EPI10 - Análise de Sobrevivência

Aplicações com o modelo de Cox

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Modelos estatísticos

Modelos estatísticos

Breiman (2001)[1] sugere que existem dois objetivos na análise de dados:

- **Predição:** ser capaz de prever o que as respostas vão ser para futuras variáveis de entrada.
- **Informação:** extrair algumas informações sobre como a natureza está associando as variáveis de resposta às variáveis de entrada.

[1] Breiman, L. Statistical modeling: the two cultures. *Statistical Science*, 16:199-231, 2001.

Modelos estatísticos

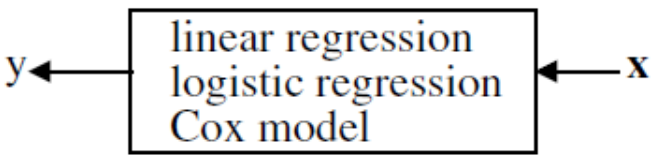
Ainda, para **Breiman (2001)**, existem duas abordagens diferentes para esses objetivos:

- **A cultura de modelagem de dados**, em que a análise começa assumindo um modelo de dados estocástico para o interior da "caixa preta". Por exemplo, um modelo de dados comum é que os dados são gerados por seleções independentes de

$$\text{variáveis resposta} = f(\text{variáveis aleatórias, ruído aleatório, parâmetros})$$

Modelos estatísticos

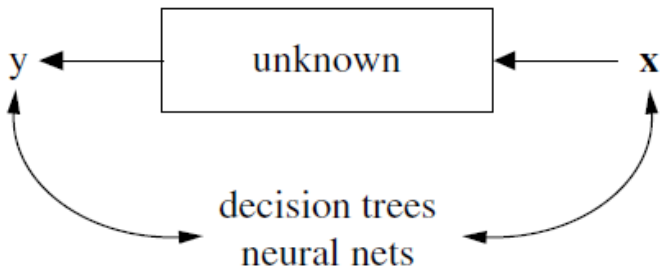
- Os valores dos parâmetros são estimados a partir dos dados e o modelo então usado para informação e/ou previsão.



- **Validação do modelo.** Sim-não usando testes de adequação e análise de resíduos.
- **População estimada da cultura.** 98% de todos os estatísticos.

Modelos estatísticos

- **A cultura de modelagem algorítmica**, que considera o interior da caixa complexo e desconhecido. A abordagem é encontrar uma função $f(\mathbf{x})$ - um algoritmo que opera em $\mathbf{x}$ para prever as respostas y.



- **Validação do modelo.** Medido por precisão preditiva.
- **População estimada da cultura.** 2% dos estatísticos, muitos em outras áreas.

Modelos estatísticos

Shmueli (2010) em ***To Explain or to Predict?***[2] sugere três tipos de modelagem:

- **Modelagem explicativa:** aplicação de modelos estatísticos aos dados para testar hipóteses causais.
- **Modelagem preditiva:** aplicação de modelos estatísticos **(e aprendizado estatístico/máquina)** para predição/classificação de novas ou futuras observações.
- **Modelagem descritiva:** aplicação de modelos estatísticos para representar de maneira compacta a estrutura dos dados; captura a associação entre as variáveis dependente e independentes **(ausência de hipóteses causais)**.

[2] Shmueli, G. To explain or to predict. *Statistical Science*, 25:289-310, 2010.

Modelos estatísticos

As abordagens explicativa e preditiva são diferentes.

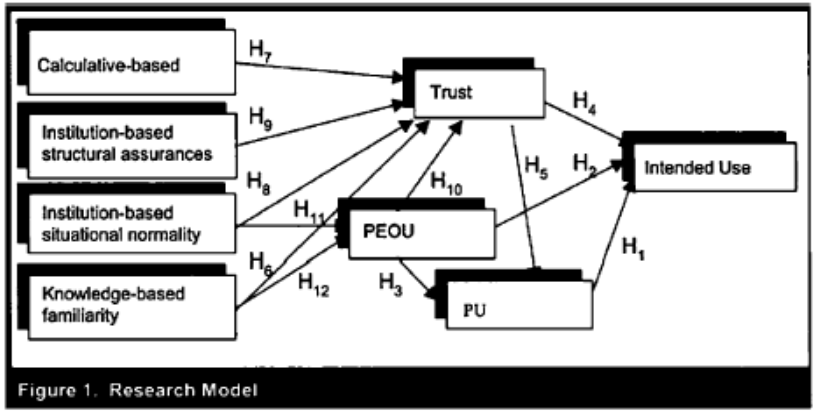
- Relação **Viés-Variância:** O **erro de previsão esperado** (EPE) para uma nova observação com valor x, usando uma função de perda quadrática, é dado por

$$\begin{aligned} EPE &= \mathrm{E}\,[Y - \hat{f}(x)]^2 \\ &= \mathrm{E}\,[Y - \hat{f}(x)]^2 + \{\mathrm{E}\,[\hat{f}(x)] - f(x)\}^2 + \mathrm{E}\,\{\hat{f}(x) - \mathrm{E}\,[\hat{f}(x)]\}^2 \\ &= \mathrm{Var}\,(Y) + \mathrm{Viés}[\hat{f}(x)] + \mathrm{Var}\,[\hat{f}(x)]. \end{aligned}$$

Modelos estatísticos

- Esta decomposição revela uma fonte da diferença entre modelagem explicativa e preditiva:
  - Na modelagem explicativa, o foco está em minimizar o viés para obter a representação mais precisa da teoria subjacente.
  - Em contraste, a modelagem preditiva busca minimizar a combinação de viés e variância de estimativa, ocasionalmente sacrificando a precisão teórica para melhorar a precisão empírica.

