OBJECTIVES
In the present study, we evaluated sinus and atrioventricular (AV) node electrophysiology of endurance athletes and untrained individuals before and after autonomic pharmacologic blockade.

BACKGROUND
Endurance athletes present a higher prevalence of sinus bradycardia and AV conduction abnormalities, as compared with untrained individuals. Previous data from our laboratory suggest that nonautonomic factors may be responsible for the longer AV node refractory period found in well-trained athletes.

METHODS
Six aerobically trained male athletes and six healthy male individuals with similar ages and normal rest electrocardiograms were studied. Maximal oxygen uptake (V\textsubscript{O2max}) was measured by cardiopulmonary testing. The sinus cycle length (SCL), AV conduction intervals, sinus node recovery time (SNRT), Wenckebach cycle (WC) and anterograde effective refractory period (ERP) of the AV node were evaluated by invasive electrophysiological studies at baseline, after intravenous atropine (0.04 mg/kg) and after addition of intravenous propranolol (0.2 mg/kg).

RESULTS
Athletes had a significantly higher V\textsubscript{O2max} as compared with untrained individuals. The SCL was longer in athletes at baseline, after atropine and after the addition of propranolol for double-autonomic blockade. The mean maximal SNRT/SCL was longer in athletes after atropine and after propranolol. The WC and anterograde ERP of the AV node were longer in athletes at baseline, after atropine and after propranolol.

CONCLUSIONS
Under double-pharmacologic blockade, we demonstrated that sinus automaticity and AV node conduction changes of endurance athletes are related to intrinsic physiology and not to autonomic influences. (J Am Coll Cardiol 2002;39:1033–8) © 2002 by the American College of Cardiology Foundation.
Abbreviations and Acronyms

ANOVA = analysis of variance
AV = atrioventricular
ECG = electrocardiogram
ERP = effective refractory period
SCL = sinus cycle length
SNRT = sinus node recovery time
V\(\dot{O}\)\(_2\)max = maximal oxygen uptake
WC = Wenckebach cycle

pharmacologic blockade. All subjects were informed of the risks and discomforts involved in the experiments and gave written, informed consent. In light of the results of our previous experiments (3), as well as the risks involved with the performance of invasive electrophysiologic studies in asymptomatic individuals (4), our institution’s Research Committee approved the protocol for six athletes and six untrained individuals. The protocol was also approved by the Brazilian National Council for Research (CONEP, Brasilia, Brazil).

Measurement of V\(\dot{O}\)\(_2\)max. The subjects exercised on a motor-driven treadmill (Inbramed TK 10,200, Porto Alegre, Brazil); the 12-lead ECG was continuously monitored; and respiratory gases were analyzed by using a previously validated commercial system (Total Energy Expenditure Measurements, Aerosport, Ann Harbor, Michigan) (5). For the athletes, the exercise protocol started at a speed of 4 km/h, with additional increments of 2 km/h every 2 min until volitional fatigue. For untrained individuals, the protocol was started at speed of 2 km/h, with additional increments of 2 km/h every 2 min until volitional fatigue.

Electrophysiologic study and pharmacologic blockade. The electrophysiologic study was performed with the subjects in the postabsorptive state. The subjects rested in the supine position for 15 min, and a 12-lead surface ECG was recorded on a Funbec (São Paulo, Brazil) electrocardiograph. The PR interval and corrected QT (QTc = QT·[V\(\sqrt{R}\)]\(^{-1}\)) interval were measured. Correction of the QT interval was used to control for the different rest heart rates of the groups. The subjects were then continuously monitored by pulse oximetry and electrocardiography. A cannula was inserted in the antecubital vein, and 2 mg of midazolam was initially administered intravenously. Additional doses of midazolam were given throughout the procedure, if necessary for sedation. After local anesthesia of the right groin with 1% lidocaine, two sheaths were introduced percutaneously into the right femoral vein. Under fluoroscopic guidance (calculated radiation exposure of 28 to 42 mGy), two 7F, deflectable, multipolar electrode catheters were positioned against the high right atrial wall, near the region of the sinus node, and across the tricuspid valve in the area of the His bundle for recordings of intracardiac electrograms and pacing. Baseline intracardiac conduction intervals were then measured during sinus rhythm (6). Electrical stimulation of the atrium was performed with a programmable stimulator (UHS 20, Biotronik, Germany) using 2-ms, constant-current pulses at approximately twice the late diastolic threshold. Surface ECG leads and bipolar intracardiac electrograms filtered at a bandpass of 30 to 500 Hz were displayed and recorded simultaneously on a multichannel recorder (Mingograf 7, Siemens, Germany) at a paper speed of 50 or 100 mm/s.

