On the Influence of Heart Rate and Coupling Interval Prematurity on Heart Rate Turbulence

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Abstract*—*Objective: **Heart rate turbulence (HRT) has been successfully explored for cardiac risk stratification. While HRT is known to be influenced by the heart rate (HR) and the coupling interval (CI), nonconcordant results have been reported on how the CI influences HRT. The purpose of this study is to investigate HRT changes in terms of CI and HR by means of an especially designed protocol. *Methods:* A dataset was acquired from 11 patients with structurally normal hearts for which CI was altered by different pacing trains and HR by isoproterenol during electrophysiological study (EPS). The protocol was designed so that, first, the effect of HR changes on HRT and, second, the combined effect of HR and CI could be explored. As a complement to the EPS dataset, a database of 24-h Holters from 61 acute myocardial infarction (AMI) patients was studied for the purpose of assessing risk. Data analysis was performed by using different nonlinear ridge regression models, and the relevance of model variables was assessed using resampling methods. The EPS subjects, with and without isoproterenol, were analyzed separately. *Results:* The proposed nonlinear regression models were found to account for the influence of HR and CI on HRT, both in patients undergoing EPS without isoproterenol and in low-risk AMI patients, whereas this influence was absent in high-risk AMI patients. Moreover, model coefficients related to CI were not statistically significant, $p > 0.05$, on EPS subjects with isoproterenol. *Conclusion:* The observed relationship between CI and HRT, being in agreement with the baroreflex hypothesis, was statistically significant ($p < 0.05$), when decoupling the effect of HR and normalizing the CI by the HR. *Significance:* The results of this study can help to provide new risk indicators that take into account physiological influence on HRT, as well as to model how this influence changes in different cardiac conditions.**

***Index Terms*—Coupling interval, electrophysiological study, heart rate, heart rate turbulence, myocardial infarction.**

I. Introduction

HEART rate turbulence (HRT) is the physiological heart rate (HR) response to a spontaneous ventricular premature contraction (VPC). In normal subjects, this response consists of an initial acceleration and a subsequent deceleration in HR. Its absence has been shown to be a powerful risk predictor of cardiovascular events following acute myocardial infarction (AMI) and other cardiac conditions [1], [2]. HRT is usually characterized by turbulence onset (TO) and turbulence slope (TS) parameters. TO represents the degree of sinus acceleration following a VPC and is defined by the relative difference of the averages of the two normal R–R intervals before and after the VPC. TS represents the rate of sinus deceleration after the initial acceleration and is defined as the maximum slope of the linear regression of every five consecutive R–R intervals within the first 15 R–R intervals following the VPC (VPC tachogram) [2], [3].

The baroreflex hypothesis of HRT origin states that increased prematurity of the VPC causes a larger drop in blood pressure, which, in turn, leads to a stronger HRT response [2]. The standard approach to assessing HRT uses signal averaging of all the available isolated VPC tachograms, from which TS and TO are computed. While signal averaging improves the signal-to-noise ratio, it could also mask the influence of different physiological factors on HRT, especially when these factors are not independent [4], [5]. Several physiological factors modulate HRT, namely, HR, VPC prematurity, and circadianity [6]–[8]. However, existing studies present surprisingly contradictory results which, sometimes, are in conflict with the baroreflex hypothesis.

The aim of this study is to assess the interaction of coupling interval (CI) and HR with HRT. Instead of using signal

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averaging, HRT was measured by computing TS on each individual VPC tachogram. For this purpose, data were acquired from patients with structurally normal hearts who underwent electrophysiological study (EPS). A clinical protocol was specifically designed so that the CI was controlled with a programmed cardiac pacing protocol, and the HR was controlled using isoproterenol. The electrophysiological protocol consisted of two substudies: one for analyzing the relationship between HR and HRT, and the other for analyzing the combined effect of HR and CI on HRT. We also analyzed these interactions by using Holter recordings from patients after an AMI episode, so that EPS data, acquired during favorable conditions, could be compared to data from ambulatory monitoring where much higher noise levels are encountered. Suitable regression models were used to replicate previous results [9]–[12], and to explain the combined influence of CI and HR on HRT.

