

Beat-to-beat variability of cardiac action potential duration: underlying mechanism and clinical implications¹

Péter P. Nánási, János Magyar, András Varró, and Balázs Ördög

Abstract: Beat-to-beat variability of cardiac action potential duration (short-term variability, SV) is a common feature of various cardiac preparations, including the human heart. Although it is believed to be one of the best arrhythmia predictors, the underlying mechanisms are not fully understood at present. The magnitude of SV is basically determined by the intensity of cell-to-cell coupling in multicellular preparations and by the duration of the action potential (APD). To compensate for the APD-dependent nature of SV, the concept of relative SV (RSV) has been introduced by normalizing the changes of SV to the concomitant changes in APD. RSV is reduced by I_{Ca} , I_{Kr} , and I_{Ks} while increased by I_{Na} , suggesting that ion currents involved in the negative feedback regulation of APD tend to keep RSV at a low level. RSV is also influenced by intracellular calcium concentration and tissue redox potential. The clinical implications of APD variability is discussed in detail.

Key words: action potential duration, arrhythmia, ion channels, beat-to-beat variability.


Résumé : La variabilité battement par battement de la durée du potentiel d'action cardiaque (variabilité à court terme, VC) est une caractéristique commune de diverses préparations cardiaques, y compris de cœur humain. Bien que l'on croie que ce soit le meilleur facteur prédictif de l'arythmie, on n'en comprend pas à l'heure actuelle les modes d'action intimes. L'amplitude de la VC est déterminée fondamentalement par l'intensité du couplage intercellulaire dans des préparations pluricellulaires et par la durée du potentiel d'action (DPA). Afin de compenser le fait que la VC soit dépendante de la DPA, nous avons introduit le concept de VC relative (VCR) en normalisant les variations de la VC sur la base des variations concomitantes de la DPA. Nous avons observé qu' I_{Ca} , I_{Kr} et I_{Ks} entraînent une diminution de la VCR tandis qu' I_{Na} a l'effet inverse, ce qui laisse entendre que les courants ioniques jouant un rôle dans la régulation de la rétroaction négative de la DPA tendraient à maintenir la VCR à des valeurs basses. La VCR est aussi influencée par les concentrations intracellulaires de calcium et le potentiel redox des tissus. Les répercussions cliniques de la variabilité de la DPA sont discutées en détail. [Traduit par la Rédaction]

Mots-clés : durée du potentiel d'action, arythmie, canaux ioniques, variabilité battement par battement.

Introduction

Action potential duration (APD) is generally uniform under given experimental conditions; however, there is a small scattering in APD when consecutive action potentials are analyzed. This is defined as beat-to-beat variability or short-term variability (SV) of APD, which has been observed in a variety of mammalian cardiac preparations, including human (Hinterseer et al. 2008, 2009, 2010; Sur et al. 2013; Tereshchenko et al. 2010), canine (Abi-Gerges et al. 2010; Thomsen et al. 2004, 2006; Schneider et al. 2005; van der Linde et al. 2005), rabbit (Jacobson et al. 2011; Michael et al. 2007), and guinea pig (Zaniboni et al. 2000) hearts. SV is usually formulated by the following equation:

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

where  is the short-term variability, APD_n and APD_{n+1} indicate the durations of the n^{th} and $(n+1)^{\text{th}}$ action potentials, respectively, at 90% level of repolarization, and n_{beats} denotes the number of

consecutive beats (typically 20–50) analyzed (Johnson et al. 2010; Szentandrassy et al. 2015).