After control recordings, the atrium was paced for 30-s periods, at constant cycle lengths of 600, 500 and 400 ms, and the rhythm was monitored to ensure complete atrial capture. At least 30 s was allowed to elapse between each successive pacing period. Measurements of sinus node recovery time (SNRT) were made using bipolar electrograms recorded from the proximal two poles of the high atrial catheter; SNRT was defined as the time from the last paced stimulus to the onset of the first deflection on the electrogram of the first sinus beat. To control for differences in sinus rate, SNRT was normalized for the spontaneous sinus cycle length (SCL) (7). At least five consecutive cycles following each pacing period and after the rhythm had returned to the control cycle length were used to calculate the mean SCL. In each individual, the longest (maximal) SNRT was determined. The anterograde effective refractory period (ERP) of the AV node was defined as the cycle length during incremental atrial pacing where the AV node Wenckebach phenomenon was noted. The anterograde effective refractory period (ERP) of the AV node was measured using an eight-beat drive at a cycle length equal to the SCL – 100 ms, followed by a single premature atrial stimulus introduced decrementally at 10-ms intervals. The anterograde ERP of the AV node was defined as the longest coupled premature atrial stimuli interval that failed to propagate to the His bundle (6).

Parasympathetic blockade was induced by administration of atropine, 0.04 mg/kg body weight intravenously (8,9). After a stable sinus rate had been achieved, the electrophysiologic variables described earlier were again measured. Double-autonomic blockade was then obtained by addition of 0.2 mg/kg of propranolol intravenously, and, after SCL stabilization, a final set of electrophysiologic variables was obtained again (8,9). Sheaths were pulled out; hemostasis was obtained by pressure; and the subjects rested in a recovery room for 6 h.

Statistical analyses. Data are presented as the mean ± SD. Differences between athletes and nonathletes were compared by using the Student t test. The effects of pharmacologic blockade on the electrophysiologic variables were compared by two-way analysis of variance (ANOVA) for repeated measures. When appropriate, multiple comparisons were made by the Student Newman–Keuls method. Based on the results of our previous study using transesophageal stimulation (3), and assuming a lower variability of the data due to sedation, we estimated that a sample size of six individuals in each group would have a statistical power of...
Data are presented as the mean value ± SD. NS = not significant; $V_O_{2\text{max}}$ = maximal oxygen uptake.

80% to detect a 20% difference in the electrophysiologic variables, at $p = 0.05$.

**RESULTS**

Table 1 describes the demographic, rest ECG and exercise testing data for athletes and untrained individuals. The groups were similar in terms of age, weight and height. In athletes, the rest heart rate was significantly lower and $V_O_{2\text{max}}$ was significantly higher. The rest ECG intervals were similar in the two groups and within the normal range for all subjects.