The structure of the paper is as follows. In Section II, the EPS protocol and the Holter database are described. In Section III, the analysis methods and the nonlinear ridge regression models are presented, as well as the statistical method for benchmarking different models. In Section IV, statistical analysis and results are presented. In Section V, the present results are discussed and related to existing results in the literature. Conclusions of this work are presented in Section VI.

II. Clinical Datasets

A. EPS Protocol

Eleven patients (50 ± 15 years, seven women) with structurally normal hearts were included in the study, all of them referred for EPS in the Hospital Universitario Virgen de la Arrixaca (Murcia, Spain). The study was approved by the local Ethics Committee and all participants granted a signed informed consent. The EPS was performed during sinus rhythm after ablation procedures, and sequences of 10 single induced VPCs were delivered every 20 s from the right ventricular apex.

The study was structured into a *fixed CI protocol* (five patients) and a *variable CI protocol* (six patients), designed to investigate the influence of HR on HRT, and the combined influence of HR and CI on HRT, respectively. The HR was increased with isoproterenol, which does so by activating beta-1 adrenergic receptors in the heart [13]. Isoproterenol, 0.8 μg/ml, was delivered as a continuous infusion via a cannulated antecubital vein. The initial rate of infusion was 30 ml/h and then increased in increments of 10 ml/h every 2 min until the target HR of 20–30% above baseline was achieved.

1) Fixed CI Protocol—Influence of HR on TS (Five Patients): The purpose of this protocol was to assess the influence of HR on TS, under the assumption that high HR (short sinus cycle length, SCL) produces a lower TS. There were two phases in this protocol, a control phase and an isoproterenol infusion phase. VPCs were delivered with a prematurity of 70% of the baseline SCL as measured at the start of each phase.

2) Variable CI Protocol—Influence of HR and Prematurity on TS (Six Patients): The purpose of this protocol was twofold: First, to verify CI modulation of TS (under the assumption that a shorter CI is associated with more pronounced HRT); second, to verify the possible interaction between HR and CI suggested in [14]. The variable CI protocol was also delivered in two phases: the control phase and the isoproterenol phase. VPCs were delivered with an initial prematurity of 95% of the baseline SCL, as measured at the start of each phase, after which prematurity was decremented by 70 ms each time until the extrastimulus was no longer captured. Note that the variable CI protocol aimed to decouple the effect of HR and CI on TS modulation, by considering two scenarios: one with low HR (long SCL, control phase) and one with high HR (short SCL, isoproterenol phase). CI was modified to evaluate the isolated influence of VPC prematurity.

Both phases were repeated twice for each protocol in order to obtain enough valid VPC tachograms.

B. AMI Dataset

The AMI dataset consisted of recordings from 61 AMI patients (64 ± 9 years, 18 women) who underwent emergency coronary angiography and, when appropriate, percutaneous coronary intervention. These data were collected in a prospective study at University Hospital Virgen de la Arrixaca [15] in order to evaluate the impact of primary angioplasty on the indication for implantable defibrillator in patients with AMI. 24-h ambulatory electrocardiographic monitoring was done in patients with stable sinus rhythm between two and six weeks after the infarction, and patients with at least one VPC during the monitoring period were included in the study.

There were 58 patients with at least one VPC. The patients were split three ways according to their risk for mortality according to standard HRT classification, high risk (TS $<$ 2.5 ms/R–R interval and TO $>$ 0%), low risk (TS $>$ 2.5 and TO $<$ 0), and moderate risk (TS $<$ 2.5 exclusive or TO $>$ 0) [2], of which the first two subsets were employed. The low-risk subset was comprised of 17 patients (63 ± 12 years, five women) and the high-risk subset was comprised of six patients (70 ± 6 years, one woman). The purpose of the splitting was to compare the low-risk subset with the EPS patients and then to contrast it with the high-risk subset.

III. Regression Modeling of the HRT

We propose to use a data-driven model of HRT as a function of HR and CI for analyzing the hypothesis that TS can be partially explained as a nonlinear function of HR and CI. A nonlinear ridge regression model is considered, which accounts for linear and nonlinear interactions of HR and CI. A nonparametric bootstrap resampling procedure is also proposed for estimating both the standard error and the confidence intervals of the model coefficients [16]. HR is represented as SCL in ms, as in previous studies [9], [17].

