Proceedings of the 28th IEEE
EMBS Annual International Conference
New York City, USA, Aug 30-Sept 3, 2006

The time constants for cathodic make stimulation of electrical syncytia: an application to cardiac pacing

Roberto E. Suárez-Antola.
Electrical Engineering Department, Catholic University of Uruguay.
8 de Octubre 2738.
Montevideo 11600 – Uruguay.
rsuarez@ucu.edu.uy

Abstract : **In the framework of cardiac pacing, measured chronaxies are different for current and for voltage pulses. They increase with the distance between the pacing cathode and the myocardium, and with the size of the electrode. Mathematical formulae that relate the time constants (and the chronaxies) of the strength duration curves with the parameters of the system composed by the electrode, the volume conductor and the myocardium are used to explain the aforementioned experimental results and to discuss, from an engineering standpoint, some aspects related with thresholds for cardiac pacing, both for unipolar and bipolar pacing. These formulae are derived from a mathematical model of the electric stimulation of a syncytium framed in the bidomain theory. The time constants are given as increasing functions of a non dimensional number, equal to the quotient between a a certain characteristic length and myocardium's space constant. In the case of pacing electrodes, the characteristic length is a function of the size and shape of a region of influence of the cathode on the excitable tissue located adjacent to the electrode.**

I. INTRODUCTION

The myocardium is composed by a mass of excitable cells tightly coupled, so that an electrical syncytium is formed [1]. Let us consider an active cathode located in a volume conductor, near the mass of excitable cells that make the tissue (an active electrode at the tip of a lead for cardiac pacing, for example). An anode is used to close the circuit (a ring electrode in the lead mentioned before, perhaps at 2cm or less from the tip, or a truly indifferent electrode located in the pulse generator, perhaps at 5 to 10cm from the tip) [2]. For a rectangular cathodic current pulse of a given duration, there is a threshold amplitude such that a little above it the electric stimulation succeeds (an AP is produced), and a little below it the stimulation fails. If the duration of the pulse decreases, its threshold amplitude (strength) increases, so that the strength-duration curve looks like a hyperbola with a horizontal asymptote for long pulses and a vertical asymptote for short ones[3]. The results of many laboratory experiments and clinical practice show that the parameters of the strength-duration curve depend not only of the excitability properties of the membranes of the target element (myocardium), but depend also of certain geometric and bioelectric parameters of the system formed by the electrodes, the tissues and the target element[4],[5]. The least threshold current for long pulses is the rheobase I_R, and the product of pulse duration (t_p) and threshold amplitude (I_T) is the threshold charge Q_T. This charge decreases when t_P decreases. There is a limit threshold charge ($Q_{T,0}$) for vanishing pulse duration. Then the time constant for electric current pulses is defined as

$$t_{S,I} = \frac{Q_{T,0}}{I_R} \qquad (1)$$

The chronaxy t_C is defined as the duration of a pulse with a threshold amplitude twice the rheobase. It results that t_C is closely related with t_S. Usually both behave in the same way when system's parameters vary. For the same myocardium, the chronaxy measured using a point active electrode, acting as anode and located inside a cell, is different from the chronaxies measured using the same electrode acting as cathode and located in the volume conductor outside the tissue. Furthermore, for external electrodes, measured chronaxies increase with the distance between the electrode and the tissue and with electrode's size. When a pacing electrode is located near enough to myocardium, measured chronaxies depend of electrode's shape [6].

In cardiac pacing for medical purposes, a rectangular voltage pulse is applied to the electrodes, instead of the rectangular current pulse mentioned before [4], [7]. Due mainly to the polarization of the electrode-tissue interface, the electric load seen by the pulse generator is not an ohmic one. The amplitude of the current pulse now decreases from the beginning to the end of the pulse while the amplitude of the voltage pulse remains constant. A strength duration curve may be measured for threshold voltage pulses, and a voltage rheobase U_R, a threshold value of the product between pulse duration and threshold voltage amplitude $U_T(t_p)$, and a voltage chronaxy (or a time constant $t_{S,U}$) may be determined from this measured curve.

The purpose of this paper is twofold: (a) to extend a previous work reported in reference [8] on the time constants for cathodic make excitation of nerve and skeletal muscle fibres, to embrace an electric syncytium like myocardium, and (b) to discuss the relation between thresholds for rectangular current and voltage pulses from an engineering standpoint.

The approach to the strength-duration curves by people working in cardiac pacing has been mainly an empirical one.

