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L-Type Ca^{2+} Current in Cardiac Arrhythmias

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1. Introduction

Cardiac arrhythmias result from the confluence of structural and functional changes in the heart and genetic predisposition, reflecting an interaction between a susceptible substrate (e.g. an anatomically defined circuit, a myocardial scar, fibrosis or a monogenic arrhythmia syndrome) and a specific electrophysiological triggering event. Such triggered activities arises from delayed afterdepolarizations (DADs) or early afterdepolarizations (EADs), in which action potential prolongation and aberrant Ca^{2+} fluxes are a recurrent theme.

Ca^{2+} channels in cardiomyocytes provide the main influx pathway for Ca^{2+}. Three types of high threshold Ca^{2+} channels are expressed in heart: two L-type channels, $Ca_v1.2$ and $Ca_v1.3$ and a P-type channel, $Ca_v2.1$. The $Ca_v2.1$ channel protein is expressed at a very low level the in heart (Starr et al., 1991) while $Ca_v1.3$ is mainly expressed in fetal hearts and only in adult sinoatrial and atrioventricular nodes and atrial tissues of adult (Lipscombe et al., 2004; Qu et al., 2005). We will focus attention on the $Ca_v1.2$ L-type Ca^{2+} channel (LTCC) which is the main player in electrical activity and excitation-contraction coupling (EC coupling) in the ventricular cardiomyocyte.

The LTCC of cardiomyocytes is a complex multimeric molecular sarcolemmal ensemble that during an action potential (AP) allows Ca^{2+} to flow down its electrochemical gradient into the cardiac cell. LTCCs are mostly localized in the transverse tubular system of cardiomyocytes (Wibo et al., 1991; Kawai et al., 1999; Brette et al., 2004). Activation of LTCC generates a Ca^{2+} current (I_{CaL}) through the sarcolemma large enough to be involved in AP overshoot and in the control of AP duration (APD) in different cardiac cells types (Bers, 2001). I_{CaL} serves as a trigger for Ca^{2+} release from the sarcoplasmic reticulum (SR) during the excitation-contraction coupling by a mechanism known as calcium-induced calcium release (CICR, Fabiato & Fabiato, 1975; Bers, 2001). LTCC activation can also play a role in transcription mechanisms in cardiomyocytes (Atar et al., 1995; Brette et al., 2006). Several hormones and neuromediators modulate the activity of LTCC via complex intracellular signaling pathways and, as well, several intracellular molecules and the cytoskeleton can influence LTCC activity (Benitah et al., 2010). However, intracellular Ca^{2+} concentration is strictly controlled in normal cells by different mechanisms (Bers, 2001) since a Ca^{2+} overload can have deleterious effects including arrhythmias and myocardial remodeling via a genetic reprogramming of the cardiac cell (Benitah et al., 2003).

2. Macromolecular structure

The typical structure of LTCC in ventricular cardiomyocytes is a macromolecular multimeric complex consisting of a ~240 kDa pore-forming unit α_1C (encoded by the CACNA1C gene) and two auxiliary (modulator) subunits: an intracellular β subunit (mainly β_{2A}, encoded by the CACNB2A gene) and the dimer $\alpha_2\delta$ subunit (mainly $\alpha_2\delta$-1, encoded by the CACNA2D1 gene) in a 1:1:1 ratio (Catterall et al., 2005). The α_1C subunit consists of four homologous repeating motifs (I–IV), each one composed of six membrane-spanning α-helices (S1 to S6) linked by variable extracellular and cytoplasmic loops (linkers). This subunit contains all the necessary structures to allow the channel to gate (activation and inactivation) and confers the Ca^{2+} selectivity as well as the electrophysiological and pharmacological properties of the LTCC (Takahashi & Catterall, 1987; Catterall, 2000; Carafoli et al., 2001; Lacinová & Hoffmann, 2001; Bodi et al., 2005; Lacinova & Hofmann, 2005; Brette et al., 2006; Benitah et al., 2010). However, more native LTCC properties can be achieved when all three subunits are present (Lacinová & Hoffmann, 2001; Lacinova & Hofmann, 2005; Benitah et al., 2010). The β_{2A} subunit seems to be involved in membrane targeting of α_1C and influence LTCC inactivation (Bodi et al., 2005; Lacinova & Hofmann, 2005; Brette et al., 2006). Its structure reveals a module of two interacting domains, a Src homology 3 (SH3) domain and a Guanylate Kinase (GK) domain (Chen et al., 2004; Bodi et al., 2005). It was initially believed that its conserved sequence, BID (Beta Interaction Domain), interacted directly with the Alpha Interaction Domain (AID) within the intracellular loop between domains I and II of the α_1C subunit (De Waard et al., 1996; Arikkath & Campbell, 2003). However, recent data indicate that BID is largely buried in the $Ca_v\beta$ core and is unavailable for protein-protein interactions (Chen et al., 2004; Van Petegem et al., 2004). The AID is bound in a hydrophobic groove (α-binding pocket, ABP) in the GK domain and positions the β-subunit near the intracellular pore-lining segment I6 (which is important in Ca^{2+} channel inactivation) thus providing evidence that $Ca_v\beta$ influence Ca^{2+} channel gating by direct modulation of this segment (Van Petegem et al., 2004). Although the BID does not participate directly in binding the α_1C subunit, structural integrity and bridging of the SH3 and GK domains are greatly influenced by BID. The $\alpha_2\delta$-1 subunit seems to be involved in targeting (or stabilization) of the α_1C to the sarcolemma (Lacinová & Hoffmann, 2001; Lacinova & Hofmann, 2005; Brette et al., 2006; Benitah et al., 2010) and could confer more native LTCC properties. The δ subunit is composed of a single transmembrane segment with a very short intracellular C-term and links by disulphide bonds the α_2 subunit that is entirely extracellular (Davies et al., 2007). The α_2 subunit contains a Von Willebrand factor A domain (VWA) that has a metal-ion-dependent adhesion site that seems to be key in trafficking the α_1C subunit to the membrane (Canti et al., 2005).

