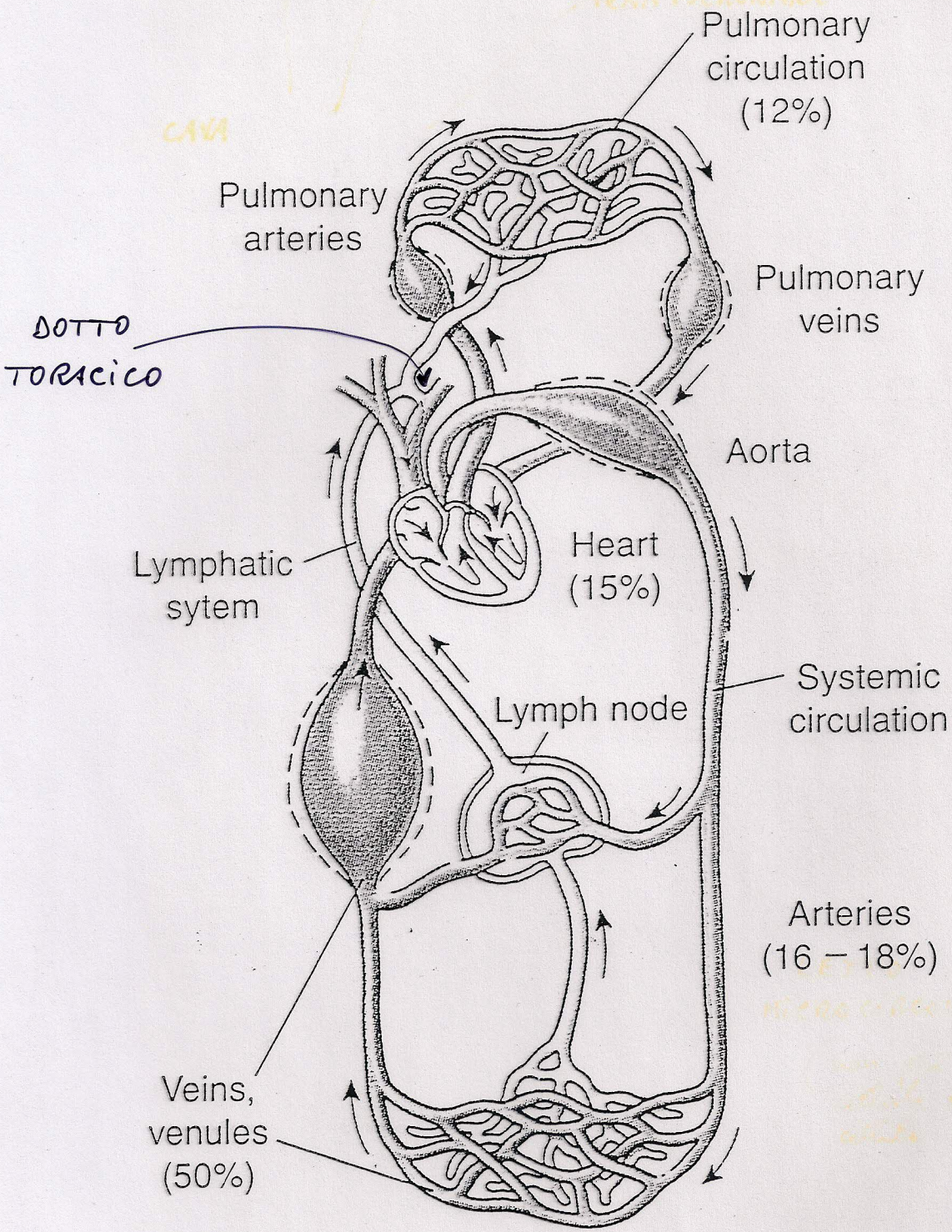
Da: Randall et al., Animal Physiology, 4th edition, Freeman & Company, 1997.

