Electrophysiological Characteristics of Canine Superior Vena Cava Sleeve Preparations

Effect of Ranolazine

Serge Sicouri, MD; Jonathan Blazek, BS; Luiz Belardinelli, MD; Charles Antzelevitch, PhD, FAHA

Background—In addition to extrasystoles of pulmonary vein (PV) origin, those arising from the superior vena cava (SVC) can precipitate atrial fibrillation (AF). The present study evaluates the electrophysiological properties of canine SVC sleeve preparations and the effect of ranolazine on late phase 3 early and delayed afterdepolarization (EAD and DAD)-induced triggered activity in SVC sleeves and compares SVC and PV sleeve electrophysiological properties.

Methods and Results—Action potentials (APs) were recorded from superfused SVC and PV sleeves using microelectrode techniques. Acetylcholine (1 μmol/L), isoproterenol (1 μmol/L), high calcium ([Ca2+]o=5.4 mmol/L), or a combination were used to induce EADs, DADs, and triggered activity. A marked diversity of action potential characteristics was observed in the SVC sleeve, including action potentials with short and long APs, with and without phase 4 depolarization. Rapid pacing induced hyperpolarization, accentuating the slope of phase 4 depolarization. Phase 4 depolarization and rapid pacing-induced hyperpolarization were reduced or eliminated after atropine (10 μmol/L) or ranolazine (10 μmol/L). APs displaying phase 4 depolarization (n=19) had longer APDs, smaller amplitude and Vmax, and a more positive take-off potential than APs lacking phase 4 depolarization (n=15). Ranolazine (5–10 μmol/L) eliminated late phase 3 EAD- and DAD-induced triggered activity as well as isoproterenol-induced automaticity elicited in SVC sleeves. Compared with PV, SVC sleeves display phase 4 depolarization, smaller Vmax, and longer APs.

Conclusions—Autonomic influences promote spontaneous automaticity and triggered activity in SVC sleeves, thus generating extrasystolic activity capable of initiating atrial arrhythmias. Ranolazine can effectively suppress these triggers. (Circ Arrhythm Electrophysiol. 2012;5:371-379.)

Key Words: atrial fibrillation | antiarrhythmic drugs | sodium channel blocker | electrophysiology | pharmacology

Pulmonary veins (PV) have been shown to be a major site of ectopic foci capable of initiating atrial fibrillation (AF). In addition to PV, extrasystoles arising from a number of non-PV sites have been shown to be capable of initiating AF as well as other atrial arrhythmias, among them, the superior vena cava (SVC), left atrial posterior free wall, crista terminalis, coronary sinus ostium, ligament of Marshall, and the interatrial septum. Of these sites, the SVC is thought to be the most common source of ectopy, harboring 26% to 30% of non-PV foci. As in PV sleeves, atrial myocardial tissue has been demonstrated to extend into the SVC sleeves for approximately 2 to 5 cm. Extrasytolic activity arising from non-PV atrial structures, such as SVC, may compromise the success of PV isolation for the treatment of AF. In addition to PV isolation, SVC isolation improves the outcome of AF ablation in patients with paroxysmal AF.

Clinical Perspective on p 379

Previous studies have shown that ranolazine exerts antiarrhythmic effects in canine PV sleeves by suppressing late phase 3 early and delayed afterdepolarization (EAD and DAD)-induced triggered activity generated by parasympathetic and/or sympathetic stimulation. The effect of ranolazine on arrhythmias induced in SVC is unknown.

The present study was designed to evaluate the electrophysiological properties of canine SVC sleeve preparations and establish the effectiveness of ranolazine to suppress arrhythmias induced in SVC sleeve preparations. Electrophysiological properties of SVC sleeve preparations were compared with those of PV sleeve preparations.

Methods

The experiments of this investigation conform to the Guide for Care and Use of Laboratory Animals published by the National Institutes of Health (NIH publications No 85–23, Revised 1996) and was approved by the Animal Care and Use Committee of the Masonic Medical Research Laboratory.