The intended theoretical derivations of well known empirical formulae like Lapicque's (1907) or Weiss' (1901) for myocardial stimulation by pacing electrodes were sometimes very ingenious, as the one presented in reference[7], but not in accord with standard electrophysiological knowledge. In 1977 Lindemans obtained experimental data that suggest that **an initial depolarization, above uniform membrane threshold, of a critical mass of cardiac cells is needed to produce a propagated AP** [9]. This pointed towards the existence of **liminal volumes** for the excitation of a three dimensional syncytium, analogous to the **liminal lengths** introduced by Rushton (1937) in the case of nerve or muscle fibres [8]. However, it lacked an appropriate theory to give an explanation of these findings. Under the name of **bidomain theory of electro-cardiology**, in 1978 began the construction of a sound, albeit phenomenological theoretical framework [10]. Most work was done in applying bidomain theory to digital simulation of AP propagation and of cardiac far-field stimulation (due to its importance in cardioversion and defibrillation), and comparatively much less effort was done on near-field stimulation, which is the situation of interest for cardiac pacing [11], [12]. In 1994 appeared a fully analytical non-linear approach to threshold phenomena in biological tissues stimulated by external electrodes [8], [13], [14], [15]. This approach, framed in the bidomain model, allows an explanation of the liminal volumes discovered by Lindemans, as well as a derivation of their geometric dimensions. The polarizing effect of an external electrode on the excitable electrical syncytium is described by a **bounded region of influence**. This allows the application of methods of non-linear modal analysis closely related with the methods of Synergetics [16].

II. MATHEMATICAL FORMULAE FOR THE TIME CONSTANTS

A Time constants for current pulses.

In order to simplify as much as possible the mathematics of threshold phenomena, let us consider first a **homogeneous** and **isotropic** electric syncytium. Let us further assume that membrane's recovery variables are frozen at their rest values, but membrane's activation variables are always fully relaxed to equilibrium with the local value of membrane's voltage. Then the density of ionic current through the membrane is only a function of membrane voltage. A cubic polynomial, with three real roots, may be a good approximation for the cardiac muscle [17]. In this case the three dimensional non-linear Cable Equation of the continuum of excitable membranes reduces to the Nagumo Equation. Assuming that in the bidomain's boundary the electric current goes to or comes from the surrounding tissues only through the interstitial domain, in the surface of the cardiac muscle the current density in the intracellular continuum must vanish. The region of influence of the applied current field over the membranes of the myocardium cells may be represented by half an ellipsoid of revolution [13], [15] (Fig1).

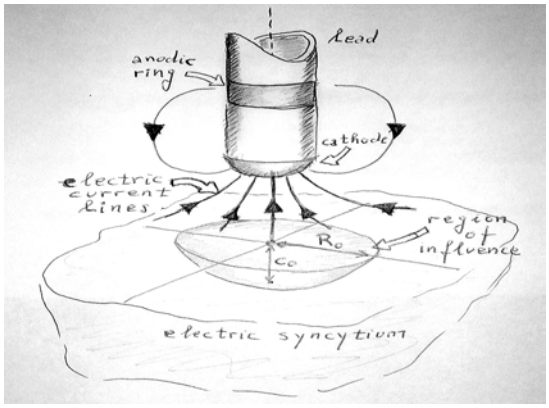

Fig.1. Electrode, myocardium and region of influence

The radius R_0 of the circle located on the boundary of the excitable tissue, nearest to the cathode, is given by

$$R_0 = \gamma(r_0 + e) \tag{2}$$

r_0 is a cathode's radius, e is the thickness of the layer of non-excitable tissues interposed between the electrode and the myocardium, and γ is a non-dimensional parameter (related with the spatial distribution of the electric current density) that will be explained below. The minor axis of the half-ellipsoid, c_0, that gives a measure of the depth of penetration of the polarizing effect in the syncytium, is a function of R_0 and of the syncytium's space constant λ_M [13], [15] :

$$\frac{c_0}{\lambda_M} = \frac{\beta(R_0/\lambda_M)}{\sqrt{{\alpha_1}^2 + (R_0/\lambda_M)^2}} \tag{3}$$

(Here β is near 1). ${\alpha_1}^2 \approx 5.783$. It can be seen that c_0 is a monotonically increasing function that tends to $\beta.\lambda_M$ when the radius of the half ellipsoid of influence goes to ∞. A necessary condition for AP generation is that the region of influence of the electrode includes a liminal volume of syncytium. So $R_0 > R_{0,c}$, being $R_{0,c}$ a minimum value for excitation [13], [15]. Membrane voltage is supposed to be at its rest value on the curved surface of the half-ellipsoid, and the normal derivative of membrane voltage on the flat face is proportional to the applied cathodic current $I(t)$. Using this region of influence it is possible to carry on with the methods of non-linear modal analysis, and after doing that and making several simplifications, the following results are obtained [13], [15].

