Ventricular rate smoothing for atrial fibrillation: a quantitative comparison study

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Aims To quantitatively compare the ventricular rate-smoothing (VRS) effects of different ventricular pacing (VP) protocols for atrial fibrillation (AF).

Methods and results Using a recently developed open-source model that can simulate the ventricular response in AF and VP, the performance of fixed-rate pacing and four previously published VRS algorithms were assessed by the mean RR (mRR), the root mean square of successive RR differences (RMSSD), the percentage of ventricular senses (VS%), and the percentage of short RR intervals (sRR%). All pacing protocols cause rate-dependent reduction of RMSSD, VS%, and sRR% with or without shortening of mRR compared to spontaneous AF. Fixed-rate pacing was more sensitive to the intrinsic rate than the VRS algorithms. The performance was generally comparable between different VRS algorithms, although higher mRR and VS% can be achieved at the expense of larger RMSSD and sRR%.

Conclusion The effect of VP on ventricular rhythm in AF depends on both intrinsic rate and the aggressiveness of the pacing protocol. Adequate rate control is necessary for effective operation of the VRS algorithm. Choosing VRS algorithm should balance between the beneficial effects of rate regularization and the negative effects of increasing heart rate and percentage of VP.

KEYWORDS
Ventricular rate smoothing; Ventricular pacing; Atrial fibrillation; RR interval

Introduction

Atrial fibrillation (AF) remains the most common clinical tachyarrhythmia that causes significant morbidity and mortality. Converging evidence suggests that the irregular ventricular rhythm in AF had adverse haemodynamic effects independent of the fast ventricular rate.

Previous studies have demonstrated that some specially designed ventricular pacing (VP) protocols could reduce the ventricular irregularity in AF. The ventricular rate-smoothing (VRS) algorithms were perceived advantageous than the fixed-rate VP scheme because the former could automatically vary the pacing cycle length (PCL) based on measured ventricular rate and/or its regularity. On the other hand, some of these VRS algorithms can result in aggressive VP and unconditional suppression of intrinsic ventricular depolarization, which may offset the benefit offered by the rate regularization. Moreover, what has been missing is the objective comparison between various VRS methods under different rate and rhythm conditions present in different AF populations. Unfortunately, a clinical trial to address this challenge, albeit highly desired, is not practical due to the heterogeneity of pacemaker models from different manufactures, the difficulty of patient enrolment, and the lack of financial support.

An alternative solution is to compare different VRS algorithms through computer simulations based on a standard test platform. Although several models have been proposed to explain the rate stabilization effect of VP in AF, controversy remains due to some conflicting evidence. By treating the AV junction (AVJ) as a lumped structure, Cohen et al. showed that their model could account for most known statistical properties of the RR intervals in AF. However, several important physiological properties of the heart were missing from their model, and the effect of VP was also omitted.

Recently, a novel AF–VP model was developed to elucidate the effects of VP on the ventricular rhythm during AF. This model can be viewed as an extension and enhancement of Cohen’s AF model, by taking into account VP, physiological conduction delays, and electrotonic modulation in the AVJ. It has been demonstrated that this model could explain most experimental observations, including the various patterns of RR interval distribution in AF, the biphasic relationship between atrial and ventricular rates in AF, and the intrinsic rate-dependent stabilization effects of VP. We have further validated this model through simulated atrial pacing protocols, which are simpler-case scenarios by factoring out the randomness of AF and the interactions with VP. Specifically, we have shown this model could reproduce the following major findings reported in a previous study during application of standard atrial pacing protocols in isolated rat hearts: (a) a step change of the atrial cycle length is accompanied by a
transient adaptation of the AV conduction time towards a new steady state; (b) the AV conduction time of a premature atrial stimulus is related to steady-state AV conduction time of the preceding cycles; (c) a blocked impulse within the AV node affects its refractoriness and conduction properties; (d) an atrial extrasystole following a sequence of steady atrial intervals can result in longer or shorter RR interval; (e) alternately short and long atrial cycle lengths can result in relatively stable RR intervals; and (f) sufficiently high atrial rate can result in progressively lengthening of AV conduction time and periodic AV block (Wenckebach phenomena). More recently, we have applied this AF–VP model to further examine the role of ventricular conduction time in rate stabilization for AF, inspired by a clinical study that found no measurable difference in VRS effect between pacing the right ventricular apex and the His bundle. We have found that longer ventricular conduction time results in slightly longer PCL to achieve 95% VP. The limited effect of ventricular conduction time on rate stabilization could be attributed to the multi-level interactions between antegrade waves induced by AF and the retrograde waves induced by VP.

