Atrial selectivity in Na\(^+\) channel blockade by acute amiodarone

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Aims

Na\(^+\) channel blockers are often used to treat atrial fibrillation (AF), but may sometimes cause ventricular contractile dysfunction. However, amiodarone, a multi-channel blocker with Na\(^+\) channel block, causes less contractile dysfunction. In this study, we tested the hypothesis that Na\(^+\) channel block by amiodarone is selective in atrial myocytes (AM) compared with ventricular myocytes (VM).

 Methods and results

Na\(^+\) currents (\(i_{\text{Na}}\)) were measured using whole-cell patch-clamp technique in isolated rabbit AM and VM. Amiodarone inhibited \(i_{\text{Na}}\) in AM (IC\(_{50}\) 1.8 ± 1.1 μM; \(n = 8\)) much more than in VM (40.4 ± 11.9 μM; \(n = 7\), \(P < 0.01\)). Amiodarone at 10 μM shifted the steady-state inactivation relationship in AM (−16.2 ± 1.7 mV shift; \(n = 12\)) compared with VM (−5.9 ± 0.7 mV shift; \(n = 13\), \(P < 0.01\)). For mexiletine, the inhibition of \(i_{\text{Na}}\) and inactivation curve shifts were comparable for AM and VM. The effects of amiodarone and mexiletine on conduction velocity (CV) in Langendorff-perfused rabbit hearts were evaluated using an optical mapping system. The decrease of CV by 3 μM amiodarone was significantly larger in the atrium (−18.9 ± 3.8% change; \(n = 5\)) compared with the ventricle (−3.7 ± 3.7%; \(n = 5\), \(P < 0.01\)). In contrast, mexiletine reduced CV equally in the atrium and the ventricle.

Conclusion

Amiodarone preferentially inhibits \(i_{\text{Na}}\) of AM compared with VM. Atrial selective Na\(^+\) channel block by amiodarone may contribute to treating AF with less effect on ventricular contractility than other Na\(^+\) channel blockers.

Keywords

Amiodarone • Atrial selectivity • Na\(^+\) channel • Patch-clamp • Optical mapping

1. Introduction

Na\(^+\) channel blockers are usually applied for a rhythm control-based treatment of atrial fibrillation (AF).\(^1\)–\(^4\) However, Na\(^+\) channel blockers also suppress ventricular contractility as a common deleterious side effect.\(^5\)–\(^6\) Consequently, atrial-selective Na\(^+\) channel blockers have been suggested.\(^7\)–\(^9\)

Amiodarone is useful in the treatment of AF\(^1\)\(^0\)–\(^1\)\(^2\) and has been reported to block Na\(^+\) channel as well as other channels.\(^1\)\(^3\) Compared with other Na\(^+\) channel blockers, amiodarone has less effect on haemodynamics.\(^1\)\(^4\)–\(^1\)\(^6\) Based on these pharmacological profiles, we hypothesized that amiodarone may have atrial selectivity in its Na\(^+\) channel blocking effect. The purpose of this present study was to compare the Na\(^+\) channel block by amiodarone in the atrium and ventricle of rabbits.

2. Methods

2.1 Electrophysiological recording

Animal use protocols were approved by the Institutional Animal Care and Use Committee at Nagoya University. Japanese white male rabbits weighing 2.4–3.0 kg were anaesthetized with an intravenous bolus injection of thiamylal sodium (30 mg/kg) and the hearts were removed. The adequacy of anaesthesia was monitored by the animal’s reaction to pain stimulation. Single cardiomyocytes were isolated enzymatically from the left-atrial appendage and the apical region of the right ventricle. The whole-cell mode of the patch-clamp technique was used for recording sodium currents (\(i_{\text{Na}}\)) and resting membrane potentials (RMP).\(^1\)\(^7\)–\(^1\)\(^8\) \(i_{\text{Na}}\) and RMP were recorded using Axopatch 200B, Digidata 1440A, and pClamp 9.2 software (Axon Instruments Inc., Foster City, CA, USA) for amplification and acquisition of signals and for data analysis. \(i_{\text{Na}}\) and RMP recordings

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were started after 30 min superfusion with normal Tyrode’s solution. Cell capacitances of atrial and ventricular cardiomyocytes were 85.5 ± 4.1 pF (n = 25) and 99.6 ± 4.2 pF (n = 27), respectively. Concentration–response relationships were fitted to the Hill equation (Eq. 1) to determine the concentration of drug required for 50% inhibition (IC50).