A current pulse of duration t_p is just threshold, $I_T(t)$, if

$$\int_o^{t_p} G(t_p - t) I_T(t).dt \approx Q_{T,0} \tag{4}$$

$Q_{T,0}$ is the limit threshold charge, $G(t) = e^{-\frac{t}{t_S}}$ (5)

$$t_S = \tau_{\mathrm{M}} \cdot \frac{\left({R_0}^2/{\lambda_M}^2\right)}{a + b\left({R_0}^2/{\lambda_M}^2\right)} \tag{6}$$

τ_M is the linear membrane time constant with the activation variables relaxed to equilibrium with membrane voltage, R_0 and λ_M were defined before, and the non-dimensional parameters a and b may be taken $a \approx 38.41$ and $b \approx 6$. If the amplitude of the current pulse is constant $I_{T,0}$, from Equations (4) and (5) we obtain Lapicque's formula for cathodic make excitation of an electric syncytium, like myocardium:

$$I_{T,0}(t_p) = \frac{I_R}{1 - e^{-\frac{t_p}{t_S}}} \qquad (7)$$

The rheobase is $I_R = Q_{T,0} / t_{S,I}$ so that t_S, given by formula (6) as a well defined function of the parameters of the electrode, of the excitable tissue, and of the geometry of the electric current field, **is the time constant $t_{S,I}$ for cathodic make excitation.** Figure 2 shows the relation between the dimensionless variables $t_{s,I} / \tau_M$ and R_0 / λ_M.

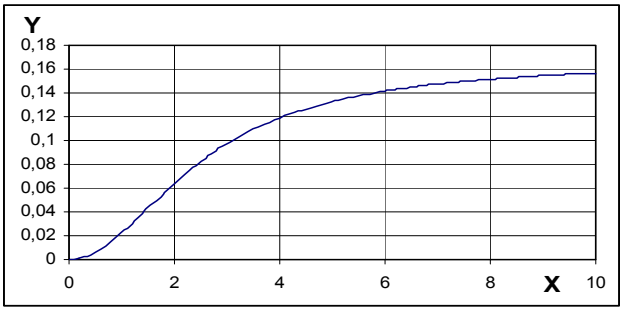

Fig.2.Relation between $Y = t_{s,I} / \tau_M$ and $X = R_0 / \lambda_M$

The time constant increases with the radius of the electrode, with the thickness of the layer of non-excitable tissues and with the parameter γ. For unipolar stimulation by a convex cathode, $\gamma \approx 1.33$, but it increases in bipolar stimulation when the distance between the ring anode and the cathode decreases [13], [15]. All this is in accord with experimental results [4], [7], [18], [19], [20].

B Time constants for voltage pulses.

Modern permanent pulse generators use constant voltage pulses to pace the heart. While the voltage remains at the programmed value, the electric current suffers variations that reflect the changes in the load impedance seen by the pulse generator. This impedance is the sum of an ohmic resistance R_p and the impedance produced by the polarization of the electrochemical double layer located at the interface between the electrodes and the tissues [4], [7], [18]. The voltage drop between the anode and the cathode $U(t)$ can be written, in a linear approximation, as the ohmic voltage drop in the cables and the tissues plus the voltage drop in the double layer:

$$U(t) = R_p . I(t) + \int_0^t K(t-u) . I(u) . du \qquad (8a)$$

$K(t)$ is positive and $\int_0^\infty K(u) . du = R_d$, R_d is the D.C. resistance of the interface. As $U(t)$ is given by the voltage pulse generator, it is convenient to invert (8a), thus obtaining:

$$I(t) = \frac{1}{R_p} . \left(U(t) - \int_0^t L(t-u) . U(u) . du \right) \qquad (8b)$$