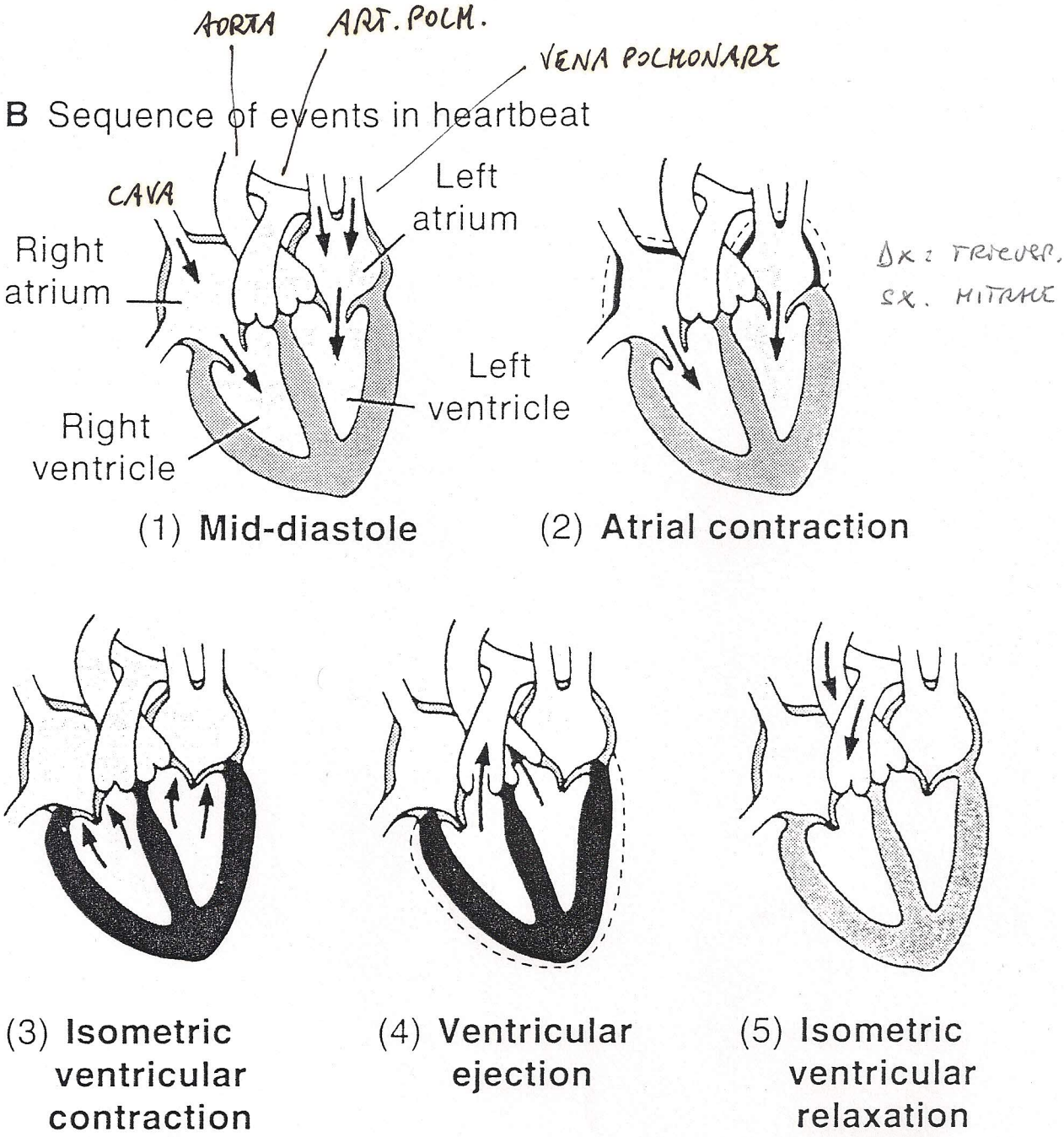


fino a 15-20%

SIST. CIRCOLATORIO CHIUSO (ALTA P SISTEMICA, PIÙ V E MENO VOL.)

CIRCOLAZIONE DOPPIA (P DIVERSE NEI POLMONI E NELLA CIRC. SISTEMICA)

SISTEMA IN PARALLELO (EFFICACE PER LA DISTRIBUZIONE NEI DIVERSI LETTI CIRCOLATORI)



Da: Randall et al., Animal Physiology, 4th edition, Freeman & Company, 1997.

REGOLAZIONE CARDIACA

EFFETTO
+ o -

CRONOTROPO (frequenza, nodo SA)

INOTROPO (forza, miocardio)

BATMOTROPO (eccitabilità)

DROMOTROPO (conduzione)

a) Come e dove viene generato il ritmo (PACEMAKER)

b) Conduzione dell' impulso

c) Proprietà del P.A. nelle diverse regioni cardiache
(e significato funzionale)

d) Regolazione da parte del sistema autonomo
- a breve termine
- su canali ionici

Da: Guyton & Hall. Fisiologia Medica, II edizione. EdiSES, 2002.

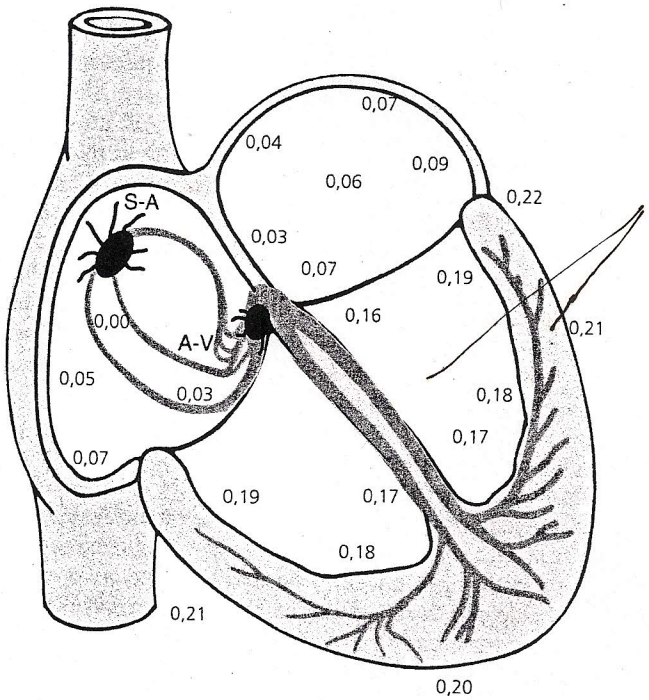


FIGURA 10-4

Propagazione dell'impulso nel cuore che mostra i tempi di comparsa, in frazioni di sec, nelle diverse parti.