Modelos estatísticos



H_1: *PU will positively affect intended use of a business-to-consumer (B2C) Web site.*

H_2: *PEOU will positively affect intended use of a business-to-consumer (B2C) Web site.*

H_3: *PEOU will positively affect PU of a business-to-consumer (B2C) Web site.*

FIG. 1. *Causal diagram* (left) *and partial list of stated hypotheses* (right) *from Gefen, Karahanna and Straub* (2003).

FIG. 2. *Steps in the statistical modeling process.*

Aplicações com o modelo de Cox: escore de risco cardiovascular (em 10 anos) de Framingham

Escore de risco (Framingham)

Epidemiology

General Cardiovascular Risk Profile for Use in Primary Care

The Framingham Heart Study

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Escore de risco (Framingham)

predicting an individual CVD component. Indeed, there are occasions when a physician would like to target risk assessment and preventive measures to a specific cardiovascular end point such as myocardial infarction or stroke depending, for example, on an individual patient's family history, age, diabetic status, or predisposition to a particular outcome by valve disease. However, with this exception, primary care physicians engaged in preventive health maintenance want to assess risk of developing any major atherosclerotic CVD event using a general CVD risk assessment tool. Accordingly, the purpose of the present investigation was to formulate a single multivariable risk assessment tool that would enable physicians to identify high-risk candidates for any and all initial atherosclerotic CVD events using measurements readily available at the clinic or office.

Escore de risco (Framingham)

Study Design and Sample

The design and selection criteria for the original Framingham Heart Study and the Framingham Offspring Study have been detailed elsewhere.[25,26] Detailed descriptions of the examination procedures and criteria for CVD events also have been reported.[27] Participants were eligible for the present investigation if they attended the 11th biennial examination cycle of original cohort (1968 to 1971, when measurement of high-density lipoprotein [HDL] cholesterol was available) or the first (1971 to 1975) or third (1984 to 1987) examination cycles of the Offspring cohort and were free of CVD. All participants provided written informed consent, and the study protocol was approved by the Institutional Review Board at the Boston Medical Center.

The study sample consisted of attendees of the baseline examinations free of prevalent CVD who were 30 to 74 years of age with nonmissing data on covariates. After exclusions, 8491 participants (mean age, 49 years; 4522 women) remained eligible.

Escore de risco (Framingham)

Measurement of CVD Risk Factors

At each heart study examination, participants underwent a physical examination, anthropometry, blood pressure determination, and phlebotomy for vascular risk factors. Blood pressure measurements were made on the left arm of the seated participants with a mercury-column sphygmomanometer and an appropriately sized cuff; the average of 2 physician-obtained measures constituted the examination blood pressure. Serum total and HDL cholesterol levels were determined with standardized enzymatic methods. Cigarette smoking status was ascertained by self-report. Diabetes was defined as fasting glucose ≥126 mg/dL (offspring cohort) or 140 mg/dL (original cohort) or use of insulin or oral hypoglycemic medications. Antihypertensive medication use was ascertained by the physician examiner at the heart study and based on self-report.

+ sexo + idade

Escore de risco (Framingham)

Follow-Up and Outcome Events

All study participants were under continuous surveillance for the development of CVD events and death. The Framingham Heart Study defines CVD as a composite of CHD (coronary death, myocardial infarction, coronary insufficiency, and angina), cerebrovascular events (including ischemic stroke, hemorrhagic stoke, and transient ischemic attack), peripheral artery disease (intermittent claudication), and heart failure.[1] Information about CVD events on follow-up was obtained with the aid of medical histories, physical examinations at the study clinic, hospitalization records, and communication with personal physicians. All suspected new events were reviewed by a panel of 3 experienced investigators who evaluated all pertinent medical records. A separate review committee that included a neurologist adjudicated cerebrovascular events, and a heart study neurologist examined most participants with suspected stroke.

Escore de risco (Framingham)

Statistical Analyses

Multivariable Models and Estimation of General CVD Risk Functions

We used sex-specific Cox proportional-hazards regressions[28] to relate risk factors to the incidence of a first CVD event during a maximum follow-up period of 12 years after confirming that the assumption of proportionality of hazards was met. From these models, we estimated mathematical CVD risk functions,[28] referred to as a general CVD risk function (Appendix); these functions were used to estimate 10-year absolute CVD risk.

análise de resíduos

Appendix

Risk Estimation From Cox Model and From Score Sheet

The following examples illustrate the direct application of the Cox model and the use of the score sheet to estimate CVD risk in women and men.

General formula:

$$\hat{p} = 1 - S_0(t)^{\exp(\Sigma_{i=1}^{p} \beta_i X_i - \Sigma_{i=1}^{p} \beta_i \bar{X}_i)},$$

where $S_0(t)$ is baseline survival at follow-up time t (here t=10 years; see Table 2), βi is the estimated regression coefficient (log hazard ratio; see Table 2), Xi is the log-transformed value of the ith risk factor, (if continuous), $\bar{X}_i$ is the corresponding mean, and p denotes the number of risk factors.