$L(t)$ is also positive and $\int_0^\infty L(u) . du = \frac{R_p}{R_p + R_d}$. For a voltage pulse of constant amplitude U_0, Equation (8b) may be rewritten thus:

$$I(t) = \frac{U_0}{R_p + R_d} . (1 + \varphi(t)) \qquad (9)$$

$\varphi(t)$ is positive, monotonically decreasing from $\varphi(0) = \frac{R_d}{R_p}$ towards zero when $t \to \infty$. It can be given as a function of $\int_0^t L(u) . du$. From (9) it follows that $I(t)$ decreases from the beginning to the end of the voltage pulse. A voltage pulse of constant amplitude will be a threshold pulse $U_{T,0}$ if the corresponding current pulse $I_T(t)$ verifies Equation (4). After having substituted the threshold current pulse given by Equation (9) for $U_{T,0}$, in Equation (4), we obtain:

$$U_{T,0}(t_p) = (R_p + R_d) Q_{T,0} / \left(\int_0^{t_p} G(t) dt + \int_0^{t_p} G(t_p - t) . \varphi(t) dt \right) \qquad (10)$$

If $G(t) = e^{-\frac{t}{t_{S,I}}}$, it is possible to show that: $\lim_{t_p \to \infty} \int_0^{t_p} G(t_p - t) \varphi(t) dt = 0$. But $\int_0^\infty G(t) dt = t_{S,I}$, so taking into account that $I_R = Q_{T,0} / t_{S,I}$, the rheobase of voltage is: $U_R = \lim_{t_p \to \infty} U_{T,0}(t_p) = (R_p + R_d) I_R \qquad (11)$

Voltage rheobase and **current rheobase** are connected by the total resistance (D.C. impedance) seen by the pulse generator.

The **s**trength-duration formula for **rectangular voltage pulses, given by Equation (10), may be rewritten thus**:

$$U_{T,0}(t_p) = \frac{(t_{S,I} . U_R)}{\int_0^{t_p} G(t) dt + \int_0^{t_p} G(t_p - t) . \varphi(t) dt} \qquad (12)$$

The strength-duration formula for **rectangular current pulses obtained from Equation (4) may be rewritten thus**:

$$I_{T,0}(t_p) = \frac{(t_{S,I} . I_R)}{\int_0^{t_p} G(t).dt} \quad (13)$$

For short pulses they both behave proportional to t_p^{-1}, but for longer pulses the threshold amplitude of rectangular voltage pulses approaches to its rheobase faster than the threshold amplitude of rectangular current pulses of the same durations. All this is in accord with experimental results [7], [18], [20].

From Equation (12), taking into account that, by definition, $t_{S,U} = \frac{\lim_{t_p \to 0} (t_p . U_{T,0}(t_p))}{U_R}$, it follows that:

$$t_{S,U} = \frac{t_{S,I}}{1+\varphi(0)} = \frac{R_p}{R_p + R_d} . t_{S,I} \quad (14)$$

Thus **the time constant for excitation with voltage pulses** is always less than **the time constant for excitation by current pulses**, and the difference between them increases with the increase in the D.C. impedance of the electrochemical double layer relative to the ohmic impedance of the lead cables and the tissues. All this is in accord with known experimental results [4], [7],[18], [19], [20] (Figure 3)

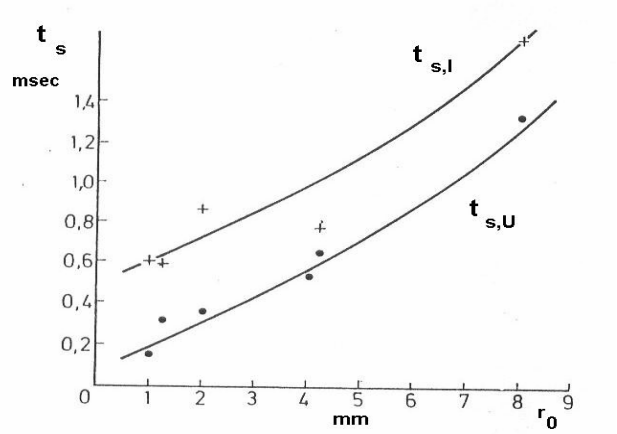

Fig.3. Relation between t_S and r_0 (modified from [7]).

III. CONCLUSIONS

The theoretical results for the time constants, both for current pulses and voltage pulses agree fairly well with known experimental results from electrophysiological experiments and from clinical practice. The quantitative predictions implicit in the formulae given in this paper should be tested against laboratory experiments or digital simulations of the emergence of an AP in electrical syncytia like cardiac tissue. Also, they could help in the design both of complex digital simulations of threshold phenomena and in the assessment of electrodes for chronic cardiac pacing.