Adult mongrel dogs weighing 20 to 35 kg were anticoagulated with heparin (180 IU/kg) and anesthetized with sodium pentobarbital (35 mg/kg, IV). The chest was opened via a left thoracotomy, and the heart was excised and placed in a cold cardioplegic solution ([K+]o=8 mmol/L, 4°C).
Superfused SVC and PV Sleeve Preparations

SVC and PV sleeve preparations (approximately 2.0×1.5 cm) were isolated from the right and left canine atria, respectively. The thickness of the preparations was approximately 2 mm. The preparations were placed in a small tissue bath and superfused with Tyrode solution of the following composition (mmol/L): 129 NaCl, 4 KCl, 0.9 NaH2PO4, 20 NaHCO3, 1.8 CaCl2, 0.5 MgSO4, 5.5 glucose, buffered with 95% O2/5% CO2 (35–37°C). SVC and PV sleeve preparations were stimulated at a basic cycle length (BCL) of 1000 ms during the equilibration period (1 hour), using electric stimulation (1–3 ms duration, 2.5×diastolic threshold intensity) delivered through silver bipolar electrodes insulated except at the tips. Transmembrane potentials were recorded using glass microelectrodes filled with 3 mol/L KCl (10–20 MΩ DC resistance) connected to a high input-impedance amplification system (World Precision Instruments, model KS-700, New Haven, CT). The following parameters were measured: action potential duration at 85% and 50% repolarization (APD85, APD50), action potential amplitude (APA), maximum rate of rise of action potential upstroke (Vmax), resting membrane potential, and take-off potential. Transmembrane APs were recorded at a sampling rate of 41 kHz.

Induction of Arrhythmias

In 22 SVC sleeve preparations, we evaluated the effect of exposure of SVC to ACh (1 μmol/L), isoproterenol (0.5–1 μmol/L), and high...
calcium (5.4 mmol/L) or their combination, conditions known to promote arrhythmias. This arrhythmia model has been previously shown to generate late phase 3 EAD- and/or DAD-induced triggered activity in 100% PV sleeve preparations.12–14,16

Drugs
Ranolazine (Gilead, Foster City, CA) was dissolved in distilled water to form a stock solution of 10 mmol/L and used at a final concentration of 5 to 10 μmol/L. Isoproterenol (Sigma-Aldrich, St Louis, MO) was dissolved in distilled water to form a stock solution of 1 mmol/L and used at a final concentration of 1 μmol/L.

Acetylcholine (ACh) was dissolved in distilled water to form a stock solution of 10 mmol/L and used at a concentration of 1 μmol/L.

Atropine (Sigma-Aldrich) was dissolved in distilled water to form a stock solution of 10 mmol/L and used at a final concentration of 1 μmol/L. Ouabain (Sigma-Aldrich) was dissolved in distilled water to form a stock solution of 1 mmol/L and used at a final concentration of 1 μmol/L.

Statistics
Statistical analysis was performed using 1-way, repeated-measures ANOVA followed by Bonferroni test. Mean values were considered to be different at P<0.05. All data are reported as mean±SD.

Results
We tested the viability and stability of superfused SVC and PV sleeve preparations by exposing them to normal Tyrode solution and continuously recording the electric activity for a period of 120 minutes. No significant changes in AP morphology were observed over a 120-minute period.

Figure 1A illustrates a representative example of diversity of AP morphologies recorded form a SVC sleeve preparation. At a BCL of 1000 ms, AP1 shows a narrow AP and no phase 4 depolarization, whereas AP2 and AP3 display a wider AP, decreased amplitude, and phase 4 depolarization, which is more accentuated in AP3. Similar heterogeneity of AP characteristics was observed in all SVC sleeve preparations (n=9). Figure 1B illustrates an SVC sleeve preparation, showing how the muscular extension originating from the right atrium covers the endocardial (Endo) surface of the SVC. AP recordings were always obtained from the Endo surface of the SVC preparation. Figure 2 shows the effect of rapid pacing in 2 SVC sleeve preparations displaying phase 4 depolarization. Rapid pacing led to a marked hyperpolarization of maximum diastolic potential and accentuation of phase 4 diastolic depolarization. Similar behavior was observed in 9 experiments. APs hyperpolarized 1.4±0.6 mV at a BCL of 2000 ms; 2.8±1.1 mV at BCL 1000 ms; 3.7±1.7 mV at BCL 500 ms; 4.4±1.9 mV at BCL 300ms; 4.7±1.7 mV at BCL 200 ms; and 5.6±2.7 mV at BCL of 100 ms.