28. Cox DR. Regression models and life tables. *J Royal Stat Soc*. 1972; 34(series B):187–220.

Escore de risco (Framingham)

(1) Covariates included in Cox models were age, total cholesterol, HDL cholesterol, systolic blood pressure, antihypertensive medication use, current smoking, and diabetes status.(2) Other variables such as diastolic blood pressure, body mass index, and triglycerides also were considered, but they were not statistically significant.(3) The use of low-density lipoprotein cholesterol did not improve model fit or performance.(4) All the continuous variables were naturally logarithmically transformed to improve discrimination and calibration of the models and to minimize the influence of extreme observations.(5) We adjusted for the use of antihypertensive medication by modeling the impact of a participant's systolic blood pressure differently on the basis of use of such medications.

interação

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Assessment of Model Performance (validação)

We evaluated the ability of the risk prediction model to discriminate persons who experience a CVD event from those who do not using an overall c statistic,[29,30] expanding on a suggestion by Harrell et al.[31] This c statistic is analogous to the area under the receiver-operating characteristic curve. Briefly, 2 subjects are described as comparable if we can determine which one survived longer and concordant if their predicted probabilities of survival and survival times go in the same direction, and we can define the overall c statistic as the probability of concordance given comparability. The degree of overoptimism resulting from model assessment on the same data on which it was developed was estimated on the basis of bootstrap resampling of the original set.

Discriminação (Estatística c)

We evaluated the calibration of our risk prediction model, a measure of agreement between observed and predicted events within 10 years, using a modified Hosmer-Lemeshow χ^2 statistic with 9 *df*.[29] For this purpose, we used the Kaplan-Meier estimator to obtain the observed incidence of CVD events, which was then compared with the CVD risk predicted by the model and classified into deciles.[29] We also calculated the proportion of CVD events that occurred in the top quintile of predicted risk (ie, sensitivity of the top quintile of predicted risk for identifying CVD events) and the proportion of individuals without events who are not in the top quintile of predicted risk (ie, specificity of the top quintile for CVD events).

Calibração (H-L)

Sensibilidade Especificidade

Escore de risco (Framingham)

events).

The performance of the new CVD risk prediction model presented here was compared with that of another popular Framingham risk score developed by Wilson et al.[16] Because the latter score was developed for predicting CHD and not CVD, we performed a simple recalibration by multiplying the risk of each individual by the ratio of CVD incidence rate and the mean predicted risk based on the CHD risk function. Thus, we assessed how well the Framingham CHD risk functions[16] predicted CVD relative to the new CVD prediction model. A test for difference in 2 correlated c statistics proposed by Antolini et al[32] was used, along with the net reclassification improvement proposed by Pencina et al.[33] Reclassification improvement is defined as an increase in risk category for individuals who develop events and as a decrease for those who do not. Net reclassification improvement accounts for movement between categories in the wrong direction and applies different weights to events and nonevents. We used 0% to 6%, 6% to 20%, and >20% as risk categories.

Comparação de modelos

Reclassificação

NRI

classes de risco

baixo risco

médio risco

alto risco

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Results

The risk factor characteristics of men and women in our sample at the baseline examinations are shown in Table 1. In our middle-aged sample, mean levels of serum total cholesterol and systolic blood pressure were similar in men and women, as were the prevalences of cigarette smoking and use of antihypertensive treatment. The prevalence of diabetes was substantially higher in men, whereas mean serum HDL levels were higher in women.

Table 1. Summary Statistics for Risk Factors Used in Risk Models

Characteristics	Women (n=4522, 28% FOC)	Men (n=3969, 22% FOC)
Age, mean (SD), y	49.1 (11.1)	48.5 (10.8)
Total-C, mean (SD), mg/dL	215.1 (44.1)	212.5 (39.3)
HDL-C, mean (SD), mg/dL	57.6 (15.3)	44.9 (12.2)
Systolic BP, mean (SD), mm Hg	125.8 (20.0)	129.7 (17.6)
BP treatment, n (%)	532 (11.76)	402 (10.13)
Smoking, n (%)	1548 (34.23)	1398 (35.22)
Diabetes, n (%)	170 (3.76)	258 (6.50)
Incident CVD events, n (%)	456 (10.08)	718 (18.09)

FOC indicates Framingham original cohort; Total-C, total cholesterol; HDL-C, HDL cholesterol; and BP, blood pressure.

Escore de risco (Framingham)

General CVD Risk Prediction Models

The multivariable-adjusted regression coefficients and hazard ratios for incident CVD events are presented in Table 2. We observed highly statistically significant relations of all risk factors evaluated and incident CVD.