Hinterseer and coworkers emphasized the predictive value of the increased variability regarding arrhythmia incidence in patients with cardiomyopathy or heart failure and in individuals having ion channel mutations leading to cardiac arrhythmias (Hinterseer et al. 2008, 2009, 2010). These results have been corroborated later using in vivo and in vitro animal models of drug-induced torsades de pointes type arrhythmias by applying D-sotalol, dofetilide, or setindole to suppress the rapidly activating delayed rectifier K^+ current (Abi-Gerges et al. 2010; Thomsen et al. 2004, 2006; van der Linde et al. 2005). Now, it is generally accepted that SV is a good predictor of the torsade-related arrhythmia incidence (Abi-Gerges et al. 2010; Jacobson et al. 2011; Tereshchenko et al. 2010; Thomsen et al. 2004; van der Linde et al. 2005), even better than triangulation or QT prolongation itself (Abi-Gerges et al. 2010; Hinterseer et al. 2008, 2009, 2010; Thomsen et al. 2006). This is because the elevation of SV results automatically in an increased temporal inhomogeneity, which is considered as a substrate for reentrant arrhythmias.

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In spite of the potential clinical importance of SV, its ionic mechanism remained hidden for a long period of time. Although it was evident that stochastic gating of cardiac ion channels is the basic underlying mechanism of SV (Lemay et al. 2011; Pueyo et al. 2011), contribution of the individual ion currents have been elucidated only in the recent years. In the present paper, we review all aspects of SV in multicellular and single cell cardiac preparations, including its ionic mechanism and the factors influencing SV.

SV in multicellular cardiac tissues: role of cell-to-cell coupling

When comparing the variability in healthy multicellular and single cell mammalian preparations, it turned out that SV is much smaller in multicellular cardiac tissues than in single cells (Magyar et al. 2015). This is due to the balancing effect of the neighboring myocytes through the open gap junctions. Zaniboni et al. have elegantly shown, using cell pairs coupled electrically through a 100 M Ω resistance, that SV was decreased in both myocytes after electrical coupling (Zaniboni et al. 2000). In line with this, rotigapeptide, a gap junction opener peptide, was shown to suppress arrhythmogenic discordant alternans in ischemic guinea pig hearts. This indicates that intact cell-to-cell coupling is an important factor to keep APD variability at a low level in vivo (Kjølbye et al. 2008). Because SV is very low in multicellular preparations and, more importantly, because its magnitude is mostly influenced by the degree of cell-to-cell coupling, multicellular preparations are not really suitable for studying the specific ionic mechanisms involved in governing SV.

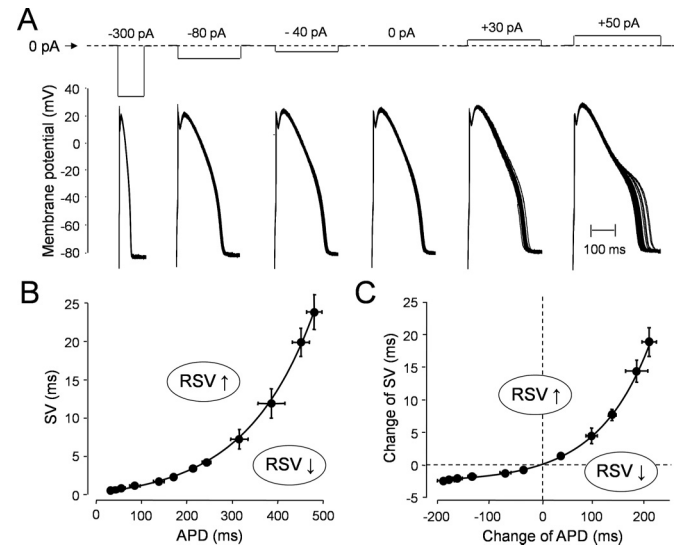
SV in single cardiomyocytes: role of APD and the concept of relative SV

Ion substitution and the application of selective blockers and activators of ion channels are the simplest strategies to identify the role of individual ion currents in SV. Following the latter approach, it became evident that APD itself has a strong influence of SV: SV was sharply increasing with lengthening of action potentials (Heijman et al. 2013; Johnson et al. 2010; Szentandrassy et al. 2015). Indeed, SV was shown to be an exponential function of APD, when APs were lengthened and shortened using inward and outward current pulses, respectively, injected throughout the entire plateau (Szentandrassy et al. 2015; Fig. 1). APD elongation and shortening, induced by current injections, can be basically considered as an "ion-channel-independent" manipulation of APD. Therefore, the exponential curve in Fig. 1B can be used as a reference allowing to visualize the pure consequences of APD changes, which are generally apparent in response to drug actions targeting cardiac ion channels. To eliminate the APD-related changes of SV, the term relative SV (RSV) has been introduced by plotting SV as a function of APD (Fig. 1B). Similar results were obtained when the changes in SV were plotted against the concomitant changes in APD (Fig. 1C). Accordingly, data points located above the curves correspond to increased RSV, while those located under the curves indicate reduction of RSV. Thus, RSV is suitable for studying the specific effect of a drug or intervention on beat-to-beat variability of APD.