PACEMAKER MIOGENO

VELOCITÀ DI CONDUZIONE

ATRIO	~ 0.3 m/s
VIE INTERNODALI	1.0 m/s
FIBRE DI TRANSIZIONE	0.05
NODO ATRIO-VENTRICOL.	0.10
HIS - PURKINJE	4-5 m/s
ENDO → EPICARDIO	0.5 m/s

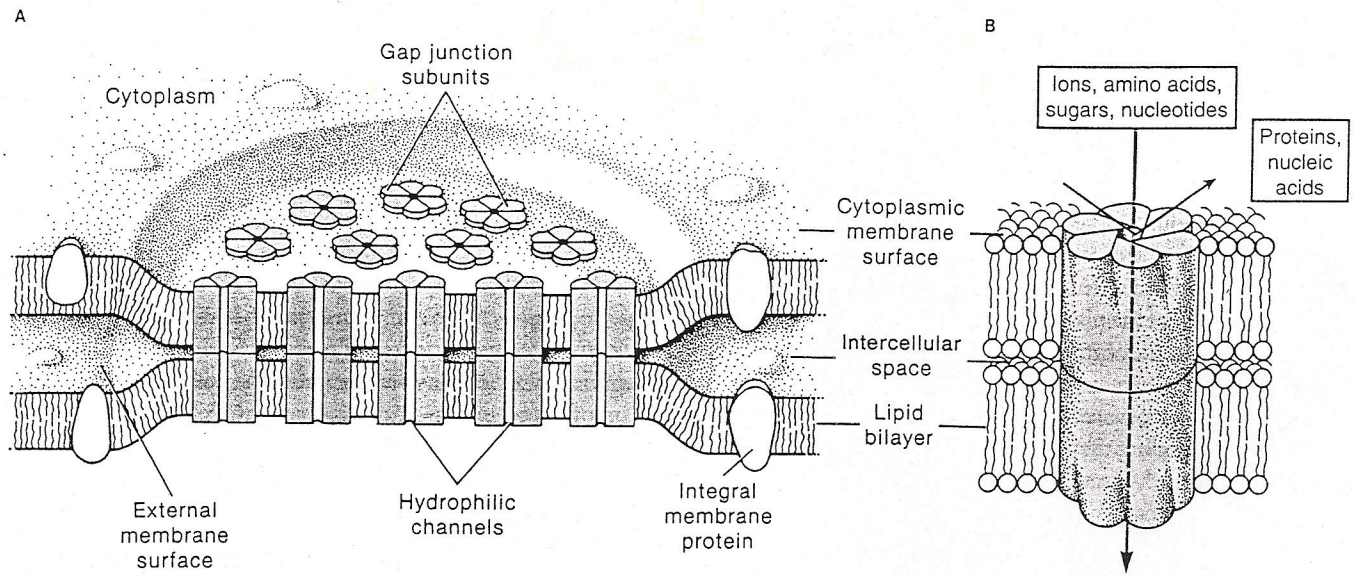
RAGIONI DELLA BASSA V DI CONDUZIONE NELLA ZONA DEL NODO AV:

- FIBRE PICCOLE
- TENDENZIALMENTE DEPOLARIZZATE
- POCHE GIUNZIONI (O P MINORE)

DISTRIBUZIONE: NEURONI, EPITELI, GLIA, CELLULE MUSC. LISCE E CARDIACHE, BLASTOMERI ...

PERMEABILITÀ: MOLECOLE FINO A N 1000 PM

PORO DI CIRCA 16 Å DI DIAMETRO



From: RANDALL et al. ANIMAL PHYSIOLOGY 4th ES. FREEMAN

SPAZIO INTERMEMBRANE: 20 Å = 2 nm

SINGOLA SUBUNITÀ: CONNESSINA (250-500 aa)

(ALMENO 16 NOTE NE' VERTEBRATI)

ESAMERO = CONNESSONE = EMICANALE

REGOLAZIONE = VARIA DA TESSUTO A TESSUTO

(V_m, pH, Ca^{2+} ...)

Da: Aidley D.J., The Physiology of Excitable Cells. Cambridge Univ. Press, 1998.