In view of above, in this study, we apply this computer model to quantitatively evaluate the performance of four previously published VRS algorithms and compare with the fixed-rate VP protocols.

**Methods**

**Computer model**

The AF–VP model was described in detail in Lian et al. To facilitate its use and further improvement, the model’s source code has been made freely available on PhysioNet, an online forum for the dissemination and exchange of recorded and simulated biomedical signals and archives of open-source software. Recently, the software architecture and design flowcharts of the AF–VP model have also been provided in an open access format.

The model consists of four inter-connected modules: AF generator, AVJ, ventricle, and electrode. The AF generator outputs random AF impulses whose arrival is modelled as a truncated Poisson process with a mean rate . Conversely, retrograde conducted waves escaping the AVJ can collide with an imminent AF impulse or reset the timing cycle of the AF generator.

The AVJ is treated as a lumped structure with defined electrical properties mimicking those of individual AV nodal cells. As illustrated in Figure 1A, the action potential of the AV nodal cells has five phases. The cell is depolarized (Phase 0) when its membrane potential crosses the depolarization threshold. Then the cell repolarizes (Phases 1–3) and returns to the resting potential (Phase 4).

The refractory period, when no new action potential can be initiated, begins with Phase 0 and extends into Phase 3. The AV nodal cells can depolarize spontaneously due to gradual increase of the membrane potential in Phase 4. These properties are abstracted in the AVJ module depicted in Figure 1B. The AVJ fires when its membrane potential \( V_n \) reaches the threshold \( V_r \). The activation of AVJ starts a refractory period, when the AVJ is not responsive to any stimulation. After the refractory period, \( V_m \) returns to the resting potential, \( V_s \), and starts to rise linearly at a rate \( dV/dt \). During Phase 4, each AF impulse invading the AVJ causes a step increase of \( V_n \) by the amount \( \Delta V \), whereas the \( V_m \) is brought to \( V_r \) immediately if the AVJ is penetrated by a VP-induced retrograde wave. The firing of the AVJ generates an activation wave, which starts an antegrade or retrograde AV conduction according to the direction of activation. If the AVJ is retrograde activated while an antegrade wave has not finished its AV conduction (or vice versa), a collision within the AVJ occurs that annihilates the waves in both directions. Realistic properties of the AVJ, such as the recovery-dependent conduction delay and refractory period, as well as the electrotonic modulations in AVJ due to concealed impulses, are also incorporated in the model.

The ventricle is simplified as a conduction compartment with bi-directional conduction delays. The completion of an antegrade AV conduction starts an antegrade wave in the ventricle towards the electrode, whereas the delivery of a VP generates a retrograde wave towards the AVJ. When both antegrade and retrograde waves are present in the ventricle, a ventricular fusion beat manifests, causing the extinction of both waves.

The ventricular electrode is connected to a pacing device operating in demand mode. If an activation wave propagates to the electrode after an antegrade ventricular conduction delay, a ventricular sense (VS) occurs that inhibits the scheduled VP, whereas the timeout of the PCL triggers the delivery of VP. The PCL can be fixed (e.g. VVI mode), or dynamically adjusted according to the designed VP protocol (e.g. VRS algorithms).

**Ventricular rate-smoothing (VRS) algorithms**

Four previously published VRS algorithms are compared.

1. The dynamic overdrive pacing (DOP-VRS) algorithm increases the PCL by 10 ms after each paced beat, whereas decreases the PCL by 1 ms after each sensed beat.

2. The flywheel-VRS continuously monitors the mean ventricular rate (average over eight beats). Any sudden decrease in ventricular rate of \( >2.5 \) ppm would be interrupted by VP at a rate equal to \( 2.5 \) ppm below the measured heart rate. The rate of pacing then gradually decreases at 0.25 ppm towards the programmed lower rate limit.

3. The MADIFF-VRS continuously measures the normalized mean absolute difference (MADIFF) of eight consecutive RR intervals. The VP rate is increased by 5 ppm when MADIFF \( >0.10 \), or...
decreased by 5 ppm if MADIFF does not exceed 0.10 for 64 RR cycles.

(4) The adaptive-VRS measures RR interval and dynamically adjusts the PCL towards a predefined physiological zone with upper boundary \( P_{\text{hi}} = 800 \) ms and lower boundary \( P_{\text{lo}} = 600 \) ms. If \( RR < P_{\text{lo}} \), then set \( PCL = RR + (1000 - RR)/8 \). If \( RR > P_{\text{hi}} \), then update \( PCL = RR - (RR - 700)/8 \). If \( P_{\text{lo}} \leq RR \leq P_{\text{hi}} \), then the PCL is unchanged after a VS, or increased after a VP (same as RR \( \leq P_{\text{lo}} \)).

