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Concept of relative variability of cardiac action potential duration and its test under various experimental conditions

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Abstract. Beat-to-beat variability of action potential duration (short-term variability, SV) is an intrinsic property of mammalian myocardium. Since the majority of agents and interventions affecting SV may modify also action potential duration (APD), we propose here the concept of relative SV (RSV), where changes in SV are normalized to changes in APD and these data are compared to the control SV-APD relationship obtained by lengthening or shortening of action potentials by inward and outward current injections. Based on this concept the influence of the several experimental conditions like stimulation frequency, temperature, pH, redox-state and osmolarity were examined on RSV in canine ventricular myocytes using sharp microelectrodes. RSV was increased by high stimulation frequency (cycle lengths < 0.7 s), high temperature (above 37°C), oxidative agents (H_2O_2), while it was decreased by reductive environment. RSV was not affected by changes in pH (within the range of 6.4–8.4) and osmolarity of the solution (between 250–350 mOsm). The results indicate that changes in beat-to-beat variability of APD must be evaluated exclusively in terms of RSV; furthermore, some experimental conditions, including the stimulation frequency, redox-state and temperature have to be controlled strictly when analyzing alterations in the short-term variability of APD.

Key words: Short-term variability — Action potential duration — Cardiac ion currents — Canine myocytes

Abbreviations: SV, short-term variability; APD, action potential duration; RSV, relative variability.

Introduction

Beat-to-beat variability of action potential duration (short-term variability, SV) is an intrinsic property of various *in vivo* and *in vitro* mammalian cardiac preparations including the human heart (Hinterseer et al. 2009, 2010; Tereshchenko et al. 2010). Although SV is considered one of the best proarrhythmic predictors (Thomsen et al. 2004; Abi-Gerges et al. 2010; Jacobson et al. 2011), its exact mechanism is still not fully understood. Involvement of several factors, such as stochastic gating of ion channels (Lemay et al. 2011; Pueyo et al. 2011), intensity of cell-to-cell coupling (Zaniboni et al. 2000), action potential morphology (Heijman et al. 2013), cytosolic calcium concentration (Johnson et al. 2013) and stimulation frequency (Johnson et al. 2010) have already been implicated in modulation of SV. In these studies, however, the concomitant changes in action potential duration (APD) were ignored. Recently, we have shown that SV is a nonlinear function of APD (Szentandrássy et al. 2014) implicating that many effects of drugs and interventions studied on SV so far could modify SV unspecifically – merely due to its lengthening or shortening effect on APD. This distortion can be avoided by using the concept of *relative* SV, i.e. when changes of SV are normalized to the concomitant changes in APD. Using this concept we examined or re-examined

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the influence of some important experimental conditions like stimulation frequency, temperature, pH, redox-state and osmolarity on SV in canine ventricular myocytes. This preparation was chosen since it is believed to resemble most the human ventricular cells regarding their electrophysiological properties (Szabó et al. 2005; Szentandrássy et al. 2005), and because of the large mass of data on SV accumulated already in dogs.

Materials and Methods

Isolation of single canine ventricular myocytes

Adult mongrel dogs of either sex were anaesthetized with intramuscular injections of 10 mg/kg ketamine hydrochloride (Calypsol, Richter Gedeon, Hungary) + 1 mg/kg xylazine hydrochloride (Sedaxylan, Eurovet Animal Health BV, The Netherlands) according to protocols approved by the local ethical committee (license N^{o}18/2012/DEMáB) in line with the ethical standards laid down in the Declaration of Helsinki in 1964 and its later amendments. The hearts were quickly removed and placed in Tyrode solution. Single myocytes were obtained by enzymatic dispersion using the segment perfusion technique, as described previously (Bárándi et al. 2010). Briefly, a wedge-shaped section of the left ventricular wall supplied by the left anterior descending coronary artery was dissected, cannulated and perfused with oxygenized Tyrode solution. After removal of blood the perfusion was switched to a nominally Ca^{2+}-free Joklik solution (Minimum Essential Medium Eagle, Joklik Modification, Sigma) for 5 min. This was followed by 30 min perfusion with Joklik solution supplemented with 1 mg/ml collagenase (Type II. Worthington, Chemical Co.) and 0.2% bovine serum albumin (Fraction V., Sigma) containing 50 µM Ca^{2+}. After gradually restoring the normal external Ca^{2+} concentration, the cells were stored in Minimum Essential Medium Eagle until use. Drugs were obtained from Sigma-Aldrich Co. (St. Louis, MO, USA) except ryanodine, which was purchased from Cayman Chemical Company (Michigan, USA).