Ridge regression data model: Assuming a general form of the nonlinear regression model with $K+1$ terms

$$\widehat{T} = w_0 + w_1\varphi_1 + w_2\varphi_2 + \cdots + w_K\varphi_K \tag{1}$$

the independent variables $\varphi_k, k = 1, \ldots, K$, represent the individual variables SCL, CI, and nonlinear combinations and powers of these variables, and $\widehat{T}$ represents a parameter assessing the HRT, which in this work is TS. If the model coefficients are arranged in a column vector $\boldsymbol{w}$, then the nonlinear regression

TABLE I
DIFFERENT NONLINEAR RIDGE REGRESSION MODELS ANALYZED

Model	Name
$\boldsymbol{\varphi} = [\mathrm{CI}]$	M_1
$\boldsymbol{\varphi} = \left[\mathrm{SCL}, \mathrm{CI}, \mathrm{SCL}^2, \mathrm{CI}^2, \mathrm{SCL}\cdot\mathrm{CI}\right]^T$	M_2
$\boldsymbol{\varphi} = \left[\mathrm{SCL}, \mathrm{CI}, \mathrm{SCL}^2, \mathrm{SCL}^3, \mathrm{CI}^2, \mathrm{CI}^3, \mathrm{SCL}\cdot\mathrm{CI}\right]^T$	M_3

model can be written as

$$T_i = \boldsymbol{w}^T \boldsymbol{\varphi}_i + \varepsilon_i = \widehat{T}_i + \varepsilon_i, \quad i = 1, \ldots, N \tag{2}$$

where $\boldsymbol{\varphi}_i = [1, \varphi_{1,i}, \ldots, \varphi_{K,i}]^T$, and N is the total number of VPCs. In matrix notation, (2) can be rewritten as

$$\boldsymbol{T} = \boldsymbol{\Phi}\boldsymbol{w} + \boldsymbol{\varepsilon} \tag{3}$$

where $\boldsymbol{\Phi} = [\boldsymbol{\varphi}_1 \ \ \boldsymbol{\varphi}_2 \ \ \ldots \ \ \boldsymbol{\varphi}_N]^T$, $\boldsymbol{T} = [T_1, \ldots, T_N]^T$, $\boldsymbol{w} = [w_0, \ldots, w_K]^T$, and $\boldsymbol{\varepsilon} = [\varepsilon_1, \ldots, \varepsilon_N]^T$ is the error term.

To compute $\boldsymbol{w}$, we used the least-squares criterion modified by including a regularization term. This term provides a tradeoff between bias and variance for the model [18], [19]. The influence of the regularization term is controlled by parameter λ

$$\min_{\boldsymbol{w}} \left\{ \|\boldsymbol{T} - \boldsymbol{\Phi}\boldsymbol{w}\|_2^2 + \lambda \|\boldsymbol{w}\|_2^2 \right\}. \tag{4}$$

The solution is given by

$$\boldsymbol{w} = \left(\boldsymbol{\Phi}^T\boldsymbol{\Phi} + \lambda\mathbb{I}\right)^{-1}\boldsymbol{\Phi}^T\boldsymbol{T} \tag{5}$$

where λ is usually estimated using a cross-validation procedure, and $\mathbb{I}$ is the identity matrix [19].

Several regression models have been analyzed in this study. First, a linear regression model (M_1), using CI as explanatory variable, allows us to replicate the results found in the literature on low-noise EPS data. In order to isolate the effect of CI from the effect of HR, we also considered the normalized CI [10], defined as $\mathrm{CI}_n = \mathrm{CI}\ / RR_{-1}$, where RR_{-1} denotes the R–R interval preceding the VPC. Second, two nonlinear ridge regression models are proposed including quadratic (M_2) and cubic (M_3) powers of the explanatory variables, as well as a first-order interaction term. The regression models are summarized in Table I. Since some of the variables are powers, or combinations, of SCL and CI, the ranges differ widely, and variables with large values could have too much influence on the cost function. To overcome this problem, data were modified by subtracting its mean and dividing by its standard deviation [20], so that variables can be presented in normalized units.