The mathematical model was constructed for a homogeneous and isotropic syncytium. As the cardiac muscle is heterogeneous, anisotropic and with unequal anisotropy (the anisotropy ratios of the intracellular and the interstitial continua differ) the analytical approach developed here should be extended to cope with this anisotropy.

The time scales of the pulses used in cardiac pacing justify the assumptions made about the relaxation of the activation variables to equilibrium with membrane voltage and the freezing of the recovery variables. However, it is possible to take into account activation and recovery effects in the framework of a nonlinear modal analysis of threshold phenomena [13], [15], [16].

I. REFERENCES

[1] P. Baser and B. Roth "New currents in electrical stimulation of excitable tissues" *Annu. Rev. Biomed. Eng.*, Vol. 2, pp 377-397, 2000.

[2] M.Forde and P.Ridgley "Implantable cardiac pacemakers" in *The Biomedical Engineering Handbook*, J. Bronzino, Ed., Boca Raton, CRC-IEEE 2000

[3] D. Durand "Electric stimulation of excitable tissue" in *The Biomedical Engineering Handbook*, J. Bronzino, Ed., Boca Raton, CRC-IEEE 2000.

[4] S.Furman, D.Hayes, and D.Holmes "A practice of cardiac pacing",San Francisco: Futura, 1993.

[5] C.Brooks, B.Hoffman, E.Suckling, and O.Orias "Excitability of the heart", New York: Grune & Stratton, 1955.

[6] J.Laplantif "Importance de la geometrie des electrodes dans la valeur du seuil aigu de stimulation cardiaque", PhD.Thesis, Poitiers, 1983.

[7] W. Irnich "Engineering concepts of pacemaker electrodes" in Advances in Pacemaker Technology, M.Schaldach and S.Furman, Eds., New York: Springer,1975.

[8] R.Suárez-Ántola "The time constants for the electric stimulation of nerve and muscle fibres by point electrodes" in *Proceedings of the 2005 2nd International IEEE/EMBS conference on Neural Engineering,IEEE, pp652-655, 2005*

[9] F.Lindemans "Electrical stimulation of heart muscle", PhD. Thesis, Uthretch: Elinkwijk, 1977.

[10] C.Henriquez "Simulating the electrical behavior of cardiac muscle using the bidomain model" *Crit. Rev. Biomed Eng.* ,Vol.21, pp1-77, 1993.

[11] K.Simelius, J.Nenonen, V.Mäntynen, J.Clements and B.Milan "A hybrid model of cardiac electric conduction", Helsinski: Helsinski University of Technology Publications on Engineering Physics, TKK-F-A289, 2004.

[12] N.Trayanova "Far-field stimulation of cardiac tissue" Herzchr. Electrophys. Vol.10, pp137-148, 1999.

[13] R. Suárez-Antola "Thresholds : contributions to the study of excitation and propagation of the electric activity of biological tissues stimulated by external electrodes" *D. Sc. Thesis, UDELAR,* Montevideo, 1994.

[14] R. Suárez-Antola and A. Sicardi-Schifino "A modal approach to threshold dynamics for excitable tissues stimulated by external electrodes I. One state variable model for a fiber" *Physica D*, Vol. 89, pp 427-438, 1996.

[15] R. Suárez-Antola "Outline of an analytical approach to threshold dynamics for excitable tissues stimulated by external electrodes" in "Modeling the Heart",*Fifth Conference of the European Society for Engineering and Medicine*, Barcelona, June 1999.

[16] A.Sicardi-Schifino and R.Suárez-Ántola "From Synergetics to biological excitability" in Biological Complexity, E.Mizraji et al. Eds., Montevideo: DIRAC, 1997, Ch.18.

[17] J. Jack, D.Noble and R. Tsien "Electric current flow in excitable cells" Oxford : Clarendon, 1983, ch. 9 and 12.

[18] A.Ripart and J.Mugica "Electrode-heart interface: definition of the ideal electrode", PACE, Vol.6, pp 410-421, 1983.

[19] W.Irnich "Comparison of pacing electrodes of different shape and material: recommendations" , PACE, Vol.6, pp422-426, 1983.

[20] W. Irnich "The chronaxie time and its practical importance" *Pace,Vol.3, pp292-301, 1980.*