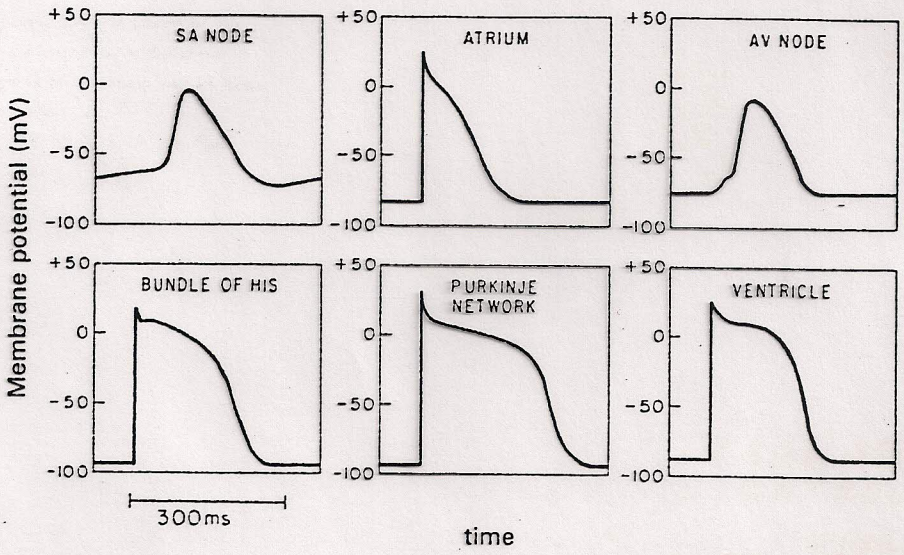


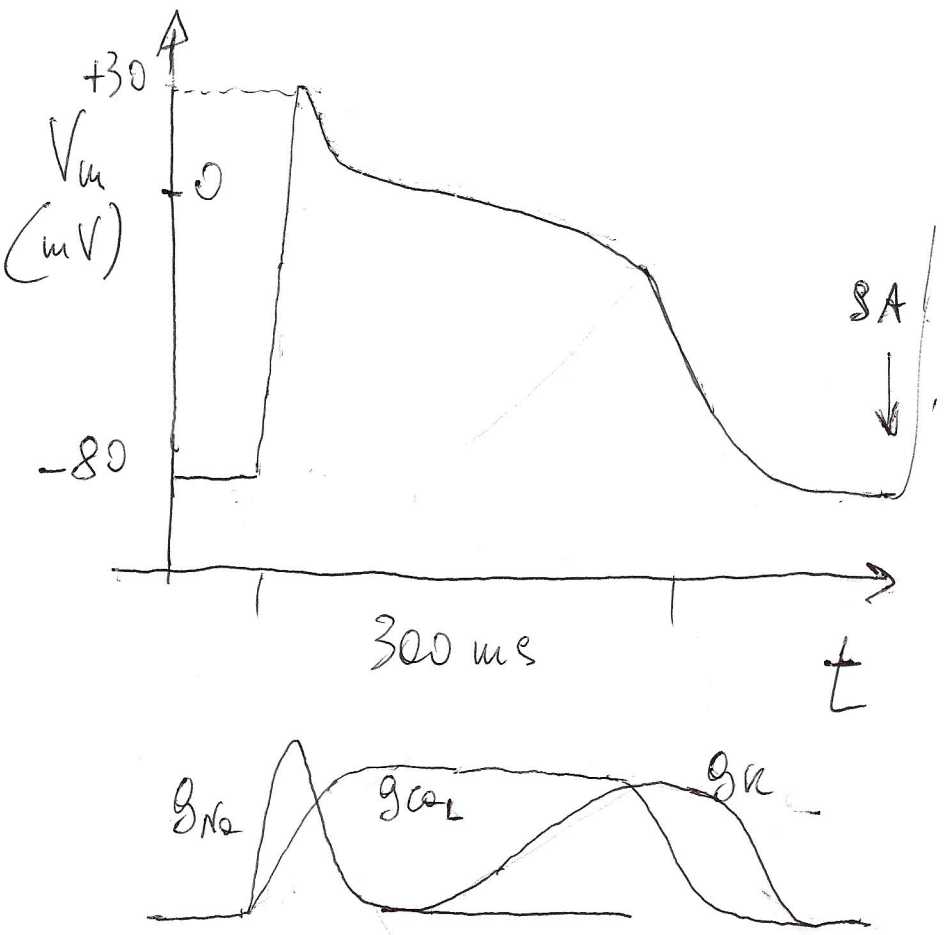
Figure 21.7. The shape of the action potential in different regions of the mammalian heart. SA, sinuatrial; AV, atrioventricular. (From Katz, 1977.)