Ionic mechanism of variability: contribution of individual ion currents

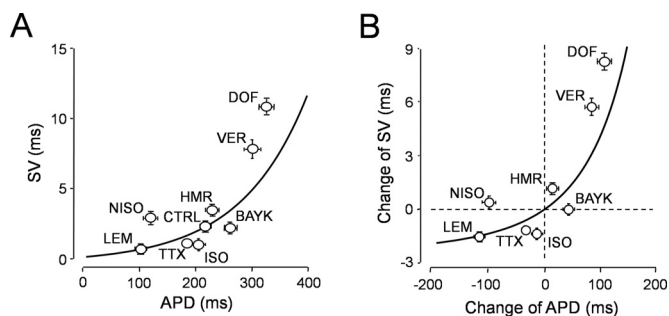
The contribution of individual ion currents to SV was revealed by using selective blockers and activators of ion channels. Suppression of I_{Kr} by dofetilide increased SV in single canine ventricular cells (Johnson et al. 2010) and in vivo rabbit hearts, but failed to modify SV in conscious dogs (Lengyel et al. 2007). In Langendorff-perfused rabbit hearts, I_{Kr} was also suppressed by low concentrations of quinidine and amiodarone: SV was increased by quinidine (Wu et al. 2008a), but not by amiodarone (Wu et al. 2008b). Similarly,

selective inhibition of I_{Ks} by HMR-1556 increased SV in isolated canine myocytes (Johnson et al. 2010), but had no effect on SV under in vivo conditions in dogs and rabbits (Lengyel et al. 2007). However, when applying simultaneous blockade of I_{Kr} and I_{Ks} (using HMR-1556 plus dofetilide), SV was largely elevated in both species (Lengyel et al. 2007). The role of I_{Na} current was studied using ATX-II to enhance and tetrodotoxin (TTX) to suppress I_{Na} . ATX-II increased SV in isolated canine ventricular cells (Johnson et al. 2010) as well as in Langendorff-perfused rabbit hearts (Wu et al. 2008a, 2008b). SV was reduced by TTX in guinea pig ventricular cells (Zaniboni et al. 2000), similarly to high concentrations of quinidine and amiodarone (applied to block I_{Na}) in Langendorff-perfused rabbit hearts (Wu et al. 2008a, 2008b). SV was decreased by isoproterenol when canine myocytes were superfused with isoproterenol in the presence of dofetilide or ATX-II, but increased when isoproterenol was applied following pretreatment with HMR-1556 (Gallacher et al. 2007; Johnson et al. 2010). These results suggest that SV was strongly reduced by I_{Kr} and increased by I_{Na} , while I_{Ks} had probably a weak suppressive effect. However, interpretation of these results is somewhat difficult because the drug actions on SV were not correlated with the concomitant changes of APD. This was performed by Szentandrassy et al., who took APD changes into account and reported the effects of several selective ion channel activators and inhibitors on RSV in canine ventricular myocytes (Szentandrassy et al. 2015; Fig. 2). According to Fig. 1, data points located above and under the curves correspond to increased and decreased RSV, respectively. RSV was increased by dofetilide, HMR-1556, the I_{Na} activator veratridine, and the I_{Ca} blocker nisoldipine. On the other hand, RSV was reduced by TTX and the I_{Ca} activator BAY K8644, while remained unaffected by the ATP-sensitive K^+ channel opener lemakalim. This was direct evidence indicating that RSV was reduced by I_{Ca} , I_{Kr} , and I_{Ks} , in-