Table 2. Regression Coefficients and Hazard Ratios

Variable	β*	P	Hazard Ratio	95% CI
Women [So(10)=0.95012]				
Log of age	2.32888	<0.0001	10.27	(5.65–18.64)
Log of total cholesterol	1.20904	<0.0001	3.35	(2.00–5.62)
Log of HDL cholesterol	−0.70833	<0.0001	0.49	(0.35–0.69)
Log of SBP if not treated	2.76157	<0.0001	15.82	(7.86–31.87)
Log of SBP if treated	2.82263	<0.0001	16.82	(8.46–33.46)
Smoking	0.52873	<0.0001	1.70	(1.40–2.06)
Diabetes	0.69154	<0.0001	2.00	(1.49–2.67)
Men [So(10)=0.88936]				
Log of age	3.06117	<0.0001	21.35	(14.03–32.48)
Log of total cholesterol	1.12370	<0.0001	3.08	(2.05–4.62)
Log of HDL cholesterol	−0.93263	<0.0001	0.39	(0.30–0.52)
Log of SBP if not treated	1.93303	<0.0001	6.91	(3.91–12.20)
Log of SBP if treated	1.99881	<0.0001	7.38	(4.22–12.92)
Smoking	0.65451	<0.0001	1.92	(1.65–2.24)
Diabetes	0.57367	<0.0001	1.78	(1.43–2.20)

So(10) indicates 10-year baseline survival; SBP, systolic blood pressure.
*Estimated regression coefficient

Escore de risco (Framingham)

The sex-specific CVD functions performed well in terms of both model discrimination and calibration. The c statistics for the risk function ranged from 0.763 (95% confidence interval [CI], 0.746 to 0.780) in men to 0.793 (95% CI, 0.772 to 0.814) in women. The degree of overoptimism was estimated at 0.001 for men and 0.003 for women, partly reflecting a large number of events and the potential limitation of the bootstrap resampling approach for assessing overoptimism.

The calibration χ^2 statistics for the CVD prediction models were 13.48 in men and 7.79 for the women, indicating excellent goodness of fit (for the lack of fit, P=0.14 and P=0.56, respectively). The Figure displays the calibration plots comparing predicted deciles of risk and actual observed risk in men and women. The top sex-specific quintiles of predicted risk identified ≈49% of men and 60% of women who experienced a first CVD event on follow-up (sensitivity). Proportions of men and women without CVD events who were not in the top quintile of predicted risk were 85% and 84%, respectively (specificity).

Escore de risco (Framingham)

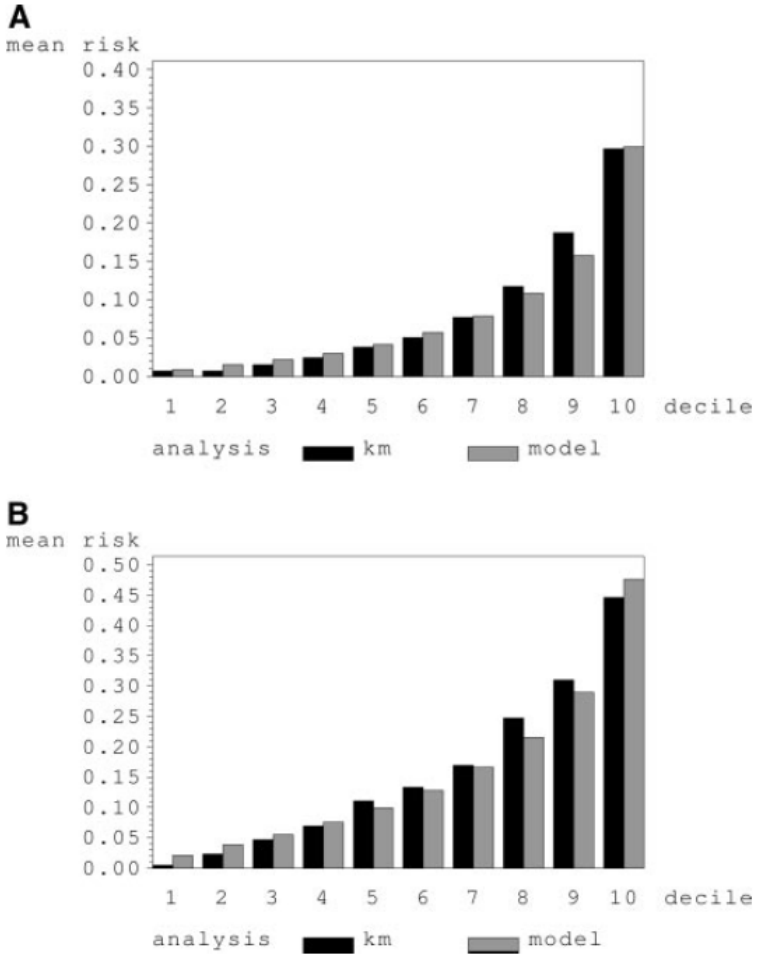

Figure. Calibration by decile for CVD function for women (A) and men (B). Vertical bars represent observed (Kaplan-Meier [km]; black) and model-based predicted (decile specific means; gray) probabilities of CVD event in 10 years in deciles of model-based predicted probabilities.

Escore de risco (Framingham)

The Framingham CHD risk functions (Wilson et al[16]) performed less well for predicting CVD risk: The c statistics were lower (0.756 [95% CI, 0.739, 0.773] in men; for difference compared with our new model, P=0.051; 0.778 [95% CI, 0.756, 0.799] in women; for difference compared with our new model, P=0.003) and calibration was worse (χ^2=32.37 in men and 12.42 in women) relative to that noted above for the new CVD risk prediction models. The sensitivity of the top quintile of predicted risk using the CHD risk functions was slightly lower (47% in men and 56% in women) although specificity was similar (85% in men and 83% in women). The net reclassification improvement from using the new model was statistically significant for both men and women and reached 6.65% (P<0.001) and 7.95% (P=0.003), respectively.

