

Different electrophysiological effects of the levo- and dextro-rotatory isomers of mexiletine in isolated rabbit cardiac muscle

Zsolt Gurabi, Bence Patocskai, Balázs Györe, László Virág, Péter Mátyus, Julius Gy. Papp, András Varró, and István Koncz

Abstract: Racemic mexiletine is a widely used antiarrhythmic agent that blocks sodium channels. The effects of R(-) and S(+) mexiletine stereoisomers on maximum rate of depolarization (\dot{V}_{\max}), conduction time, and repolarization have not yet been investigated in isolated cardiac preparations. We studied the effect of the R(-) and S(+) mexiletine on rabbit cardiac action potential parameters by using the conventional microelectrode technique. Both enantiomers at 20 $\mu\text{mol/L}$ of the therapeutically and experimentally relevant concentration, significantly depressed the \dot{V}_{\max} at fast heart rates (BCLs 300–700 ms). R(-) mexiletine has more potent inhibitory effect than S(+) mexiletine. Both R(-) and S(+) mexiletine significantly inhibited the \dot{V}_{\max} of early extrasystoles measured at 70 ms diastolic interval induced by S1–S2 stimuli. R(-) mexiletine has more pronounced inhibitory effect than S(+) mexiletine. Both R(-) and S(+) mexiletine increased significantly the ERP/APD₉₀ ratio. The time constant (τ) of recovery of \dot{V}_{\max} was found to be $\tau = 376.0 \pm 77.8$ ms for R(-) mexiletine and $\tau = 227.1 \pm 23.4$ ms for S(+) mexiletine, which indicates a slower offset kinetics for R(-) mexiletine from sodium channels than that of the S(+) enantiomer. These data suggest that R(-) mexiletine might be a more potent antiarrhythmic agent than S(+) mexiletine.

Key words: R(-) mexiletine, S(+) mexiletine, papillary muscles, \dot{V}_{\max} , conduction time, early extrasystoles.

Résumé : La mexilétine racémique est un antiarythmique bloqueur des canaux sodiques largement utilisé. Les effets de la D(-) et de la L(+) mexilétine, des stéréoisomères, sur la vitesse maximale de dépolarisation (\dot{V}_{\max}), le temps de conduction et la repolarisation n'ont pas encore été étudiés dans des préparations de cœur isolé. Nous avons étudié l'effet de la D(-) et de la L(+) mexilétine sur les paramètres du potentiel d'action cardiaque de lapin par la technique de microélectrode conventionnelle. À des concentrations pertinentes sur le plan thérapeutique et expérimental de 20 $\mu\text{mol/L}$, nous avons observé avec les deux énantiomères une diminution importante de la \dot{V}_{\max} à des fréquences cardiaques élevées (longueur des cycles de base de 300 à 700 ms). La D(-) mexilétine avait un effet inhibiteur plus puissant que la L(+) mexilétine. La D(-) et la L(+) mexilétine entraînaient toutes deux une inhibition marquée de la \dot{V}_{\max} pour les extrasystoles précoces mesurées après un intervalle diastolique de 70 ms induit par des stimuli S1–S2. La D(-) mexilétine avait un effet inhibiteur plus prononcé que la L(+) mexilétine. La D(-) et la L(+) mexilétine entraînaient toutes deux une augmentation notable du rapport PRE/DPA₉₀ (période réfractaire effective sur durée du potentiel d'action à 90 % de la repolarisation). Nous avons observé que la constante de temps (τ) de la récupération de la \dot{V}_{\max} était de 376,0 \pm 77,8 ms avec la D(-) mexilétine et de 227,1 \pm 23,4 ms avec la L(+) mexilétine, ce qui montre que la cinétique de la diminution de l'effet de la D(-) mexilétine sur les canaux sodiques est plus lente que celle de l'énantiomère L(+). Ces données laissent entendre que la D(-) mexilétine pourrait être un antiarythmique plus puissant que la L(+) mexilétine. [Traduit par la Rédaction]

Mots-clés : D(-) mexilétine, L(+) mexilétine, muscles papillaires, \dot{V}_{\max} , temps de conduction, extrasystoles précoces.

Introduction

The compound Kö 1173, later denominated mexiletine, exerted anticonvulsant activity in animal experiments. Since 1972, mexiletine has been recognized as an antiarrhythmic agent with characteristics similar to those of lidocaine (Vaughan Williams 1998). The racemic mexiletine had been classified as a Class IB antiarrhythmic compound (Vaughan Williams 1998), which blocks so-

dium channels in a use-dependent manner with relatively fast onset and offset kinetics of \dot{V}_{\max} block (Campbell 1983; Varró et al. 1985). The most important advantage of mexiletine over lidocaine is its good oral availability and longer half-life. Mexiletine reduces use-dependently the magnitude of fast sodium current (Hering et al. 1983), markedly slows premature conduction (Hohnloser et al. 1982), suppresses abnormal automaticity in Purkinje fibers (Sarkozy and Dorian 2007), and shortens the durations

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Table 1. The electrophysiological effects of R(-) and S(+) mexiletine enantiomers in rabbit ventricular papillary muscle at basic cycle length of 1000 ms.

Parameters	MDP (mV)	APA (mV)	APD ₉₀ (ms)	APD ₅₀ (ms)	\dot{V}_{\max} (V/s)	ERP/APD ₉₀
Control	-85.1±1.2 (8)	108.7±1.3 (8)	192.2±8.4 (8)	156.0±8.0 (8)	200.2±13.1 (8)	0.953±0.021 (6)
R(-) Mexiletine 20 μ mol/L	-85.2±1.7 (8)	104.2±2.5 (8)	193.3±6.9 (8)	155.7±7.3 (8)	162.7±7.9* (8)	1.031±0.028* (6)
Control	-83.4±1.7 (8)	105.9±1.7 (8)	184.2±11.9 (8)	148.9±13.9 (8)	205.1±12.3 (8)	0.942±0.021 (6)
S(+) Mexiletine 20 μ mol/L	-83.9±1.1 (8)	106.9±1.8 (8)	198.7±13.1 (8)	161.3±12.4 (8)	167.2±10.5* (8)	0.997±0.015* (6)