\[
y = \frac{V_{\text{max}} x^n}{(k^n + x^n)}
\]

(1)

The voltage dependence of \( I_{Na} \), activation and inactivation was determined by fitting appropriate currents measurements to the Boltzman function (Eq. 2).

\[
y = A_1 + \frac{(A_1 - A_2)}{[1 + \exp((x - x_0)/dx)]}
\]

(2)

2.2 Optical mapping

The experimental model and procedures of optical mapping used here were essentially the same as reported previously. In brief, isolated rabbit hearts were perfused on a Langendorff apparatus with modified Krebs–Ringer solution at 37°C. The tissue was treated with a voltagesensitive dye, di-4-ANEPPS (4 μM), and fluorescence images (256 × 256 pixels) were recorded at 1000 frames/s. Cytochalasin D (20 μM) was applied to minimize motion artefacts, unless otherwise specified. Conductance (CV) was measured during constant stimulation at the centre (EQ 3).

The Tyrode’s solution used for cell isolation and patch clamp experiments was maintained at 37°C and was composed of the following (mM): NaCl 143, KCl 5.4, CaCl2 1.8, MgCl2 0.5, NaH2PO4 0.25, HEPES 5.0, and glucose 5.6 (pH 7.4 adjusted with NaOH). For RMP measurements, the pipette resistance was 3–5 MΩ and the internal pipette solution was composed of the following (mM): KOH 60, KCl 80, aspartate 40, HEPES 5, EGTA 10, Mg ATP 5, sodium creatine phosphate 5, and CaCl2 0.65 (Pc, 8.0) at pH 7.2. To record \( n_{Na} \), the external solution was maintained at room temperature (22–25°C) and was composed of following (mM): NaCl 10, TEA-Cl 130, CaCl2 1, CoCl2 1, CsCl 3, MgCl2 0.5, HEPES 10. The glass pipette for the \( n_{Na} \) measurement had a resistance of 1–1.5 MΩ after filling with the internal pipette solution containing (mM): NaCl 5, CsF 145, EGTA 10, HEPES 10, MgATP 5. The Krebs–Ringer solution used for Langendorff perfusion in the optical map recording was composed of the following (mM): NaCl 118.6, KCl 5.4, CaCl2 1.8, MgSO4 1.3, NaH2PO4 1.2, NaHCO3 25.2, and glucose 5.8 (equilibrated with 95% O2–5% CO2, pH 7.4).

Amiodarone hydrochloride (Sigma–Aldrich) was dissolved in dimethyl sulfoxide (DMSO). The final concentration of DMSO in the external solution was <0.1%. This concentration of DMSO had no significant effect on inward currents or resting membrane potentials in rabbit atrial and ventricular myocytes. Mexiletine (Sigma–Aldrich) was dissolved in distilled water.

2.4 Statistical analysis

Data are expressed as mean ± SEM (n = number of cells or tissue preparations). Unless otherwise noted, statistical significance was assessed with Student’s t-test for simple comparisons and ANOVA followed by Bonferroni’s test for multiple comparisons. Differences at \( P < 0.05 \) were considered to be significant (* \( P < 0.05 \), ** \( P < 0.01 \)).

3. Results

3.1 Effects of amiodarone on \( I_{Na} \) in atrial and ventricular myocytes

The effects of 10 μM amiodarone on \( I_{Na} \) in atrial (AM) and ventricular myocytes (VM) were summarized in Figure 1. Depolarizing pulses for 100 ms from −90 to 0 mV in 5 mV intervals were applied from the holding potential at −90 mV at 1 Hz (Figure 1A). Averaged current–voltage (I–V) relationships for \( I_{Na} \) in AM (n = 10) and VM (n = 12) were demonstrated in Figure 1B. In control, the densities of peak \( I_{Na} \) were similar in AM and VM (−57.5 ± 6.4 pA/pF at −30 mV (n = 10) in AM vs. −51.0 ± 3.4 pA/pF at −30 mV (n = 12) in VM; P = 0.36). Amiodarone (10 μM) reduced \( I_{Na} \) density in AM from control by 74.8 ± 2.8% at −30 mV (n = 10). However, less reduction was observed in VM by 39.8 ± 0.04% at −30 mV (n = 12, P < 0.01 vs. AM). The IC50 calculated from the dose–response curves of inhibitory action at −30 mV (Figure 1C) was lower in AM than that in VM (IC50: 1.4 ± 0.3 μM (n = 8) in AM vs. 40.4 ± 11.9 μM (n = 7) in VM; P < 0.01).