In coltura: 70/80 min^{-1} NODO SA

40/60 AV

15/40 Purkinje

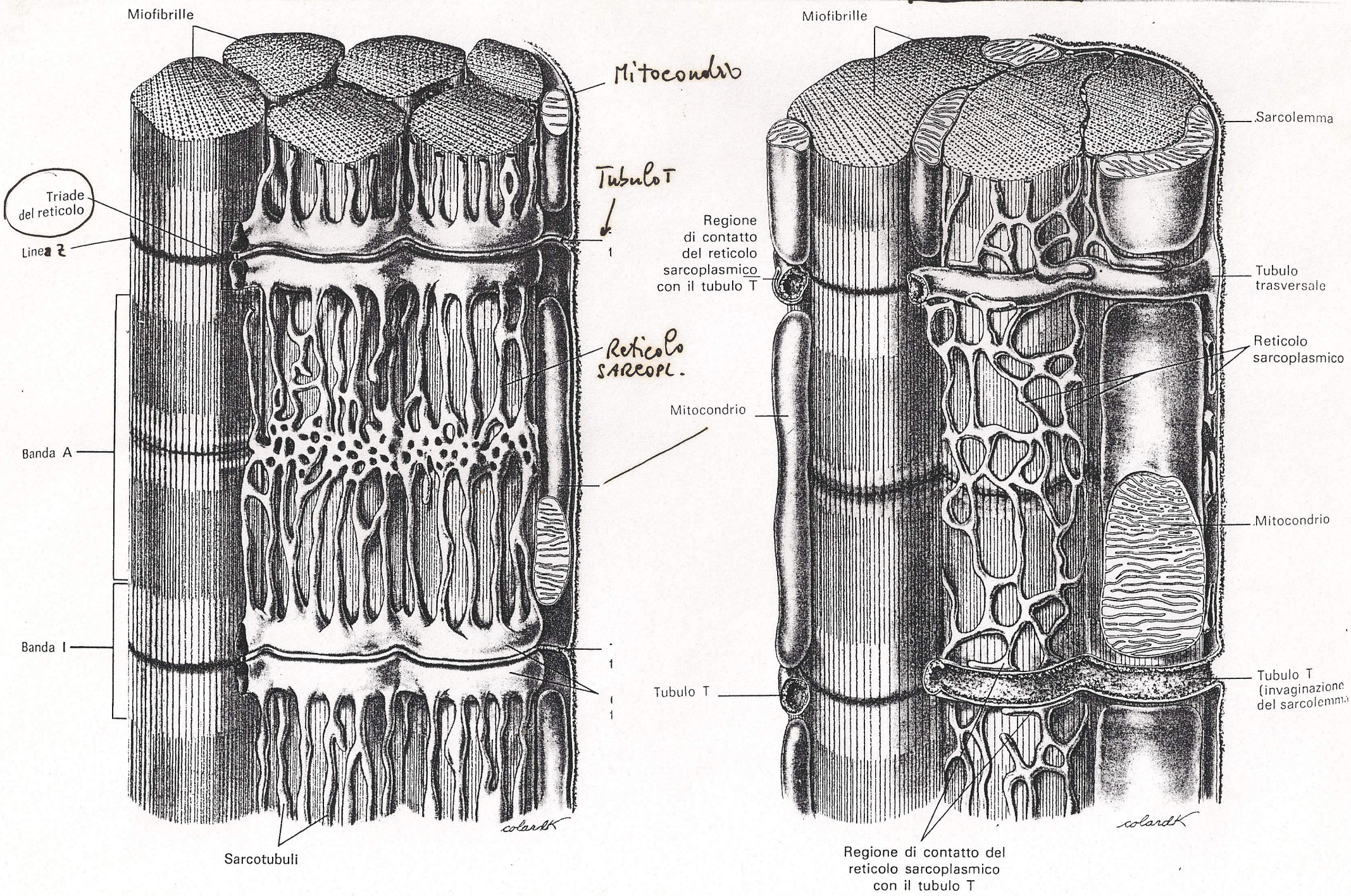
CELLULE DEL VENTRICOLO



SCHELETRICO

Da: Bloom & Fawcett, Trattato di Istologia
II ed., Piccin, 1981

CARDIACO



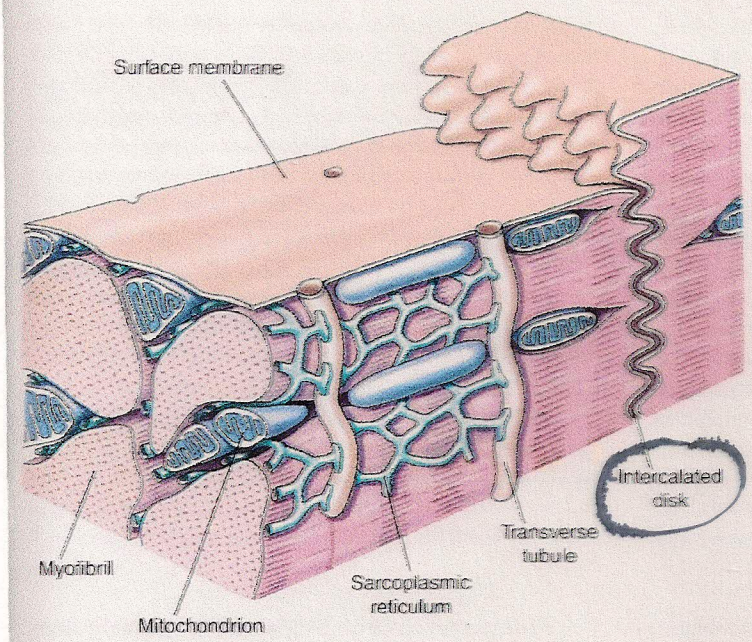


Figure 10-50 Adult mammalian ventricular cardiac muscle has an extensive sarcoplasmic reticulum. The cells are connected electrically through intercalated disks, at which the extensive membranes of neighboring cells are joined by numerous gap junctions and desmosomes. (Adapted from Threadgold, 1967.)

Randall et al.
Animal Physiology

The relative importance of the SR and the plasma membrane for Ca^{2+} regulation varies among species. Cardiac muscle of the frog has only a rudimentary reticulum and tubular system. The myocytes of the frog heart are much smaller than adult mammalian cardiac muscle fibers, and their relatively large surface-to-volume ratio reduces the need for an elaborate intracellular reticulum for the storage, release, and uptake of Ca^{2+}. Instead, most of the Ca^{2+} regulating contraction in amphibian heart cells enter through the surface membrane as a result of the membrane's increased calcium permeability during depolarization. Adult mammalian hearts, on the other hand, largely depend on calcium release from the sarcoplasmic reticulum.