Recording of action potentials

All electrophysiological measurements were performed at 37°C except for those where the effect of temperature was studied. As presented in Fig. 1, the rod-shaped viable cells, showing clear striation were sedimented in a plexiglass chamber of 1 ml volume allowing continuous superfusion (at a rate of 2 ml/min) with modified Krebs solution gassed with a mixture of 95 % O_2 and 5 % CO_2 at pH = 7.4. The modified Krebs solution contained (in mM): NaCl, 128.3; $NaHCO_3$, 21.4; KCl, 4.0; $CaCl_2$, 1.8; $MgCl_2$, 0.42; and glucose 10. Transmembrane potentials were recorded using 3 M KCl filled sharp glass microelectrodes having tip resistance between 20 and 40 MΩ. These electrodes were connected to the input of Multiclamp 700A, 700B or Axoclamp-2B amplifiers (Molecular Devices, Sunnyvale, CA, USA). The cells were paced through the recording electrode at steady cycle length of 1 s using 1–2 ms wide rectangular current pulses having amplitudes of twice the diastolic threshold. Since the cytosol was not dialyzed, time-dependent changes in action potential morphology were negligible for the period of our experimental protocol lasting typically shorter than 30 min. Action potentials were digitized (at 200 kHz using Digidata 1322A, 1440A and 1200 A/D card, purchased from Axon Instruments Inc., Foster City, CA, USA) and stored for later analysis. Series of 50 consecutive action potentials were analyzed to estimate SV according to the following formula:

$$SV = \Sigma (|APD_{n+1} - APD_n|) / [n_{beats} * \sqrt{2}]$$

where SV is short-term variability, APD_n and APD_{n+1} indicate the durations of the n^{th} and $n+1^{th}$ APs, respectively, at 90% level of repolarization and n_{beats} denotes the number of consecutive beats analyzed (Johnson et al. 2010; Szentandrássy et al. 2015). Experiments were not performed in preparations when APD was not stabilized under baseline conditions within 5 min. Also, records containing AP alternant were excluded from the analysis.

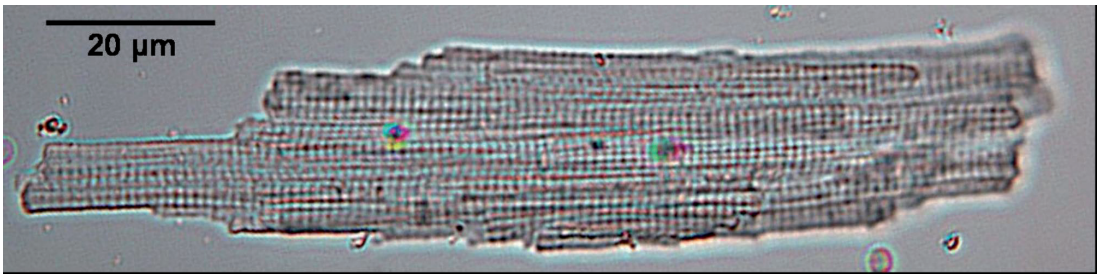

Figure 1. Photograph of a typical canine ventricular myocyte.

Statistics

Results are expressed as mean ± SEM values. Statistical significance of differences from control was evaluated using one-way ANOVA followed by Student's *t*-test. Differences were considered significant when p was less than 0.05.