Escore de risco (Framingham)

Derivation of CVD Prediction Scores and Heart Age/Vascular Age

Tables 5 and 6 and 7 and 8 provide score sheets that can be used for estimating the multivariable risk of CVD for women and men, respectively. Tables 9 and 10 give a different quantification of the same risk in the form of heart age/vascular age. We illustrate the use of these tables in the Appendix, and they are available at www.framinghamheartstudy.org/risk/index.html.

A presentação dos resultados

Presentations

The CVD risk functions of Table 2 are easily programmed, for example, as an Excel spreadsheet or as the score sheets of Tables 5 through 10. This was done with the Adult Treatment

Escore de risco (Framingham)

Table 11. Case 1

Risk Factor	Value	Points
Age	61	9
Total cholesterol	180	1
HDL	47	0
Nontreated SBP	124	0
Treated SBP	...	0
Smoker	Yes	3
Diabetes	No	0
Point total	13	
Estimate of risk, %	10.0	
Heart age/vascular age, y	73	

SBP indicates systolic blood pressure.

Escore de risco (Framingham)

Case 1—Women (baseline 10-year survival=0.95012). A 61-year-old woman not treated for high blood pressure has a total cholesterol of 180 mg/dL, HDL of 47 mg/dL, and systolic blood pressure of 124 mm Hg and is a current smoker but is not diabetic (see Table 11).

The risk estimate based on the Cox model is computed as follows:

$$\sum_{i=1}^{p} \beta_i X_i = 2.32888*\log(\mathbf{61}) + 1.20904*\log(\mathbf{180})$$

$$-0.70833*\log(\mathbf{47}) + 2.76157*\log(\mathbf{124}) + 2.82263*0$$

$$+0.52873*\mathbf{1} + 0.69154*\mathbf{0} = 26.9653.$$

$$\sum_{i=1}^{p} \beta_i \bar{X}_i = 2.32888*3.8686 + 1.20904*5.3504$$

$$-0.70833*4.0176 + 2.76157*4.2400$$

$$+2.82263*0.5826 + 0.52873*0.3423$$

$$+0.69154*0.0376 = 26.1931.$$

$$\hat{p} = 1 - S_0(t)^{\exp(\Sigma_{i=1}^{p} \beta_i X_i - \Sigma_{i=1}^{p} \beta_i \bar{X}_i)} = 1 - 0.95012^{\exp(26.9653 - 26.1931)}$$

$$= 0.1048 \approx 10.5\%$$

Escore de risco (Framingham)

Table 12. Case 2

Risk Factor	Value	Points
Age	53	8
Total cholesterol	161	1
HDL	55	−1
Nontreated SBP	...	0
Treated SBP	125	2
Smoker	No	0
Diabetes	Yes	3
Point total	13	
Estimate of risk, %	15.6	
Heart age/vascular age, y	64	

SBP indicates systolic blood pressure.

Escore de risco (Framingham)

Case 2—Men (baseline 10-year survival=0.88936). A 53-year-old man on treatment for systolic blood pressure has a total cholesterol of 161 mg/dL, HDL of 55 mg/dL, and systolic blood pressure of 125 mm Hg and is diabetic but is not a current smoker (see Table 12).

The risk estimate based on the Cox model is computed as follows:

$$\sum_{i=1}^{p} \beta_i X_i = 3.06117*\log(\mathbf{53}) + 1.12370*\log(\mathbf{161}) - 0.93263*\log(\mathbf{55}) + 1.93303*\mathbf{0} + 1.99881*\log(\mathbf{125}) + 0.65451*\mathbf{0} + 0.57367*\mathbf{1} = 24.3509.$$

$$\sum_{i=1}^{p} \beta_i \bar{X}_i = 3.06117*3.8560 + 1.12370*5.3420 - 0.93263*3.7686 + 1.93303*4.3544 + 1.99881*0.5019 + 0.65451*0.3522 + 0.57367*0.0650 = 23.9802.$$

$$\hat{p} = 1 - S_0(t)^{\exp(\Sigma_{i=1}^{p} \beta_i X_i - \Sigma_{i=1}^{p} \beta_i \bar{X}_i)} = 1 - 0.88936^{\exp(24.3509 - 23.9802)} = 0.1562 \approx 15.6\%$$

Aplicações com o modelo de Cox: resposta autonômica cardíaca e doença coronariana - ARIC Study

Resposta autonômica cardíaca e CHD - ARIC

American Journal of Epidemiology

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Does the Cardiac Autonomic Response to Postural Change Predict Incident Coronary Heart Disease and Mortality?