Two TS values were computed for each patient in variable CI protocol, both in control and in isoproterenol phase, using the classical approach of averaging a minimum of five tachograms grouped according to short and long CI.

Model performance: The accuracy of the nonlinear regression model was assessed using cross validation and obtaining the mean squared error (MSE):

$$\mathrm{MSE} = \frac{1}{N}\sum_{i=1}^{N}(\widehat{T}_i - T_i)^2 \tag{6}$$

and the R^2 statistic

$$R^2 = 1 - \frac{\mathrm{RSS}}{\mathrm{TSS}} \tag{7}$$

where $\mathrm{RSS} = N \cdot \mathrm{MSE}$ is the residual sum of squares, $\mathrm{TSS} = \sum_{i=1}^{N}(T_i - \overline{T})^2$ is the total sum of squares, and $\overline{T}$ is the average of all T_i values. The parameter R^2 measures the fraction of the total variance of TS that is explained by the model variables and varies between 0 and 1. We applied a tenfold cross-validation procedure, often used in the literature [21]. In this procedure, the dataset is randomly divided into ten groups of equal size, named folds, and ten nonlinear regression models are constructed. Each model is fitted by using data from ninefolds, while the remaining fold is used as a validation set to compute the accuracy measures. This process is repeated ten times, so that the validation set corresponds to a different fold every time. The final estimation of the measures is computed by averaging the results obtained for the ten validation sets.

Bootstrap procedure. Empirical distributions of the coefficients of the nonlinear ridge regression model were computed by using a nonparametric resampling procedure. Bootstrapping is a powerful statistical tool that emulates the process of obtaining new datasets by resampling of an existing dataset with replacement [16]. It allows us to obtain coefficient estimates from different datasets by repeatedly resampling observations from the original dataset [21].

Let us denote an observation as the pair $(T_i, \boldsymbol{\varphi}_i)$, where $i = 1, \ldots, N$, and N is the number of observations in the original dataset. Therefore, the complete original dataset is $Z = (\boldsymbol{T}, \boldsymbol{\Phi})$. The bootstrap procedure consists of randomly selecting N observations with replacement from Z to obtain a bootstrap dataset Z^{*1}. Since resampling is performed with replacement, a given observation can be included more than once in Z^{*1}. Coefficients are estimated using Z^{*1}, leading to a bootstrap estimate for $\boldsymbol{w}$, called $\hat{\boldsymbol{w}}^{*1}$. This procedure is repeated B times to produce B bootstrap datasets, $\{Z^{*i}\}_{i=1}^{B}$, and accordingly, to produce B bootstrap estimates of the coefficients $\{\hat{\boldsymbol{w}}^{*i}\}_{i=1}^{B}$ [21].

From those estimated distributions, it is straightforward to test the null hypotheses for each of the coefficients in the model. We test the null hypothesis that parameter $w_j = 0$, meaning that the associated variable does not explain TS. The alternative hypothesis is that $w_j \neq 0$, meaning that the corresponding variable is relevant, i.e., there is a linear relationship between variable and response. This can be stated as follows:

$$\begin{cases} H_0 : w_j = 0 \\ H_1 : w_j \neq 0. \end{cases} \tag{8}$$

This hypothesis test can be readily performed from the bootstrap empirical distribution of parameter w_j. The null hypothesis H_0 is rejected if the 95% confidence interval of the parameters does not contain the zero value.

IV. RESULTS

First, the linear regression model M_1 is fitted to the EPS database control phase (i.e., without isoproterenol), aiming to reproduce the conclusions in the literature [9]. Second, linear regression models are fitted by using data separated into fixed

