Predictive Value of Resting Heart Rate for Cardiovascular and All-cause Mortality

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Abstract

Background: Resting heart rate (which ranges from 60 to 80 bpm) is one of the simplest cardiovascular parameters, and has been considered as a predictor of cardiovascular and all-cause mortality.

Objective: To determine the predictive value of resting heart rate (RHR) before exercise stress testing (ET) for cardiovascular (CV) and all-cause mortality.

Methods: This was a case-control study using data from the database of the Exercise Testing Laboratory of a cardiac hospital and the death records of the Health Department of a city located in the South of Brazil from January 1995 to June 2007. A total of 7,055 patients were studied; 1,645 (23.3%) in the case group (deceased) and 5,410 (76.7%) in the control group (alive). The cut-off value of RHR for mortality was derived from the ROC curve, and a multivariate analysis was performed for the selected variables. The study's outcome measures were cardiovascular and all-cause mortality.

Results: Six hundred and seventy-four patients died of cardiovascular diseases (9.5%); the cut-off value was RHR ≥ 78 bpm). After adjusting for selected variables, the odds ratio (OR) of RHR ≥ 78 bpm was 3.5 (95% CI 2.9 to 4.2) for CV mortality and 3.6 (95% CI 3.2 to 4.0) for all-cause mortality.

Conclusion: Resting heart rate ≥ 78 is an independent predictor of cardiovascular and all-cause mortality. (Arq Bras Cardiol 2010;95(6):713-719)

Keywords: Predictive value of tests; heart rate; exercise test/mortality.

Introduction

Intrinsic heart rate (HR), in the absence of any neurohumoral influence, is approximately 100 to 120 bpm. In the healthy individual, heart rate at rest reflects a balance between the tonically active sympathetic and parasympathetic systems, with a predominance of the latter. Such predominance results in a resting heart rate (RHR) that is lower than the intrinsic heart rate, one of the simplest cardiovascular parameters that usually ranges from 60 to 80 bpm[1]. Resting HR, or baseline HR, refers to the number of heartbeats per minute at rest[2].

Since 1980, it is known that resting heart rate is a prognostic factor for coronary artery disease (CAD) and that it is associated with cardiovascular[3] and all-cause[4] mortality.

Several past long-term follow-up studies have demonstrated the impact of elevated resting HR in the general population[5], elderly subjects[6], and hypertensive[7] as well as acute myocardial infarction pacients[6], on both cardiovascular[8,9] and all-cause[8,10]. This finding has been confirmed by more recent studies.[9,11,12]. In multivariate analyses, many studies have found that the relative risk (RR) for elevated RHR remained high even after being adjusted for several cardiovascular risk factors. These studies also found that increased RHR is a predictor of cardiovascular and all-cause mortality[11,13,14].

This study sought to evaluate the predictive value of resting (pre-exercise) heart rate for cardiovascular and all-cause mortality, establishing a cut-off value in a sample of patients undergoing exercise stress testing (ET). Investigating the relationship between RHR and mortality is extremely important. The findings of our study both support and add new evidence to the existing literature regarding the predictive value of RHR for cardiovascular and all-cause mortality.

Methods

This was a case-control study using data from the database of exercise tests of a cardiac hospital and the death records of a city located in the South of Brazil from January 1995 to June 2007. The case group (deceased) consisted of patients selected from the Death Registry who had undergone exercise testing, and the control group (alive) consisted of patients extracted from the database of the Exercise Testing Laboratory (aged 25 or older). Patients who had the same name in the database were excluded from the study when there was insufficient data to determine if they were one and the same person. The Probabilistic Record Linkage Software (Link Plus)[15] developed

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by the U.S Centers for Disease Control (CDC), a sophisticated linkage mechanism, was used to mach the names from the database of the Exercise Testing Laboratory with those of the Death Registry. Matching was done by gender and the same year at which the exercise test had been performed. After data analysis, a total of 7,055 patients were selected: 1,645 for the case group (deceased) and 5,410 for the control group (the number of patients was greater in this group to minimize any potential bias resulting from deaths away from home).