The Atherosclerosis Risk in Communities Study

Mercedes R. Carnethon,[1] Duanping Liao,[2] Gregory W. Evans,[3] Wayne E. Cascio,[4] Lloyd E. Chambless,[5] Wayne D. Rosamond,[6] and Gerardo Heiss[6]

Resposta autonômica cardíaca e CHD - ARIC

Supine heart rate variability (HRV) is an estimate of parasympathetic modulation of the autonomic nervous system that is inversely associated with incident coronary heart disease (CHD) (1–3) and all-cause mortality (4, 5) in the population. However, the basis of normal cardiac autonomic

autonomic balance and correlate it with prevalent disease (6–10). The HRV response to postural change is hypothesized to be a more sensitive measure of cardiac autonomic modulation than is supine HRV because cardiac damage is thought to occur primarily through sympathetic impairment, which can only be estimated with a stimulus (11, 12).

Using HRV measures with a postural change, our primary objective was to determine whether small changes in parasympathetic autonomic modulation and heart rate or large decreases in overall autonomic modulation (indicating an absent reciprocal increase in sympathetic modulation) predict nonfatal myocardial infarction (MI), fatal MI or fatal CHD, and non-CHD mortality. Additionally, we investi-

Resposta autonômica cardíaca e CHD - ARIC

MATERIALS AND METHODS

Study population

This was an ancillary investigation to the Atherosclerosis Risk in Communities (ARIC) Study. A biracial probability sample of men and women aged 45–64 years were recruited from the Minneapolis suburbs, Minnesota; Forsyth County, North Carolina; and Washington County, Maryland. Black adults were sampled exclusively in a fourth community, Jackson, Mississippi, and oversampled in Forsyth County, North Carolina. Between 1987 and 1989, 15,792 eligible persons (46 percent in Jackson, Mississippi, and 66 percent in the other communities) were interviewed and examined. A detailed description of the study design and methods is published (14).

Participants were excluded sequentially from the cohort for the following reasons: HRV records collected prior to establishing the final protocol ($n = 804$); prevalent or missing CHD information ($n = 1,037$); unusable HRV records in the supine ($n = 2,106$) and standing ($n = 4,046$) positions (total = 4,586); age younger than 45 years ($n = 32$); race other than Black or White, or Black race in Minnesota or Maryland ($n = 27$); and antiarrhythmic medication use ($n = 39$). This report includes 9,267 participants.

Resposta autonômica cardíaca e CHD - ARIC

HRV measurement (Exposição)

Measures to estimate the shift in autonomic balance with postural change take the general form: supine HRV – standing HRV = ΔHRV. Standing HF should decline, and R-R intervals should be shorter to reflect the decrease in parasympathetic modulation and increased heart rate, relative to supine measures. Smaller Δ HF and Δ R-R intervals represent an attenuated parasympathetic response to postural change that we hypothesize to predict incident events. Conversely, the shift from parasympathetic to sympathetic modulation should cause little change in the overall modulation of cardiac autonomic balance as estimated by SDNN. Thus, we hypothesize that participants with a large Δ SDNN are at higher risk of incident events.

Resposta autonômica cardíaca e CHD - ARIC

Event ascertainment (Desfecho)

All events were identified and processed according to the ARIC protocol for event follow-up and surveillance (18). Potential events that occurred among cohort participants between the baseline clinic visit (1987–1989) and December 31, 1997, were identified annually by telephone interview with the participant (or next-of-kin of a decedent) and through community hospital surveillance. Hospitalizations or deaths with specific cardiac-related discharge or underlying cause-of-death codes (*International Classification of Diseases*, Ninth Revision, codes 402, 410–414, 427, 428, and 518.4) were investigated further for classification.

Copies of the electrocardiograms were sent to the University of Minnesota and classified according to the Minnesota code (19). A combination of symptoms, cardiac enzymes, and electrocardiogram evidence was used to determine a diagnosis, and physician reviewers on the ARIC Morbidity and Mortality Classification Committee validated and classified all events (18). Fatal CHD was defined as death within 4 weeks of hospitalization for an MI, death preceded by chest pains within 72 hours, a history of chronic ischemic heart disease, or death certificate codes consistent with the underlying cause of death related to CHD. Death during the follow-up period in the absence of an MI or fatal CHD was classified as non-CHD mortality on the basis of death certificate information and/or annual follow-up information.

Resposta autonômica cardíaca e CHD - ARIC

Covariates (variáveis de ajuste)

Demographic characteristics and CHD risk factors were measured according to standardized protocols common to all ARIC study sites and were subject to regular quality-control checks (20, 21). Prevalent CHD was defined as a history of coronary artery bypass surgery, balloon angioplasty, or MI based on electrocardiograph or self-report. Age, race/ethnicity, gender, education level, and smoking history were identified on the basis of self-report. Education was dichotomized to compare participants with less than a high school education to those with a high school education or greater. Smoking status (current, former, or never) was dichotomized to compare current with never or former smokers. Medication use was identified and defined by coding all reported medications, vitamins, and supplements used in the 2 weeks prior to the clinic examination. Heart rhythm control medications included beta-blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, antianginals, antihypertensives (excluding diuretics), vasodilators, and digoxin.