For all VRS algorithms, the lower and upper rate limits are respectively set to 50 and 120 ppm. In addition, the rate-smoothing effects of three fixed-rate pacing protocols were evaluated with PCL = 800, 700, and 600 ms, respectively.

**Simulation protocol**

Three AF-VP model parameters that directly affect intrinsic ventricular rate were varied to simulate different patterns of RR intervals in AF: the mean arrival rate of AF impulses \( \lambda \), the strength of the AF impulse \( \Delta V \), and the AVJ spontaneous depolarization rate \( dV/dt \). In all simulations, we fixed the difference between depolarization threshold and the resting potential \( V_t - V_r \) to 50 mV.

For each model configuration and each VP protocol, 100 trains of 500 RR intervals were generated by the model. Each sequence of steady-state RR intervals (last 300 cycles) [The initial 200 RR intervals of the sequence were excluded in calculating the metrics because it can take 100 beats or more for DOP-VRS and MADIFF-VRS to reach the steady state (see Results).] was analysed to obtain the following metrics: the mean RR interval (mRR), the root mean square of successive RR differences (RMSSD), the percentage of ventricular senses (VS%), and the percentage of short RR intervals (sRR%) that are \(<500\) ms.

**Statistical analysis**

Each of the above four metrics were first summarized by calculating their mean and standard deviation from the 100 runs of RR series that corresponds to specific model configuration and VP protocol. For data in which two variables were compared, the paired t-test was used and a level of \( P < 0.05 \) was required for statistical significance. Specifically, the metrics of AF (no VP) were compared with those of VP protocols (fixed-rate VP and four VRS algorithms), and the metrics of DOP-VRS, flywheel-VRS, and MADIFF-VRS were respectively compared with those of the adaptive-VRS.

**Results**

**Figure 2** plots some exemplary RR intervals (500 beats each) in AF with (a) no VP, (b) fixed-rate VP with PCL = 800 ms, (c) fixed-rate VP with PCL = 700 ms, (d) fixed-rate VP with PCL = 600 ms, (e) DOP-VRS, (f) flywheel-VRS, (g) MADIFF-VRS, and (h) adaptive-VRS, respectively. In these examples, \( \lambda = 5/s, \Delta V = 15 \text{ mV}, dV/dt = 30 \text{ mV/s} \).

The RR intervals of spontaneous AF are random and irregular, ranging between 0.2 and 1.2 s (Figure 2A). As expected, all VP protocols (Figure 2B–H) effectively regularize the ventricular rate through ventricular pacing that eliminates long RR intervals. In agreement with previous studies, the incidence of rapid intrinsic beats (e.g. with RR \(<500\) ms) is also reduced. Fixed-rate VP protocols (Figure 2B–D) result in unconditional elimination of all RR intervals longer than the programmed PCL. In addition, higher pacing rate is associated with more suppression of the intrinsic ventricular cycles. On the other hand, all four VRS algorithms (Figure 2E–H) dynamically adjust the pacing rate (or PCL), while the paced beats tend to be clustered. Particularly, the adaptive-VRS (Figure 2H) shows wider range of PCL, and the paced cycles are intercalated with many sensed cycles that are around the predefined physiological zone (600–800 ms). In contrast, all other three VRS algorithms (Figure 2E–G) result in more aggressive VP and fewer intrinsic RR intervals. Also note that while the flywheel-VRS and adaptive-VRS algorithms immediately take control of the rhythm from the beginning of the episodes, it takes about 100 beats or more for the DOP-VRS and MADIFF-VRS algorithms to reach the steady states (i.e. relatively stable range of PCL).

**Figure 3** compares the metrics of RR intervals in AF with fixed-rate VP protocols (PCL = 800, 700, and 600 ms) at three different AF rates (\( \lambda = 3, 5, 7/s \)), while fixing \( \Delta V = 15 \text{ mV} \) and \( dV/dt = 30 \text{ mV/s} \). Compared to AF, all fixed-rate VP protocols cause regularization of the ventricular response, suppression of conducted beats, and reduction of short intrinsic cycles, as evidenced by the decrease of RMSSD, VS%, and sRR%, respectively. The fixed-rate VP protocols have relatively less impact on the ventricular rate, and the mRR could be shorter or no different than that of lone AF.