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Fig. 2. Effects of selective ion channel activators and inhibitors on relative short-term variability (SV) to demonstrate the contribution of the corresponding current to beat-to-beat variability (Szentandrassy et al. 2015). Panels (A) and (B) show plots of SV versus action potential duration (APD) and drug-induced changes of SV versus drug-induced APD changes, respectively. CTRL, pooled control; DOF, 300 nmol/L dofetilide; VER, 100 nmol/L veratridine; HMR, 500 nmol/L HMR 1556; NISO, 1 μ mol/L nisoldipine; LEM, 300 nmol/L lemakalim; BAYK, 20 nmol/L BAY K8644; TTX, 3 μ mol/L tetrodotoxin; and ISO, 10 nmol/L isoproterenol. The exponential curves are identical to those shown in Fig. 1.



creased by I_{Na^+} and not influenced by background K^+ conductances, like I_{K-ATP} or I_{K1} (Szentandrassy et al. 2015).

Without questioning the role of the stochastic nature of channel gating in beat-to-beat variability (Lemay et al. 2011; Pueyo et al. 2011), the above results provided an essentially new interpretation of the phenomenon. This interpretation suggests that the well-known negative feedback regulation of APD (based on the finely tuned and voltage-coupled interplay between the amplitude of I_{Ca} and the activation of repolarizing K^+ currents) may be an important factor in the modulation of SV. In line with this theory, I_{Na} is not expected to decrease SV, because the late Na^+ current is activated predominantly during the terminal phase of the plateau (Horváth et al. 2013; Liu et al. 1992; Zaza and Rocchetti 2013), where there is no room for further activation of I_{Kr} or I_{Ks} . In contrast to $I_{Na-late}$, I_{Ca} has the highest amplitude at the beginning of the plateau phase having stronger influence on the subsequent activation of I_{Kr} and I_{Ks} (Bányász et al. 2003). In addition, because the membrane resistance is extraordinarily high during the late plateau (Zaniboni et al. 2000), a relatively small inward shift in the net membrane current may result in a large instability of APD (Bányász et al. 2009; Bárándi et al. 2010). This also gives the physical basis of the logarithmic relationship between SV and APD, as was predicted by the simulations of Heijman et al. (2013) and confirmed experimentally by Szentandrassy et al. (2015). As shown in Fig. 2, RSV was decreased by a low concentration of isoproterenol giving a strong support to this interpretation, because isoproterenol is known to increase massively both I_{Ca} and I_{Ks} , and to a smaller extent I_{Kr} , in canine ventricular myocardium (Harmati et al. 2011).

I_{Kr} , I_{Ks} , and I_{Ca} , therefore, appear to reduce SV. Blocking these currents directly using class 3 and class 4 antiarrhythmics, or indirectly by class 2 drugs (beta receptor blockers), on the other hand, results in increased SV. An important clinical implication of these findings is that the antiarrhythmic potency of ion channel blockers acting on I_{Kr} , I_{Ks} , and I_{Ca} may be limited by the concomitant effect of these drugs to increase beat-to-beat variability of APD.

Factors influencing RSV

Ischemia-reperfusion injury, a massive source of life-threatening cardiac arrhythmias, is also associated with increased beat-to-beat variability of APD (Kormos et al. 2014; Sarusi et al. 2014). Reperfusion of the ischemic tissue leads to increased Ca^{2+} load, acidosis, and oxidative shift in the tissue redox potential. Elevation of

$[Ca^{2+}]_i$ and decrease of intracellular pH results in disconnection of gap junctions (Dekker et al. 1996; Maurer and Weingart 1987; White et al. 1990) causing conduction block (De Groot and Coronel 2004; Kléber 1992). In addition, reduced electrical coupling also increases SV in multicellular preparations (Kjølbye et al. 2008; Zaniboni et al. 2000). Beyond these effects, evident in multicellular cardiac tissues, recent results indicated that RSV was increased by elevation of $[Ca^{2+}]_i$ in single cardiomyocytes as well. Reduction of $[Ca^{2+}]_i$ by chelating intracellular Ca^{2+} using BAPTA-loaded cells (BAPTA-AM) decreased, while increasing intracellular Ca^{2+} using the Ca^{2+} ionophore A23187 increased RSV (Kistamás et al. 2015a).