Note: Values are means \pm SEM with number of observations (i.e., number of preparations obtained from different animals) in parentheses. MDP, maximum diastolic potential; APA, action potential amplitude; APD₉₀, action potential duration at 90% of repolarization; APD₅₀, action potential duration at 50% of repolarization; \dot{V}_{\max} , maximum rising velocity of the action potential upstroke; ERP, effective refractory period. * $p < 0.05$.

of action potentials (Arita et al. 1979; Yamaguchi et al. 1979). The main cardiac indication of mexiletine is the treatment of ventricular arrhythmias (Mason 1993; Singh et al. 1990). At present, there is a need for available pharmacotherapy to target directly the ionic basis of most long QT syndromes (LQTS) for the acute termination of torsades de pointes (TdP) arrhythmia. In a recent article, it was reported that mexiletine may be an effective treatment approach to terminate refractory TdP from several acquired causes of LQTS (Badri et al. 2015). Mexiletine is applied in extra-cardiac disorders, too. It is widely administered in the therapy of myotonic disorders (Logigian et al. 2010; Statland et al. 2012), in Timothy syndrome (Y. Gao et al. 2013), in neuropathies (O'Connor and Dworkin 2009), and in chronic pain (Park and Moon 2010). A recent study (Weiss et al. 2016) has provided Class I evidence that mexiletine has been safe when given daily to patients with amyotrophic lateral sclerosis (ALS). Mexiletine therapy has resulted in large dose-dependent decreases in muscle cramp frequency and severity. The racemic mexiletine preparations containing both isomers (R(-) and S(+)) mexiletine, are used therapeutically. De Luca et al. demonstrated the stereoselective effects of mexiletine enantiomers on sodium currents and excitability of skeletal muscle fibers (De Luca et al. 1995). They found that R(-) isomers were more potent in sodium current blockade and they highlighted the probable usefulness of low doses of R(-) mexiletine in the therapy of the abnormal hyperexcitability of the myotonic muscles, with an expectable reduction of unwanted side effects. However, the detailed cardiac electrophysiological effects of the R(-) and S(+)) mexiletine isomers on cardiac ventricular preparations have not been investigated yet. We examined whether a significant difference exists between the cardiac electrophysiological effects of the 2 enantiomers. Our research group analysed the effects of the enantiomers on action potential parameters in different protocols performed on rabbit right ventricular papillary muscle preparations. The main findings of our study are that the R(-) mexiletine displays slower offset kinetics than S(+) mexiletine, and R(-) mexiletine displays a tendency to more potent inhibitory effect than S(+) mexiletine on \dot{V}_{\max} , especially at early premature action potentials, i.e., this enantiomer might exert stronger antiarrhythmic effect especially in terminating early ventricular extrasystoles.

Materials and methods

Conventional microelectrode technique

All experiments were carried out in compliance with the *Guide for the Care and Use of Laboratory Animals* (NIH Publication No. 85-23, revised 1996). The protocols were approved by the Review Board of the Committee on Animal Research of the University of Szeged (54/1999 OEj). Young male New Zealand rabbits (1000–2000 g) were euthanized by a blow on the neck and the hearts were removed. Free right ventricular wall and the right papillary muscles were prepared and placed into the tissue bath (50 mL) and allowed to equilibrate for at least 1 h while superfused (flow rate 4–5 mL/min) with Locke's solution containing (in mmol/L): NaCl 120, KCl 4, CaCl₂ 2, MgCl₂ 1, NaHCO₃ 22, and glucose 11. The pH of this solution was 7.40–7.45 when gassed with 95% O₂ and 5% CO₂ at 37 °C. During the equilibration period, the ventricular muscle tissues

were stimulated at a basic cycle length of 1000 ms. Electrical pulses of 2 ms in duration and twice diastolic threshold in intensity (S_1) were delivered to the preparations through bipolar platinum electrodes. Transmembrane potentials were recorded with the use of glass capillary microelectrodes filled with 3 mol/L KCl (tip resistance: 5–15 M Ω). The microelectrodes were coupled through an Ag–AgCl junction to the input of a high impedance, capacitance-neutralizing amplifier (Experimetria 2004). Intracellular recordings were displayed on a storage oscilloscope (Hitachi V-555) and led to a computer system (APES) designed for online determination of the following parameters: resting membrane potential, action potential amplitude, action potential duration at 10%, 25%, 50%, and 90% repolarization, and the maximum rate of rise of the action potential upstroke (\dot{V}_{\max}). The following types of stimulation were applied in the course of the experiments: stimulation with a constant cycle length of 1000 ms (ventricular muscles); stimulation with different constant cycle lengths ranging from 300 to 5000 ms. To establish the recovery of \dot{V}_{\max} , extra test action potentials were elicited by using single test pulses (S_2) in a preparation driven at a basic cycle length of 1000 ms (S_1). The S_1 – S_2 interval was gradually increased from the end of refractory period. The action potential characteristics of the potentials evoked by each S_2 were determined. The diastolic interval preceding the test action potential was measured from the point corresponding to 90% repolarization of the preceding basic action potential to delivery of S_2 . The effective refractory period (ERP) of the preparation, defined as the shortest S_1 – S_2 interval that evoked a propagated action potential using a stimulus amplitude equal to twice the diastolic threshold intensity, was also determined. Once control measurements had been obtained, the preparation was superfused either for 45 min with 20 μ mol/L R(-) mexiletine or S(+) mexiletine. The therapeutically and experimentally relevant concentration of mexiletine amounts to about 20 μ mol/L (Paalman et al. 1977). Same concentration was applied at both stereoisomers. Following these periods of exposure, all action potential parameters were again obtained.

Statistical analysis

Statistical differences were evaluated with Student's *t* test and differences were considered significant when $p < 0.05$. Data are expressed as mean \pm SEM (standard error of the mean).