Results

Concept of relative SV

According to previous results, the beat-to-beat variability of APD is a nonlinear function of baseline APD (Szentandrássy et al. 2015). Consequently, the effect of any intervention on SV has to be assessed only in terms of *relative* SV (RSV), i.e. by comparing the changes in SV to the concomitant changes in APD. The baseline SV-APD relationship was obtained by injecting outward and inward current pulses in current clamp mode throughout the full time of action potential plateau and repolarization. Application of these current pulses with a relatively wide range of amplitude (between –500 and +70 pA) resulted in modification of APD also within a reasonably wide range (between 20 and 500 ms) in a way not directly related to any specific ionic mechanism. SV was shown to be an exponential function of APD (Fig. 2B), and more importantly, a similar relation was obtained between the *changes* of these parameters as well (Fig. 2C, see the legend for further details). Using this approach, RSV is considered to be increased when data points are above, while decreased when they are located below the exponential solid curves in Fig. 2B,C.

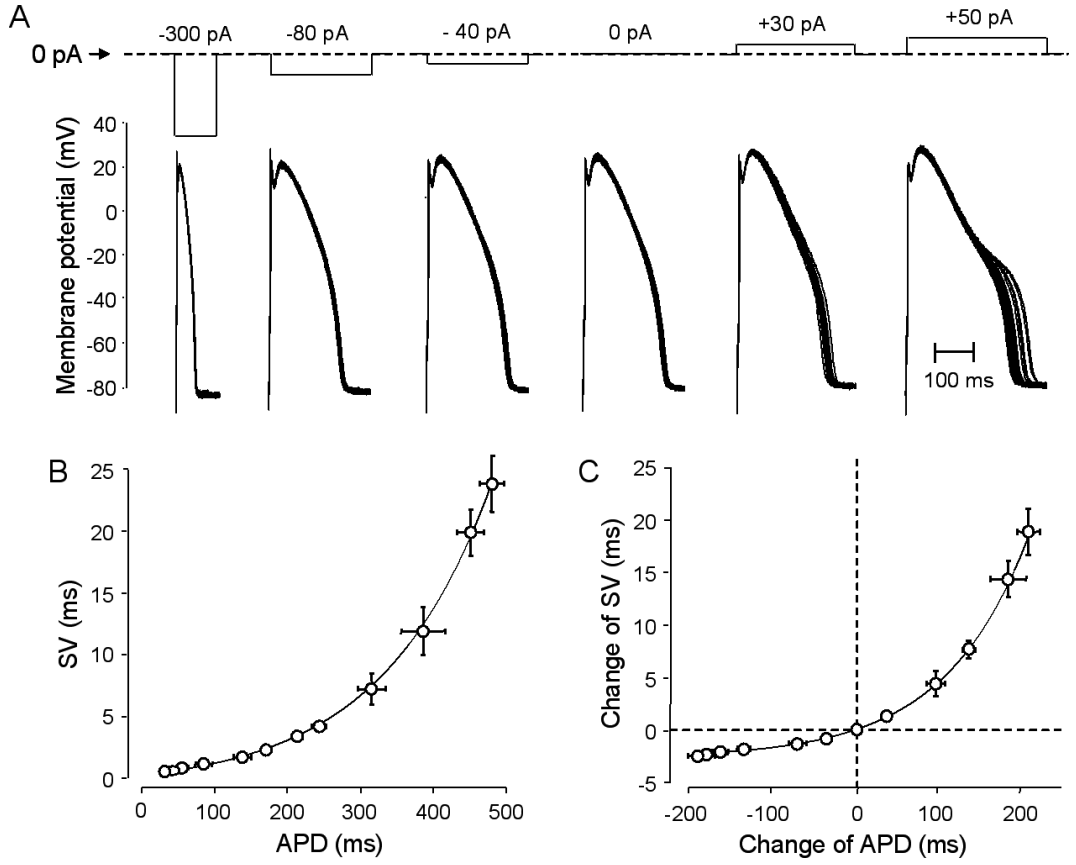

Figure 2. Effect of action potential duration (APD) on its beat-to-beat variability. Data were collected from 9 myocytes by injecting outward or inward current pulses starting immediately after the upstroke and ending after full repolarization of the action potential in order to increase and decrease APD, respectively. Current amplitudes were –500, –400, –300, –200, –80, –40, 0, +30, +40, +50, +60 and +70 pA from left to right on the bottom panels (**B, C**). The exponential curve in panel B was obtained by fitting the data to $SV = A * e^{APD/T}$, where SV and APD have their conventional meanings and T is time constant, while in panel **C** to $\Delta SV = \Delta SV_0 + A * e^{\Delta APD/T}$, where ΔSV_0 is the minimum value of the ordinate, ΔAPD and ΔSV represent the changes induced by current injections. The regression coefficient was 0.99 in both cases. Selected superimposed sets of 50 consecutive action potentials are presented in the top panel (**A**) together with the current injection applied. Symbols and bars indicate arithmetic means ± SEM values, respectively. SV, short-term variability.