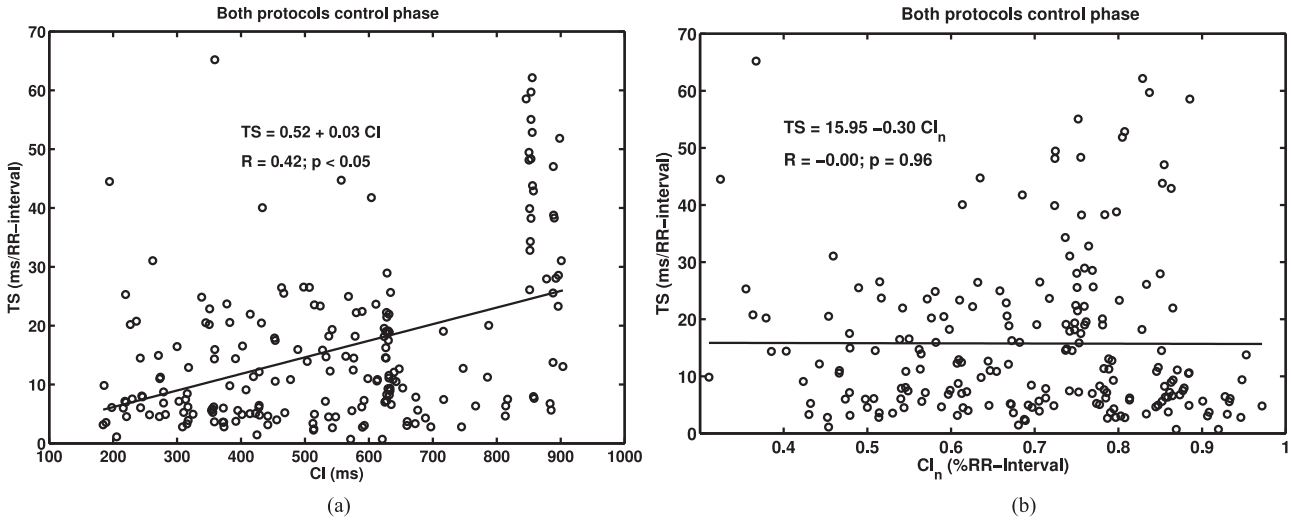

Fig. 1. Linear regression of (a) TS versus CI and (b) TS versus CI_n, in a population of 11 patients with no structural heart disease from both protocols in the control phase (without isoproterenol).

CI and variable CI protocol, aiming to check whether the design of the protocol allows us to determine the influence of CI on HRT. Finally, nonlinear ridge regression models are fitted to the EPS and AMI databases to explain the influence of HR and CI on HRT.

TS as a linear function of CI: To compare with results in the literature, we analyzed the EPS database using M_1, which was fitted using control phase patients of both the fixed and variable CI protocols.

Fig. 1(a) shows a positive relationship between CI and TS that is statistically significant (given by $\mathrm{TS} = 0.52 + 0.03\ \mathrm{CI}$, $R = 0.42, p < 0.05$). This result is the opposite of what is expected from the baroreflex hypothesis. We found no correlation between TS and CI_n ($R = -0.06$, n.s.) in agreement with results in [9] [see Fig. 1(b)].

TS as a linear function of CI and interaction effect of HR: The two phases, control and isoproterenol, of the variable CI protocol allowed us to study the effect of SCL on CI, by fitting M_1 for each of the phases.

Fig. 2 represents the results of simple linear regression models, M_1, for control and isoproterenol phases, showing no significant relationship ($p > 0.05$) between TS and CI ($R = -0.16$ and $R = -0.006$, respectively). However, using CI_n yielded TS models with significant negative slope, given by $\mathrm{TS} = 25.48 - 21.56\ \mathrm{CI}_n$, with $R = -0.37$, $p < 0.01$, and by $\mathrm{TS} = 19.24 - 16.74\ \mathrm{CI}_n$ with $R = -0.36$, $p < 0.05$. This behavior is consistent with the HRT baroreflex hypothesis. Moreover, the slope coefficient was lower with high HR (low SCL), hence proving an interaction effect of HR on CI according to other previous results [14]. Fig. 2(e) and (f) shows individual TS values calculated from averaged tachograms from the six patients in the variable CI protocol. Similar to the graphs above them, higher CI_n produces smaller TS, and the negative relationship between CI and TS is damped at higher HR, achieved with isoproterenol.