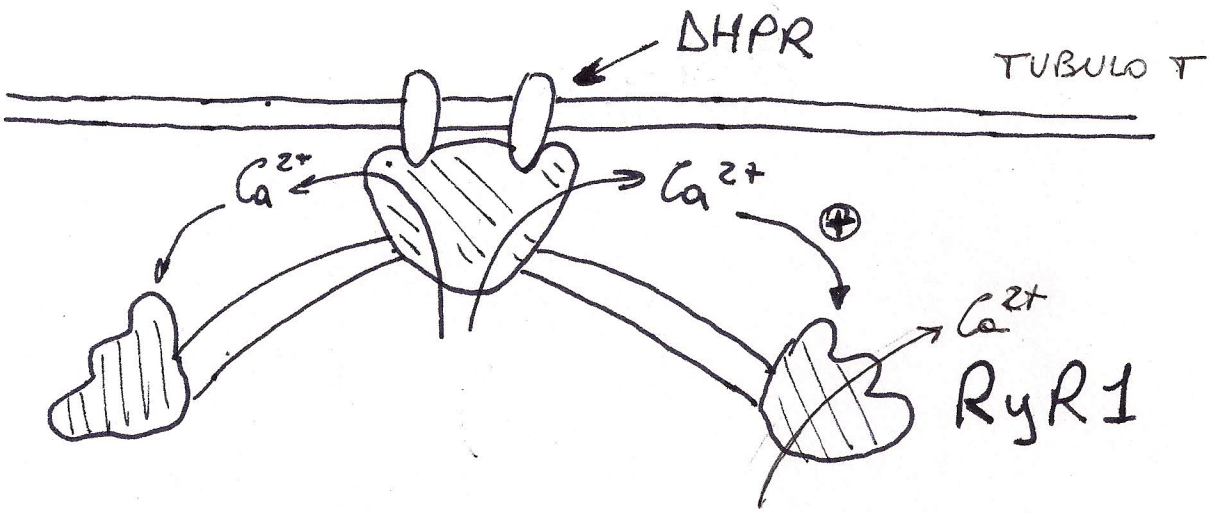
As in skeletal muscle, ryanodine receptors mediate excitation-contraction coupling in mammalian cardiac muscle. Low concentrations of ryanodine (in the nanomolar range) lock the calcium channels in cardiac SR membrane in the open state (see Figure 10-24). The Ca^{2+} released from the sarcoplasmic reticulum following ryanodine treatment at low concentrations is removed from myocytes by Na^+/Ca^{2+} exchange across the sarcolemma. The end result is that SR calcium stores are reduced, the capacity to release Ca^{2+} from the SR is diminished, and cardiac contractility falls. Because the effects of ryanodine vary with the importance of the SR in regulating cardiac contraction, this drug has little effect on the contraction of the frog heart but a marked effect on the contraction of the adult rat heart.

The amount of tension that can be developed by a cardiac muscle depends on the amount of Ca^{2+} in the myoplasm. In the frog heart, when muscle cells are depolarized, Ca^{2+} flows into the cell because of the increased calcium permeability of the depolarized membrane. Because the influx of Ca^{2+} is voltage dependent, tension develops as a function of depolarization, with greater depolarization producing greater tension (Figure 10-51A). Reduction of the extracellular Ca^{2+} concentration leads to a weaker contraction for a given depolarization, because less Ca^{2+} enters the cell (Figure 10-51B). The intracellular Ca^{2+} concentration in cardiac muscle is determined not only by depolarization but also by a number of other factors including the action of catecholamines on the heart. The catecholamines epinephrine and norepinephrine that circulate in the blood or are released from neuron terminals activate α- and β-adrenoreceptors on the surface of cardiac cells. Stimulation of α-adrenoreceptors activates the inositol phospholipid second-messenger system (see Figures 9-14 and 9-15), resulting in increased release of Ca^{2+} from the sarcoplasmic reticulum. In contrast, β-adrenoreceptor stimulation activates the adenyl cyclase second-messenger system (see Figures 9-11 and 9-12), resulting in increased calcium flux across the sarcolemma. Thus stimulation of both types of adrenoreceptors augments cardiac contraction.

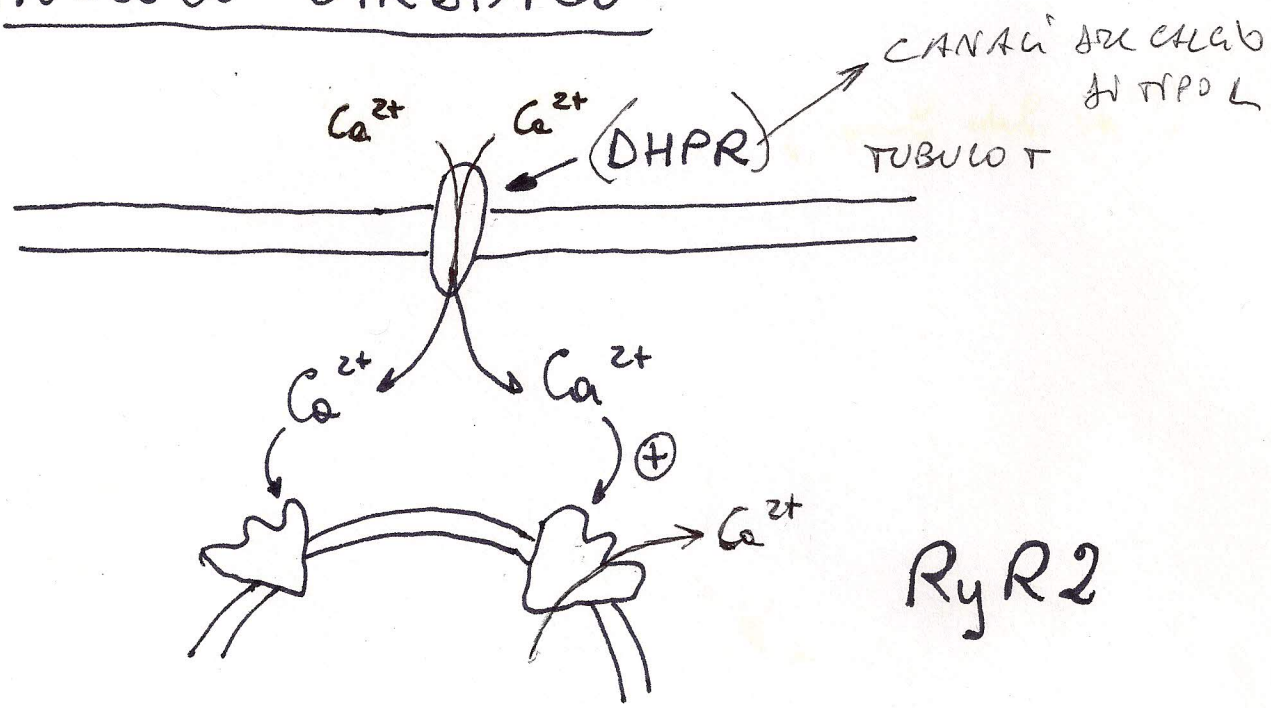
The time course of cardiac contraction is determined by the duration of the increase in cytosolic Ca^{2+} concentration and the cross-bridge cycling rate, both of which may be temperature dependent. Rapid cooling of the mammalian heart from 30 to 10°C produces a prolonged contracture because the reduction in temperature slows the calcium pump in the SR membrane and Na^+/Ca^{2+} exchange across the sarcolemma, increasing the duration of the calcium pulse. Animals living at low temperatures can maintain high heart rates because they have enhanced calcium release and removal mechanisms compared with mammalian hearts at the same low temperature. Some animals, such as carp, that use their muscles over a wide temperature range produce two different forms of myosin: a low-temperature (winter) form and a high-temperature (summer) form. These different forms of myosin allow a carp to maintain a reasonably stable time

