Effect of Physiological Changes in Heart Rate Turbulence Using a Lumped Parameter Model

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Abstract

Heart Rate Turbulence (HRT) is a strong risk stratification criterion in patients with cardiac disorders. Several physiological factors affect HRT, e.g., previous heart rate, circadian rhythm. However, the relationship between these factors and HRT still needs to be further clarified. We propose to use a modified version of a detailed lumped parameter model to study the relationship between different physiological factors and the HRT, as quantified by the usual Turbulence Slope (TS) and Turbulence Onset (TO) parameters. We modified a detailed model of cardiac regulation previously developed by Ursino and Magosso, in order to generate the hemodynamic effect of ectopic beats and the subsequent HRT response. The modified version of the model allows to vary three different physiological factors, namely, prematurity, maximum contraction and systole duration of the ectopic beat. Changes in these physiological factors modify the resulting HRT pattern. These results should be taken into account when quantifying HRT by TS and TO parameters, just as the ulterior risk stratification procedure using them.

1. Introduction

Heart Rate Turbulence (HRT) is the physiological response to a spontaneous ventricular premature complex (VPC). In normal subjects consists of an initial acceleration and subsequent deceleration of the sinus heart rate. It has been shown to be a strong risk stratification predictor in patients with high-risk of cardiac disease [1, 2]. Assessment of the HRT is performed using the so-called VPC tachogram, which is constructed averaging the RR-intervals sequences surrounding isolated VPCs, that is, local VPC tachograms. The aim of this averaging procedure is to reduce the noise that masks the HRT pattern in isolated VPCs tachograms. There exists other approaches to filter individual VPCs tachograms using robust denoising techniques [3].

The HRT is assessed by two parameters, Turbulence Onset (TO) and Turbulence Slope (TS). TO represents the amount of sinus acceleration following a VPC, and it is defined as the percentage difference between the heart rate immediately following the VPC and the heart rate immediately preceding the VPC. TS represents the rate of sinus deceleration that follows sinus acceleration, and it is defined as the maximum positive regression slope assessed over any 5 consecutive sinus rhythm RR-intervals within the first 15 sinus rhythm RR-intervals after the VPC [2]. In normal subjects, the initial sinus acceleration following the VPC is characterized by negative values of TO parameter, whereas the subsequent sinus deceleration is characterized by positive values of TS parameter.

It has been documented in the literature the influence of several physiological factors on the HRT [2]. The heart rate modulates the strength of the HRT response. Thus, HRT is reduced at high heart rate. There exist some approaches to correct HRT indexes for heart rate, or to propose new ones [4, 5]. Presence of circadian rhythms in HRT was demonstrated in some studies [6,7]. VPC prematurity also modulate the HRT response. So, in agreement with the baroreflex source of HRT, the more premature the VPC, the stronger the HRT response is. Nevertheless, the effects of VPC prematurity on HRT were analyze in different studies with somewhat conflicting results [2].

Although it has been shown the existence of various physiological factors influencing the HRT, it is necessary to gain a more detailed knowledge on the way these factors modulate the HRT. The usual procedure to assess the HRT implies averaging all the available isolated VPC tachograms. However this procedure could mask the influence of the different physiological factors, considering HRT responses to isolated VPC as equivalents, when they may have different physiological conditions.

In this work, we propose to use a lumped parameter model of the short-term cardiovascular regulation, properly modified in order to reproduce the hemodynamic effect of an ectopic beat (VPC), and the following response

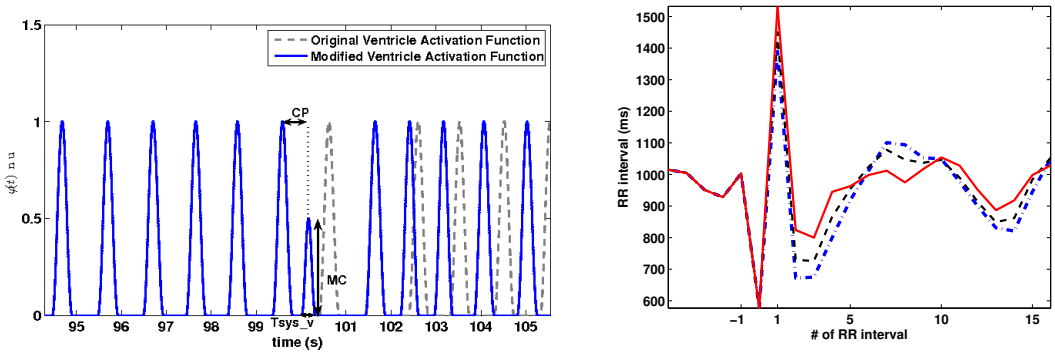

Figure 1. *(a) Ventricle activation function, $\varphi(t)$, modified to generate the hemodynamic effect of an ectopic beat. (b) Simulation of an ectopic beat and the subsequent HRT responses for three different values of the MC parameter using the lumped parameter model with the modified ventricle activation function.*

corresponding to HRT. This controlled environment would allow to analyze the influence of different physiological factors on the HRT pattern.