TS as a nonlinear function of CI and HR: Next, we present the results after fitting nonlinear regression models M_2 and M_3 to EPS and AMI databases. Table II and Fig. 3 (M_3 only) show the coefficient values of the nonlinear models fitted to the EPS data with and without isoproterenol and the low and high mortality risk AMI data. In M_3 and for the EPS without isoproterenol and AMI low-risk databases, the CI coefficient was significantly, and negatively, correlated with TS, in agreement with the hypothesis of baroreflex source of HRT. Coefficients relating SCL and TS were significant, and positive, for M_2 and M_3. Interaction term SCL·CI was also significant for M_2 and M_3. Models M_2 and M_3 fitted to EPS with isoproterenol dataset obtained the highest value of R^2, since TS for these subjects had a small variability around the fit line due to the high basal HR.

The model coefficients of M_2 and M_3, fitted to the AMI high-risk database, exhibited a relationship between TS and CI that was completely different from that obtained when analyzing the EPS and AMI low-risk databases. Fig. 3 shows the mean and 95% confidence intervals, as estimated with bootstrap resampling, for the coefficients of nonlinear ridge regression model M_3 fitted to EPS control [see Fig. 3(a)] and isoproterenol phase [see Fig. 3(b)], AMI low-risk, and AMI high-risk database. Changes in the relationship between TS and CI due to the interaction of the HR can be observed in Fig. 3(b). In the fitted model M_3 for EPS patients with high HR, isoproterenol phase, none of the coefficients related to CI was significant. The $\mathrm{SCL}^*\mathrm{CI}$ term was significant in all the models except M_2 for AMI high risk. The inclusion of this interaction term in the model may decouple the effect of HR on CI.

V. Discussion

In this study, HRT parameters were computed on single VPC tachograms. They were also compared with the classical procedure of averaging a number of individual tachograms. Previous works focused on methods for reliable estimation of HRT parameters from individual VPC responses. For instance, HRT statistical detection was addressed by using an extension of the integral pulse frequency modulation model accounting for HRT [22]–[24]. In this approach, the tachogram was assumed