Likewise, **Figure 4** shows the metrics of RR intervals in AF and four VRS algorithms at various AF rates (\( \lambda = 3, 5, 7/s \)), with fixed \( \Delta V = 15 \text{ mV} \) and \( dV/dt = 30 \text{ mV/s} \). Compared to AF, all VRS algorithms decrease the mRR, RMSSD, VS%, and sRR% (all \( P < 0.0001 \), except that \( P = NS \) for mRR of adaptive-VRS vs. AF). The efficacy of VRS was generally comparable between DOP, flywheel, and MADIFF with respect to mRR, RMSSD, VS%, and sRR%. In contrast, adaptive-VRS tends to have higher mRR and VS% at the expense of larger RMSSD and sRR%. In addition, **Figures 3 and 4** show that the fixed-rate VP protocols are more sensitive to the intrinsic rate than the VRS algorithms, evidenced by steeper increase in VS% as the intrinsic rate goes higher.

Similar comparisons between AF and VRS algorithms are shown in **Figure 5** (for various \( \Delta V = 15, 20, \) and 25 mV, while fixing \( \lambda = 5/s \) and \( dV/dt = 30 \text{ mV/s} \)), and **Figure 6** (for various \( dV/dt = 20, 30, \) and 40 mV/s, while fixing \( \lambda = 5/s \) and \( \Delta V = 15 \text{ mV} \)), respectively. Consistent to **Figure 4**, all VRS algorithms (vs. AF) significantly reduces mRR, RMSSD, VS%, and sRR%, whereas the effect of adaptive-VRS is more moderate compared to other three VRS algorithms.

**Figures 3–6** also show that for all VP protocols, the rate-smoothing effect depends on the intrinsic ventricular rate in AF. Lower intrinsic rate (smaller \( \lambda, \Delta V, dV/dt \)) results in more paced beats that eliminate long cycles. Contrariwise, VP becomes less effective at higher intrinsic rate (larger \( \lambda, \Delta V, dV/dt \)) due to more frequent sensing of sRR.

**Discussion**

This study represents the first quantitative comparison of different pacing protocols for VRS in AF. The optimal use of the VRS algorithms remains uncertain, partially because the initial clinical studies have been limited to small and specific patient populations. In this regard, the recently developed AF–VP model provides a unique platform to quantitatively evaluate different VRS algorithms under different AF conditions.

In this study, four metrics have been used to assess different aspects of the RR interval dynamics. The mRR is the reciprocal of heart rate, which must be adequately controlled
during VRS to avoid pacing-induced tachycardiomyopathy. The RMSSD is a metric comparable to the mean absolute difference between consecutive RR intervals, both of which measure beat-to-beat RR variance. They are preferable regularity indices than the standard deviation or range of RR intervals, because the target of VRS is to smooth the beat-to-beat (rather than global) cycle length variation, which has adverse haemodynamic effects. The VS% is a metric reflecting the VP aggressiveness, which should be balanced while seeking to regularize the ventricular rate. The sRR% is another important metric (yet has received little attention), because sRR can severely compromise the stroke volume in AF.

Consistent with previous findings, we have shown that all VRS algorithms, including the fixed-rate VP protocols, not only can eliminate long ventricular pauses, but also can suppress short intrinsic RR intervals. Although the underlying mechanism has been a matter of debate, our previous analysis suggested it could be explained by the multi-level interactions between the AF-induced antegrade waves and the VP-induced retrograde waves.

Previous studies have yielded mixed results regarding the effect of VRS on ventricular rate. While some studies found no difference in ventricular rate while running VRS, others showed increased heart rate during VRS compared.
These discrepancies could be explained by: (1) the differences in the VRS algorithms (fixed-rate VP, DOP, flywheel, and MADIFF); (2) the difference in intrinsic rate and rhythm of the AF episodes (e.g. intrinsic heart rate varied from 65 bpm to 80–95 bpm and up to 100 bpm); (3) the difference in experimental protocols (e.g. rest vs. exercise, acute vs. chronic); and (4) the difference in sample size (ranged from n=8 to n=90). Using the present AF–VP model as a standard test platform, we have demonstrated that all VP protocols cause rate-dependent reduction of ventricular irregularity (RMSSD) with or without shortening of the mean cycle length (mRR) compared to AF (Figures 3–6).
Figure 5  Summary of (A) mRR, (B) RMSSD, (C) VS%, and (D) sRR% in AF with four VRS algorithms at various $\Delta V$ (15, 20, and 25 mV), with fixed $\lambda = 5/s$ and $dV/dt = 30$ mV/s. Statistical comparison was performed between the metrics of AF and those of the VRS algorithms, as well as between the metrics of DOP-VRS, flywheel-VRS, MADIFF-VRS, and those of the adaptive-VRS. *$P < 0.0001$ vs. AF, **$P < 0.0001$ vs. adaptive-VRS.