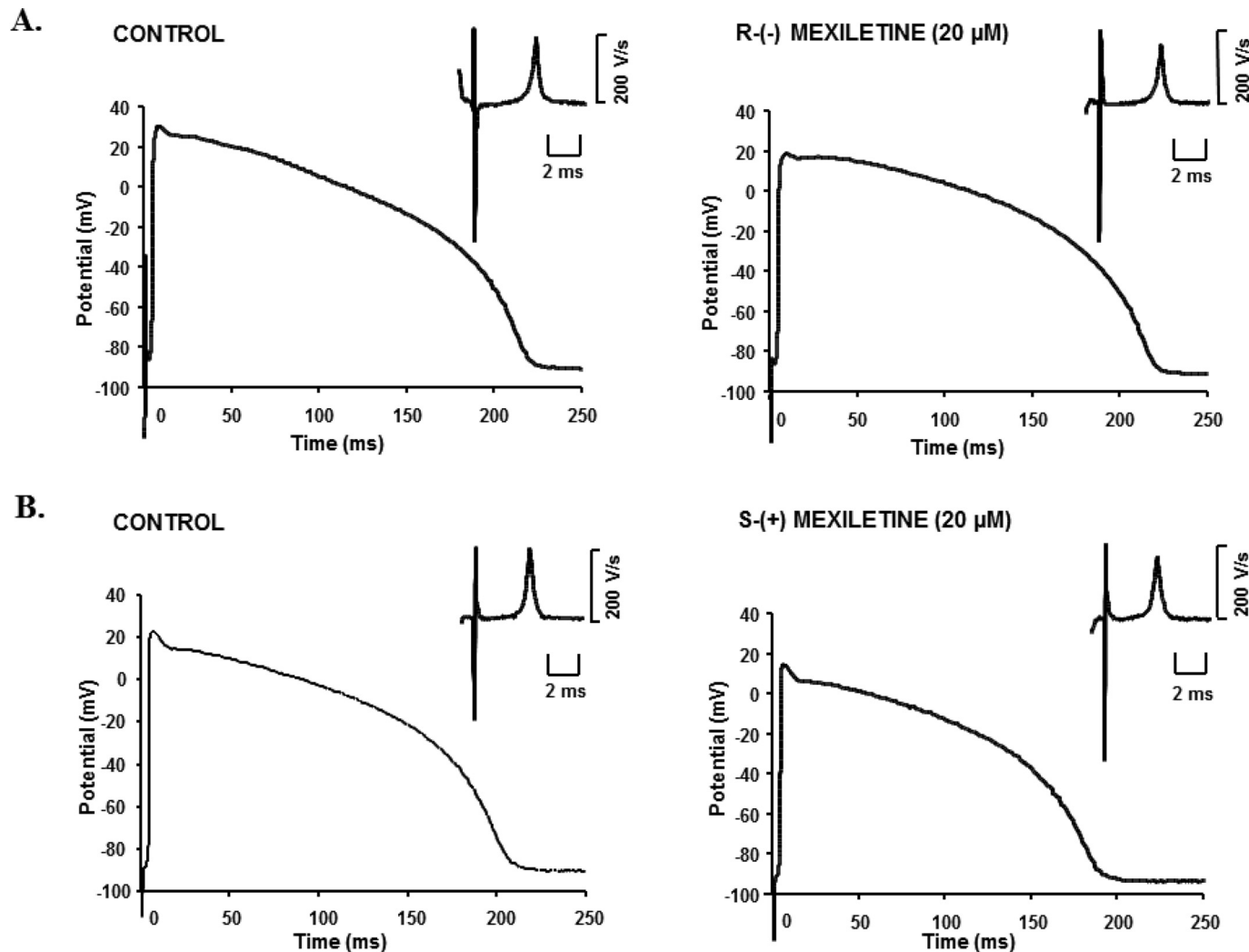
Results

Effects of mexiletine enantiomers on transmembrane action potentials

The effects of 20 μ mol/L R(-) and S(+) enantiomers of mexiletine on action potential characteristics in rabbit ventricular and papillary muscle preparations are summarized in Table 1, with examples illustrated in Fig. 1. At a stimulation cycle length of 1000 ms, the enantiomers did not change ventricular repolarization (Table 1 and Fig. 1). Neither R(-) nor S(+) mexiletine had effects on the action potential amplitude, the maximal diastolic potential/membrane resting potential. Both R(-) and S(+) mexiletine significantly increased the ERP/APD₉₀ ratio (Table 1). Both enantiomers at 20 μ mol/L concentration significantly depressed the \dot{V}_{\max} (Table 1) at a stimulation cycle

T1
F1

Fig. 1. Effect of R(-) mexiletine (A) and S(+) mexiletine (B) on action potential waveform of rabbit ventricular muscle at stimulation cycle length of 1000 ms. The amplitude and time scales for the recording of the first derivative of the transmembrane voltage with respect to time (\dot{V}_{\max}) are indicated to the right.



length of 1000 ms. The depression of maximal rate of rise of depolarization (\dot{V}_{\max}) evoked by the stereoisomers (Figs. 2A and 2B) was strongly dependent upon stimulation frequency (“use dependent”); i.e., as pacing cycle length was decreased (basic cycle lengths 300–700 ms), the depression of \dot{V}_{\max} was increased. There was no statistically significant difference between mexiletine isomers in the degree of inhibition of \dot{V}_{\max} (Fig. 2C), although R(-) mexiletine demonstrated a somewhat more potent inhibitory effect. Impulse conduction time (CT), another sodium channel-mediated parameter, i.e., the time between the stimulus signal and the action potential upstroke was also prolonged significantly (Figs. 3A and 3B) by the enantiomers at fast rates. The effects of mexiletine enantiomers on early premature action potentials following final repolarization of the previous basic action potential (i.e., at a diastolic interval = 70 ms) are summarized in Table 2. Both R(-) and S(+) mexiletine significantly depressed the \dot{V}_{\max} (Table 2) of early premature action potentials and R(-) mexiletine caused a more potent inhibitory action. At the stimulation cycle length of 1000 ms, mexiletine enantiomers inhibited the recovery of \dot{V}_{\max} (Fig. 4). The time constants for recovery of \dot{V}_{\max} in the presence of 20 μmol/L mexiletine enantiomers were $\tau = 376.0 \pm 77.8$ ms for R(-) mexiletine and $\tau = 227.1 \pm 23.4$ ms for S(+) mexiletine. The R(-) mexiletine seems to display slower offset kinetics, i.e., dissociation from the sodium channels, and the difference was significant