Composite data of the electrophysiological characteristics of SVC sleeve preparations with and without phase 4 depolarization are shown in Figure 3. APs with phase 4 depolarization (n=19) displayed significantly longer APD85 and APD50, smaller APA and Vmax, and exhibited a more positive take-off potential at slow rates, compared with APs lacking phase 4 depolarization (n=15) (P=0.04, P=0.03, P=0.001,
V_{\text{max}} showed a progressive decrease with acceleration in APs with no phase 4 but a biphasic relationship in AP with phase 4 (Figure 3D). This was a constant feature in all SVC sleeve preparations studied.

Development of Late Phase 3 EADs and DADs in SVC Sleeves

Effect of Ranolazine

Previous studies have shown that phase 3 EAD- and DAD-induced triggered activity are observed in PV sleeves after exposure to ACh, isoproterenol, high calcium, or their combination and that ranolazine, in concentrations within the therapeutic range (2–10 \( \mu \text{mol/L} \)), is capable of suppressing triggered activity and reducing or suppressing EADs and DADs.\(^9,10,12,15\) We performed a series of experiments to establish whether similar behavior is observed in SVC sleeve preparations. Figure 4A illustrates the development of ACh and high calcium–induced late phase 3 EADs in an SVC sleeve preparation. Late phase 3 EADs are observed at slow rates in beats immediately after rapid pacing (BCL = 200 ms). Ranolazine (10 \( \mu \text{mol/L} \)) completely eliminated the late phase 3 EAD activity (Figure 4B). Figure 4C illustrates the development of DAD-induced triggered responses in an SVC preparation after exposure to isoproterenol and high calcium. Ranolazine (5 \( \mu \text{mol/L} \)) eliminated the triggered beats, but DADs persisted (Figure 4D).

Late phase 3 EADs and/or DADs and triggered activity and/or increased automaticity could be induced in all SVC preparations exposed to ACh, isoproterenol, or high calcium, alone or in combination (n = 22). Isoproterenol, alone or combined with high calcium, often caused an increase in automaticity. Figure 5 illustrates an example of isoproterenol-induced increase in automaticity. Spontaneous activity due to an increase in phase 4 depolarization was observed after pacing at BCL of 500 ms. Ranolazine (10 \( \mu \text{mol/L} \), 30 minutes of exposure) suppressed the spontaneous activity as well as phase 4 depolarization. In SVC sleeves, ranolazine (5–10 \( \mu \text{mol/L} \)) eliminated late phase 3 EADs, DAD-induced triggered activity, and decreased automaticity in 10 of 11 preparations.

Effects of Ouabain, Atropine, and Ranolazine on SVC With Phase 4 Depolarization

To determine the mechanism of phase 4 depolarization and pacing-induced hyperpolarization and increase in phase 4 depolarization, we evaluated the effects of ouabain, a Na\(^+/\)K\(^+\)-pump inhibitor, atropine, a muscarinic ACh receptor blocker, and ranolazine, a late sodium channel blocker, on SVC sleeve preparations exhibiting phase 4 depolarization. Ouabain (1 \( \mu \text{mol/L} \)) exerted no effect on phase 4 or pacing-induced hyperpolarization in any of the SVC preparations studied (n = 4). Atropine markedly reduced or eliminated phase 4 depolarization as well as rapid pacing-induced hyperpolarization (Figure 6A and 6B). Similar results were
observed in 4 of 4 SVC preparations. Subthreshold pulses (50–100 Hz) delivered to SVC preparations induced a 6-mV hyperpolarization and development of phase 4 depolarization (Figure 6C), suggesting stimulation of parasympathetic nerves innervating the SVC sleeve as the basis for the hyperpolarization and enhanced phase 4 depolarization accompanying rapid pacing. Similar effects of subthreshold stimulation were observed in 3 SVC sleeve preparations.