Effects of stimulation frequency, temperature, redox-state, pH and osmolarity on RSV

The cycle length of stimulation was gradually decreased from the longest (5 s) to shorter cycle lengths up to 0.3 s, allowing APD to reach steady-state level at each frequency. Both APD and SV were decreased monotonically at higher pacing rates (Fig. 3A). However, when changes of SV were plotted against the concomitant changes of APD, and these data point were compared to the position of the control SV-APD relationship, determined using current injections (as demonstrated in Fig. 2), data points obtained at lower frequencies were strictly on the curve, while those obtained at higher stimulation rates (at cycle lengths < 0.7 s) deviated to upward direction indicating that RSV is increased at this range of stimulation frequency (Fig. 3B).

In the next series of experiments the temperature of the incubating solution was altered within a wide range (between 34 and 41°C). The measurement started always at 37°C (control), and abrupt shifts in temperature were induced either to colder or warmer directions; the cells were exposed to each temperature for 3 min allowing equilibration of APD. Both SV and APD were increased by cooling, while the opposite change was observed on warming, as indicated in Fig. 3C. These changes were statistically significant, except for the reduction of SV at lower temperatures. Plotting the temperature-dependent changes of SV as a function of changes in APD clearly indicated that RSV was increased by warming, while reduced by cooling (Fig. 3D).

To study the effect of redox-potential changes on variability, reductive shifts were evoked by superfusion of a reductive cocktail (containing 1 mM DL-dithiothreitol, 1 mM reduced L-glutathione and 1 mM L-ascorbic acid), while oxidative shifts were evoked by pretreatment with of 10 μM H_2O_2 for 6 min. As demonstrated in Fig. 4, RSV was decreased by reductive, while increased by oxidative environments. This