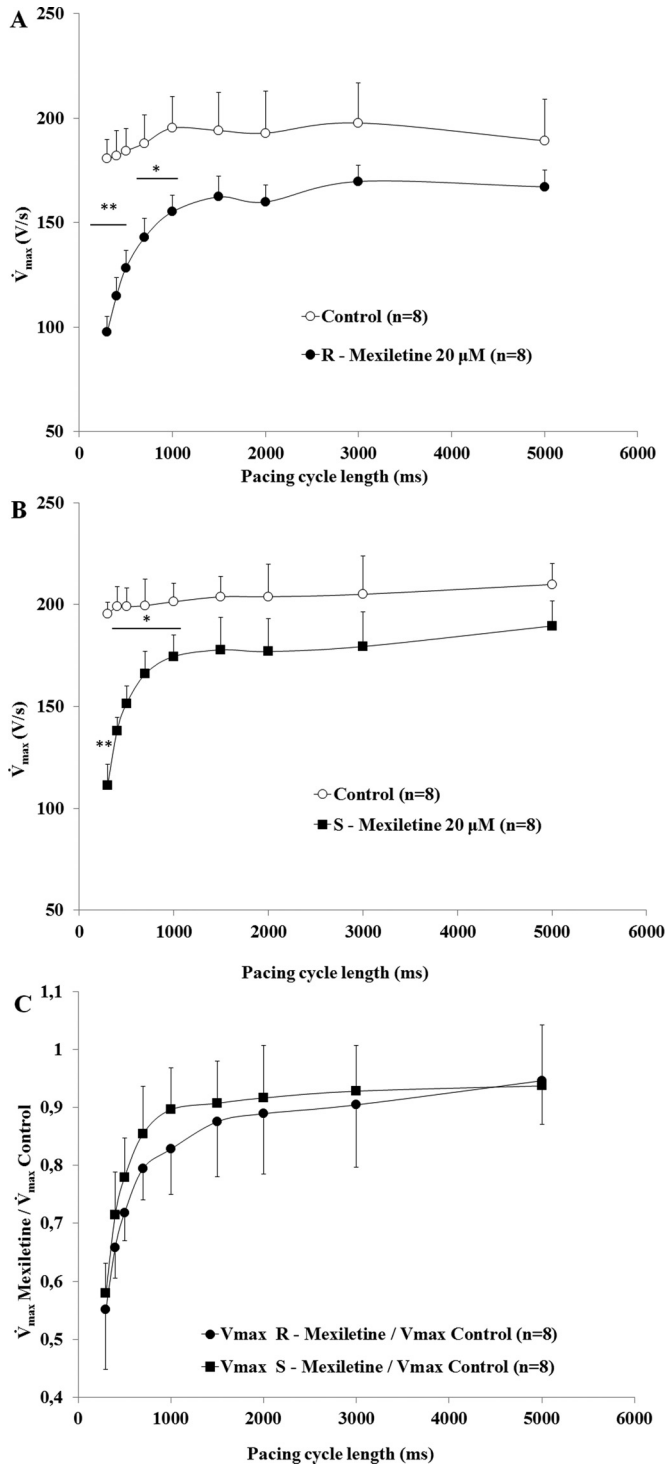
($p < 0.05$) between mexiletine isomers in the degree of inhibition of recovery. The depression was predominant over the range of early extrasystoles.

Discussion

Possible mechanisms

Mexiletine, a widely used antiarrhythmic drug, exists as a racemic mixture, i.e., the available drug preparations contain both S(+) and R(-) enantiomers. It has been extensively studied and established that racemic mexiletine inhibits \dot{V}_{\max} in different cardiac preparations with relatively fast recovery like lidocaine and, as such, it was classified as a Class IB antiarrhythmic drug (Campbell 1983; Varró et al. 1985). Although the enantiomers, like with sotalol, may have different effect, so far the cellular cardiac electrophysiological effect of the S(+) and R(-) enantiomers have never been studied and analysed. Therefore, we have studied the cardiac electrophysiological effects of mexiletine enantiomers (20 μmol/L) on isolated rabbit ventricular preparations. To establish whether the R(-) and S(+) enantiomers had different properties, we first examined the effect of the stereoisomers on \dot{V}_{\max} , which is the maximum rising velocity of the action potential upstroke. \dot{V}_{\max} measurements are indicative for I_{Na} function (i.e., cycle length dependent \dot{V}_{\max} block in rabbit ventricular muscles is

Fig. 2. Rate-dependent effect of R(-) mexiletine (A) and S(+)-mexiletine (B) on the maximum rate of depolarization (\dot{V}_{\max}). Results are mean \pm SEM, * $p < 0.05$, ** $p < 0.01$ vs. control, $n = 8-8$. Comparison of the rate-dependent effects of R(-) mexiletine and S(+)-mexiletine on the maximum rate of depolarization (\dot{V}_{\max}) (C). Values indicated on ordinate are calculated by dividing the \dot{V}_{\max} value measured in the presence of either R(-) or S(+)-mexiletine with its own control \dot{V}_{\max} value.



attributable to the inhibitory effect of mexiletine enantiomers on the fast Na^+ current, but cannot be applied for quantitative estimation of sodium channel availability, which could be underestimated by such measurements (Sheets et al. 1988), because \dot{V}_{\max} can

be considered as a nonlinear indicator of the fast inward sodium current (Cohen et al. 1984). We have found that both the R(-) and S(+)-enantiomers of mexiletine at 20 $\mu\text{mol/L}$ produced a rate-dependent inhibition of the \dot{V}_{\max} value (Figs. 2A and 2B), but the inhibition was more pronounced in the case of the R(-) mexiletine (Fig. 2C). The stronger depression of \dot{V}_{\max} by the R(-) enantiomer can be attributed to the slower offset kinetics comparing to its S(+)-enantiomer. Indeed, at cycle length range of 400–1000 ms the R(-) enantiomer caused more pronounced \dot{V}_{\max} depression than the S(+)-one. R(-) mexiletine suppressed \dot{V}_{\max} of early premature action potentials significantly (Table 2), and this inhibition was also more pronounced than that of S(+)-mexiletine. Therefore, we can speculate that application of medications containing only the R(-) mexiletine might decrease the probability of a second conducted impulse occurring at short premature intervals and thereby reduces the possibility of developing re-entrant tachyarrhythmias. De Luca et al. (1995) demonstrated the stereoselective effects of mexiletine enantiomers (tested at 50 and 100 $\mu\text{mol/L}$) on sodium currents and excitability of frog skeletal muscle fibers. They found that R(-) isomers were more potent in sodium current blockade. Inhibition of sodium current has been found to be more pronounced when the resting membrane potential is partly depolarized (Pu et al. 1998), e.g., in ischaemic tissues. Therefore, the stereoselective effect of mexiletine isomers on \dot{V}_{\max} , what we have found, could be further investigated in future experiments in cardiac preparations exposed to in vitro ischemia protocols, mimicking ischemic heart diseases. We also measured another important parameter reflecting the availability of sodium channels, next to \dot{V}_{\max} , the impulse conduction time (CT). Before administration of each enantiomer, impulse conduction time was independent of the stimulation cycle length (300–5000 ms, Fig. 3). Both enantiomers were capable of exerting marked rate-dependent impulse CT changes (Fig. 3). The time constant for recovery of \dot{V}_{\max} in the case of R(-) mexiletine displays slower offset kinetics than the S(+)-mexiletine (Fig. 4). The mexiletine stereoisomers did not affect repolarization (Fig. 1) at basic cycle length of 1000 ms as shown earlier (Vaughan Williams 1998).