Figure 6  Summary of (A) mRR, (B) RMSSD, (C) VS%, and (D) sRR% in AF with four VRS algorithms (DOP, flywheel, MADIFF, and adaptive) at various $dV/dt$ (20, 30, and 40 mV/s), with fixed $\lambda = 5/s$ and $\Delta V = 15$ mV. Statistical comparison was performed between the metrics of AF and those of the VRS algorithms, as well as between the metrics of DOP-VRS, flywheel-VRS, MADIFF-VRS, and those of the adaptive-VRS. *$P < 0.0001$ vs. AF, **$P < 0.001$ vs. AF, †$P < 0.0001$ vs. adaptive-VRS.
impact on the ventricular rate could be attributed to the suppression of rapidly conducted beats (sRR%).

This study demonstrated that the fixed VP protocols are sensitive to the intrinsic rate and unconditionally suppress all intrinsic beats slower than the programmed pacing rate (Figures 2 and 3). The efficacy of VRS was generally comparable between DOP, flywheel, and MADIFF algorithms. On the other hand, the adaptive-VRS tends to have slower ventricular rate and preserve more intrinsic cycles, but is associated with more variation in RR intervals and less suppression of short cycles as a trade-off (Figures 4–6). Although it remains unclear how to translate these findings into effects on haemodynamics, symptoms or quality of life, they do provide guidance for choosing appropriate VRS algorithm for individual AF patient with specific ventricular rate and rhythm profile. Also notably, the DOP-VRS and MADIFF-VRS may take some time before reaching stable state of VP (Figure 2). For proximal AF, this delayed response of VRS (e.g. after device mode-switching) may potentially compromise its therapeutic efficacy.

Clinical implications

While the goal of VRS is to improve haemodynamics, it is also known that frequent right ventricular pacing and rapid ventricular rate are both associated increased risk of developing congestive heart failure. Therefore, choosing VRS algorithm should balance between the beneficial effects of ventricular rate stabilization and the negative effects of increasing heart rate and percentage of VP. Individually tailored VRS should be an integral part of the optimal AF management. This study also revealed the potential limitations of the VRS algorithms. On one hand, lower intrinsic ventricular rate could render more aggressive VP and even result in VP saturation. On the other hand, higher intrinsic ventricular rate could reduce the efficacy of VRS due to VP suppression, as being reported during exercise. Therefore, adequate rate control (either drug-based or device-based), which brings the spontaneous ventricular rate to an appropriate level for pacing intervention, should be a prerequisite for gaining additional benefits of rhythm control offered by the VRS algorithm.

Limitations

This study is limited by the nature of simulation. Certainly, a direct experimental validation of the model as well as the findings of this study is needed. On the other hand, the present AF–VP model incorporates many realistic properties of the cardiac conduction system, and can account for most known experimental observations.

In this study, only three model parameters were varied to generate RR intervals in AF, which may not cover all possible scenarios. For example, different random or deterministic processes (other than the Poisson process) can be used to model the AF generator. The antegrade/regrograde AV conduction and/or ventricular conduction can be modified to simulate various degrees of AV–VP interactions. The AVJ refractory properties, including the electrotonic modulation by blocked impulses, can also affect the RR intervals in AF. These variations can be easily implemented using the open-source AF–VP model and our experience with above scenarios has confirmed all major findings of the present study.

In addition, all parameters of the VRS algorithms were fixed in our simulation, although the performance of each VRS algorithm depends on its specific parameter settings. For instance, the flywheel-VRS can be programmed to slow mode or fast mode, and the physiological zone of the adaptive-VRS can be adapted to the sensor rate or the mean heart rate prior to the AF episode. Despite of these limitations, the results of this study provide valuable insights into the behaviour of various VRS algorithms. More importantly, the present AF–VP model provides a unified platform wherein comprehensive AF modelling and variants of VRS algorithms (including future development of new or improved VRS algorithms) could be tested.

Conclusion

The effect of VP on ventricular rhythm in AF depends on both intrinsic rate and aggressiveness of the pacing protocol. Choosing VRS algorithm should balance between the beneficial effects of ventricular rate stabilization and the negative effects of increasing heart rate and percentage of VP. Effective rhythm control by means of VRS requires adequate rate control in AF.

Conflict of interest: J.L., D.M., and V.L. are employees of Micro Systems Engineering Inc. a subsidiary of Biotronik GmbH.

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