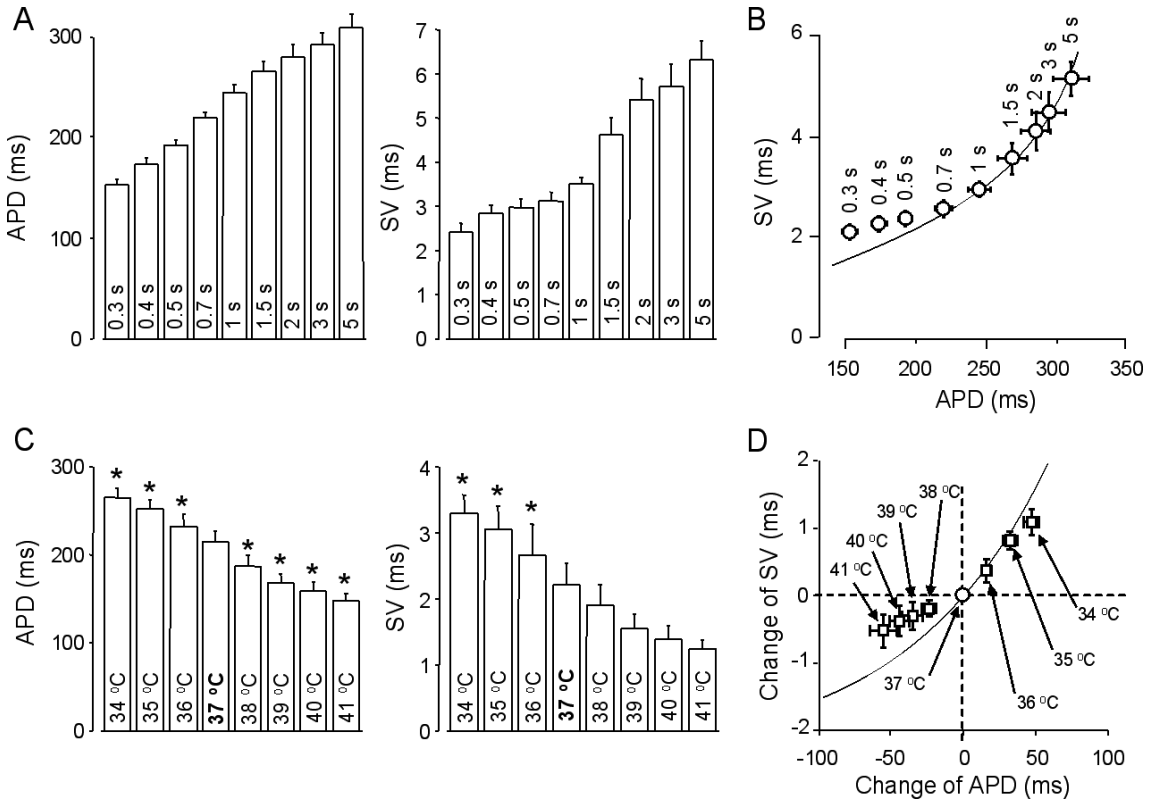

Figure 3. Effects of the stimulation frequency and temperature on SV and APD. **A.** The cycle length of stimulation was gradually decreased from 5 s to 0.3 s, allowing APD to reach steady-state level at each frequency. **B.** Average SV values plotted as a function of the corresponding APDs obtained in 8 myocytes at the full range of cycle lengths studied. (**C, D**) When studying the effect of temperature, SV and APD values were first recorded at 37°C (control) then the temperature of the superfusate was gradually increased or decreased. The cells spent 3 min period of time at each temperature. Symbols and columns are mean values obtained in 5 myocytes; bars indicate SEM and asterisks denote significant differences from the controls measured at 37°C. Here and in the subsequent figures the solid lines represent control SV-APD relationships obtained from Fig. 2.

was the case in spite of the fact that both SV and APD were increased by H_2O_2 significantly.

In contrast to the redox state, changes of pH within 1 pH unit had no significant effect on RSV. As demonstrated in Fig. 4C, neither SV nor APD was changed by an acidic shift of pH (from 7.4 to 6.4 using HCl). On the other hand both SV and APD were reduced significantly by an alkaline shift of identical magnitude (from 7.4 to 8.4 with NaOH). Since these changes were fully proportional, RSV was not altered within the studied range of pH Fig. 4D.

Finally, the osmotic concentration of the bathing solution was set to 250 mOsm by decreasing its NaCl content by 25 mM, while hyperosmotic medium (350 mOsm) was produced by the addition of 50 mM glucose. The temperature and pH of the medium was kept at 37°C and pH = 7.4, respectively, and the cells were exposed to these solutions for 10 min to allow full equilibration. Although, changing the osmotic concentration of the medium failed to modify SV or APD significantly, there was a slight (statistically not significant) increase in both APD and SV in hypertonic and a similar reduction of both parameters in hypotonic solution (Fig. 5A) However, when these data were displayed in a diagram plotting changes in SV against changes in APD (Fig. 5B), all data points were found on the solid line.

Discussion

Critically important message of the present study is that changes in beat-to-beat variability of APD has to be evaluated exclusively in terms of RSV under *all* experimental conditions, including the temperature, pH, osmolarity, redox state and stimulating frequency. Furthermore, the stimulating