Clinical implications

A retrospective study (D. Gao et al. 2013) performed on patients with an implantable cardioverter defibrillator (ICD) revealed that when mexiletine was added to amiodarone in case of amiodarone ineffectiveness, the combination of these drugs reduced ventricular tachycardia and fibrillation events, which might mean appropriate therapy in these patients. In another retrospective study (Mazzanti et al. 2016), it was recently demonstrated that long-term treatment with mexiletine shortened the QT interval and resulted in a major reduction of life-threatening arrhythmic events in LQT3 patients. Another recent study (Badri et al. 2015) concluded that in patients with acquired LQT and TdP refractory to conventional treatments, the application of mexiletine may be considered. Given the possible cellular cardiac electrophysiological explanations for the latter observations, we should note that many years ago mexiletine was found to be able to abbreviate the APD of the M cells and to suppress the development of EADs (Sicouri et al. 1997) and was also found to be highly effective in decreasing dispersion of repolarization and preventing TdP in LQT2 and LQT3 models (Shimizu and Antzelevitch 1997). Turgeon et al. (1991) demonstrated in their study that R(-) mexiletine was more efficient in the prevention of ventricular tachycardia after coronary ligation in dogs than the S(+)-stereoisomer. Their work raised the possibility that R(-) mexiletine may possess stronger antiarrhythmic characteristics than the opposite enantiomer (Turgeon et al. 1991). On the basis of De Luca's (greater potency of R(-) mexiletine to inhibit I_{Na}) and Turgeon's and our findings, it might be worth examining the effects of the mexiletine stereoisomers, but especially those of the R(-) mexiletine in different patient groups, i.e., patients with an implantable cardioverter

Fig. 3. Rate-dependent effect of R(-) mexiletine (A) and S(+) mexiletine (B) on the conduction time (CT). Results are mean \pm SEM, * $p < 0.05$, ** $p < 0.01$ vs. control, $n = 8-8$. The increase in CT in the presence of S(+) isomer is less than that following exposure to the R(-) isomer.

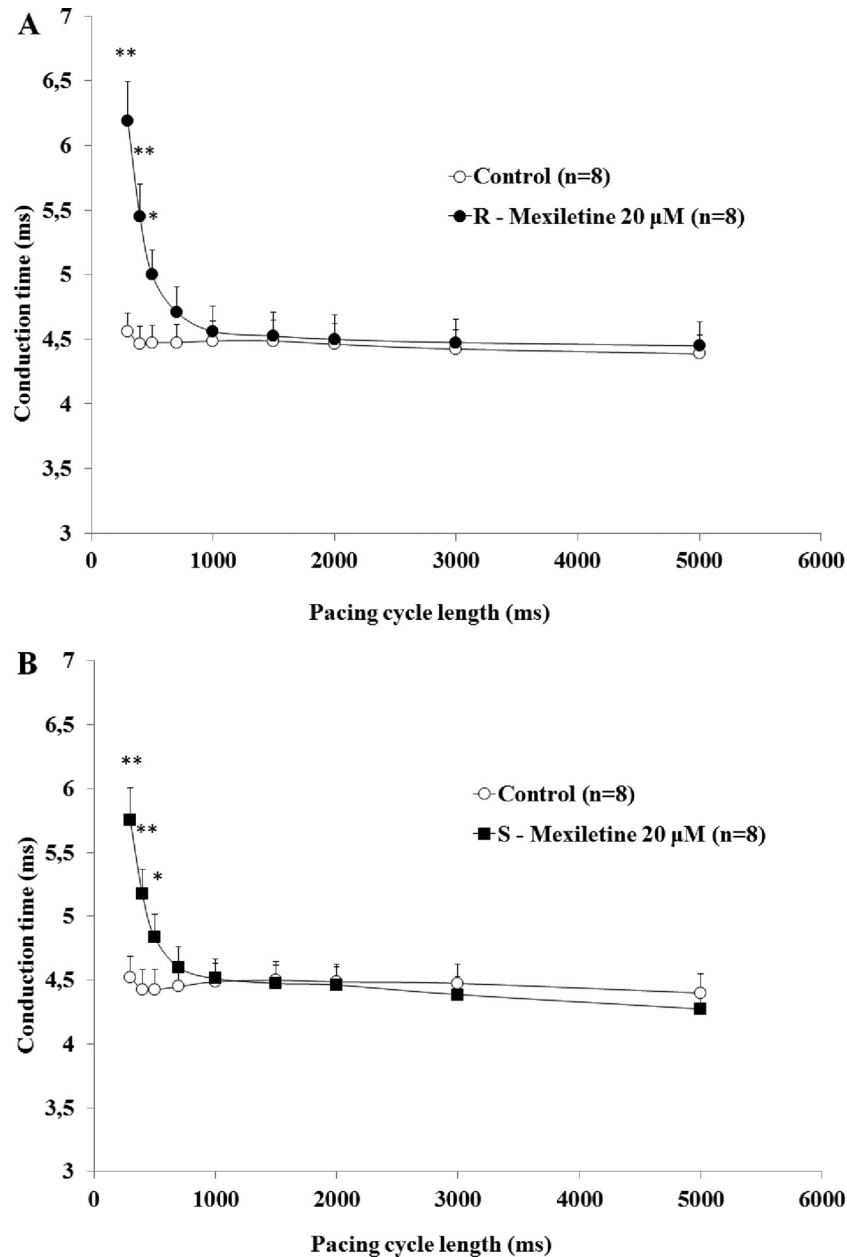


Table 2. The electrophysiological effects of R(-) and S(+) mexiletine enantiomers on the premature action potential at 70 ms of diastolic interval in rabbit ventricular papillary muscle.