3. Biophysics of the cardiac L-type Ca^{2+} channel

3.1 Selectivity and permeation

The cardiac LTCC is a multi-ion pore in which a Ca^{2+} ion bound to a high affinity site can be repelled by a second Ca^{2+} ion entering the pore thus allowing selectivity with high ionic flux (Hess & Tsien, 1984). The LTCC pore exhibits two different affinities for Ca^{2+}: a K_D ~ 1 μM for Ca^{2+} block of monovalent current through the channel and a K_D ~ 10-14 mM for saturation of divalent current (which can be lower if surface charge screening is taken into account at high divalent concentrations), suggesting the existence of two Ca^{2+} binding sites

within the channel's pore (Almers & McCleskey, 1984; Hess & Tsien, 1984). In the absence of Ca^{2+} other ions can pass the channel and unitary conductance measurements gave the following sequence $Ca^{2+} < Ba^{2+} < Li^{+} < Na^{+} < K^{+} < Cs^{+}$ (Hess et al., 1986). Four glutamate residues, one in each of the four P-loops of the LTCC (the EEEE locus), are important for channel selectivity (Tang et al., 1993; Yang et al., 1993). The current view of the selectivity filter considers that the EEEE locus is physically flexible (Sather & McCleskey, 2003). Some recent results suggest that an EEEE locus is not enough to explain selectivity and permeation in LTCC and other high voltage activated Ca^{2+} channels. A set of non conserved (channel specific) charged residues (Divalent Cation Selection or DCS locus) located in the upper half of the channel (pointing toward the pore) could form a second Ca^{2+} binding site important in defining a Ca^{2+} permeability profile. It was proposed that the number of charged residues in the DCS locus is critical for Ca^{2+} binding. In the cardiac LTCC the DCS locus contains three negative charges (DSED) that seem to be important for the high Ba^{2+} conductance (Cens et al., 2007).

3.2 Activation, inactivation and reactivation of LTCC

In a ventricular cardiomyocyte at rest (resting potential ~ -80 mV) there is a transmembrane Ca^{2+} concentration gradient (~ 2 mM outside, ~ 100 nM inside) that generates a huge driving force (electrochemical gradient) for Ca^{2+} that tends to move it into the cell. Activation of LTCC allows Ca^{2+} to enter the cardiomyocyte during the AP and constitutes the major Ca^{2+} entry pathway. With a threshold at -40 mV (or slightly positive to), activation of I_{CaL} is fast with a time constant of 2-3 ms and time-to peak inward current ranging around 4-5 ms or less at the membrane potentials at which maximal inward current occurs (0 to +10 mV), and even faster at higher depolarizations (McDonald et al., 1994; Bers, 2001). Similar to Na^{+} channels, LTCC inactivate but with a much slower inactivation time course. With Ca^{2+} as charge carrier, I_{CaL} inactivation is usually a biexponential process with an "U-shaped" voltage-dependence. Minimal values for time constants of 4 to 10 ms (τ_{fast}) and 40 to 60 ms (τ_{slow}) occur at around 0 and +10 mV depending on cardiomyocyte type (McDonald et al., 1994; Bers, 2001). Deactivation of peak I_{CaL} after a short depolarizing pulse and repolarization to a negative holding potential is fast with a time constant ranging between 0.2 and 0.5 ms (Josephson et al., 1984; Cohen et al., 1992). However, it can be slower in rat cardiomyocytes (~1 ms) (Richard et al., 1993).

3.2.1 Current-to-Voltage relationship

Current-to-voltage relationship for I_{CaL} is bell-shaped with a threshold around -40 or -30 mV and a peak inward current at 0 (or +10 mV); it is almost linear at positive potentials and reverses around +60 to +70 mV at normal Ca^{2+} concentrations. At potentials beyond its reversal, I_{CaL} exhibits some inward going rectification (McDonald et al., 1994; Bers, 2001). Whole cell I_{CaL} can be roughly described by a Hodgkin-Huxley formalism considering that

$$I_{CaL} = G_{CaL} \cdot d_{\infty} f_{\infty} (V_m - V_{Ca})$$

where G_{CaL} is the maximal Ca^{2+} conductance, d_{∞} is the activation gate variable, f_{∞} the inactivation gate variable, V_m is the membrane potential and V_{Ca} is the Ca^{2+} reversal potential (Luo & Rudy, 1994). Since I_{CaL} inactivation is both voltage- and Ca^{2+}-dependent (see below), the formalism can be more complex and could include a variable related to the Ca^{2+}-dependent inactivation (CDI) process (Hirano & Hiraoka, 2003; Findlay et al., 2008). However, since the Hodgkin-Huxley formalism does not represent kinetic states of the ion

channel, single channel-based Markov models could be more useful to fully describe coupling between kinetic gating transitions and molecular interactions in LTCC (Faber et al., 2007). At the single channel level, current-to-voltage relationship for LTCC is essentially ohmic over the whole potential range with some inward rectification near the reversal potential (McDonald et al., 1994). Since the single channel current i_{CaL} can be described as

$$i_{CaL} = \gamma_{Ca} (V_m - V_{Ca})$$

where γ_{Ca} is the unitary conductance, the relationship between whole cell I_{CaL} and i_{CaL} is

$$I_{CaL} = NP_o\, i_{CaL} = NP_o\, \gamma_{Ca} (V_m - V_{Ca})$$

where N is the total number of functional channels and P_o the probability that a channel is open.

Unitary conductance of LTCC is 3-5 pS when Ca^{2+} is the charge carrier and 15 - 25 pS with Ba^{2+} as charge carrier (McDonald et al., 1994; Bers, 2001; Guia et al., 2001). However, subconductance levels of 50% to 70% of the major conductance have been also demonstrated (McDonald et al., 1994). On depolarization LTCC activity can vary between different modes: gating mode 0 (or "null mode") in which the channel is not available to open; gating mode 1 (or "normal") consisting of short bursts of brief openings and closings and gating mode 2 (with high P_o) in which the channel show long openings interrupted by short closings. This gating mode 2 is induced by phosphorylation, "Ca^{2+} channel agonists" (such as BAY K 8644) or strong depolarizations (Pietrobon & Hess, 1990; McDonald et al., 1994).

3.2.2 Voltage-dependence of activation and inactivation

Steady-state activation of I_{CaL} (d_∞) has a sigmoidal relationship with the membrane potential with a half-activation potential around -15 mV. The relationship for the inactivation variable (f_∞; availability) is more complex since for potentials from -80 to 0 mV it is sigmoidal with a half-inactivation potential around -35 mV; however an "overshoot" can often be seen at potentials negative to -50 mV in cells clamped at negative holding potentials (> -80 mV). Other singularities of the availability curve of I_{CaL} are that f_∞ rarely attains a zero value but a minimum between 0 and +10 mV and that the curve bends up at potentials positive to +10 mV, a phenomenon that is related to the CDI of I_{CaL} (Mentrard et al., 1984). These characteristics d_∞ and f_∞ are consistently seen in cardiomyocytes from different species including humans (McDonald et al., 1994; Bers, 2001; Treinys & Jurevicius, 2008; Benitah et al., 2010).