This effect of intracellular BAPTA was more pronounced when early afterdepolarizations were evoked by dofetilide pretreatment (Horváth et al. 2015). It was revealed that Ca^{2+} released from the sarcoplasmic reticulum plays a critical role, because RSV was equally decreased by ryanodine and cyclopiazonic acid (Kistamás et al. 2015a). The former inhibits the ryanodine receptor (Meissner 1986), whereas the latter blocks the refilling of the sarcoplasmic reticulum (Takahashi et al. 1995; Yard et al. 1994). However, both agents result in a smaller Ca^{2+} release from the sarcoplasmic reticulum. Spontaneous diastolic Ca^{2+} release, evoked by high concentrations of isoproterenol (100 nmol/L), was also shown to increase SV and APD (Johnson et al. 2013). Low concentrations of isoproterenol (10 nmol/L), on the other hand, reduced both parameters in the same species (SV to a larger extent than APD, so RSV was markedly decreased by 10 nmol/L isoproterenol) (Szentandrassy et al. 2015). The concentration-dependent differences observed in the isoproterenol effects are likely consequences of the combination of 2 actions of isoproterenol: the enhancement of I_{Ca} , I_{Ks} , and I_{Kr} , and the elevation of $[Ca^{2+}]_i$. A relatively low concentration of isoproterenol is sufficient to activate the transmembrane ion currents (the respective EC_{50} values are 15.3, 14.5, and 13.7 nmol/L for I_{Ca} , I_{Ks} , and I_{Kr}) (Szentandrassy et al. 2012), while higher isoproterenol concentrations are required to overload the cells with Ca^{2+} . As it has been discussed previously, RSV is reduced by the former but increased by the latter effect of isoproterenol.

The role of the sodium-calcium exchanger (NCX) in beat-to-beat variability has been also studied (Kistamás et al. 2015a). A moderate concentration (300 nmol/L) of SEA0400, a relatively selective inhibitor of NCX, increased SV, while APD was concomitantly shortened, indicating an elevation of RSV by SEA0400. It is not clear, however, that this effect was a direct consequence of suppression of the NCX current (in this case, NCX itself should be considered as a reducer of RSV) or, alternatively, the changes in RSV were associated with the consecutive changes in Ca^{2+} handling.

The mechanism of the $[Ca^{2+}]_i$ -dependent modulation of RSV is not fully understood, although alterations in Ca^{2+} -dependent ion currents (e.g., augmentation of the Ca^{2+} -dependent inactivation of I_{Ca} resulting in a reduction of I_{Ca} amplitude) are likely to be involved. It must be borne in mind, however, that the proarrhythmic potency of Ca^{2+} overload is accentuated in multicellular preparations by the concomitant disconnection of gap junctions.

Gross changes in redox potential occur in cardiac tissues during ischemia-reperfusion injury, characteristically accompanied by an increased incidence of arrhythmias (Becker and Ambrosio 1987). In a recent study, the effect of redox potential changes on beat-to-beat variability has been demonstrated (Kistamás et al. 2015b). RSV was decreased by applying a reductive environment (containing DL-dithiothreitol, reduced L-glutathione, and L-ascorbic acid). However, shifting the redox potential in the oxidative direction by H_2O_2 strongly increased RSV and resulted in development of early afterdepolarizations. These effects of H_2O_2 could be prevented by pretreatment with reducing agents, indicating that the elevation of RSV was really caused by the oxidative shift (Kistamás et al. 2015b). Because similar changes are known to occur under conditions of oxidative stress, it is plausible to assume that the increased RSV due to oxidative shifts may contribute to the higher arrhythmia incidence observed under these pathological condi-