The structure of the paper is as follow. In Section 2, the lumped parameter model, the proposed modification, and the experimental setup are described. In Section 3 the results of the experiments are reported. Finally, in Section 4, conclusions are presented.

2. Methods

The mathematical model of the short-term cardiovascular regulation, which is the base of this work, was presented in [8]. This model allows to investigate the physiological mechanisms leading to heart rate variability, which extends a previous model [9], by including: a separate distinction of system and pulmonary circulation, sympathetic feedback control loops working on systemic resistance, unstressed volume and heart contractility, sympatho-vagal control of heart period, and the mechanical effect of respiration on venous return. These characteristics were simulated on the basis of existing, previously reported clinical and experimental data.

The regulation mechanisms includes both arterial baroreceptors and lung stretch receptors, which modulate various cardiovascular parameters, namely, systemic peripheral resistance, venous unstressed volume, heart contractility and heart period. Both information sources from the receptors are weighted using proper gains, and combined to modulate the corresponding cardiovascular factor. The heart period control is the only one that involves a balance between the vagal and sympathetic activities, whereas the control is purely sympathetic in the remaining cardiovascular parameters.

The ventricle activity, in the model, is characterize by means of the function $\varphi(t)$, called ventricle activation function. Function $\varphi(t)$ ranges from 0 (complete relaxation) to 1 (maximum contraction).

$$\varphi(t) = \begin{cases} \sin^2\left(\frac{\pi T(t)}{T_{sys}(t)}u\right) & 0 \leq u \leq T_{sys}/T \\ 0 & T_{sys}/T \leq u \leq 1 \end{cases} \quad (1)$$

where T is the heart period, T_{sys} is the duration of systole, and u is a dimensionless variable, that represents the fraction of cardiac cycle (ranging from 0, beginning of systole, to 1, end of systole). The expression for $u(t)$ is.

$$u(t) = \text{frac}\left[\int_{t_0}^{t} \frac{1}{T(\tau)} \text{d}\tau + u(t_0)\right] \quad (2)$$

where the function *fractional part* (frac()) resets the variable $u(t)$ to zero as soon as it reaches the value $+1$.

The ventricle activation function $\varphi(t)$ was modified, in this work, in order to generate the hemodynamic effect of ventricular ectopic beats, so that the model was able to reproduce the physiological response to a VPC, that is, to reproduce the HRT response, which in a healthy subject corresponds to an initial sinus acceleration followed by a sinus deceleration, within the 15-20 beats after the VPC. Figure 1 (a) shows the modified ventricle activation function, including the generation of one ectopic beat. Figure 1 (b) shows the resultant tachogram using the modified model. It can be shown that the model is able to reproduce the usual response to a VPC, that is, the HRT pattern.

The ectopic beat was characterized by three parameters, namely: complementary prematurity (CP), maximum contraction (MC), and systole duration of the ventricular ectopic beat ($Tsys\_v$). CP is defined as a percentage of the original RR-interval, that is, the one that is missed due to the ectopic beat. MC is defined as the maximum value reached by $\varphi(t)$ when the beat is a ventricular ectopic. Generally, MC is in the range $[0, x]$, where $x < 1$.

$Tsys\_v$ is defined as the systole duration of the ventricular ectopic beat, and it is in the range $[0, 0.5]$ seconds.

The aim of the experimental setup was to analyze, using a detailed model, the relationships between the physiological parameters that describe the ectopic beat and the HRT pattern. Parameters TS and TO were computed in order to assess the HRT, for combinations among the physiological parameters, namely:

1. MC = 0.5, $Tsys\_v$ = 0.3 sec, and CP = [10, 20, 30, 40, 50] %;
2. MC = 0.5, CP = 20%, and $Tsys\_v$ = [0.1, 0.2, 0.3, 0.4, 0.5] sec.;
3. $Tsys\_v$ = 0.3 sec., CP = 20%, MC = [0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7].

3. Results

Table 1 shows TS and TO parameters, assessing the HRT, computed simulating the model for 5 different values of the parameter CP, which controls the ectopic beat prematurity. In this experiment, parameters MC and $Tsys\_v$ were fixed to 0.5 and 0.3 sec. respectively. In accordance with the results, the lower the value of the parameter CP (i.e. the greater the prematurity of the ectopic beat) the greater the absolute values of the parameters TS and TO. This implies that the greater the prematurity, the stronger the HRT response is; while the smaller is the prematurity, the flatter is the HRT response. These results are in agreement with the baroreflex source of the HRT, according to which, the HRT responses are stronger to more premature, and thus less hemodynamically efficient VPCs with longer compensatory pauses [2].