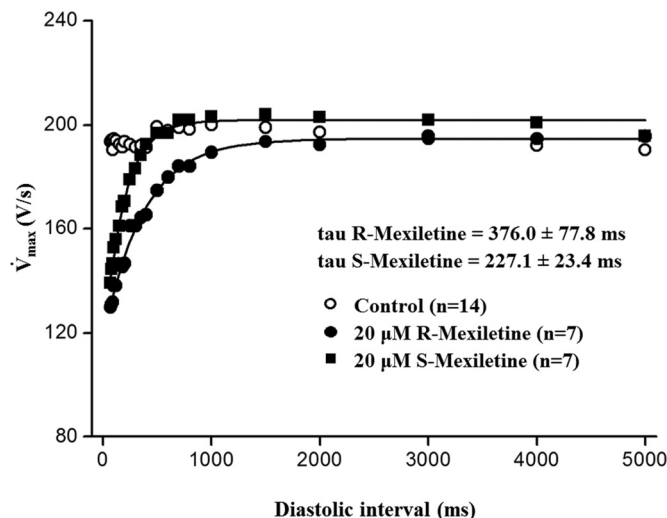
Parameters	MDP (mV)	APA (mV)	APD ₉₀ (ms)	APD ₅₀ (ms)	\dot{V}_{max} (V/s)
Control	-83.4 \pm 1.5 (7)	109.6 \pm 2.1 (7)	204.4 \pm 14.5 (7)	165.9 \pm 15.7 (7)	208.2 \pm 30.2 (7)
R(-) Mexiletine 20 μ mol/L	-86.0 \pm 0.9 (7)	107.9 \pm 2.1 (7)	202.5 \pm 9.5 (7)	161.5 \pm 11.6 (7)	129.7 \pm 29.9* (7)
Control	-85.0 \pm 1.8 (7)	111.3 \pm 2.6 (7)	200.7 \pm 13.4 (7)	164.2 \pm 13.9 (7)	185.6 \pm 18.4 (7)
S(+) Mexiletine 20 μ mol/L	-87.4 \pm 1.2 (7)	110.0 \pm 2.5 (7)	198.9 \pm 18.5 (7)	162.0 \pm 14.6 (7)	142.3 \pm 13.6* (7)

Note: Values are means \pm SEM with number of observations (i.e., number of preparations obtained from different animals) in parentheses. MDP, maximum diastolic potential; APA, action potential amplitude; APD₉₀, action potential duration at 90% of repolarization; APD₅₀, action potential duration at 50% of repolarization; \dot{V}_{max} , maximum rising velocity of the action potential upstroke; ERP, effective refractory period. * $p < 0.05$.

defibrillator and receiving amiodarone or in LQT3 patients. It has emerged from experiments performed on Purkinje fibers (Varró and Lathrop 1990) that combined application of sotalol and mexiletine may produce beneficial electrophysiological effects by possibly exerting intensified antiarrhythmic efficacy and less

proarrhythmic complications in patients; therefore, it might be of value to examine the combined effects of sotalol and R(-) mexiletine in future experiments and clinical studies. Regarding extracardiac implications, the R(-) mexiletine could be studied in patients with myotonic dystrophy. The pharmacokinetic parame-

Fig. 4. Effects of R(-) and S(+) enantiomers of mexiletine on recovery of \dot{V}_{\max} . Means are shown. The abscissa indicates diastolic intervals in milliseconds, and the ordinate shows the \dot{V}_{\max} . The time constants for recovery of \dot{V}_{\max} were $\tau = 376.0 \pm 77.8$ ms for R(-) mexiletine and $\tau = 227.1 \pm 23.4$ ms for S(+) mexiletine. The difference was significant ($p < 0.05$) between mexiletine isomers in the degree of inhibition of recovery.



ters of the enantiomers should always be considered. Kwok et al. (1995) observed a pharmacokinetic difference between mexiletine stereoisomers in 12 healthy human subjects. In their study (Kwok et al. 1995), it was described that after oral administration of 200 mg racemic mexiletine, the mean serum total R(-) mexiletine concentrations were significantly higher than those for S(+) mexiletine during the first 6 h following drug administration. It was found in a human study (McErlane et al. 1987) involving 5 healthy subjects that the serum protein binding was significantly greater for R(-) mexiletine than its antipode and the free fraction of S(+) mexiletine was $28.32\% \pm 1.45\%$ and that of the R(-) enantiomer was $19.80\% \pm 1.49\%$. Another study (Igwemezie et al. 1989) involving 5 healthy subjects revealed that the elimination half-life of S(+) mexiletine was 11.0 ± 3.80 h, which was significantly longer than that of the R(-) enantiomer, 9.10 ± 2.90 h. A study in rats (Mehvar et al. 2002) uncovered non-stereoselective distribution of the isomers to most tissues with the exception of the liver, where the concentration of the S(+) stereoisomer was more than twice of that of its antipode. This study also established a 2-fold higher tissue/serum concentration ratio for S(+) mexiletine enantiomer as compared with the ratio for the R(-) isomer. The most frequently seen adverse effects of mexiletine are often dose related and they affect mainly the central nervous system. Tremors, nystagmus, blurred vision, dizziness, drowsiness, confusion, ataxia, paresthesia, dysarthria, insomnia, tinnitus, and convulsions are the most common side effects. Gastrointestinal disturbances can also develop during mexiletine therapy (Vaughan Williams 1998). Detailed studies are still needed to establish the pharmacokinetic difference between the 2 stereoisomers and its possible therapeutic and toxicological significance.