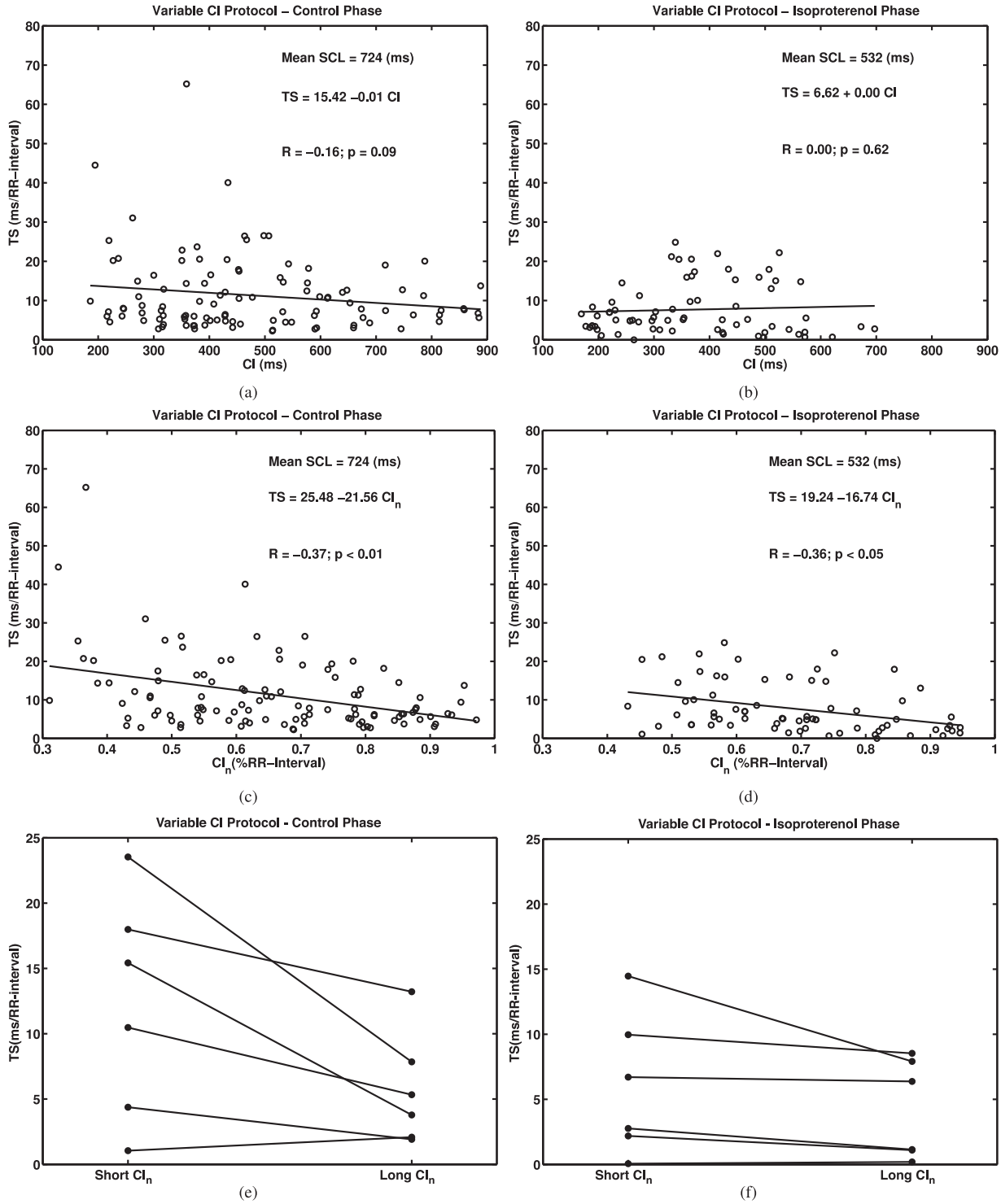

Fig. 2. Analysis of the interaction between HR and CI using data from patients in variable CI protocol, control phase (a), (c), and isoproterenol phase (b), (d). Mean and standard deviation of SCL for each phase are reported. Interaction between HR and CI using TS computed from an averaged tachogram grouped by CI_n, control phase (e), and isoproterenol phase (f). Solid lines connect TS values from the same subject.

to reflect the combination of HR variability (modeled as white Gaussian noise) and HRT (modeled as a linear combination of Karhunen-Loève basis functions). Another approach consisted of filtering individual VPC tachograms by using a robust method based on support vector machines [4].

Several physiological factors modulate the HRT pattern [6]–[8]. The dependence of HRT on HR is attributed to a shared sympathovagal modulation, i.e., HRT is attenuated at high-HR conditions. Although some studies support this physiological hypothesis by showing a strong correlation between HR and

TABLE II
COEFFICIENT VALUES OF NONLINEAR RIDGE REGRESSION MODELS FITTED TO EPS DATABASE

EPS Control	SCL	CI	SCL^2	SCL^3	CI^2	CI^3	SCL · CI	MSE	R^2
M_2	**2.08***	−0.65	**3.01***	–	0.76	–	**1.70***	145.41	0.22
M_3	**1.36***	**−1.02***	**2.05***	**2.74***	−0.13	**1.11***	**0.91***	149.67	0.20
EPS ISO	SCL	CI	SCL^2	SCL^3	CI^2	CI^3	SCL · CI	MSE	R^2
M_2	**1.32***	0.06	**1.69***	–	**0.52***	–	**1.05***	52.23	0.33
M_3	**1.01***	−0.09	**1.25***	**1.36***	0.23	0.45	**0.68***	52.65	0.32
AMI low-risk	SCL	CI	SCL^2	SCL^3	CI^2	CI^3	SCL · CI	MSE	R^2
M_2	**3.44***	**−1.55***	**3.32***	–	**−1.83***	–	**0.82***	300.93	0.13
M_3	**2.65***	**−1.05***	**2.49***	**2.28***	**−1.26***	**−1.43***	**0.63***	297.20	0.15
AMI high-risk	SCL	CI	SCL^2	SCL^3	CI^2	CI^3	SCL · CI	MSE	R^2
M_2	**1.13***	**1.63***	**−0.69***	–	0.14	–	0.02	16.77	0.21
M_3	**1.18***	**1.47***	0.08	**−1.12***	**0.59***	−0.58	**0.57***	16.82	0.20

Statistically significant variables are highlighted and denoted by *. Symbol – means that the variable was not included in the model.