The voltage dependence of Na⁺ channel activation in AM and VM were compared (Figure 2). Activation curves were calculated by current–voltage relation. The activation of Na⁺ channel (\( G_{Na} \)) was studied by measuring the peak Na⁺ conductance (\( G_{Na} \)). \( G_{Na} \) was calculated from \( G_{Na} = I_{Na}(V_{rev} - V_{Na}) \), where \( I_{Na} \) is the peak Na⁺ current during the test depolarization \( (V_t) \), and \( V_{Na} \) is the Na⁺ reversal potential. Data were normalized to maximum peak conductance (\( G_{max} \)). The voltages at half-maximum activation (\( V_{0.5 \text{act}} \)) were estimated from fitting the data to a Boltzmann function. Under control conditions, \( V_{0.5 \text{act}} \) was similar in AM and VM \( (V_{0.5 \text{act}}: −44.1 ± 0.7 \text{mV} \) (n = 17) in AM vs. −42.2 ± 0.8 mV (n = 18) in VM; P = 0.08) (Figure 2A and B). In AM, amiodarone (10 μM) did not affect activation curves significantly (\( V_{0.5 \text{act}}: −44.0 ± 0.9 \text{mV} \) in control vs. −43.3 ± 1.4 mV in amiodarone at 10 μM administered group; n = 10, P = 0.67) (Figure 2A). In contrast, amiodarone (10 μM) shifted activation curves of VM significantly (\( V_{0.5 \text{act}}: −41.4 ± 1.0 \text{mV} \) in control vs. −44.5 ± 1.1 mV in amiodarone group; n = 12, P < 0.05) (Figure 2B).

The voltage dependence of Na⁺ channel inactivation was measured using a different voltage protocol. A 1 s pre-pulse applied to variable voltages that ranged from −160 to −30 mV was followed by a test depolarization to −30 mV (Figure 2C). The voltage at half-maximum inactivation potential (\( V_{0.5 \text{inact}} \)) was estimated from Boltzmann fitting of the data. In control, the inactivation curves for AM were hyperpolarized by 9.8 mV compared with that in VM \( (V_{0.5 \text{inact}}: −89.4 ± 1.3 \text{mV} \) (n = 19) in AM and −79.6 ± 1.2 mV (n = 19) in VM; P < 0.01) (Figure 2D and E). These data indicate that a larger fraction of Na⁺ channels are inactivated in AM compared with VM. Amiodarone shifted the inactivation curve in AM markedly by −19.6 ± 2.1 mV (\( V_{0.5 \text{inact}}: −89.1 ± 1.6 \text{mV} \) in control vs. −108.7 ± 2.9 mV after amiodarone administration; n = 12, P < 0.01) (Figure 2D). In VM, the shift in the inactivation curve (−6.3 ± 0.8 mV) was significantly less (P < 0.01) than in AM (\( V_{0.5 \text{inact}}: −77.5 ± 1.1 \text{mV} \) in control vs. −83.7 ± 1.5 mV after amiodarone administration; n = 13) (Figure 2E).
3.2 Effects of mexiletine on $I_{\text{Na}}$ in atrial and ventricular myocytes

Mxelitine at 10 $\mu$M reduced $I_{\text{Na}}$ in both AM and VM (Figure 3A and 8). The inhibitions by mexiletine (10 $\mu$M) were comparable in AM and VM (IC50: 3.7 ± 0.5 $\mu$M (n = 7) in AM vs. 6.5 ± 1.9 $\mu$M (n = 8) in VM; $P = 0.20$) (Figure 3C).

In AM, mexiletine (10 $\mu$M) did not shift the voltage dependence of $I_{\text{Na}}$ activation ($V_{0.5 \text{act}}$: −44.2 ± 1.3 mV in control vs. −45.4 ± 1.2 mV in mexiletine group; n = 7, $P = 0.52$) (Figure 4A). In VM, similar to AM, activation curves were not affected by mexiletine ($V_{0.5 \text{act}}$: −43.9 ± 1.1 mV in control vs. −44.9 ± 0.7 mV in mexiletine group; n = 6, $P = 0.46$) (Figure 4B).