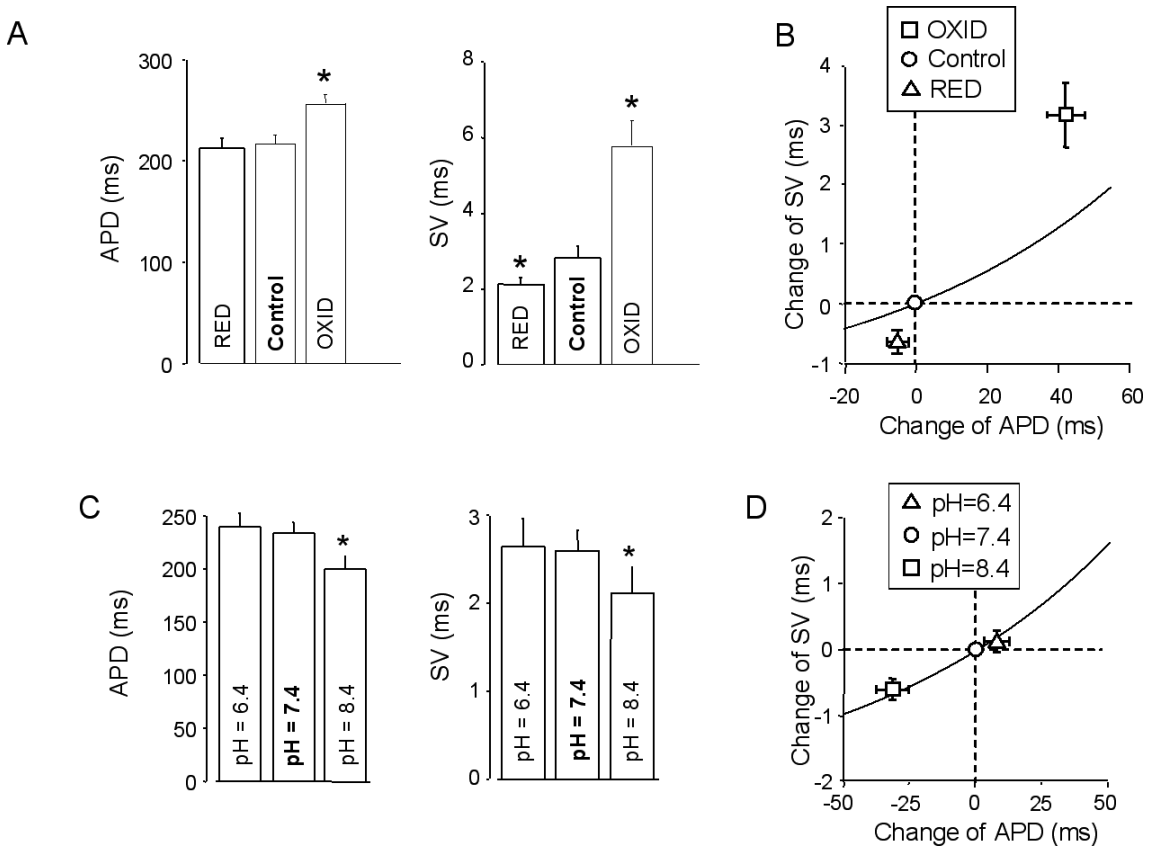

Figure 4. Effect of the redox state and pH on SV and APD. **A.** Effects of 6 min pretreatment with a reductive cocktail (RED: containing: 1 mM DL-dithiothreitol, 1 mM reduced L-glutathione and 1 mM L-ascorbic acid) and oxidative (OXID: 10 μM H_2O_2) environment on SV and APD. **B.** Average SV values plotted against the corresponding APDs. Data were obtained in 10 myocytes exposed to control, reductive and oxidative environments. **C.** SV and APD values obtained under control conditions (pH = 7.4) and after shifting the pH towards acidic (pH = 6.4) or alkaline (pH = 8.4) directions for 10 min. **D.** Average SV values plotted against the corresponding APDs, obtained in 9 myocytes exposed to pH of 7.4, 6.4 and 8.4. Symbols and columns are mean values; bars indicate SEM and asterisks denote significant differences from the control values.