3.2.3 Voltage- and Ca^{2+}-dependent inactivation of LTCC

Time-dependent inactivation of I_{CaL} during depolarization is both voltage- and Ca^{2+}-dependent (Kass & Sanguinetti, 1984; Mentrard et al., 1984; Lee et al., 1985; Hadley & Hume, 1987). A very slow inactivation has also been described in the heart including human ventricular myocytes (Schouten & Morad, 1989; Benitah et al., 1992). CDI can be considered as the result of a two-component process, one due to Ca^{2+} ions passing through the channel and another due to Ca^{2+} release from the SR in the vicinity of the LTCC (Imredy & Yue, 1992; Richard et al., 2006; Faber et al., 2007). CDI can be easily shown up by using Ba^{2+} instead of Ca^{2+} as charge carrier which markedly prolonged LTCC inactivation time course. An increase in current amplitude is also seen since the LTCC has less affinity for Ba^{2+} than for Ca^{2+} (Hess et al., 1986). It is generally believed that under this condition, LTCC

inactivation is essentially controlled by a voltage-dependent inactivation mechanism (VDI). However, this paradigm has been called into question since it has been well demonstrated that Ba^{2+} can induce ion (or current) -dependent inactivation (Markwardt & Nilius, 1988; Ferreira et al., 1997; Ferreira et al., 2003) and thus the "apparent VDI" with Ba^{2+} as charge carrier also shows fast and slow components. Evidences exist that VDI can also have fast and slow components (Hering et al., 2000; Ferreira et al., 2003; Findlay, 2004). The situation could be even more complicated since, at least for N-type Ca^{2+} channels, the permeant ion could interact in a complex way with the voltage sensor (Shirokov, 1999).

The relative contribution of CDI to total inactivation of I_{CaL} is still under dispute. It is commonly accepted that the fast inactivation phase of I_{CaL} represents the CDI component (Findlay, 2004). However, it has been shown that the fast inactivation time constant of I_{CaL} of rat ventricular cardiomyocytes was "unexpectedly" slowed down after I_{CaL} was increased by β-adrenergic stimulation, as well as after manipulations not involving CDI (Alvarez et al., 2004; Haase et al., 2005; Alvarez et al., 2010). This makes difficult to ascertain which one of CDI or fast VDI predominates in the fast inactivation phase of I_{CaL} with Ca^{2+} as charge carrier. Nevertheless, it has been suggested that VDI could be more important under control conditions and that after β-adrenergic stimulation, CDI becomes the main inactivation mechanism due to a slow down of VDI (Findlay, 2004). It should be noted that CDI could be visualized as a "Ca^{2+}-dependent brake for a pre-existing voltage-dependent inactivation" based on the conserved regulation of both VDI and CDI by the auxiliary β-subunit, and that the I-II intracellular loop, essential for VDI, could also play a role in CDI (Cens et al., 1999; Cens et al., 2006). The precise mechanisms underlying CDI are not completely well defined. However, a general picture emerged in which in the presence of Ca^{2+} (entering through the LTCC or released from the SR) a calmodulin (CaM) molecule binds to the C-terminal tail of the α_1C subunit to promote CDI. CaM binds to two segments (LA and IQ), in a Ca^{2+}-dependent manner (Xiong et al., 2005) and it has been shown that the amino acid sequence of the IQ region in the α_1C subunit is critical for CaM binding and CDI (Ohrtman et al., 2008). Several other structures seem to be involved in CDI such as an EF-hand locus in the C-terminus of α_1C subunit (Peterson et al., 2000), the $Ca_v\beta$ subunit (Zhang et al., 2005), the N-terminus of the α_1C subunit, the I-II intracellular linker (Pitt et al., 2001; Erickson et al., 2003; Kobrinsky et al., 2005) and the pore region involved in slow inactivation (Shi & Soldatov, 2002).

3.2.4 Reactivation

Reactivation (removal of inactivation) of LTCC has been described as a mono or biexponential process, however, the time for half reactivation (t_{50}) can be considered as a reliable parameter and has been reported to be in the range of 70-100 ms in cardiomyocytes clamped at negative holding potentials (-80 mV or more negative) and an overshoot at short coupling intervals is often seen. At more depolarized holding potentials, t_{50} can be notably increased and the overshoot disappears (Argibay et al., 1988; Tseng, 1988; Schouten & Morad, 1989; Alvarez & Vassort, 1992). A voltage-dependent transition into a closed available state and/or reopenings from the inactivated state could explain in part the reactivation of LTCC (Jones, 1991; Slesinger & Lansman, 1991). However, reactivation of LTCC is a more complex phenomenon since it is Ca^{2+}-dependent (Argibay et al., 1988; Tseng, 1988) and thus related to CDI. The overshoot in I_{CaL} reactivation could be of physiological relevance since it is, at least in part, related to the well-known increase in premature (extrasystolic) APD in well polarized cardiomyocytes but not in partially depolarized ones (Hiraoka & Sano, 1976).

3.3 Facilitation of LTCC

The overshoots seen in the availability and reactivation curves of I_{CaL} are both a manifestation of a "facilitation" phenomenon of LTCC. In both cases an increase in τ_{fast} is commonly observed and both seem to be related to the pacing-dependent (staircase) facilitation of I_{CaL} (Lee, 1987). However, the "overshoots" and the staircase phenomena could be dependent on the basal I_{CaL} density disappearing at higher current densities (Argibay et al., 1988; Alvarez & Vassort, 1992; Piot et al., 1996). Facilitation of LTCC has been more extensively studied by stimulating cardiomyocytes at high rates after a rest period or by applying prepulses of moderate and high amplitude (Richard et al., 2006). At negative holding potentials (> -80 mV) the frequency-dependent changes in I_{CaL} amplitude upon stimulation can be variable: significant (Lee, 1987), modest or absent (Piot et al., 1996; Delgado et al., 1999) and even modestly decrease (Argibay et al., 1988; Alvarez & Vassort, 1992; Alvarez et al., 2004). However, an increase in τ_{fast} has been consistently reported in these conditions, resulting, independently of what happens with I_{CaL} amplitude, in a significant increase in Ca^{2+} influx (Delgado et al., 1999). The mechanism of this "Ca^{2+}-dependent facilitation" (CDF) or potentiation seems to be related to a negative feedback involving less CDI at frequencies at which Ca^{2+} load and release from the SR are decreased (Delgado et al., 1999). This phenomenon has often been related to phosphorylation by cyclic AMP-dependent protein kinase (Tiaho et al., 1994; Piot et al., 1996) although there are also reports that β-adrenergic stimulation significantly diminished I_{CaL} facilitation (Zygmunt & Maylie, 1990; Delgado et al., 1999; Alvarez et al., 2004). Disruption of the interaction between α_1C and β_{2A} subunits also abolished CDF (Alvarez et al., 2004). In this sense, this phenomenon is still far to be completely understood. CDF also involves CaM and the Ca^{2+}/CaM kinase II (CaMKII). Similar to CDI, the CDF requires the binding of CaM to the IQ motif located in the α_1C C-terminus but to a structural frame different to that involved in CDI (Zuhlke et al., 1999). Activation of CaMKII by Ca^{2+} entry or release from the SR is also involved in I_{CaL} facilitation (Anderson et al., 1994; Yuan & Bers, 1994; Anderson, 2004). More recently phosphorylation of β_{2A} has been reported to be critical for CaMKII-dependent I_{CaL} facilitation (Grueter et al., 2006).