The effects of ranolazine on phase 4 depolarization were evaluated in 4 experiments. Figure 7 (A and B) shows an example of the effect of ranolazine on an SVC preparation exhibiting phase 4 depolarization. Ranolazine (10 μmol/L) eliminated spontaneous phase 4 depolarization as well as rapid pacing-induced hyperpolarization and enhanced phase 4 depolarization. Ranolazine (5–10 μmol/L) reduced or eliminated phase 4 depolarization and rapid pacing-induced hyperpolarization in 4 of 4 experiments. Isolated spontaneous ectopic beats were often observed in SVC preparations; however, spontaneous beating was only observed in 1 of 24 SVC sleeve preparations. In this preparation (Figure 7C), ranolazine (10 μmol/L) reduced phase 4 depolarization from a CL of 550 to of 700 ms after 10 minutes of exposure and subsequently totally suppressed automaticity.

Comparison of SVC and PV Sleeve Preparations
In SVC sleeve preparations, muscular atrial extensions (sleeves) are observed on the endocardial side (luminal) of the SVC, whereas in PV sleeve preparations atrial extensions penetrate on the epicardial side (abluminal) of the PV. Compared with PV, SVC sleeve preparations exhibit phase 4 depolarization, display smaller $V_{\text{max}}$ ($P<0.001$) and APA ($P<0.001$), and a longer APD$_{50}$ ($P<0.001$) and APD$_{85}$ ($P=0.07$) and exhibited a more negative take-off potential ($P=0.01$) (Figure 8). Isoproterenol-induced DADs and triggered activity were observed in both PV and SVC sleeves. However, isoproterenol-induced automaticity was observed more frequently in SVC preparations than in PV sleeve preparations.

Discussion

The superior vena cava is the main non-PV site of origin of extrasystoles capable of triggering AF.6–8 Paroxysmal atrial tachycardia is known to originate from the SVC.17,18 Similar to extensions of left atrial muscle into PV, right atrial muscle extends into the SVC.5,6 Chen et al.18 previously described in canine SVC cardiomyocytes the presence of spontaneously beating APs displaying phase 4 depolarization. The results of our study demonstrate a marked diversity of AP characteristics in the canine SVC sleeve, including APs with short and long durations, with and without phase 4 depolarization. As in PV sleeves, APs of cells in SVC sleeves develop late phase 3 EADs and DAD-induced triggered activity after exposure to ACh, isoproterenol, high calcium, or their combination. In addition, SVC sleeves exhibit increased automaticity secondary to an increase in phase 4 depolarization after isoproterenol or isoproterenol combined with high calcium.
Phase 4 Depolarization in SVC

The presence of phase 4 depolarization was consistently observed in the SVC preparations. It should be noted that spontaneous beating was only rarely observed in SVC preparations (1 of 24), and phase 4 depolarization was of relatively modest magnitude and only increased after stimulation of vagal efferents. These characteristics and behavior of phase 4 depolarization differ markedly from phase 4 depolarization typically observed in sinus node, AV node, or Purkinje fiber pacemakers cells. Phase 4 depolarization was observed at slow rates in SVC sleeves and was markedly enhanced after rapid pacing-induced hyperpolarization. Atropine and ranolazine but not ouabain were able to markedly decrease and/or eliminate phase 4 depolarization as well as hyperpolarization induced by fast pacing. The effect of atropine to suppress rapid pacing-induced hyperpolarization and the ability of subthreshold stimulation to induce this phenomena are consistent with concomitant stimulation of parasympathetic nerves coursing through the SVC. Stimulation of human parasympathetic efferent nerves that lie along the surface of the SVC induces negative chronotropic and dromotropic effects.19 Lu et al20 showed that superior vena cava–aorta ganglionated plexi can act as “the head stage” for the autonomic mechanism underlying rapid SVC firing that initiates AF. We did not systematically study the effect of the site of stimulation and are therefore unable to determine whether the presence of neuronal clusters could have influenced the effect of subthreshold stimulation. The development of phase 4 depolarization in SVC may also be linked to the Lakatta calcium clock hypothesis described for sinus node cells, suggesting that spontaneous calcium releases may contribute to accentuation of phase 4 depolarization.21,22 Interestingly Chen et al18 showed that densities of I_{Ca-L} and I_K are similar, but I_{Na} densities differ between cardiomyocytes with and without phase 4 depolarization.