Table 2 shows TS and TO parameters computed simulating the model for 5 different values of the parameter $Tsys\_v$, which controls the systole duration of the ectopic beat. In this experiment, parameters CP and MC were fixed to 20% and 0.5 respectively. According to the results, the greater the duration of systole, the lower the absolute value of the parameters TS and TO. These results are consistent with the hypothesis of baroreflex origin, so that the greater the duration of systole, more hemodynamically efficient the ectopic beat is, resulting in a more attenuated HRT response.

Table 3 shows TS and TO parameters computed simulating the model for 7 different values of the parameter MC, which controls the intensity of the ventricle contraction of the ectopic beat. In this experiment, parameters $Tsys\_v$ and CP were fixed to 0.3 sec. and 20% respectively. According to the results, the lower the ventricle contraction, the greater the absolute value of the parameters TS and TO. Again, these results are consistent with the hypothesis of baroreflex origin.

$MC = 0.5$ / $Tsys\_v = 0.3$	CP				
	10%	20%	30%	40%	50%
HRT-TS	75.3	72.4	70.6	69.8	68.9
HRT-TO	−22.8	−21.3	−20	−18.9	−17.9

Table 1. TS and TO parameters, assessing HRT, for different values of the CP parameter.

$MC = 0.5$ / $CP = 20\%$	$Tsys\_v(sec.)$				
	0.1	0.2	0.3	0.4	0.5
HRT-TS	89.0	79.4	72.4	67.3	64.2
HRT-TO	−26.1	−23.4	−21.3	−19.7	−18.4

Table 2. TS and TO parameters, assessing HRT, for different values of the $Tsys\_v$ parameter.

4. Conclusions

We modified a detailed lumped parameter model of the short-term cardiovascular regulation in order to analyze relationships between different physiological factors and HRT, using the controlled simulation environment provided by the model. The ventricle activation function of the original model was modified to model the behavior of the HRT, so that it reproduced the hemodynamic effects of an ectopic beat and the subsequent response of the baroreflex and the autonomic nervous system forming the characteristic pattern of HRT. The ectopic beat was described by three different parameters, namely, complementary prematurity (CP), maximum contraction (MC), and systole duration ($Tsys\_v$).

Three different experiments were performed, each one consisted on the generation of an ectopic beat for different combination of values of the parameters characterizing it. The aim was to study the influence of these parameters in the subsequent HRT response, as assessed by TS and TO parameters.

Thus, we studied the influence of variations in each of the characteristic parameters of the ectopic beat on the subsequent response in the form of HRT, quantified by the usual parameters, TS and TO.

The results show that variations in the characteristic parameters of the ectopic beat modify the HRT response, and therefore change the value of parameters TS and TO. The modification in the HRT response, in the experiments, always agreed with the hypothesis that the baroreflex is a major cause of HRT. Thus, in experiments where the ectopic beat was hemodynamically less efficient, the subsequent HRT was more pronounced, and vice versa. The results were consistent for variations in any of the three parameters studied.

The results of this study support the conclusion that it is necessary to pay attention to the physiological factors affecting the HRT, as these factors may change the pattern of HRT clearly, and by extension modify the values of the parameters TS and TO. Hence, it must be noted that an

$Tsys\_v = 0.3$ $CP = 20\%$	MC						
	0.1	0.2	0.3	0.4	0.5	0.6	0.7
HRT-TS	104.1	106.4	100.1	86.2	72.4	60.6	51.1
HRT-TO	-30.4	-30.2	-28.2	-24.6	-21.3	-18.4	-15.9

Table 3. TS and TO parameters, assessing HRT, for different values of the CM parameter.

attenuation of the HRT can be caused by specific physiological conditions, and not simply by different cardiac situations, which is the basis for risk stratification by HRT.

On the other hand, the usual procedure to quantify the HRT, which implies the averaging of all available VPCs in a monitoring interval (usually 24-hour Holter), may mask the influence of various physiological factors, which obviously will not be constant throughout the monitoring period. This procedure leads to greater complexity in understanding and analyzing the results of HRT quantification by the usual parameters TS and TO, as there is no reference to the physiological conditions for each individual VPC.

Extensions are needed in the model to take into account the influence of physiologically relevant factors, such as heart rate or circadian rhythm. There is clear evidence in the literature of the influence of these physiological factors on HRT. There is also need to establish a comprehensive validation of the modified model using real data, so that it is possible to establish valid quantitative conclusions from the results of the simulation.

The ultimate goal is to establish a characterization framework of the HRT that would allow, in some way, include information of the different physiological condition for individual VPC. Therefore, the characteristic parameters of the HRT would be associated, or normalized, to their environmental physiological conditions.

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