Similar to frequency-dependent facilitation, prepulse-induced facilitation of I_{CaL} is characterized by an increase in τ_{fast} (Barrere-Lemaire et al., 2000) and its underlying mechanism seems to involve a negative feedback on LTCC related to CDI as discussed above (Guo & Duff, 2003) and a positive feedback on LTCC following CaMKII activation by membrane potential and Ca^{2+} entry (Xiao et al., 1994).

3.4 LTCC "window" current

Activation and inactivation (availability) curves overlap at membrane potentials between the threshold for I_{CaL} at -40 to potentials of 0 or +10 mV thus defining a "window" Ca^{2+} current ($d_\infty.f_\infty > 0$) in the plateau range of the cardiac AP. The peak window current (which is proportional to $d_\infty.f_\infty$) is between -25 and -20 mV and could be as large as 10% of maximal I_{CaL} (McDonald et al., 1994). Its existence has been verified in whole cell recordings (Hirano et al., 1992; McDonald et al., 1994). Within this window LTCC channels can cycle between closed, open and inactivated states but a transition again to the closed state and reopenings are possible before inactivating again (Shorofsky & January, 1992). Such reopenings have been clearly demonstrated in single channel recordings (Shorofsky & January, 1992; McDonald et al., 1994) and constitute the underlying mechanism for the EAD (January et al., 1988). EADs are more frequently observed at low rates when the APD is increased and

during interventions that increase I_{CaL} (e.g. after activation of β-adrenergic receptors). They are supposed to underlie the cellular mechanism of "Torsades de Pointes" (TdP) in long QT syndromes (Napolitano & Antzelevitch, 2011). Transient K^+ outward current (I_{to}) reactivation at low rates could contribute to generation of EADs since it drives the membrane (plateau) potential to more negative "take off" potentials and warrants higher peak amplitude of EADs (January et al., 1988). β-adrenergic stimulation increases I_{CaL} and shifts the window current to more negative potentials due to an increase in channel's P_o at more negative potentials (hyperpolarizing shifts in d_∞) and a shift of f_∞ to more hyperpolarized potentials (McDonald et al., 1994) thus favoring the appearance of EADs. It is to be noted that, at these membrane potentials, the fast Na^+ current (I_{Na}) and I_{to} are inactivated, the inward rectifier current I_{K1} is decreased and outward rectifier currents are just activating. As a result the total membrane resistance is increased (Weidmann, 1951) thus making the membrane space constant high enough to guarantee a rather high safety margin for the slow response to be conducted for a given I_{CaL} density.

3.4.1 A note on "EADs" recorded in multicellular cardiac preparations

It is possible that in some cases EADs recorded in multicellular cardiac preparations represent a reentry from a distant site rather than a true EAD arising from the recording site. In any case, the mechanism underlying this activity is the same as the previously described for EAD. This reentry mechanism, at these short coupling intervals (during the AP plateau) is due to "slow response" APs that can be conducted with a large enough safety margin and are due to the activation of LTCC (Cranefield, 1975). The biophysical properties of LTCC described above, can fully account for the conducted slow response APs in partially depolarized cells. Under several pathological conditions these slow responses can be conducted and are at the origin of reentry, for example in depressed fibres in ischemia (Cranefield, 1975) since the slow response APs are rather resistant to hypoxia (Alvarez et al., 1981), in TdP associated to long QT syndromes (Antzelevitch & Burashnikov, 2001) (see below) or during the verapamil-sensitive reentrant intranodal tachycardia involving the AV node (Wellens et al., 1977).

3.4.2 A role for a second window current?

The characteristics of the activation and inactivation curves of I_{CaL} could predict the existence of a "second window" current at potentials positive to +10 mV since at these values, the product $d_\infty.f_\infty$ is > 0. Whether the overlap between d_∞ (=1) and the increasing f_∞ at positive prepulse potentials could represent a true "secondary" window current or not is debatable, but it is clear that after these prepulse potentials LTCCs recover from inactivation and reopen in a sort of "facilitation" (Pietrobon & Hess, 1990). Nonetheless, the physiological (or physiopathological) relevance of this window current is uncertain since at these membrane potentials the fast I_{Na} is the main depolarizing current and physiologically membrane potentials over +40 mV never exist. This property, however, has been important for the characterization of the CDI of LTCC in cardiac cells (Mentrard et al., 1984).

4. Role of I_{CaL} in the cardiac arrythmogenesis associated to acquired pathophysiological states

4.1 Myocardial ischemia and ventricular fibrillation

Ventricular fibrillation (VF) and myocardial ischemia are inseparable. In general terms, myocardial ischemia is defined as disequilibrium between myocardial oxygen demand

versus supply, which episodes can trigger serious and fatal arrhythmic events. Thus, in the clinical setting around 80% of all sudden cardiac deaths (SCD) are due to myocardial ischemia. The most common sequence of events leading SCD appears to be the degeneration of ventricular tachycardia (VT) into ventricular fibrillation (VF) (Rubart & Zipes, 2005). VF is thought as a disorganized cardiac activation in which electrical waves propagate through the ventricles haphazardly and unpredictably (Jalife, 2000). The last consequence of this disorganized process is strong alteration in the adequate contractions of the ventricles that fail to eject blood effectively as a consequence of a strong electrical dysfunction, which is detected in the heart even during the first minutes after acute myocardial ischemia (usually lasting for 30 min) where abundant arrhythmogenesis is detected. During acute ischemia, in the border zone between the ischemic and normal tissue the excitability is increased resulting in spontaneous activation of Purkinje fibers initiating VT. During reperfusion the rapid inhomogeneous improvement in tissue excitability contributes to arrhythmogenesis again (Opthof et al., 1993; Luqman et al., 2007).