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After a 12-hour fast, blood was drawn from the antecubital vein of seated participants by using a butterfly needle and vacutainers and shipped to a central laboratory for assay. Glucose was measured by a hexokinase/glucose-6-phosphate dehydrogenase method on a Coulter DACOS device (Beckman Coulter, Inc., Fullerton, California). Diabetes was defined as fasting serum glucose of 126 mg/dl or more, non-fasting glucose of 200 mg/dl or more, or self-reported current use of medications for diabetes or a self-reported previous diagnosis. Insulin was measured by radioimmunoassay using an Insulin Kit (Cambridge Medical Diagnosis, Inc., Billerica, Massachusetts). Sitting blood pressure was measured three times by using a random zero sphygmomanometer after a 5-minute rest; the average of the last two measurements was used in this study. Hypertension was defined as any of the following: 1) systolic blood pressure of 140 mmHg or more; 2) diastolic blood pressure of 90 mmHg or more; or 3) reported use of hypertension-lowering medications during the 2 weeks preceding the clinic examination.

Body mass index was calculated as the ratio of weight (km) to standing height $(m)^2$; participants with a body mass index of 30 or more were classified as obese. The modified Baecke questionnaire was used to assess physical activity by deriving a score based on the frequency of overall sport and exercise participation and the duration and intensity of up to four activities (22).

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Statistical methods

After confirming previous findings that the relation between HRV and events is not linear (1–5) (data not shown), we created indicator variables to correspond to the quartiles of the distribution of HRV, using the highest quartile as the referent for each index. Multivariable Cox proportional hazards models were used to test the association between HRV and the time to event while accounting for varying follow-up time between the baseline examination and the event or censoring date. All two-way interactions between the main exposure and other covariates in the model were evaluated as a set by using a likelihood ratio test. If the likelihood ratio test was significant ($p < 0.05$), individual interaction terms were examined by using stepwise regression procedures. Log-log survival plots and time/covariate interaction terms were used to evaluate the proportional hazards assumption. No covariates violated this assumption.

The joint significance of the three indicator variables as a group were tested in relation to each event with a Wald χ^2 test. Next, we calculated the hazards of each event by comparing each individual quartile (quartiles 1–3) of HRV with the uppermost quartile (quartile 4) for each index. For evaluation of effect modification by diabetes, quartiles were collapsed to compare the lowest quartile (quartile 1) with the upper three (quartiles 2–4) of each HRV index. The significance of an interaction term between diabetes and each index was tested in proportional hazards models. Proportional hazards models were then stratified by diabetes. All analyses were conducted using the SAS system version 6.12 (SAS Institute, Inc., Cary, North Carolina).

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RESULTS

Over an average of 8.9 years of follow-up, 297 (3.2 percent) cases of incident MI, 63 (0.7 percent) cases of fatal CHD, and 540 (5.9 percent) deaths due to causes other than CHD were identified. On average, participants included in this study were younger, less likely to be male, and more often of Black race than the remainder of ARIC participants (table 1). Despite these demographic differences, the distri-

TABLE 1. Distribution of baseline covariates (1987–1989) and incident events, stratified by study inclusion status, Atherosclerosis Risk in Communities Study, 1987–1989

	Available data (n = 9,267)				Missing data (n = 4,550)				p value*
	Mean	(SE)†	No.	%	Mean	(SE)	No.	%	
Covariates									
Age	53.63	(0.06)			54.41	(0.09)			<0.01
Gender (% male)			3,752	40.5			2,222	49.0	<0.01
Race (% Black)			2,669	28.8			1,029	22.7	<0.01
Education (% with less than high school education)			2,108	22.8			1,025	22.6	0.85
Current smoking (%)			2,371	25.6			1,221	26.9	0.10
Physical activity score	2.42	(0.01)			2.39	(0.01)			0.08
Obesity (body mass index (kg/m^2) ≥30)			2,415	26.1			1,338	29.5	<0.01
Insulin (pmol/liter)	94.83	(2.15)			94.59	(2.69)			0.81
Glucose (mg/dl)	107.24	(0.42)			107.84	(0.58)			0.20
Diabetes			1,009	11.0			537	11.9	0.10
Systolic blood pressure (mmHg)	120.97	(0.20)			120.12	(0.28)			0.04
Diastolic blood pressure (mmHg)	73.50	(0.12)			73.14	(0.16)			0.18
Hypertension			3,137	33.9			1,504	33.4	0.50
Medication use									
Definition 1‡			1,270	13.7			659	14.5	0.19
Definition 2§			1,581	17.1			813	17.9	0.21
Incident events									
Myocardial infarction			297	3.2			186	4.1	<0.01
Fatal CHD†			63	0.7			57	1.2	<0.01
Non-CHD mortality			540	5.8			308	6.8	0.03

* p values derived from t tests of means and chi-square tests of proportions.
† SE, standard error; CHD, coronary heart disease.
‡ Medication use–definition 1, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and antianginals.
§ Medication use–definition 2, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, antianginals, and antihypertensives (excluding diuretics).