The voltage dependence of inactivation was shifted by mexiletine (10 $\mu$M) in AM ($V_{0.5 \text{inact}}$: −90.0 ± 2.3 mV in control vs. −100.1 ± 1.6 mV in mexiletine group; n = 7, P < 0.01) (Figure 4C). In VM, 10 $\mu$M mexiletine shifted the inactivation curve significantly ($V_{0.5 \text{inact}}$: −84.1 ± 1.7 mV in control vs. −92.9 ± 2.4 mV in mexiletine group; n = 6, P = 0.01) (Figure 4D). Mexiletine (10 $\mu$M) shifted inactivation curves to hyperpolarizing direction to the similar extent between AM (−10.9 ± 0.8 mV, n = 7) and VM (−8.9 ± 1.0 mV, n = 6, P = 0.31). In AM, the shift of inactivation curve by 10 $\mu$M mexiletine (−10.9 ± 0.8 mV, n = 7) was significantly less than that by amiodarone (10 $\mu$M) (−19.6 ± 2.1 mV, n = 12, P < 0.01). In VM, the shift of inactivation curve was comparable between amiodarone and mexiletine groups (P = 0.07). In summary, unlike amiodarone, mexiletine did not have differential effects on $I_{\text{Na}}$ in AM and VM.

3.3 Effect of amiodarone on action potentials and resting membrane potentials

Action potentials (APs) were elicited at 1 Hz by application of a 2 ms current injection at an intensity ~20% over threshold. Action potential durations measured at 90% repolarization (APD90) were averaged from five beats at frequencies of 1 Hz in AM (83.1 ± 6.2 ms; n = 5) and VM (161.5 ± 8.9 ms; n = 9) (Figure 5A and B). RMPs were significantly less negative in AM (−75.0 ± 1.0 mV, n = 5) compared with VM (−82.1 ± 1.1 mV, n = 9, P < 0.01) (Figure 5A and C). In both AM and VM, amiodarone (10 $\mu$M) had no effect on either APD90 or RMPs.

3.4 Effect of amiodarone and mexiletine on conduction velocities in atrium and ventricle

Conduction properties under constant stimulation were examined in 18 hearts (both atrium and ventricle) for amiodarone (n = 5) and mexiletine (n = 4). The effects of amiodarone on CV are presented in Figure 6. In left-atrial appendage, we measured CVs from isochronal
maps which were drawn in a 10 mm square from the stimulated point. Figure 6A shows a picture of left-atrial appendage and 10 mm square used for CV measurement. In the 10 mm square, conduction times represented by isochrones were propagated concentrically (Figure 6B). Intervals between each isochrones were shortened by addition of amiodarone (3 mM), indicating that amiodarone decreased CV in the left-atrial appendage (Figure 6C). We also measured maximum CV (max CV) in the square. In the atrium, amiodarone (3 mM) significantly reduced max CV (−18.9 ± 3.8%, n = 5) using a stimulation interval of 200 ms (Figure 6G and J).

In the left-ventricular free wall (Figure 6D), the isochrones of activation exhibited a smooth symmetric elliptical pattern (Figure 6E). The long axis corresponded to the fibre orientation of subepicardial cardiac muscle. CVL (CV of longitudinal direction) and CVT (CV of transverse direction) were the fastest and the slowest CV in the left-ventricular free wall, respectively. The intervals between isochrones were unchanged by amiodarone (3 mM) in both the longitudinal and transverse directions (Figure 6F). In the ventricle, the influence of amiodarone (3 mM) on CVL (−3.7 ± 3.7%, n = 5, PCL = 200 ms) was significantly less than that in atrium (P < 0.01) (Figure 6H and J).

The effects of mexiletine on CVs are demonstrated in Figure 7. In the left-atrial appendage (Figure 7A), mexiletine (5 mM) shortened the intervals between isochrones (Figure 7B and C). Similar to the atrium, the isochrone intervals were shortened by mexiletine (5 mM) in the left-ventricular anterior wall in both the longitudinal and transverse directions (Figure 7D–F). In contrast to amiodarone, mexiletine (5 mM) significantly reduced CVs in both the atrium and the ventricle (Figure 7G–I). These reductions of CVs by mexiletine (5 mM) were comparable between the atrium (−24.1 ± 1.0%, n = 4, PCL = 200 ms) and the ventricle (−27.8 ± 1.9%, n = 4, P = 0.09) (Figure 7J).