tions. Regarding the possible underlying mechanism, it was speculated that the increased late Na^+ current combined with the elevated $[\text{Ca}^{2+}]_i$ may probably be responsible for the elevation of RSV. Both changes are known to be consequences of an oxidative shift in the redox potential. The amplitude of Na^+ current was increased by H_2O_2 in rabbit ventricular cells due to the impaired fast inactivation (Xie et al. 2009), and I_{Na} was shown to increase RSV (Heijman et al. 2013; Szentandrassy et al. 2015). In addition, elevation of $[\text{Na}^+]_i$ is known to be followed by intracellular Ca^{2+} accumulation. Indeed, accumulation of cytosolic Ca^{2+} was observed with H_2O_2 in rabbit ventricular cells (Anzai et al. 2000; Goldhaber and Liu 1994; Xie et al. 2009; Zissimopoulos and Lai 2006) and elevated $[\text{Ca}^{2+}]_i$ has been reported to increase the beat-to-beat variability of APD (Johnson et al. 2013; Kistamás et al. 2015a; Szentandrassy et al. 2015). However, in the absence of relevant voltage clamp data, the role of I_{Na} remains to be supported experimentally.

Acidosis, the third consequence of an ischemia-reperfusion injury, increases beat-to-beat variability of APD in multicellular preparations due to the H^+ -induced closure of the gap junctions and, therefore, it is proarrhythmic (White et al. 1990). In contrast, RSV was not influenced by ± 1 pH unit change in isolated canine ventricular myocytes (Magyar et al. 2016), suggesting that RSV is increased during ischemia-reperfusion injury by the Ca^{2+} overload and the redox shift, but not by acidosis.

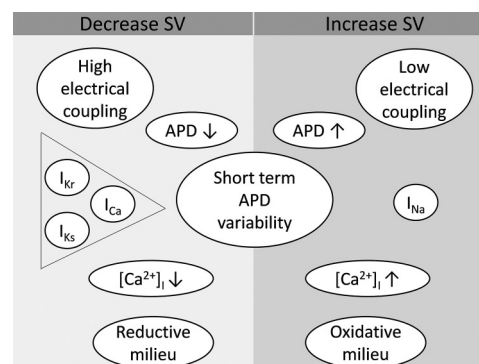
RSV was also increased at high driving rates in canine ventricular cells (Johnson et al. 2010) even if the records with action potential alternans were excluded from the analysis (Szentandrassy et al. 2015). Although the underlying mechanism was not studied directly, it is reasonable to assume that the Ca^{2+} overload, caused by the high stimulation frequency, might be responsible for this effect.

Changes in temperature also have influence on RSV, which was increased when the superfusate was warmed from 37 to 38–41 °C in canine cardiomyocytes (Magyar et al. 2016). 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).

In silico analysis

Because SV is believed to be a consequence of stochastic gating of ion channels, the relative contribution of stochastic fluctuation of the individual channels/currents were analyzed in silico. Depending on the animal model used for the analysis, the contribution of 3 currents was dominant. In a guinea-pig-based model, the stochastic fluctuation of I_{Ks} and late I_{Na} were the major sources of APD variability (Lemay et al. 2011; Pueyo et al. 2011), while in a canine/human model, late I_{Na} and I_{Kr} were the major sources of APD variability (Heijman et al. 2013). Notably, the relative contribution of these currents to ventricular repolarization is different in these species. In dogs and humans, I_{Kr} is the main repolarizing ion current, while in guinea pigs, I_{Ks} is the main repolarizing ion current (Varró et al. 2000; Virág et al. 2001). Interestingly, fluctuations of I_{Ca} , the current mediating inward current during almost the entire plateau, had much less impact (Heijman et al. 2013; Lemay et al. 2011). These simulations can detect correlation between APD variability and the fluctuation of channel gating of a particular ion channel type, while keeping the total conductance for the given ion (number of channels \times single channel conductance) constant. Under real-life conditions, such as when an ion channel blocker is applied, specific membrane conductances are modified. This should be taken into consideration when the experimental results obtained with selective ion channel blockers (Szentandrassy et al. 2015) are compared with predictions of in silico models.