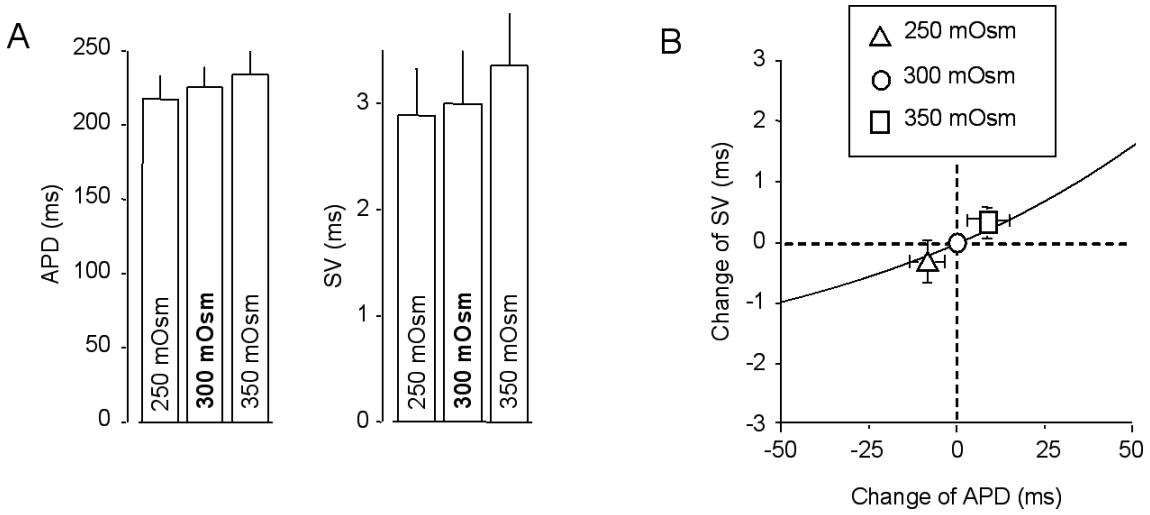

Figure 5. Effect of osmolarity on SV and APD. **A.** Average values of APD and SV obtained under control conditions (300 mOsm) and after 10 min exposure to hypoosmotic (250 mOsm) or hyperosmotic (350 mOsm) solutions. **B.** SV values plotted as a function of the corresponding APDs, obtained in 5 myocytes exposed to control, hypoosmotic and hyperosmotic solutions. Symbols and bars indicate arithmetic means ± SEM values, respectively.

frequency, temperature and redox state has to be controlled strictly when analyzing alterations in the short-term variability of APD. The significance of the first statement can easily be understood when analyzing the effect of any drug SV. The majority of cardioactive agents are likely to alter SV and APD simultaneously, since both actions are consequences of interactions with cardiac ion channels. The best example to demonstrate this principle is probably related with the effect of the calcium channel blocker nisoldipine, which had no significant effect on SV, but strongly increased RSV due to the marked concomitant reduction of APD in canine ventricular cells (Szentandrássy et al. 2015). The distorting effects of APD changes can be recognized and eliminated by using the concept of RSV.

Present study is the first report analyzing the effects of temperature, pH and osmolarity on beat-to-beat variability of cardiac action potential duration. Changes in temperature had a significant impact on RSV. This may contribute to the increased incidence of cardiac arrhythmias under conditions of fever in addition to many other factors (Amin et al. 2008, 2010; Chockalingam et al. 2011). The largest shift in RSV was observed after shifting the redox potential of the solution toward an oxidative direction. Similar changes are known to occur in patients with ischemia/reperfusion injuries together with an acidic shift in the pH (Turer and Hill 2010; Hausenloy and Yellon 2013). Present results clearly indicate that RSV is modified exclusively by the redox shift, but not pH, under these pathological conditions. The insensitivity of RSV to pH changes was an unexpected finding, since most channel gating properties are pH-dependent; more specifically, acidosis is known to cause a rightward, while alkalosis a leftward shift in the voltage dependence of channel gating. It is possible, however, that a certain shift in pH results in a more-or-less comparable change in many ion channels involved in ventricular repolarization (some of these mediating inward, while others outward current), so finally the net change in current is not significant.

RSV was also increased by high stimulation frequencies in spite of the fact that records with AP alternant were strictly excluded from the analysis. Although the underlying mechanisms of these effects are not revealed by this study, involvement of alterations in calcium handling may be a possible candidate for the link between the increased variability and the elevated arrhythmia incidence. This is line with the positive staircase phenomenon, a common characteristic of most mammalian cardiac preparations, including dogs and humans, suggesting the role of the elevated cytosolic calcium concentrations at higher driving rates, similarly to patients with coronary occlusion.

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