RyRs (RECETTORI PER LA RIANODINA)

A) MUSCOLO SCHELETRICO



B) MUSCOLO CARDIACO



biomolecules

MDPI

Review

Modeling Calcium Cycling in the Heart: Progress, Pitfalls, and Challenges

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Abstract: Intracellular calcium (Ca) cycling in the heart plays key roles in excitation–contraction coupling and arrhythmogenesis. In cardiac myocytes, the Ca release channels, i.e., the ryanodine receptors (RyRs), are clustered in the sarcoplasmic reticulum membrane, forming Ca release units (CRUs). The RyRs in a CRU act collectively to give rise to discrete Ca release events, called Ca sparks. A cell contains hundreds to thousands of CRUs, diffusively coupled via Ca to form a CRU network. A rich spectrum of spatiotemporal Ca dynamics is observed in cardiac myocytes, including Ca sparks, spark clusters, mini-waves, persistent whole-cell waves, and oscillations. Models of different temporal and spatial scales have been developed to investigate these dynamics. Due to the complexities of the CRU network and the spatiotemporal Ca dynamics, it is challenging to model the Ca cycling dynamics in the cardiac system, particularly at the tissue sales. In this article, we review the progress of modeling of Ca cycling in cardiac systems from single RyRs to the tissue scale, the pros and cons of the current models and different modeling approaches, and the challenges to be tackled in the future.

Keywords: calcium cycling; excitation–contraction coupling; arrhythmias; computer modeling

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1. Introduction

The heart is probably the most intensively and accurately modeled biological system compared to other organs [1–5]. So far, more than 100 action potential models (or modified versions) have been developed for different types of myocytes and species. Tissue and organ scale models, including one-dimensional (1D) cable, two-dimensional (2D) sheet, three-dimensional (3D) slab, and anatomically based ventricle and atrium models, have been developed. These mathematical and computational models have been widely used to investigate cardiac excitation-contraction coupling and arrhythmias under physiological and pathophysiological conditions.

Modeling of the voltage in the heart is relatively well executed, mainly following the Hodgkin–Huxley (HH) modeling approach [6]. The governing equation for the transmembrane potential (V) of a myocyte is simply described by the following differential equation: $\frac{dV}{dt} = -I_{ion}/C_m$, in which I_{ion} is the total ionic current density and C_m is the cell membrane capacitance. In cardiac myocytes, there are many types of ionic currents (Figure 1A) which are modeled either using the HH formulation or Markovian approaches. In the HH formulism, the ionic current density is described as $I_s = G_s x^m y^n z^k (V - E_s)$, in which G_s is the maximum conductance, and E_s is the reversal potential. x, y, and z are the gating variables described by differential equations with properties (steady states and time constants) from experimental measurements of whole-cell voltage clamp recordings [6]. In the Markovian approaches, there are two ways of modeling. In the first way, single ion channel openings and closings are simulated using stochastic Markovian transitions, and

the total ionic current of an assembly of ion channels is described as $I_s = g_s N_o(V - E_s)$, in which g_s is the single-channel conductance and N_o is the number of open channels at a given time. In the second way, differential equations are used to describe the probabilities of states in the Markovian scheme, and the ionic current of an assembly of ion channels is described as $I_s = G_s P_o(V - E_s)$, in which P_o is the open probability of the ion channels. Note that a ventricular myocyte is a 3D entity with its dimension being roughly [7] $150 \times 30 \times 15$ μm^3, but in the current action potential models, voltage is considered uniform over the entire cell membrane. In other words, at any moment, the ion channels in the entire cell membrane are assumed to sense the same voltage. Moreover, in the Markovian scheme, it is assumed that the ion channels are statistically independent, and thus the whole-cell current is simply the summation of the single-channel currents.

However, Ca cycling and its dynamics are much more complex to model. Ca cycling not only is required for contraction but also plays important roles in regulating ionic currents (Figure 1A). Ca is stored in the sarcoplasmic reticulum (SR), which forms a complex network inside the cell. Ca is released from the SR into the cytoplasmic space through the opening of the ryanodine receptors (RyRs) in the SR membrane. Opening of the RyRs is activated by Ca on both the cytoplasmic and luminal sides. Under the normal condition, SR Ca release is mainly triggered by Ca entry from the L-type Ca channels (LCCs). Under diseased or Ca overload conditions, spontaneous Ca release occur more frequently. In cardiac myocytes, RyRs form clusters (Figure 1B), which combine with their associated LCC clusters to form basic units of Ca signaling, called Ca release units (CRUs). A cell contains hundreds to thousands of CRUs [8–10], which form a coupled network via Ca diffusion in the cytoplasmic space and SR. A rich spectrum of spatiotemporal Ca dynamics is observed in cardiac myocytes and other cell types, including Ca sparks, waves, and oscillations [11–21]. Due to the complex spatiotemporal Ca dynamics, it has been challenging to model Ca cycling dynamics in the cardiac system, particularly at the tissue scales. Models of different temporal and spatial scales have been developed to investigate these spatiotemporal dynamics. In this article, we review the progress of modeling of Ca cycling in cardiac systems from single RyRs to tissue scales, the pros and cons of the current models and different modeling approaches, and the challenges to be tackled in the future.