The outcome measures selected were cardiovascular and all-cause mortality. Death was considered as due to cardiovascular disease if the death certificate listed acute myocardial infarction (AMI), cardiorespiratory arrest, angina pectoris, ischemic heart disease, cardiogenic shock, sudden death, congestive heart failure, arrhythmias, or other causes of death included in chapter IX of the International Classification of Diseases, 10th Revision (ICD-10)[16]. Before beginning the test, a seated resting heart rate was measured with a heart rate monitor and blood pressure (BP) was taken manually. The Bruce protocol[17] was used for most patients, and the indication for the test (about 98%) was based on the diagnosis.

The following variables were analyzed: gender, age, smoking status, use of cardiovascular drugs, resting BP ≥ 140/90 mmHg, VO_2max ≤ 28 ml/kg/min, body mass index (BMI) ≥ 25 kg/m^2, hypercholesterolemia, and diabetes. The latter two were validated based on the analysis of a subsample of 1,198 Registration Forms for Exercise Testing (on cardiovascular risk factors) and compared with laboratory tests using the Kappa Index of Agreement[18] (considered acceptable when ≥ 0.40): hypercholesterolemia and cholesterol ≥ 200 mg/dl (K = 0.510); diabetes and blood glucose ≥ 126 mg/dl (K = 0.621).

In this study, VO_2 max (maximal oxygen uptake) was determined indirectly, taking into account age, gender, and tolerated workload, as described in the Brazilian Consensus on Ergometry[17].

Statistical analyses were performed using the SPSS™ software package (version 15.0). The following tests were applied: the Student's t-test, Pearson's chi-square test, ROC curve, confidence intervals, and multivariate analysis with odds ratio. P values < 0.05 were considered statistically significant, and the confidence interval was 95%.

This study protocol was approved by the Research Ethics Committees of the local Health Department and the Institutional Review Board.

Results

A total of 7,055 patients were evaluated, 1,645 (23.3%) of whom were in the case group (deceased) and 5,410 (76.7%) in the control group (alive). The mean age of the study population was 55.43 ± 10.48 years, and 61.3% of the patients were male. The follow-up period was 12 years. Cardiovascular mortality rate was 9.5% (674 patients).

The distribution of the remaining variables between groups is shown in Table 1. Mean resting HR of the case group (deceased), for both cardiovascular and all-cause death, was similar (83.18 ± 15.50 and 83.19 ± 15.50), but when it was compared with the control group (72.13 ± 12.64), there was a significant difference (p < 0.001). Smoking, diabetes, resting BP ≥ 140/90 mmHg and VO_2max ≤ 28 ml/kg/min were more prevalent in the case group (CV and all-cause death) than in the control group (p < 0.001); cardiovascular drugs were more frequently used in the case group (CV death) (69%) than in the control group (57.5%), p < 0.001. Hypercholesterolemia and BMI ≥ 25 kg/m^2 were equally distributed among groups (p > 0.005).

Regarding age distribution, Table 2 shows that approximately 30% of the patients who died were in the 51 to 60 and 61 to 70 age groups; 6.4% (CV death) and 6.9% (all-cause death) were in the 25 to 40 age group; and 16.8% (CV death) and 15.3% (all-cause death) were in the 71 to 88 age group, greater than in the control group (3.5%). The age difference between groups was statistically significant (p < 0.001).

Table 1 - Distribution of variables among groups

Variables	Control group (A) (%) (n = 5,410)	Case group - CV death (B) (%) (n = 674)	Case group - all-cause death C (%) (n = 1,645)	p* Group A x B	p* Group A x C
Male gender	3,372 (62.3)	444 (65.9)	1,058 (64.3)	0.73	0.144
Smoking	1,096 (20.3)	187 (27.7)	430 (26.1)	<0.001	<0.001
Diabetes	428 (7.9)	114 (16.9)	212 (12.9)	<0.001	<0.001
Cardiovascular drugs	3,114 (57.5)	465 (69.0)	1,005 (61.1)	<0.001	0.011
Resting BP ≥ 140/90 mmHg	2,946(54.5)	434(64.4)	1,011 (60.9)	<0.001	<0.001
VO_2 max ≤ 28 ml/kg/min (~ 8 METs)	1,926 (35.6)	380 (56.4)	870 (52.9)	<0.001	<0.001
Hypercholesterolemia	1,392 (25.7)	165 (24.5)	417 (25.3)	0. 483	0.757
BMI ≥ 25 kg/m^2	3,506 (64.8)	437 (64.8)	1,035 (62.9)	0. 999	0.161
RHR	72.13(±12.64)	83.18 (± 15.50)	83.19 (±15.50)	<0.001	<0.001