Conclusion

Our findings have particular importance as mexiletine is still an important drug with a wide range of indications (cardiac arrhythmias, myotonic dystrophy, lidocaine-responsive neonatal epilepsy, etc.). Slower detachment kinetics of R(-) mexiletine from the sodium channels than that of S(+) mexiletine and pronounced suppression the \dot{V}_{\max} of early extrasystoles by R(-) mexiletine might be of therapeutic value. Using lower doses of the probably

more potent R(-) mexiletine in the therapy of different disease conditions (arrhythmias, abnormal hyperexcitability of the myotonic muscles, neuropathic pain, ALS), might result in the reduction of unwanted adverse effects mentioned. To establish, whether the application of R(-) mexiletine alone would result in enhanced antiarrhythmic efficacy requires further in vitro and in vivo studies.

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References

- Arita, M., Goto, M., Nagamoto, Y., and Saikawa, T. 1979. Electrophysiological actions of mexiletine (K61173) on canine Purkinje fibres and ventricular muscle. *Br. J. Pharmacol.* **67**(1): 143–152. PMID:497518.
- Badri, M., Patel, A., Patel, C., Liu, G., Goldstein, M., Robinson, V.M., et al. 2015. Mexiletine prevents recurrent torsades de pointes in acquired long QT syndrome refractory to conventional measures. *JACC Clin. Electrophysiol.* **1**(4): 315–322. doi:10.1016/j.jacep.2015.05.008.
- Campbell, T.J. 1983. Resting and rate-dependent depression of maximum rate of depolarisation (V_{\max}) in guinea pig ventricular action potentials by mexiletine, disopyramide, and encainide. *J. Cardiovasc. Pharmacol.* **5**(2): 291–296. doi:10.1097/00005344-198303000-00021. PMID:6188905.
- Cohen, C.J., Bean, B.P., and Tsien, R.W. 1984. Maximal upstroke velocity as an index of available sodium conductance. Comparison of maximal upstroke velocity and voltage clamp measurements of sodium current in rabbit Purkinje fibers. *Circ. Res.* **54**(6): 636–651. doi:10.1161/01.RES.54.6.636. PMID:6329543.
- De Luca, A., Natuzzi, F., Lentini, G., Franchini, C., Tortorella, V., and Conte Camerino, D. 1995. Stereoselective effects of mexiletine enantiomers on sodium currents and excitability characteristics of adult skeletal muscle fibers. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **352**(6): 653–661. doi:10.1007/BF00171325.
- Gao, D., Van Herendaal, H., Alshengeiti, L., Dorian, P., Mangat, I., Korley, V., et al. 2013. Mexiletine as an adjunctive therapy to amiodarone reduces the frequency of ventricular tachyarrhythmia events in patients with an implantable defibrillator. *J. Cardiovasc. Pharmacol.* **62**(2): 199–204. doi:10.1097/FJC.0b013e31829651fe. PMID:23609328.
- Gao, Y., Xue, X., Hu, D., Liu, W., Yuan, Y., Sun, H., et al. 2013. Inhibition of late sodium current by mexiletine: a novel pharmacotherapeutic approach in Timothy syndrome. *Circ.: Arrhythmia Electrophysiol.* **6**(3): 614–622. doi:10.1161/CIRCEP.113.000092.
- Hering, S., Bodewei, R., and Wollenberger, A. 1983. Sodium current in freshly isolated and in cultured single rat myocardial cells: frequency and voltage-dependent block by mexiletine. *J. Mol. Cell. Cardiol.* **15**(7): 431–444. doi:10.1016/0022-2828(83)90263-8. PMID:6620395.
- Hohnloser, S., Weirich, J., and Antoni, H. 1982. Effects of mexiletine on steady-state characteristics and recovery kinetics of V_{\max} and conduction velocity in guinea pig myocardium. *J. Cardiovasc. Pharmacol.* **4**(2): 232–239. doi:10.1097/00005344-198203000-00011. PMID:6175806.
- Igwemezie, L., Kerr, C.R., and McErlane, K.M. 1989. The pharmacokinetics of the enantiomers of mexiletine in humans. *Xenobiotica*, **19**(6): 677–682. doi:10.3109/00498258909042305. PMID:2763576.
- Kwok, D.W., Kerr, C.R., and McErlane, K.M. 1995. Pharmacokinetics of mexiletine enantiomers in healthy human subjects. A study of the in vivo serum protein binding, salivary excretion and red blood cell distribution of the enantiomers. *Xenobiotica*, **25**(10): 1127–1142. doi:10.3109/00498259509061913. PMID:8578769.
- Logigian, E.L., Martens, W.B., Moxley, R.T., McDermott, M.P., Dilek, N., Wiegner, A.W., et al. 2010. Mexiletine is an effective antimyotonia treatment in myotonic dystrophy type 1. *Neurology*, **74**(18): 1441–1448. doi:10.1212/WNL.0b013e3181dc1a3a. PMID:20439846.
- Mason, J.W. 1993. A comparison of seven antiarrhythmic drugs in patients with ventricular tachyarrhythmias. *N. Engl. J. Med.* **329**(7): 452–458. doi:10.1056/NEJM199308123290702. PMID:8332150.
- Mazzanti, A., Maragna, R., Faragli, A., Monteforte, N., Bloise, R., Memmi, M., et al. 2016. Gene-specific therapy with mexiletine reduces arrhythmic events in patients with long QT syndrome type 3. *J. Am. Coll. Cardiol.* **67**(9): 1053–1058. doi:10.1016/j.jacc.2015.12.033. PMID:26940925.
- McErlane, K.M., Igwemezie, L., and Kerr, C.R. 1987. Stereoselective serum protein binding of mexiletine enantiomers in man. *Res. Commun. Chem. Pathol. Pharmacol.* **56**(1): 141–144. PMID:3589151.
- Mehvar, R., Brocks, D.R., and Vakily, M. 2002. Impact of stereoselectivity on the pharmacokinetics and pharmacodynamics of antiarrhythmic drugs. *Clin. Pharmacokinet.* **41**(8): 533–558. doi:10.2165/00003088-200241080-00001. PMID:12102640.