4. Discussion

The major observations in the present study are as follows. Amiodarone was a more potent inhibitor of hNa in AM than in VM, whereas mexiletine inhibited hNa without atrial selectivity. Additionally, in Langendorff-perfused rabbit hearts, the reduction in CV by amiodarone was more significant in the atrium than in the ventricle.

In this present study, four findings support atrial selectivity in Na+ channel block by amiodarone.
**Figure 3** Acute effect of mexiletine on $I_{\text{Na}}$ in atrial and ventricular myocytes. (A) Representative Na$^+$ current traces before and after application of mexiletine (10 μM) in AM and VM. (B) Current–voltage relationships for $I_{\text{Na}}$ before and after application of mexiletine (10 μM) in AM ($n = 7$) and VM ($n = 6$). (C) Concentration–response curves for block of $I_{\text{Na}}$ by mexiletine in AM (open triangle: $n = 7$) and VM (open circle: $n = 8$).

**Figure 4** Changing kinetics of Na$^+$ channel by mexiletine. (A) Effect of mexiletine (10 μM) on activation curve in AM ($n = 7$). (B) Effect of mexiletine (10 μM) on activation curve in VM ($n = 7$). (C) Steady-state inactivation curve in AM before and after application of mexiletine at 10 μM ($n = 7$). (D) Effect of mexiletine (10 μM) on inactivation curve in VM ($n = 7$).
The combination of a larger inactivated fraction of Na\(^+\) channels at the normal RMP and a stronger inhibition of inactivated Na\(^+\) channels in AM than in VM results in relative atrial selectivity by amiodarone and induces greater conduction delay in the atrium than in the ventricle. In contrast, mexiletine inhibited inactivated Na\(^+\) channels in AM as much as VM. Therefore, mexiletine did not exhibit a significant difference of potency for Na\(^+\) channel blockade between AM and VM. The efficacy of amiodarone in the prevention of atrial arrhythmia may be at least partly explained by this atrial selective Na\(^+\) channel blockade.

### 4.1 Other atrial selective drugs

Several reports of atrial-selective Na\(^+\) channel blockers have been published. Burashnikov and Antzelevitch\(^7\)–\(^9\) reported that ranolazine, an anti-anginal agent, has an atrial selective Na\(^+\) channel blocking effect and is efficacious on AF in experimental models. Other agents, such as AZD1305,\(^21\) AZD7009,\(^22\) and Wenxin Keli\(^23\) are also reported to exhibit atrial selective Na\(^+\) channel blockade. Similar to amiodarone in this study, AZD1305 and Wenxin Keli preferentially shifted the atrial Na\(^+\) channel inactivation curve. However, these previously described atrial selective agents are not used clinically and have not yet been demonstrated to have anti-arrhythmic activity in humans. Therefore, at present, amiodarone may be the only clinically available anti-arrhythmic drug with atrial selectivity.

### 4.2 Atrial selective effects of amiodarone

Chronic amiodarone also has been reported to reduce the maximum upstroke velocity of action potentials with atrial dominance\(^24\) and to strengthen the atrial selective Na\(^+\) channel blockage by ranolazine.\(^25\) Grande et al.\(^26\) reported a case in which chronic amiodarone treatment caused a rise in the atrial, but not ventricular threshold in a patient implanted with a dual-chamber pacemaker. However, difference comparison between the atrium and the ventricle of the direct effects of acute amiodarone on Na\(^+\) current and CV have not been tested yet. This paper is the first report that acute amiodarone has atrial selective Na\(^+\) channel block by direct recording of \(I_{Na}\) in isolated myocytes and by measurement of CV in isolated hearts.