*CV - cardiovascular; n - number; BP - blood pressure: VO_2 max - functional capacity METs - metabolic equivalents; BMI - body mass index; RHR - resting heart rate; *Pearson's chi-square test for heterogeneity and Student's t-test for comparison of RHR among groups.*

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Table 2 - Distribution of age among groups

Age (years)	Control group (A)	Case group - CV death (B) (%)	Case group - all-cause death (C) (%)
25 to 40	404 (7.5)	42 (6.4)	113 (6.9)
41 to 50	1,491 (27.6)	126 (18.9)	307 (18.6)
51 to 60	1,852 (34.2)	185 (27.5)	465 (28.3)
61 to 70	1,469 (27.2)	207 (30.4)	508 (30.9)
71 to 88	194 (3.5)	114 (16.8)	252 (15.3)
Mean age. SD	54.51(±9.99)	59.03(±11.55)	58.49(±11.43)
Total	5410	674	1645

n - number; ST - standard deviation; CV - cardiovascular; Pearson's chi-square test to compare groups: A x B = p < 0.001 and A x C = P < 0.001. Student's t-test to compare means between groups A x B = P< 0.001 and A x C = P< 0.001.

Figure 1 depicts the ROC curves for the case group, both for CV and all-cause death, which were similar to one another; minimal resting HR was 41 bpm, and maximum resting HR was 134 bpm. The ROC curve analysis showed the optimal sensitivity (Se) and specificity (Sp) of the cut-off value of resting heart rate for all-cause death (sensitivity of 0.618 and 1 and specificity of 0. 315) and CV death (sensitivity of 0.614 and 1 and specificity of 0.315), resulting in 61% and 68%, respectively. The cut-off value for mortality, therefore, was RHR ≥ 78 bpm.

Tables 3 and 4 show the correlation between the cut-off value for mortality and the significant variables of the study.

Table 3 shows that more women than men had RHR ≥ 78 bpm (OR 1.32, CI 1.19 -1.46). Smoking (OR 1.21, CI 1.08 -1.36), diabetes (OR 1.65, CI 1.41-1.95), VO_2max ≤ 28 ml/kg/min (OR 2.04, CI 1.71-2.43), and resting BP ≥ 140/90 mmHg (OR 1.36, CI 1.24 -1.50) were associated with resting HR ≥ 78 bpm. Cardiovascular drugs were found to have a protective effect, since only 37.5% of the patients who were using them had resting HR ≥ 78 bpm.

Table 4 summarizes the association of RHR ≥ 78 bpm with age distributed among groups, showing that most patients with RHR ≥ 78 bpm belonged to the case group (deceased) in all age brackets. In the quintile of the 25 to 40 age group, OR was 3.54 (CI 1.82-6.89) for cardiovascular death and 3.73 (CI 2.41-5.80) for all-cause death when resting HR was ≥ 78 bpm, compared to the control group. In the 51-60 age group, the odds ratio for cardiovascular and all-cause mortality was about four times higher than that of the control group. In the 71-88 age group, the likelihood of cardiovascular (OR 3.02; CI 1.85-4.93) and all-cause (OR 3.46, CI 2.30 -5.21) mortality increased in patients with resting HR ≥ 78 bpm.

Table 5 shows the logistic regression analysis for the case group (CV death). Male gender (OR 1.36, CI 1.12-1.65), smoking (OR 1,92, CI 1.58-2.35), diabetes (OR 1.91; CI 1.50-2.43), use of cardiovascular drugs (OR 1.27, CI 1.04-1.55), resting BP ≥ 140/90 mmHg (OR 1.20, CI 1.003-1.440), and VO_2max ≤ 28 ml/kg/min (OR 1.35, CI 1.003-1.820) were associated with cardiovascular mortality. Age was significant only in the oldest age group (71 to 88), with odds ratio of 6.38 (CI 4.11-9.88). When evaluated separately, resting HR ≥ 78 bpm was found to be an independent variable (OR 3.56, CI 2.99-4.24).