One of the mechanisms responsible for the initiation of AF is the increase in automaticity due to spontaneous firing and diastolic depolarizations.23,24 It has been demonstrated that some AF episodes are initiated by rapid firing of non-PV triggers, such as the SVC, in particular in patients with obesity and sleep apnea.25

The effect of ranolazine to suppress phase 4 as well as fast pacing-induced hyperpolarization suggest a role of the late sodium current in the genesis of phase 4 depolarization. In fact, using the enhancer of late I_{Na}, anemone toxin II (ATX-II), Song et al26 demonstrated that an increase of late I_{Na} contributes to the development of diastolic depolarization and spontaneous activity in guinea pig atrial myocytes and that ranolazine can suppress spontaneous diastolic depolarization and action potential firing in these myocytes. Similarly, in our experiments, ranolazine markedly reduced or eliminated phase 4 depolarization occurring either spontaneously or after fast pacing or isoproterenol. Moreover, preliminary experiments in SVC sleeves indicate that phase 4 depolarization increases after exposure to ATX-II (4 nmol/L) (Sicouri et al, unpublished observation). The presence of Ca^{2+}+-activated K\(^+\) channels (SK channels)27 leading to the development of phase 4 depolarization in SVC is yet another hypothesis that remains to be evaluated.

Arrhythmias Induced in SVC Sleeves

The development of late phase 3 EAD- and DAD-induced triggered activity in SVC sleeves after ACh, isoproterenol, high calcium, or their combination are similar to observations in canine PV models reported by Patterson et al,28,29 Sicouri et al,12–14,16 and Burashnikov et al10 in coronary-perfused atrial preparations. Similar characteristics of late phase 3 EADs were observed in PV sleeve preparations.12,14,16 Late phase 3 EADs and late phase 3 EAD-induced triggered activity, originally described by Burashnikov and Antzelevitch30 in coronary-perfused atrial preparations, represent a relatively new concept of arrhythmogenesis. Abbreviated
repolarization permits normal sarcoplasmic reticulum calcium release and associated sodium-calcium exchange inward current to induce a late phase 3 EAD, resulting in closely coupled triggered responses when it reaches threshold.9 Conditions permitting intracellular calcium loading (isoproterenol, high calcium, fast pacing rates) facilitate the development of late phase 3 EADs. Autonomic stimulation can also give rise to this phenomenon in canine PV sleeves and in some cases result in a run of triggered responses.12,14,16,28,29

Inhibition of peak and late INa have been shown to have important consequences on intracellular calcium homeostasis. Inhibition of peak and late INa can reduce calcium overload. Suppression of DADs by ranolazine, similarly to TTX and other Na channel blockers, is probably due to a decrease in INa as a consequence of the decrease in intracellular diastolic calcium concentration (via NCX). Song et al31 showed that ranolazine (10 μmol/L) and TTX (2 μmol/L) abolish DADs by inhibiting INa caused by Na-dependent calcium overload due to exposure to ATX-II. Inhibition of late INa has also been shown to lead to a decrease in spontaneous diastolic depolarizations due to inhibition of a slowly inactivating TTX-sensitive sodium current in atrial myocytes26 and in newborn rabbit sinoatrial node cells.32 The reduction of phase 4 depolarization by ranolazine in SVC cells could in part be mediated by this mechanism as well as by a reduction in the activity of the calcium clock.33

In addition to the development of EADs and DADs, isoproterenol frequently induced an increase in automaticity. This was a mechanism of arrhythmia induced by isoproterenol or isoproterenol plus high calcium in the SVC sleeves. The increase in automaticity led to an increase in the slope of phase 4 depolarization leading to spontaneous beating in SVC preparations (Figure 6). Therefore, the presence of phase 4 depolarization in APs of SVC sleeve preparations suggests a role for enhanced automaticity in the genesis of atrial arrhythmias of SVC origin.