At intracellular level, an important ionic imbalance occurs during myocardial ischemia. This electrophysiological imbalance is characterized by the opening of ATP-sensitive potassium channels (I_{KATP}) and causes acidosis and hypoxia of myocardial cells together with an aberrant intracellular Ca^{2+} handling that is determinant to trigger arrhythmias. Because I_{CaL} constitutes the first trigger for the EC coupling necessary for each beat in the heart, a lot of attention has been focused in the involvement of I_{CaL} in the conversion of VT to VF. With myocardial ischemia, the abrupt cessation of blood flow provokes a new distribution of a number of ions. The abnormal increase in the intracellular Na^+ concentration ($[Na^+]_i$) consequently results in an increase in the intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) due to an increase in the Ca^{2+} influx via the Na^+/Ca^{2+} exchanger (NCX) working in the reverse manner and also via depolarization-activated LTCCs. These events induce cellular Ca^{2+} overload (as a consequence of cellular Na^+ overload) favoring the presence of spontaneous (non-voltage dependent) diastolic Ca^{2+} release as Ca^{2+} waves that induce depolarization of myocyte membrane triggering DAD and finally DAD-related arrhythmias (Schlotthauer & Bers, 2000). The presence of DADs also can trigger abnormal electrical activity with the wavebreak causing VF (Koretsune & Marban, 1989; Lakatta & Guarnieri, 1993).

It is important to point out that cardiac ischemia is also characterized by a significant increase in circulating and tissue cathecholamine levels, which increase the probability of VT and SCD (Dorian, 2005). In the presence of β-adrenergic receptor (β-AR) stimulation and hypoxic conditions, a significant increase in Ca^{2+} influx through I_{CaL} is able to prolong APD and also triggers EADs (Gaur et al., 2009), which in ventricular myocytes appear not to be due to spontaneous regional increase in $[Ca^{2+}]_i$ or propagating Ca^{2+} waves. These results can be explained by the increase in the sensitivity of LTCC due to changes in gating properties by the modification of the phosphorylated state or by the modification of thiol groups of the channel, since the presence of dithiothreitol or catalase mimics the effect of acute hypoxia on I_{CaL} (Hool, 2000; Hool & Arthur, 2002; Tanskanen et al., 2005). Alterations in I_{CaL} have been also detected in simulated experimental ischemic-like conditions in single pacemaker cells isolated from the rabbit sinoatrial node (SAN). In contrast to ventricular myocytes, I_{CaL} is declined under metabolic inhibition or ischemic conditions in SAN cells (Vinogradova et al., 2000; Ju & Allen, 2003). However, it has been reported that *in vitro* ischemic conditions enhanced I_{CaL} significantly at potentials between -30 and +30 mV suggesting that the greater I_{CaL} could account for a 6 mV increase in the AP overshoot (Du & Nathan, 2007a). This is related to an increase in the G_{CaL} and a positive shift of the f_∞ curve and reduction of inactivation, likely due to a H^+- increased of I_{CaL} (Du & Nathan, 2007b).

Torsades de Pointes (TdP) is a polymorphic type of VT also associated to acquired QT prolongation and maintained bradycardia that potentially leads to SCD (Jackman et al., 1988). Several studies carried out in rabbits and dogs prone to spontaneous TdP as a consequence of the chronic atrioventricular block (AVB) showed important alterations in the control of Ca^{2+} (Sipido et al., 2000; Antoons et al., 2007; Qi et al., 2009). For example, AVB in dogs resulted in an increase in the SR Ca^{2+} content which improved Ca^{2+} release from SR as Ca^{2+} transients (Sipido et al., 2000). Although, the overall density-voltage relationship of I_{CaL} is unchanged, a depolarizing shift in the f_∞ curve resulted in an increased window current (Antoons et al., 2007). The CaM activation of CaMKII has been proposed to underlie this effect, as well the induced EADs (Qi et al., 2009).

4.2 Atrial fibrillation

Among supraventricular tachyarrhythmias, atrial fibrillation (AF) is the most common. Its prevalence is considerably increased with age, and thus AF is now classified as an epidemic (Lip et al., 2007). The cellular and molecular bases of AF electrophysiology and the underlying mechanisms have been extensively investigated (Hatem et al., 2010). The definition of the latest report of the American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) guidelines for AF is limited to a description of the pattern of irregular atrial waveforms on the electrocardiogram (ECG) as a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with a replacement of consistent P waves by rapid oscillations or fibrillatory waves (Fuster et al., 2011). At the cellular level, AF is characterized by strong alterations in the cardiac electrophysiology. The repolarizing currents such as I_{to} is almost suppressed and the voltage-gated K^+ current (I_{Kur}) is decreased by around 50% (Le Grand et al., 1994; Van Wagoner et al., 1997). While upon the onset of AF, an increase in the intracellular Ca^{2+} load is observed, in persistent AF the intracellular Ca^{2+} load is restored to normal levels. There is a consensus in the drastic reduction in I_{CaL} (around 70%) that is observed during experimental and clinical AF. Because this current is the main depolarizing current that activates during plateau phase of the AP, its reduction contributes greatly to the shortening of the AP, reducing atrial effective refractory period with a loss of physiological rate adaptation and finally favouring the formation of re-entrant circuits during AF (Le Grand et al., 1994; Van Wagoner et al., 1997; Yue et al., 1997). Several authors have postulated a significant decrease in the number of Ca^{2+} channels subunits $Ca_v1.2$ associated with AF (Brundel et al., 2001; Shinagawa et al., 2003). In fact, experiments carried out in cultured adult canine atrial myocytes subjected to *in vitro* model of atrial tachycardia by continuous tachypacing have demonstrated that during the first hours of pacing exist a Ca^{2+} overload involved in the activation of the phosphatase (PP) calcineurin (Cn) that allows the translocation of the transcriptor factor NFAT into the nucleus. This rapid Ca^{2+} overload induces the activation of the Ca^{2+}-dependent CaM-Cn-NFAT system to cause the transcriptional downregulation of α_1C subunit mRNA expression and also in the levels of $Ca_v1.2$ protein expression that is observed from 8 hours of pacing (Qi et al., 2008). These results are in conflict with others demonstrating no changes in mRNA and protein levels of the pore-forming α_1C and the regulatory β_{2A} subunits in atrial myocardium from patients with chronic AF (Schotten et al., 2003). Nevertheless, the reduction of I_{CaL} can also be the result of changes in gating properties of the channel (Bodi et al., 2005), due to alterations in the phosphorylation state of the LTCC. Indeed, it has been observed that the maximum of the current-voltage relationship of I_{CaL} is rightward shifted to more positive potentials in AF,