Table 6 shows the logistic regression analysis for all-cause mortality. Male gender (OR 1.27, CI 1.11-1.45), smoking

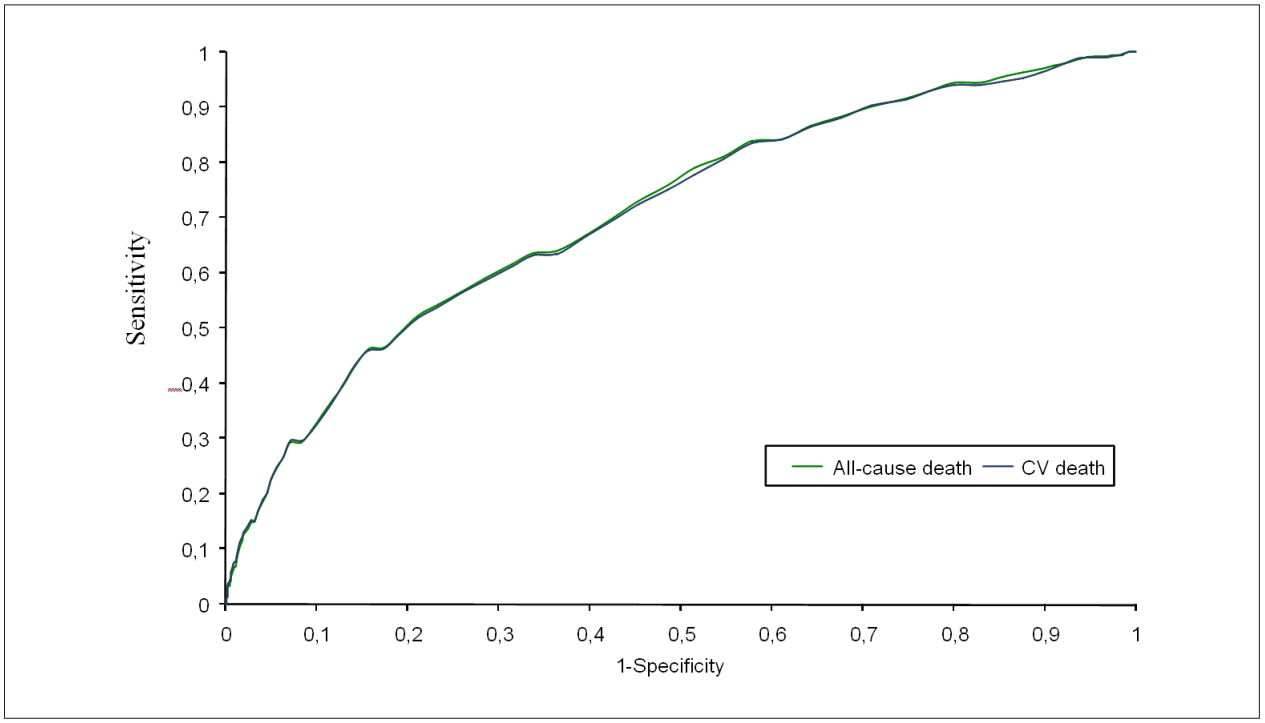

Fig. 1 - *The ROC curve for RHR of the case group (all-cause and CV death) All-cause death - area under the curve: 0.711. All-cause death - area under the curve: 0.798. CV - cardiovascular.*

Table 3 - RHR ≥ 78 bpm relative to significant variables of the total sample (n = 7,055)

Variable	RHR ≥ 78 bpm (%)	OR	95% CI
Gender			
F	(42.8)	1.32	1.19 - 1.46
M	(36.1)	1.0	
Smoking			
Yes	(42.1)	1.21	1.08 – 1.36
No	(37.6)	1.0	
Diabetes			
Yes	(49.8)	1.65	1.41 – 1.95
No	(37.5)	1.0	
Cardiovascular drugs			
Yes	(37.5)	0.89	0.81 – 0.98
No	(40.1)	1.0	
Resting BP			
≥ 140/90 mmHg.	(41.8)	1.36	1.24 – 1.50
140/90 mmHg	(34.5)		
VO_2max ≤ 28 ml/kg/min	(54.8)	2.04	1.71 – 2.43

RHR - resting heart rate; F - female M - male VO_2 max - functional capacity. BP - blood pressure: CV - cardiovascular; OR - odds ratio; CI - confidence interval.