Antiarrhythmic Effects of Ranolazine in SVC Sleeves

Previous studies in canine PV sleeves have shown that ranolazine (5–10 μmol/L) is capable of suppressing late phase 3 EAD- and DAD-induced triggered activity generated by parasympathetic and/or sympathetic stimulation.9–13,15 Inhibition of peak INa may contribute to the effect of ranolazine to suppress DAD activity in SVC. The effect of peak INa blockers to eliminate DAD activity is well established.34 In addition to blocking peak INa, all sodium channel blockers also block late INa usually at lower concentrations. Song et al31 showed that TTX suppresses DADs caused by enhanced late INa. Lidocaine is expected to do the same. Flecainide, another Na channel blocker, also suppresses DADs by inhibiting late INa.35 Rosen and Danilo34 have previously shown that other peak sodium channel blockers (tetrodotoxin, lidocaine, etc) inhibit ouabain-induced DADs. A likely explanation for these findings is that TTX and other Na channel blockers suppress DADs by reducing Na-dependent diastolic
calcium overload, leading to inhibition of $I_{Kr}$ as previously discussed. The effect of ranolazine to suppress pacing-induced hyperpolarization and associated enhancement of phase 4 is best explained by an effect of the drug to inhibit parasympathetic nerve activity. In addition to blocking NaV1.5 cardiac sodium channels, ranolazine has been reported to block NaV1.7 and NaV1.8 neuronal sodium channels. Our knowledge regarding the effect of ranolazine on nerve excitation is limited but is known to depend on the Na channel isoforms expressed in the neuronal cells. Ranolazine has been shown to inhibit NaV1.7 and 1.8 neuronal Na channel currents as well as on NaV1.1 neuronal sodium channel current. To what extent these Na channel isoforms contribute to the firing of vagal nerves remains to be established. The effects of ranolazine on vagal nerve excitability is also not well established. Because ranolazine has been shown to have no effect on heart rate, a major effect of ranolazine on vagal tone seems unlikely.

Our data demonstrate that in SVC sleeve preparations, ranolazine can diminish arrhythmias by (1) effectively eliminating EAD- and DAD-induced triggered activity induced by isoproterenol, ACh, high calcium, or their combination; (2) suppressing phase 4 depolarization (spontaneous or induced by fast pacing); and (3) possibly by inhibiting intracardiac parasympathetic nerve activity. These actions of ranolazine are in addition to those previously described involving suppression of AF by potent atrial-selective depression of peak $I_{Kr}$-dependent parameters. Thus, ranolazine, previously shown to be useful in suppressing AF triggers arising from PV sleeves, may also be useful in suppressing AF triggers originating in SVC sleeves.

**PV Versus SVC Sleeves**

Our data show that compared with canine PV sleeve preparations, SVC sleeve preparations exhibit phase 4 depolarization (always absent in PV sleeve) and display a smaller $V_{max}$ and AP amplitude but longer APDs. It remains to be established if similar differences are present in other species, including the human heart.

Late phase 3 EAD- and DAD-induced triggered activity after exposure to isoproterenol, high calcium, or their combination were observed in both PV and SVC sleeve preparations; however, isoproterenol-induced automaticity was observed much more frequently in SVC preparations.

**Conclusions**

Late phase 3 EAD- and DAD-mediated extrasystoles as well as automatic beats arising from SVC sleeves may serve as triggers of some atrial arrhythmias, including atrial tachycardia and AF. Ranolazine can effectively suppress these triggers.

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Atrial fibrillation (AF) is facilitated by the development of both an electrical substrate and triggers. The triggers are often in the form of extrasystolic activity. Although the majority of extrasystoles are of pulmonary vein (PV) origin, some are known to arise from the superior vena cava (SVC). This study evaluates the electrophysiological mechanisms by which these extrasystolic triggers arise in canine SVC sleeve preparations and the effect of ranolazine to suppress them. Rapid pacing was found to induce hyperpolarization, accentuating the slope of phase 4 depolarization, which was reduced or eliminated by either atropine or ranolazine. Ranolazine, at therapeutic concentrations, also eliminated late phase 3 early afterdepolarization-induced triggered activity. Circulation. 2003;107:2355–2360.

CLINICAL PERSPECTIVE

Ranolazine eliminates AF triggers by suppressing EAD- and DAD-induced triggered activity and by suppressing phase 4 depolarization, presumably by reducing calcium loading of cardiac cells and possibly via inhibition of intracellular parasympathetic nerve activity. Our results suggest that ranolazine may exert an anti-AF effect at least in part by suppressing triggers originating from SVC sleeves.
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