Fig. 3. Factors decreasing (left panel) or increasing (right panel) the short-term variability (SV) of action potential duration (APD). High electrical coupling reflects the physiological status of electrical cell-to-cell coupling in multicellular cardiac tissue. Low electrical coupling reflects situations resulting in compromised electrical cell-to-cell coupling. Arrows (\downarrow and \uparrow) indicate deviations from the physiologically normal range of values of the particular parameter in the negative or positive direction, respectively. I_{Kr} , I_{Ks} , and I_{Ca} are grouped together to reflect their interdependent role in the feedback regulation of APD. $[\text{Ca}^{2+}]_i$ stands for intracellular calcium concentration. Reductive and oxidative milieu indicate shifts of redox potential of the cell interior in the reductive or oxidative direction, respectively.



Summary

As has been pointed out in this review, several factors were found to modulate beat-to-beat variability in mammalian cardiac tissues (Fig. 3). Reduction of gap junction conductance in multicellular preparations and increased APD in single cardiomyocytes were the most prominent factors increasing SV. Importantly, SV was an exponential function of APD. To balance this influence of APD on SV, the concept of RSV has been introduced (Magyar et al. 2016; Szentandrassy et al. 2015). RSV was increased by elevation of temperature, heart rate, and cytosolic Ca^{2+} concentration, and also by oxidative shifts in the tissue redox potential. Accordingly, the changes in RSV during ischemia-reperfusion injury or fever have been discussed. However, the most prominent effects on RSV were observed due to alterations of the transmembrane ion currents; more specifically, RSV was increased when I_{Kr} , I_{Ks} , and I_{Ca} were suppressed, or I_{Na} was increased (Szentandrassy et al. 2015).

Implications for the future

Factors modulating beat-to-beat variability of APD are known to be present under conditions of many cardiac disorders potentially associated with severe cardiac arrhythmias. This group contains almost all types of the inherited long QT syndrome, caused by mutations of ion channels mediating I_{Kr} , I_{Ks} , and I_{Na} (Goldenberg and Moss 2008; Schwartz et al. 2012). Acquired forms of the long QT syndrome are typically related to drugs or nutrients that decrease the intensity of I_{Kr} , including anti-allergic compounds, antipsychotics, antipsychotics, nonsteroid anti-inflammatory drugs, or simple grapefruit juice (Gupta et al. 2007; Zitron et al. 2005). Common in the action of these agents is that they reduce the repolarization reserve of cardiac cells (Biliczki et al. 2002). Similarly, diseases like idiopathic cardiomyopathy, cardiac hypertrophy, or heart failure, in addition to the characteristically altered cellular Ca^{2+} handling, may cause remodeling of cardiac ion channels. Ion channel remodeling involves the reduction of K^+ current densities in many cases, compromising the repolarization reserve (Volders et al. 1999). Because SV was found to be one of the best arrhythmia predictors, it is logical to incorporate automated, ECG-aided SV analysis into the long-term follow-up strategy of these patients.

The other field where examination of SV or RSV would be highly beneficial is the screening of athletes. Although the incidence of

sudden cardiac death (typically due to ventricular fibrillation) is relatively low in the gross population (only 1/50 000 to 1/100 000), its prevalence in top athletes is close to 4-fold (Maron 2007; Pigozzi and Rizzo 2008). These individuals usually display adaptive hypertrophy (Atchley and Douglas 2007; Di Paolo and Pelliccia 2007; Scharhag et al. 2002) and may apply drugs or medications known to diminish the repolarization reserve (see the list above). Combination of a congenital or acquired long QT syndrome with the adaptive cardiomyopathy may be potentially fatal for athletes (Basavarajaiah et al. 2007; Ng and Maginot 2007; Kapetanopoulos et al. 2006). Therefore, the most risky cases could be easily screened out using determination of SV under normal, or probably more effectively, under “provoked” conditions, which could be followed by the more expensive genetic tests in the positive cases (Varró and Baczkó 2010).

Conflict of interest statement

The authors declare that there is no conflict of interest associated with this work.

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