(OR 1.68, CI 1.46-1.94), diabetes (OR 1.43, CI 1.18-1.73), VO_2max ≤ 28 ml/kg/min (OR 1.28, CI 1.03-1.59), plus age groups 61 to 70 (OR: 1.52, CI: 1.17-1.97) and age 71 to 88 (OR 6.31, CI 4.62-8.61) were associated with all-cause mortality. When resting HR ≥ 78 bpm (OR 3.62, CI 3.21-4.08) was evaluated separately, it showed the same behavior.

Discussion

In our study, elevated RHR was found to be associated with mortality, as reported by other authors[9,14,19,20].

In earlier studies, such as the National Health and Nutrition Examination Survey (NHANES), Spandau Health Test (SHT), and The Three Chicago Epidemiologic Studies, heart rate was associated with cardiovascular and noncardiovascular mortality[21].

Other studies have confirmed these data, such as the CORDIS Trial and MATISS: Kristal-Boneh et al[11], in the CORDIS trial, found that elevated RHR was strongly associated with both all-cause (RR 2.23, CI 1.4-3.6; RHR > 90 bpm) and cardiovascular mortality, even after controlling for many known risk factors. Seccareccia et al[13], in the MATISS study, found that in a low-risk Italian population heart rate increment was associated with a RR increase of 1.52 (CI 1.29-1.78) for all-cause mortality and 1.63 (CI: 1.26-2.10) for cardiovascular mortality.

It is known that individuals with elevated resting heart rate have less HR variability (reflecting an imbalance in the autonomic nervous system), which predisposes to arrhythmias, heart failure, atherosclerosis and increased risk of death[22]. In

Table 4 - RHR ≥ 78 bpm relative to age, distributed among groups (n = 7,055)

Age (years)	Control group	Case group (CV death)	Case group (all-cause death)
25 to 40			
n	407	42	113
RHR ≥ 78 bpm (%)	33.7	64.3	65.5
OR (95% CI)	1.0	3.54 (1.82 – 6.89)	3.73 (2.41-5.80)
41 to 50			
n	1,491	126	307
RHR ≥ 78 bpm (%)	33.7	59.5	59.9
OR (95% CI)	1.0	2.88 (1.99 – 4.18)	2.93(2.28 – 3.78)
51 to 60			
n	1,852	185	465
RHR ≥ 78 bpm (%)	32.3	69.7	66.2
OR (95% CI)	1.0	4.81 (3.47 – 6.69)	4.10 (3.30 – 5.09)
61 to 70			
n	1,469	207	508
RHR ≥ 78 bpm (%)	28.3	59.9	61.4
OR (95% CI)	1.0	3.78 (2.80 – 5.10)	4.02 (3.26 – 4.97)
71 to 88			
n	191	114	252
RHR ≥ 78 bpm (%)	26.2	51.8	55.2
OR (95% CI)	1.0	3.02 (1.85 - 4.93)	3.46 (2.30 – 5.21)

n - number; CV - cardiovascular; RHR - resting heart rate; OR - odds ratio; CI - confidence interval.

Table 5 - Logistic regression analysis for the case group (CV death)

Variable	OR	95% CI
Male gender	1.36	1.12 – 1.65
Smoking	1.92	1.58 – 2.35
Diabetes	1.91	1.50 – 2.43
Cardiovascular drugs	1.27	1.04 – 1.55
Age (years):	-	-
25 to 40	1.0	-
41 to 50	0.76	0.52 -1.12
51 to 60	0.89	0.60 – 1.30
61 to 70	1.36	0.92 – 2.01
71 to 88	6.38	4.11 – 9.88
RHR ≥78 bpm	3.56	2.99 – 4.24
Resting BP ≥ 140/90 mmHg	1.20	1.003 – 1.440
VO_2max ≤ 28 ml/kg/min	1.35	1.003 – 1.820

M - males; CV - cardiovascular; RHR - resting heart rate; BP - blood pressure: VO_2 max - functional capacity OR - odds ratio; CI - confidence interval.