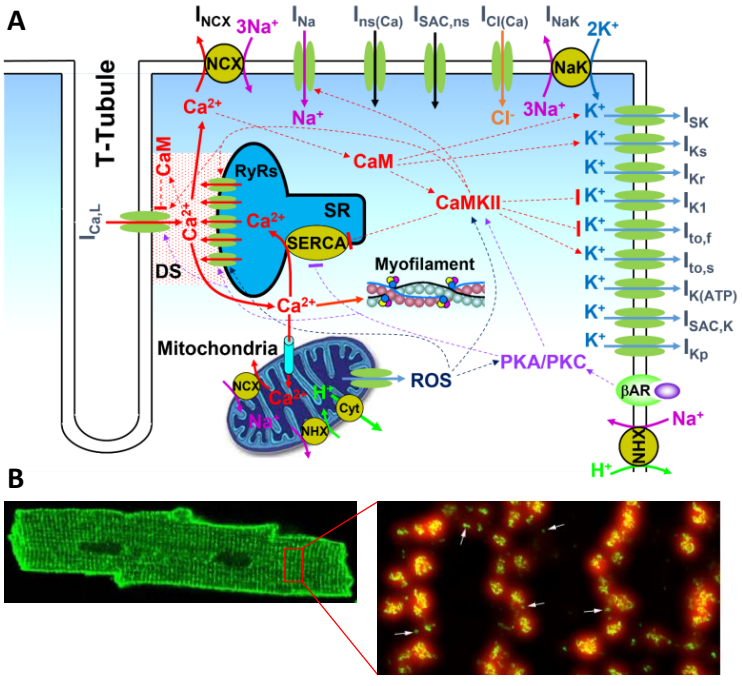

Figure 1. Ca cycling/signaling in cardiac myocytes. (**A**) Schematic diagram showing Ca cycling and signaling and its coupling with voltage, including the major components: (1) ionic currents and their

Da Randall et al. Fisiologia Animale

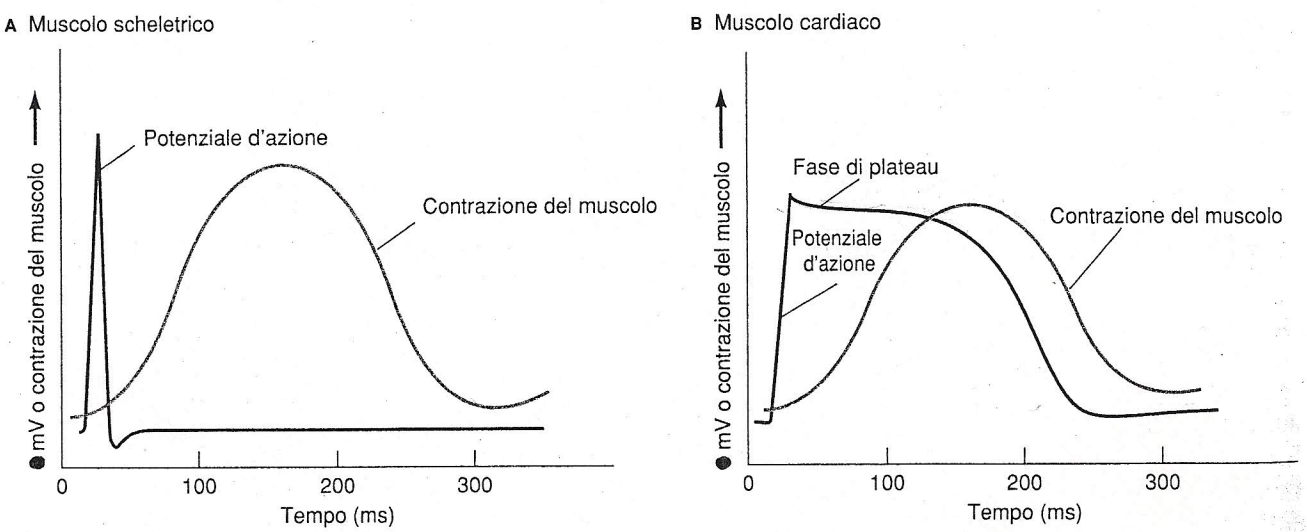

Figura 12.7 I potenziali d'azione generati nel muscolo scheletrico hanno una durata molto breve (**A**), mentre i potenziali d'azione cardiaci esibiscono una ripolarizzazione prolungata, o fase di plateau, durante la quale la membrana delle cellule rimane in uno stato refrattario (**B**). Per questo motivo, nel muscolo scheletrico, ma non nel muscolo cardiaco, è possibile la sommazione delle contrazioni e, in seguito a stimolazioni ripetitive, il tetano.

CARDIACO:

- no tetano
- no reclutamento

Forza di contrazione controllata da:

- I_{Ca}
- SERCA