suggesting phosphorylation-dependent changes in the channel regulation more than changes in its expression (Christ et al., 2004). In addition, it has been also described a high sensitivity of I_{CaL} to β-adrenergic agonists during AF, suggesting that LTCCs are in a dephosphorylated and silent state (Boixel et al., 2001; Schotten et al., 2003; Dinanian et al., 2008; Hatem et al., 2010). Moreover, the activity of CaMKII is increased in AF (Neef et al., 2010). However, increased CaMKII activity in AF seems to be offset by an increased PP activity, because CaMKII inhibitor KN-93 reduce I_{CaL} in control cells, while it did not affect I_{CaL} in AF cells (Greiser et al., 2007; Greiser et al., 2011). Moreover, the PP inhibitor, okadaic acid, increased I_{CaL} to almost normal levels in human atrial myocytes from AF patients (Christ et al., 2004; Greiser et al., 2011). In conclusion, in AF the ratio between protein kinase/phosphatase is altered in favor of increased PP activity, suggesting that the basal phosphorylation of the Ca^{2+} channel is reduced which induces lower basal I_{CaL} activity.
It seems clear that the abnormal atrial electrical remodeling associated to AF contributes to perpetuation of the arrhythmia and has profound effects on intracellular Ca^{2+} handling (Greiser et al., 2011). Contractile force of atrial tissue strips from patients with AF is also reduced around 75% and exposure to high extracellular Ca^{2+} concentration is able to restore atrial functions (Schotten et al., 2001; Schotten et al., 2004). In a sheep model of persistent AF, even with only a slight reduction in I_{CaL} (around 24%), its efficiency to highly reduced CICR (Lenaerts et al., 2009). In the presence of Ca^{2+} chelators, I_{CaL} was unchanged in AF conditions while it is increased in control cells. These results are well-matched with a possible reduction in the CDI of I_{CaL}.

4.3 Cardiac hypertrophy and heart failure

Following a pathological stress, the heart can adapt by developing cardiac hypertrophy, which improves contractile force as an adaptative mechanism to meet the new body demands. In this case, the cardiac hypertrophy is "compensated", as in physiologic cardiac hypertrophy by exercise or during the pregnancy. When the stimulus is prolonged, cardiac hypertrophy can "decompensate" toward heart failure (HF) with compromised pump function (Benitah et al., 2010). One of the best documented changes in hypertrophy and HF, both in animal models and in humans, is the prolongation of the AP, which is highly significant in the production of ventricular arrhythmias. Important abnormalities of intracellular Ca^{2+} handling has been showed in the hypertrophic and failing myocytes: reduced SERCA function, enhanced NCX function and enhanced SR Ca^{2+} leak contributing to the reduced SR Ca^{2+} load (Bers et al., 2003). It is also well known that changes in I_{CaL} in the hypertrophic and failing heart can also contribute to the electrical instability. Although the different degrees in the severity of pathological stresses as well as the variability among different models appear to influence the regulation of I_{CaL}, the amplitude of I_{CaL} is increased in hypertrophied and failing myocytes while its density (normalized to cell capacitance, as an indirect measure of cell surface) is unchanged (Benitah et al., 2002a; Benitah et al., 2003; Song et al., 2005; Loyer et al., 2008). In an early analysis of a pressure-overloaded cardiac hypertrophy model, I_{CaL} was augmented in non-hypertrophic cells (Keung, 1989). It was thus suggested that I_{CaL} could be increased before the cellular hypertrophy and then, as the cell grows, I_{CaL} density would regain control values and even decrease in models of overt HF (Aimond et al., 1999; Benitah et al., 2002b). This process involves, at least partly, the cardiac mineralocorticoid pathway (Perrier et al., 2004; Benitah et al., 2010). Although most reports agree with the idea that I_{CaL} density is normal in failing hearts, its kinetic seems to be significantly altered (Ryder et al., 1993; Bito et al., 2008). Thus, the decay of the whole-cell

I_{CaL} and its CDI have been found to be slowed, causing a reduction in the peak of the $[Ca^{2+}]_i$ transients producing less Ca^{2+}-induced inactivation of I_{CaL}. Thus, the maintained I_{CaL} density together with a slowing of its inactivation would at the end increase the total account of Ca^{2+} entry through the channel (Aimond et al., 1999; Benitah et al., 2010). Such slowing of the decay of the current has a direct effect on the EC-coupling and is involved in the prolongation of APD favoring EADs observed in failing conditions (Tomaselli & Rose, 2000). An increase in P_o and availability of LTCCs in human failing myocardium have been reported (Schröder et al., 1998), suggesting that the failing myocytes has fewer but more active channels. Hence, the response of I_{CaL} to cAMP is reduced in ventricular myocytes from failing hearts (Chen et al., 2002). The attenuated increase of I_{CaL} by β-adrenergic stimulation is consistent with a reduction in the maximal number of channels, which have a higher activity (Bito et al., 2008). This is related to the concept of "defective EC coupling" in HF (Gómez et al., 1997): The failing myocytes had a significant reduction in triggered Ca^{2+} release from the SR despite unaltered I_{CaL}, which could be due to structural alteration in the relation between LTCCs and ryanodine receptors, related to important structural changes as a loss of T-tubules density in human and experimental HF (He et al., 2001; Balijepalli et al., 2003; Louch et al., 2004; Lyon et al., 2009; Horiuchi-Hirose et al., 2011). The increased basal activity at the single Ca^{2+} channel levels is also consistent with changes in the phosphorylation state of the channel. Thus, both increases in PKA and CaMKII-dependent phosphorylation of LTCC have been described in failing myocytes (Schröder et al., 1998; Chen et al., 2008; Wang et al., 2008). PKA activation through β-adrenergic stimulation leads to increase I_{CaL}, as well as the CaMKII-dependent phosphorylation of both pore-forming α_1C and β_2 subunits, which also increased I_{CaL} CDF (Yuan & Bers, 1994; Hudmon et al., 2005; Grueter et al., 2006). In cardiac hypertrophy with prolongation of APD, these features are important since I_{CaL} can be inappropriately reactivated and contribute to EADs triggered arrhythmia (Wu et al., 2002; Anderson et al., 2011). Moreover, $Ca_v\beta_2$ expression is downregulated in the compensated phase of cardiac hypertrophy, while an upregulation is observed in failing states, which could explain the increase in the activity of LTCCs observed in single channel studies (Hullin et al., 2007).

5. Inherited channelopathies or genetically determined ion-channel disorder

The critical role of LTCCs in cardiac cells has led many to suggest that inherited defects of LTCCs could be incompatible with life. This view dramatically changed in the 2004 when the CaCNA1C gene was found to show genetic linkage to life-threatening arrhythmias associated with Timothy syndrome (Splawski et al., 2004). Since, we witnessed an explosion of information linking LTCC genes mutations (more than 25 mutations identified in the past decade) with a wide variety of inherited arrhythmia syndromes (Napolitano & Antzelevitch, 2011).