- O'Connor, A.B., and Dworkin, R.H. 2009. Treatment of neuropathic pain: an overview of recent guidelines. *Am. J. Med.* **122**: S22–S32. doi:[10.1016/j.amjmed.2009.04.007](https://doi.org/10.1016/j.amjmed.2009.04.007). PMID:[19801049](https://pubmed.ncbi.nlm.nih.gov/19801049/).
- Paalman, A.C., Siebelink, J., Roos, J.C., and Dunning, A.J. 1977. Development of a dosage scheme for simultaneous intravenous and oral administration of mexiletine. *Postgrad. Med. J.* **53**: 128–133. PMID:[876945](https://pubmed.ncbi.nlm.nih.gov/876945/).
- Park, H.J., and Moon, D.E. 2010. Pharmacologic management of chronic pain. *Korean J. Pain*, **23**(2): 99–108. doi:[10.3344/kjp.2010.23.2.99](https://doi.org/10.3344/kjp.2010.23.2.99). PMID:[20556211](https://pubmed.ncbi.nlm.nih.gov/20556211/).
- Pu, J., Balsler, J.R., and Boyden, P.A. 1998. Lidocaine action on Na⁺ currents in ventricular myocytes from the epicardial border zone of the infarcted heart. *Circ. Res.* **83**(4): 431–440. doi:[10.1161/01.RES.83.4.431](https://doi.org/10.1161/01.RES.83.4.431). PMID:[9721700](https://pubmed.ncbi.nlm.nih.gov/9721700/).
- Sarkozy, A., and Dorian, P. 2007. Anti-arrhythmic drugs. In *Principles of medical pharmacology*. Edited by H. Kalant, D.M. Grant, and J. Mitchell. Elsevier Canada, Toronto. pp. 430–447.
- Sheets, M.F., Hanck, D.A., and Fozzard, H.A. 1988. Nonlinear relation between V_{max} and I_{Na} in canine cardiac Purkinje cells. *Circ. Res.* **63**(2): 386–398. doi:[10.1161/01.RES.63.2.386](https://doi.org/10.1161/01.RES.63.2.386). PMID:[2456164](https://pubmed.ncbi.nlm.nih.gov/2456164/).
- Shimizu, W., and Antzelevitch, C. 1997. Sodium channel block with mexiletine is effective in reducing dispersion of repolarization and preventing torsade de pointes in LQT2 and LQT3 models of the long-QT syndrome. *Circulation*, **96**(6): 2038–2047. doi:[10.1161/01.CIR.96.6.2038](https://doi.org/10.1161/01.CIR.96.6.2038). PMID:[9323097](https://pubmed.ncbi.nlm.nih.gov/9323097/).
- Sicouri, S., Antzelevitch, D., Heilmann, C., and Antzelevitch, C. 1997. Effects of sodium channel block with mexiletine to reverse action potential prolongation in in vitro models of the long QT syndrome. *J. Cardiovasc. Electrophysiol.* **8**(11): 1280–1290. doi:[10.1111/j.1540-8167.1997.tb01019.x](https://doi.org/10.1111/j.1540-8167.1997.tb01019.x). PMID:[9395171](https://pubmed.ncbi.nlm.nih.gov/9395171/).
- Singh, S., Klein, R., Eisenberg, B., Hughes, E., Shand, M., and Doherty, P. 1990. Long-term effect of mexiletine on left ventricular function and relation to suppression of ventricular arrhythmia. *Am. J. Cardiol.* **66**(17): 1222–1227. doi:[10.1016/0002-9149\(90\)91104-E](https://doi.org/10.1016/0002-9149(90)91104-E). PMID:[1700592](https://pubmed.ncbi.nlm.nih.gov/1700592/).
- Statland, J.M., Bundy, B.N., Wang, Y., Rayan, D.R., Trivedi, J.R., Sansone, V.A., et al. 2012. Mexiletine for symptoms and signs of myotonia in nondystrophic myotonia: a randomized controlled trial. *J. Am. Med. Assoc.* **308**(13): 1357–1365. doi:[10.1001/jama.2012.12607](https://doi.org/10.1001/jama.2012.12607).
- Turgeon, J., Uprichard, A.C., Bélanger, P.M., Harron, D.W., and Grech-Bélanger, O. 1991. Resolution and electrophysiological effects of mexiletine enantiomers. *J. Pharm. Pharmacol.* **43**(9): 630–635. doi:[10.1111/j.2042-7158.1991.tb03552.x](https://doi.org/10.1111/j.2042-7158.1991.tb03552.x). PMID:[1685521](https://pubmed.ncbi.nlm.nih.gov/1685521/).
- Varró, A., and Lathrop, D.A. 1990. Sotalol and mexiletine: combination of rate-dependent electrophysiological effects. *J. Cardiovasc. Pharmacol.* **16**(4): 557–567. doi:[10.1097/00005344-199010000-00006](https://doi.org/10.1097/00005344-199010000-00006). PMID:[1706796](https://pubmed.ncbi.nlm.nih.gov/1706796/).
- Varró, A., Elharrar, V., and Surawicz, B. 1985. Frequency-dependent effects of several class I antiarrhythmic drugs on Vmax of action potential upstroke in canine cardiac Purkinje fibers. *J. Cardiovasc. Pharmacol.* **7**(3): 482–492. doi:[10.1097/00005344-198505000-00011](https://doi.org/10.1097/00005344-198505000-00011). PMID:[2410678](https://pubmed.ncbi.nlm.nih.gov/2410678/).
- Vaughan Williams, E.M. 1998. Class 1 antiarrhythmic action. In *Control of cardiac rhythm*. Edited by E.M. Vaughan Williams and J.C. Somberg. Lippincott-Raven Publishers, Philadelphia. pp. 11–32.
- Weiss, M.D., Macklin, E.A., Simmons, Z., Knox, A.S., Greenblatt, D.J., Atassi, N., et al. 2016. A randomized trial of mexiletine in ALS: safety and effects on muscle cramps and progression. *Neurology*, **86**(16): 1474–1481. doi:[10.1212/WNL.0000000000002507](https://doi.org/10.1212/WNL.0000000000002507). PMID:[26911633](https://pubmed.ncbi.nlm.nih.gov/26911633/).
- Yamaguchi, I., Singh, B.N., and Mandel, W.J. 1979. Electrophysiological actions of mexiletine on isolated rabbit atria and canine ventricular muscle and Purkinje fibres. *Cardiovasc. Res.* **13**(5): 288–296. doi:[10.1093/cvr/13.5.288](https://doi.org/10.1093/cvr/13.5.288). PMID:[476749](https://pubmed.ncbi.nlm.nih.gov/476749/).