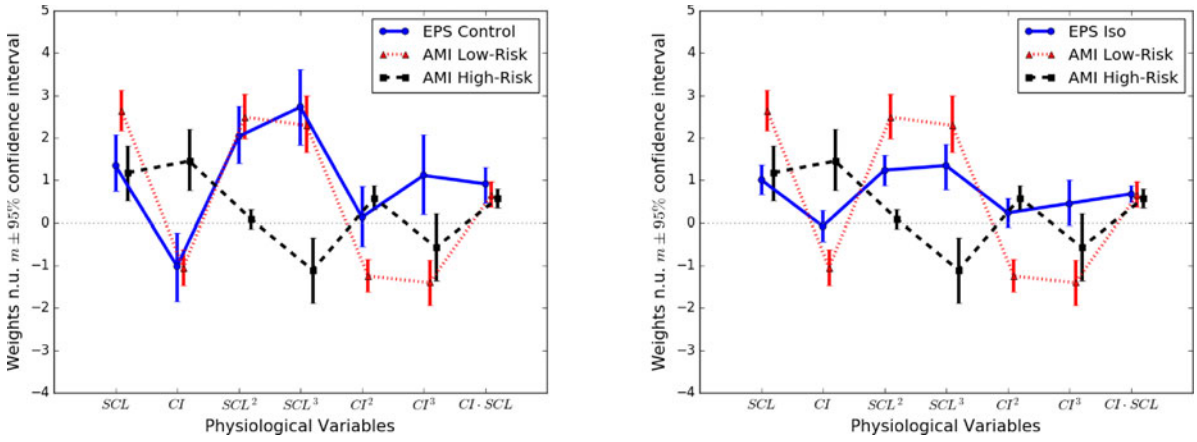

Fig. 3. Coefficient values (mean and the 95% confidence interval) of nonlinear ridge regression model M_3 fitted to EPS [control phase (a), isoproterenol phase (b)], AMI high-risk, and AMI low-risk databases.

HRT across individuals [17], [25], only weak correlation was found in individual subjects [3]. In [26], the CI was found to be correlated only with TO, but TS was not affected at all, whereas [11] and [27] reported strong correlations of both TO and TS with CI. Interestingly, this effect was less pronounced in patients with left ventricular dysfunction [11]. However, no correlation between HRT parameters and CI was found in [9], neither in a pooled population nor in individual patients. Conflicting results on correlation between HRT parameters and CI have usually been attributed to the effect of basal HR. According to [28], HRT response is severely attenuated when HR is high. In this case, HRT parameters are unlikely to be correlated with CI.

There have been some attempts to study the joint influence of CI and HR on HRT by representing TS and TO as a function of CI and HR [12]; however, no clear pattern could be observed. In our case, normalization was found to decouple the effect of SCL on CI by using only data from patients in variable CI protocol control phase, revealing the expected physiological modulation of CI on TS. The results in [9] suggested that correlation was due to strong influence of HR on HRT (low HR–high TS, and high HR–low TS), rather than an inherent relationship between HRT and CI. However, no further analysis was presented therein. In our results, the nonlinear model M_3 showed a relationship between CI and HRT which is in agreement with the baroreflex hypothesis, both in EPS control phase subjects, and in AMI low-risk patients. Interestingly, in EPS isoproterenol phase subjects, i.e., high HR, all the coefficients related to CI were statistically nonsignificant. These results may confirm the suggestion that high HR distorts the relationship between CI and HRT parameters.

VI. CONCLUSION

In this study, we have proposed a procedure to systematically assess the modulation of HRT by CI and HR. Using this approach, significant correlation was found between these physiological factors and the TS, thus supporting the baroreflex source of HRT. The proposed nonlinear model accounted for the effect of SCL and CI simultaneously. It was able to attribute weights (coefficients) that are in agreement with the physiological baroreflex explanation of HRT.

With the approach proposed in this study, two main results are obtained: First, a quantification of the effect of CI on TS, which supports the hypothesis of the baroreflex origin of HRT, and second, a nonlinear model that explains the modulation of HRT by HR and CI.

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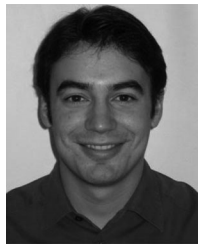

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