5.1 LQT8 or Timothy syndrome

Identified in the 1990s (Marks et al., 1995), Timothy syndrome, or syndactyly-associated LQTS or LQT8, is a dominantly inherited genetic condition characterized by multisystem dysfunction, with severe arrhythmic disorders including: QT prolongation; 2:1 atrioventricular block (due to delayed ventricular repolarisation); T-wave alternans, polymorphic VT, and TdP; and abnormal changes in multiple organs (heart, skin, eyes, teeth, immune system, brain, and dysmorphism, such as syndactyly). Patients with LQT8

may also have episodic hypoglycaemia, which can trigger arrhythmias, and structural heart anomalies, including patent ductus arteriosus, patent foramen ovale, ventricular septum defect, and tetralogy of Fallot. Prognosis is very poor and SCD often occurs during childhood.

Gain-of-function mutations in CACNA1C, localized at the end of IS6 segment that is important for the regulation of channel inactivation and the binding of the $Ca_v\beta$ subunit, have been associated with Timothy syndrome (Splawski et al., 2004; Splawski et al., 2005). A missense mutation G406R in the minor alternatively splice exon 8 of CACNA1C gene, as been first identified in all probands analysed (Splawski et al., 2004). Later, two other Gly mutations in the mutually exclusive major spliced exon 8a (G402S and G406R) were shown to cause a very similar syndrome but without the syndactyly (Splawski et al., 2005). These mutations exert powerful effect on inactivation, slowing the VDI irrespective of auxiliary β subunits, while through a proposed low-P_o gating shift speeding the kinetics of CDI (Barrett & Tsien, 2008), which was previously reported unchanged (Splawski et al., 2005). Moreover, the mutation did not affect closed-state VDI, which might explain absence of hypertension associated with LQT8, and along with impaired open-state VDI, slowed activation and deactivation (Yarotskyy et al., 2009). The later is in part consistent with spontaneous increased occurrence of mode 2 gating at single channel level, which has been associated with the generation of a consensus phosphorylation site for CaMKII (Erxleben et al., 2006). Indeed, on isolated rat cardiomyocytes infected with dihydropyridine-resistant G406R $Ca_v1.2$ channel, CaMKII autophosphorylation is increased, which mediated enhanced I_{CaL} facilitation, AP prolongation, increased Ca^{2+} spark frequency and afterdepolarizations (Thiel et al., 2008). The impaired inactivation of LTCC leads to sustained Ca^{2+} influx, AP prolongation, and Ca^{2+} overload, which promotes EADs and DADs (Jacobs et al., 2006; Sicouri et al., 2007). Roscovitine, a compound that increases the VDI, rescues the electrophysiological and Ca^{2+} homeostasis properties of Timothy syndrome cardiomyocytes (Yazawa et al.). Ca^{2+} channel blockade (eg, by verapamil and diltiazem) can control arrhythmias without affecting the QT interval, and is a possible treatment (Napolitano et al., 2006).

5.2 I_{CaL} and LQT syndrome

The QT interval is an electrocardiographic index of ventricular repolarization and a measure of the duration of the ventricular AP. Ca^{2+} influx through LTCC plays a significant role in maintaining the plateau phase of AP and hence contributes importantly to APD and QT interval. Therefore, administration of CCB is a logical strategy in all types of LQTS. In the clinical study involving recording of monophasic AP (MAP) in eight patients with LQTS, verapamil effectively abbreviated MAP duration and suppressed epinephrine-induced EADs (Shimizu et al., 1995). At the bench side, verapamil effectively abbreviates QT interval and suppresses TdP in models of congenital and acquired LQTS (LQT1+ LQT2) (Aiba et al., 2005). In a rabbit model of drug-induced LQT2, the increased I_{CaL} at the base of hearts, attributable to gender and regional difference in $Ca_v1.2$ expression, is an important determinant of the arrhythmia phenotype (Sims et al., 2008). This echoes clinical reports suggesting that Ca^{2+} channel antagonists might be appropriate as adjunctive therapy for arrhythmia suppression in LQT1, LQT2 and even LQT3 (Shimizu et al., 2005). Hence, an anti-arrhythmic effect of the specific LTCC antagonist nifedipine has been reported in mice with targeted disruption of the Na^+ channel gene (Thomas et al., 2007), as well as in intact hearts from LQT5 mice model (Balasubramaniam et al., 2003).

5.3 J wave syndromes

Because they share a common arrhythmic platform and similarities in ECG characteristics, clinical outcomes and risk factors, congenital and acquired forms of Brugada (BrS) and early repolarization (ERS) syndromes have been grouped together under the heading of J wave syndromes (Antzelevitch & Yan, 2010). Recent studies have implicated loss of function mutations in all 3 subunits of the cardiac LTCC in the generation and accentuation of electrocardiographic J waves associated with these syndromes (Antzelevitch et al., 2007; Cordeiro et al., 2009); (Burashnikov et al.).

5.3.1 Short QT syndrome

Although QT prolongation has long been known to increase the risk of SCD and overall cardiac mortality among patients with a variety of underlying etiologies, a shorter than normal QT interval could also be detrimental leading to the concept of a new clinical entity, the short QT syndrome, associated with AF and SCD (Gussak et al., 2000). Since more than 30 patients with SQTS have been reported (Schulze-Bahr et al., 1997; Gaita et al., 2003; Schimpf et al., 2005; Giustetto et al., 2006).

SQT4 and SQT5 are associated with mutations in CACNA1C and CACNB2B (Antzelevitch et al., 2007). These mutations reduce I_{CaL}, shorten QT, and are associated with asymmetrical T waves, attenuated QT-heart rate relations, and AF. More recently, a new variant of SQTS at a heterozygous state caused by a mutation in the CACNA2D1 gene has been reported (Templin et al., 2011). This mutation leads also to a decreased I_{CaL}, without modification in the $Ca_v1.2$ expression suggesting alteration of some of the biophysical single channel properties of channel.

5.3.2 Brugada syndrome

Brugada syndrome (BrS), an inherited cardiac arrhythmia syndrome associated with a relatively high risk of VF, was first described as a new clinical entity in 1992 (Brugada & Brugada, 1992). The ECG features of the Brugada patient includes an accentuated J wave displaying a real or apparent right branch bundle block and ST segment elevation in the right precordial leads. Although the BrS has thus far been linked to mutations that impede Na^+ channel expression or function, alterations in I_{CaL} current with CCBs have been implicated in the development of BrS both clinically (Shimizu, 2005) and experimentally (Fish & Antzelevitch, 2004).

