment deflection indicates negative (positive) TQ segment and positive (negative) ST segment displacement. Dark circles refer to electrode positions.

Modern theory

The effect of lesion size and tissue remodeling on ST deviation in partial-thickness ischemia

Mark Potse, PhD, Ruben Coronel, MD, PhD, Stéphanie Falcao, MSc, A.-Robert LeBlanc, PhD, Alain Vinet, PhD

From the *Research Centre for Heart Diseases, Université de Montréal, Québec, Canada. ‡The Netherlands, and †Department of Medicine, University of Amsterdam, Canada.

BACKGROUND Myocardial infarction or depression in electrocardiography (ECG) stress test due to ischemia in epicardium overlaying myocardial infarction. The ischemia is nontransmural and does not always cause ST depression. Thus, ST depression is hard to reproduce in ECG stress tests.

OBJECTIVE The purpose of the study was to examine the circumscribed pattern of ischemia and ST depression in patients with a history of myocardial infarction.

METHODS We studied ischemia in the human heart. A realistic model of ischemia was based on diffusion of extracellular potassium, transmural extent, and remodeling of the myocardium.

RESULTS Our simulations confirmed that partial-thickness ischemia, like full-thickness ischemia, typically causes ST elevation in an anisotropic model of the ventricles. However, we identified three situations in which ST depression can occur:

1. Reduced anisotropy ratio of the myocardium may result from hypertrophy or hyperemic response to ischemia.
2. ST depression may occur in very large and thin ischemic zones.
3. Myocardial reuptake and geometric factors can cause ST depression.

We note that in most circumstances, ST elevation is the only detectable feature of ischemia in partial-thickness ischemia.

STEMI: Gap junctions; Tissue remodeling; Computer model; Extracellular potassium (Heart Rhythm 2007;4:200–206) © 2007 Heart Rhythm Society. All rights reserved.
Animal model

Source of Electrocardiographic ST Changes in Subendocardial Ischemia

Danshi Li, Chuan Yong Li, Ah Chot Yong, David Kilpatrick

(Circ Res. 1998;82;957-970.)
Problem 3: *ST depression* in patients cannot be located...

**ST-elevation vectors**

**ST-depression vectors**

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... but subendocardial ischemia can!

Simulation of ST Segment Changes During Subendocardial Ischemia Using a Realistic 3-D Cardiac Geometry

Mary C. MacLachlan*, Joakim Sundnes, and Glenn Terje Lines
Occlusion and ST depression revisited

Increased heart rate → Reduced diastolic filling time
Elevated LV pressure
Reduced contractility

Global subendocardial ischemia
Local subendocardial ischemia

Primary ST depression

No ST changes

Presentation
Ischemic discomfort
Acute coronary syndrome

Working Dx
No ST elevation
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ST elevation
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Braunwald 2005

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Methods

- Reaction-diffusion model of the human heart
- Inhomogeneous boundary-element torso model
Local subendocardial ischaemia
Global subendocardial ischaemia

isotropic
anisotropic
Conclusion

- Local subendocardial ischaemia does not cause ST depression in overlying leads

- Global subendocardial ischaemia causes a “Stress-test ECG”

- Tissue anisotropy has little influence on the ECG changes due to global subendocardial ischaemia

- Primary ST depression may indicate a global perfusion problem rather than a single partial occlusion
References


references