### 4.3 Amiodarone and CV

This is also the first report to compare drug effects on conduction between the atrial and the ventricular muscle using an optical mapping system. The effect of amiodarone on CV has been reported previously in the ventricle. Nakagawa et al.\(^20\) demonstrated that amiodarone (5 \(\mu\)M) significantly decreased both CV\(_L\) and CV\(_T\) in rabbit ventricle. Their findings differ from our results. This discrepancy may be attributed to differences in experimental conditions. First, in the previous study, amiodarone was used at a concentration of 5 \(\mu\)M\(^20\) slightly higher than the 3 \(\mu\)M used in our study and the clinical dose of 1–2 \(\mu\)M. In the present study, amiodarone at 10 \(\mu\)M significantly decreased CV\(_L\) (\(P = 0.02\)) and CV\(_T\) (\(P = 0.02\)). Moreover, we measured CVs in 3-dimensional whole rabbit heart, whereas Nakagawa et al. used a 2-dimensional layer of rabbit heart to observe spiral waves during ventricular tachycardia.\(^20\)

### 4.4 Mechanisms of atrial selective Na\(^+\) channel blockade by amiodarone

A difference in the components of the Na\(^+\) channel complex between AM and VM may contribute to atrial selective Na\(^+\) channel blockade by amiodarone as Burashnikov et al.\(^7\)–\(^9\) has suggested in previous studies of ranolazine. The Na\(^+\) channel complex is composed of an \(\alpha\) subunit (SCN5a) and \(\beta\)1 subunit (SCN1b) in AM.\(^27\) In VM, a \(\beta\)3 subunit (SCN3b) is additionally required to construct Na\(^+\) channel in sheep hearts.\(^27\) The \(\beta\)3 subunit was reported to shift the inactivation curve in the depolarizing direction when channels were expressed in Xenopus oocytes.\(^27\) These data coincide with our findings that the inactivation curve in AM was more hyperpolarized compared with that in VM. However, the functional role of the \(\beta\)3 subunit has not been clarified. When Na\(^+\) channels are expressed in cultured HEK or CHO cells, \(\beta\)3 subunits are reported to shift the inactivation curve to more negative potentials.\(^28\) Na\(^+\) channel \(\beta\)-subunits may influence drug affinity. Abi-Gerges et al.\(^29\) reported that drug effects on delayed rectified K\(^+\) channel were influenced by channel...
conformation of α-subunits. Various types of Na+ channel subunits other than cited above (SCN5a, SCN1b, and SCN3b)27 have been reported in a number of mammals30,31 including human.32,33 In addition, species differences in the Na+ channel subunit distribution in cardiac tissue remains ill-defined. Such differences could also affect the regulation of cardiac Na+ currents and influences from drugs.

Further studies are required to confirm the influence of Na+ channel conformation on drug sensitivity.

5. Limitations

Amiodarone is usually used by oral administration and many studies regarding long-term amiodarone treatment have been reported.1,11,12,34 In this present study, we showed the atrial selectivity of Na+ channel blockade by acute amiodarone with a high affinity for inactivated Na+ channels, but did not compare the atrial selectivity of amiodarone between short- and long-term treatments. Chronic amiodarone also has been reported to have a high affinity for inactivated Na+ channel in guinea pig papillary muscle.35 However, to our knowledge, there are no reported studies that have compared the effects of chronic amiodarone on inactivated Na+ channels between AM and VM.

Some reports have indicated that intravenous amiodarone produces no remarkable pharmacological effects in clinical settings.36–38 Although the present study showed that acute amiodarone has atrial selectivity of Na+ channel blockade in rabbit hearts and that acute amiodarone may have potential effectiveness in treating atrial arrhythmias including AF, we do not intend to directly extrapolate our results obtained in rabbit experiments to human. Further investigations are needed to evaluate the usefulness of intravenous amiodarone for human atrial arrhythmias.

As described previously, amiodarone is a multi-channel blocker and its effects on multiple channels may affect the ability to inhibit arrhythmias. Although we only elucidated the effects of amiodarone on Na+ channels...
channels, the effects of amiodarone on other channels may also confer atrial selectivity.

Our data do not support the clinical efficacy of amiodarone on ventricular arrhythmias. Ventricular arrhythmias often arise from damaged cardiomyocytes, for example, in the ischaemic or failing heart. Na⁺ channels in the damaged cardiomyocytes tend to be more inactivated because of a less negative RMP.

6. Conclusion

Amiodarone preferentially inhibits $I_{Na}$ of AM compared with that of VM. This atrial selective Na⁺ channel block by amiodarone might contribute to the treatment of atrial fibrillation with less effect on ventricular contractility compared with other Na⁺ channel blockers.

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