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TABLE 3. Adjusted† hazard ratios and 95% confidence intervals of incident events by quartiles of supine, standing, and supine–standing (Δ) heart rate variability, Atherosclerosis Risk in Communities Study, 1987–1997

Quartile‡	Supine			Standing			Δ HRV§		
	HR§	95% CI§	*p* value*	HR	95% CI	*p* value*	HR	95% CI	*p* value*
				Myocardial infarction (n = 296)					
HF¶									
1 Low	1.12	0.79, 1.57	0.92	1.30	0.92, 1.85	0.04	0.83	0.58, 1.18	0.21
2	1.08	0.76, 7.52		1.38	0.98, 1.94		1.18	0.85, 1.62	
3	1.03	0.72, 1.47		0.90	0.62, 1.32		1.01	0.72, 1.42	
4 High	1.00			1.00			1.00		
SDNN#									
1 Low	1.76	1.23, 2.51	<0.01	2.21	1.50, 3.27	<0.01	0.75	0.54, 1.05	0.30
2	1.25	0.87, 1.78		1.47	1.01, 2.15		0.98	0.73, 1.35	
3	1.00	0.69, 1.44		1.27	0.87, 1.86		0.84	0.61, 1.15	
4 High	1.00			1.00			1.00		
R-R**									
1 Low	1.68	1.23, 2.30	<0.01	1.27	0.94, 1.71	<0.01	1.42	1.02, 1.98	0.20
2	1.10	0.78, 1.55		0.92	0.67, 1.27		1.18	0.84, 1.64	
3	1.13	0.81, 1.57		0.68	0.48, 0.96		1.13	0.81, 1.58	
4 High	1.00			1.00			1.00		

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				Fatal CHD (n = 63)					
HF									
1 Low	0.92	0.47, 1.78	0.27	2.41	1.01, 5.72	0.06	0.49	0.21, 1.16	0.09
2	0.60	0.28, 1.27		2.00	0.83, 4.79		1.24	0.65, 2.39	
3	0.52	0.23, 1.19		0.96	0.35, 2.65		0.70	0.32, 1.50	
4 High	1.00			1.00			1.00		
SDNN									
1 Low	1.04	0.48, 2.26	0.90	1.72	0.72, 4.09	0.53	0.91	0.43, 1.93	0.98
2	0.81	0.36, 1.80		1.14	0.48, 2.72		0.95	0.49, 1.84	
3	0.89	0.40, 1.98		1.19	0.50, 2.86		1.05	0.53, 2.08	
4 High	1.00			1.00			1.00		
R-R									
1 Low	0.49	0.14, 1.72	0.36	0.91	0.32, 2.61	0.55	0.87	0.41, 1.83	0.09
2	0.43	0.16, 1.13		1.31	0.57, 3.00		0.47	0.21, 1.05	
3	0.80	0.36, 1.79		0.78	0.33, 1.87		0.46	0.20, 1.05	
4 High	1.00			1.00			1.00		

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	Non-CHD mortality (n = 533)††								
HF									
1 Low	1.56	1.21, 2.01	<0.01	1.69	1.30, 2.18	<0.01	0.97	0.75, 1.27	0.01
2	1.22	0.94, 1.60		1.19	0.91, 1.56		1.38	1.09, 1.76	
3	1.26	0.97, 1.65		0.97	0.73, 1.28		1.20	0.93, 1.54	
4 High	1.00			1.00			1.00		
SDNN									
1 Low	1.30	1.00, 1.70	0.14	1.61	1.21, 2.14	<0.01	1.02	0.79, 1.31	0.58
2	1.03	0.78, 1.34		1.17	0.88, 1.54		1.11	0.88, 1.40	
3	1.10	0.84, 1.44		1.15	0.87, 1.52		1.16	0.91, 1.47	
4 High	1.00			1.00			1.00		
R-R									
1 Low	1.89	1.49, 2.40	<0.01	2.10	1.66, 2.65	<0.01	1.18	0.93, 1.52	0.53
2	1.56	1.22, 2.00		1.30	1.00, 1.68		1.10	0.86, 1.41	
3	1.07	0.82, 1.39		1.18	0.91, 1.53		1.17	0.92, 1.50	
4 High	1.00			1.00			1.00		

* p values from a 3 degrees of freedom χ^2 global test of the null hypothesis that the coefficients of the three indicator variables together are 0.

† Adjusted for age, race, gender, heart rate, and heart rhythm control medications (beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and antianginals. R-R intervals are not adjusted for heart rate.

‡ Highest quartile (quartile 4) for each index is the referent.

§ HRV, heart rate variability; HR, hazard ratio; CI, confidence interval.

¶ HF, high-frequency power, absolute units (0.15–0.40 Hz). Quartiles: supine, 4.04/9.22/20.1; standing, 1.78/4.46/10.80; supine HF −standing HF (Δ HF): −0.43/3.32/11.28.

SDNN, standard deviation of normal R-R intervals. Quartiles: supine, 24.3/33.1/45.0; standings, 23.7/32.9/44.4; supine SDNN − standing sDNN (Δ SDNN); 8.3/10/0.4.

** R-R interval lengths. Quartiles: supine, 803.2/888.2/979.3; standing, 675.8/744.1/828.0; supine R-R − standing R-R (Δ R-R), 84.2/132.2/186.5.

†† Death from any cause except myocardial infarction or fatal CHD.

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The cardiac autonomic response to postural change, as measured by short HRV records, generally did not predict incident events at the population level. The HRV response to postural change may not confer any additional predictive ability for incident cardiac and noncardiac events beyond measures in the supine or standing position when short (<5 minutes) HRV records are used. A simple measure, such as the change in heart rate with standing (Δ R-R intervals) that reflects autonomic input and additional control mechanisms, appears to be a more sensitive predictor of incident events.

Próxima aula

- Extensões do modelo de Cox.

Por hoje é só!

Bons estudos!