Recently, novel mutations of the cardiac LTCC genes responsible for shortening of the QT interval in families characterized by SCD, AF and a BrS type I ECG pattern have been reported (Antzelevitch et al., 2007). Functional analyses revealed loss-of-function missense mutations of the CACNA1C (A39V in the N-terminus and G490R in the I-II domain linker) and CACNB2 (S481L). These mutations reduce I_{CaL} amplitude (due to trafficking defect for A39V), shorten QT, and are associated with asymmetrical T waves, attenuated QT-heart rate relations, and AF. Some patients also have tall, peaked T waves. These patients can also have BrS-type ST elevation in the right precordial leads with or without drug provocation, suggesting that the same reduction in I_{CaL} underlies both SQTs and BrS. More recently, a novel missense mutation (T11L) in CACNB2B has been associated with BrS (Cordeiro et al., 2009). Characterized in heterologous expression system, this mutation induced faster inactivation kinetics and hyperpolarized shift in the steady-state inactivation without any other alteration in I_{CaL}, resulting in a reduced depolarizing current in response to epicardial AP waveform.

6. Current antiarrhythmic strategies and I_{CaL}

Current therapy to prevent cardiac arrhythmia is multidimensional and complicated. The conventional antiarrhythmic drugs have limited efficacy and safety. In the case of the most common cardiac arrhythmia, AF, treatment strategies can be pharmacological or interventional (e.g. catheter ablation techniques) but are also complicated by the presence of co-morbidities such as hypertension, diabetes, and/or pre-existing cardiovascular diseases (HF or coronary artery disease) (Prystowsky et al., 2010). Within the pharmacological strategies there are several groups of drugs including β-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), lipid-lowering and antithrombotic agents, spironolactone, among others, which have also demonstrated its efficacy in the prevention of SDC (Alberte & Zipes, 2003). From among all of them, the greatest reduction in cardiovascular mortality has been demonstrated with the treatment of β-blockers (Dorian, 2005). However, these drugs most likely exert their antiarrhythmic potential indirectly by affecting "upstream events" that contribute to the development of electrophysiological instability (Rubart & Zipes, 2005).

It has been demonstrated that the direct blockade of I_{CaL} with dihydropyridine Ca^{2+} channel blockers (CCBs) produces a strong shortening in the APD. So, blocking I_{CaL} is a potent means of suppressing VF. In Langendorff-perfused rabbit hearts, verapamil decreased the frequency of arrhythmia and changed it from disorganized VF into more organized VT (Samie et al., 2000). Similar results were also obtained using nifedipine (Choi et al., 2002). Therefore, CCBs could be considered promising antiarrhythmic drugs. However, the effects of these drugs have not emerged as unequivocally favorable in all clinical studies. Thus, verapamil and diltiazem can, in some cases, prevent episodes of acute ischemia VF in human, but they do not demonstrated to have as much of a beneficial effect on overall mortality as β-blockers or angiotensin-converting enzyme (ACE) inhibitors (Bodi et al., 2005). The problem observed with the direct blockade of I_{CaL} using CBBs is that, at the same time that VT is prevented, the contractility could be suppressed, precluding their clinical usefulness as antifibrillatory drugs. Therefore, in the last years it has been proposed that only modifying I_{CaL} kinetic properties, instead of blocking I_{CaL}, could produce equivalent anti-fibrillatory effects without impairing EC coupling (Mahajan et al., 2008).

In the clinical setting it is well established that the improvement in the current approach to treat AF is completely necessary. Amiodarone is the most effective antiarrhythmic drug for maintaining sinus rhythm in patients with AF. However, the extra-cardiac side effects have been a limiting factor, especially during chronic use, and may offset its benefits. Dronedarone is a new antiarrhythmic drug similar to amidarone that has been developed to provide rhythm and rate control in AF patients with fewer side effects. Dronedarone is considered as a potent blocker of multiple ion currents, including I_{CaL}, and also exhibits antiadrenergic effects. In myocytes from several experimental animals, it has been demonstrated that the effect of dronedarone on I_{CaL} consists in 76% block at dose of 10 μM with IC_{50}=0.18 μM (Varró et al., 2001; Gautier et al., 2003). Dronedarone has also important antiarrhythmic effects. Intravenous administration of dronedarone shortened ventricular APD, suppressed EADs, ectopic beats and also TdP (Verduyn et al., 1999). Moreover, intravenous dronedarone was able to prevent VF in a rat model of ischemia and reperfusion-induced arrhythmias (Manning et al., 1995). Similarly, several clinical trials have demonstrated that dronedarone is able to maintain sinus rhythm and control ventricular rate in AF, reducing the number of cardiovascular hospitalizations and mortality

in patients with high-risk of AF (Singh et al., 2007; Davy et al., 2008; Hohnloser et al., 2009). The current DIONYSOS clinical trial has demonstrated that in a short-term, dronedarone was less effective than amiodarone in decreasing AF recurrence and maintaining normal sinus rhythm, but had a better safety profile, specifically with regard to thyroid and neurologic events and a lack of interaction with oral anticoagulants (Le Heuzey et al., 2010). However, the ANDROMEDA clinical trial has showed that dronedarone is also contraindicated in severe or deteriorating HF (Køber et al., 2008). The reason of that is because of a negative inotropic effect of dronedarone resulting from inhibition of I_{CaL} that could have contributed to worsening of severe HF, increasing its mortality (Gautier et al., 2003; Zimetbaum, 2009). Therefore, dronedarone is still under clinical studies and has to demonstrate its real antiarrhythmic potency and effectiveness over other antiarrhythmic as well as its possible effects in the management of additional arrhythmias, e.g. VT.

7. References

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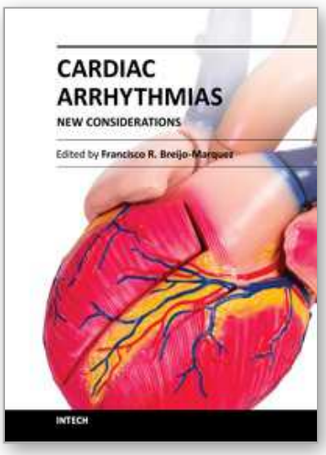

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The most intimate mechanisms of cardiac arrhythmias are still quite unknown to scientists. Genetic studies on ionic alterations, the electrocardiographic features of cardiac rhythm and an arsenal of diagnostic tests have done more in the last five years than in all the history of cardiology. Similarly, therapy to prevent or cure such diseases is growing rapidly day by day. In this book the reader will be able to see with brighter light some of these intimate mechanisms of production, as well as cutting-edge therapies to date. Genetic studies, electrophysiological and electrocardiographyc features, ion channel alterations, heart diseases still unknown , and even the relationship between the psychic sphere and the heart have been exposed in this book. It deserves to be read!

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