Table 6 - Logistic regression analysis for the case group (all-cause death)

Variable	OR	95% CI
Male gender	1.27	1.11 – 1.45
Smoking	1.68	1.46 – 1.94
Diabetes	1.43	1.18 – 1.73
CV drugs	0.93	0.82 – 1.07
Age group		
25 to 40 years	1.0	–
41 to 50	0.79	0.61 – 1.02
51 to 60	0.99	0.77 – 1.27
61 to 70	1.52	1.17 – 1.97
71 to 88	6.31	4.62 – 8.61
RHR ≥ 78 bpm	3.62	3.21 – 4.08
Resting BP ≥ 140/90 mmHg	1.12	0.99 – 1.27
VO_2max ≤ 28 ml/kg/min	1.28	1.03 – 1.59

M - males; CV - cardiovascular; RHR - resting heart rate; BP - blood pressure: VO_2 max - functional capacity OR - odds ratio; CI - confidence interval.

this study, hypercholesterolemia and BMI ≥ 25 kg/m² were equally distributed between the case and control groups. Although no variable alone was significant, the association with other risk factors, such as systemic hypertension, cigarette smoking, and diabetes may increase mortality rates[23].

All the remaining variables were associated with resting HR ≥ 78 bpm, as evidenced by several previous studies demonstrating that smoking, hypertension, diabetes, and sedentary lifestyle are associated with increased HR and mortality risk[7,24,25]. Only in the case group (CV death) was resting BP ≥ 140/90 mmHg significant, and the patients who died were 1.20 times more likely to have increased blood pressure. The impact of elevated heart rate on hypertensive as well as diabetic patients, increasing by three-to-four-fold the risk of cardiovascular events and twice the risk of dying from such an event, compared to the general population, is already well documented in the literature[4,26,27]. The adrenergic hyperactivity involved in these risk factors and the imbalance between the sympathetic and parasympathetic activities explain these findings[2].

Table 3 shows that patients with RHR ≥ 78 bpm tended to be women (42.8%), although cardiovascular death (65.9%) and all-cause death (64.3%) were more prevalent in men. Even though RHR was higher in women, the association with the development of hypertension, atherosclerosis, and CV morbidity and mortality is lower or absent in this group[28]. It is possible that women, especially premenopausal women, are protected from the deleterious effects of elevated HR due to an estrogen-associated increase in their serum HDL-cholesterol levels[29]. As shown in Table 4, patients who died from cardiovascular disease and from all causes, and who belonged to the age groups 51 to 60 and 61 to 70 years, were four times more likely to have increased RHR. In healthy individuals, HR is inversely related to age[2]. Cardiovascular risk factors are known to be associated with increased HR, therefore the effects of elevated HR in said age groups are even more deleterious[30,31].

Evaluated separately, RHR ≥ 78 bpm was found to have an impact on cardiovascular and all-cause mortality. In our study, the patients who died were more than three times as likely to have increased RHR than those who did not (OR 3.56 and 3.62, respectively). This finding supports the association of increased RHR with mortality. The deleterious effects of elevated HR have already been demonstrated in the Framingham study[21]. In this study, in a cohort of 5,070 subjects free of cardiovascular diseases at baseline, cardiovascular mortality increased progressively with resting heart rate.

The large number of patients included in our study makes it possible to confirm the hypothesis that the association of elevated RHR with mortality is not accidental.

Concluding, our findings suggest a relationship between RHR and mortality, from a cut-off value of RHR ≥ 78 bpm, found both in CV and all-case deaths, with greater risk in the 71 to 88 age group. In our study, RHR ≥ 78 bpm, even after adjustment for gender, diabetes, smoking, use of cardiovascular drugs, resting BP ≥ 140/90 mmHg, and VO_2max ≤ 28 ml/kg/min, was found to be an independent predictor of cardiovascular and all-cause mortality.

Study limitations

Possible limitations to our results include the following: the origin, not described, of all patients undergoing exercise test (some may have come from the ER and have increased RHR); the method used to consider patients as alive in the study (i. e., the fact that they were not included in the death records of the Health Department); the reliability of the information abstracted from the Death Certificates; and the fact that the Kappa test was the only statistical method used to validate the study variables.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any post-graduation program.

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