The mean AV conduction intervals and atrial P-wave, atrial His-bundle and ventricular His-bundle values were similar, within the normal range, and responded typically and alike during the pharmacologic interventions in athletes and nonathletes (Table 2). The mean SCLs in athletes and nonathletes were $1,030 ± 111$ and $913 ± 90$ ms, $737 ± 59$ and $653 ± 43$ ms and $831 ± 71$ and $722 ± 43$ ms at baseline, after parasympathetic blockade and after double-autonomic blockade, respectively (ANOVA: $p < 0.01$ for group effect; $p < 0.01$ for drug effect; $p = 0.365$ for interaction). Atropine increased and propranolol decreased the heart rate ($p < 0.05$) in similar proportions in both groups—that is, the SCL of the athletes always remained longer than the SCL of the nonathletes (Fig. 1). The mean maximal SNRT/SCL ratios in athletes and nonathletes were $1.56 ± 0.16$ and $1.5 ± 0.09$, $1.36 ± 0.19$ and $1.26 ± 0.06$ and $1.45 ± 0.09$ and $1.31 ± 0.05$ at baseline, after parasympathetic blockade and after double-autonomic blockade, respectively (ANOVA: $p < 0.01$ for group effect; $p < 0.01$ for drug effect; $p = 0.640$ for interaction). As expected, atropine decreased and propranolol increased ($p < 0.05$) the mean maximal SNRT/SCL ratio, but, unexpectedly, the recovery time of the athletes was significantly longer than that of the nonathletes after both parasympathetic and double-autonomic blockade, despite being expressed as a ratio of SCL (Fig. 1). The mean length of the WC of the AV node in athletes and nonathletes was $575 ± 73$ and $453 ± 51$ ms, $423 ± 46$ and $342 ± 25$ ms and $493 ± 56$ and $413 ± 28$ ms at baseline, after parasympathetic blockade and after double-autonomic blockade, respectively (ANOVA: $p < 0.01$ for group effect; $p < 0.01$ for drug effect; $p = 0.370$ for interaction) (Fig. 1). The mean anterograde ERP of the AV node in athletes and nonathletes was $425 ± 46$ and $313 ± 44$ ms, $338 ± 47$ and $257 ± 26$ ms and $408 ± 53$ and $282 ± 43$ ms at baseline, after parasympathetic blockade and after double-autonomic blockade, respectively (ANOVA: $p < 0.01$ for group effect; $p < 0.01$ for drug effect; $p = 0.690$ for interaction) (Fig. 1). As with SCL, the WC and anterograde ERP were reduced by atropine and increased by propranolol, but the values for athletes remained significantly longer than those for nonathletes.

**DISCUSSION**

The rest ECGs of the well-trained endurance athlete may show certain distinguished features that are similar, in many respects, to those seen in patients with cardiovascular disease. Among the most frequent rhythm changes are sinus bradycardia and AV conduction abnormalities. Rest sinus bradycardia may be found in the great majority of endurance athletes, and borderline or first-degree AV block may be observed in 10% to 33% and second-degree Wenckebach block in 2% to 10% of long-distance runners (10). These abnormalities have been related to higher parasympathetic activity owing to their association with training and detraining, as well as their disappearance after sympathetic or vagolytic maneuvers (11).

Because of the invasive nature of electrophysiologic studies, there is little information on atrial automaticity and AV node conduction of healthy athletes. Mezzani et al. (12) performed invasive electrophysiologic studies in a group of athletes and a group of untrained individuals, all with Wolff-Parkinson-White syndrome. In that study, athletes showed a longer SCL, atrial effective and functional refractory periods and anterograde ERP of the accessory pathway; these findings were attributed to autonomic influences. In our previous study of endurance-trained athletes and untrained individuals evaluated by transesophageal stimula-
Sinus automaticity in athletes. Some investigators who also used pharmacologic blockade have attributed training-induced sinus bradycardia to an imbalance of the two branches of the autonomic nervous system—that is, increased parasympathetic activity, decreased sympathetic activity or a combination of these (13). In contrast, other studies using pharmacologic blockade have proposed that alterations in the intrinsic properties of the sinus node, the so-called “nonautonomic component,” were responsible for rest bradycardia of athletes (14,15). Likewise, some studies that used heart rate variability methods, which may detect vagal adaptations (16), demonstrated an increase in parasympathetic activity (17,18), although others were not able to demonstrate this effect (3,19). The effects of autonomic blockade on the SCL of our endurance athletes are consistent with the concept that long-term, training-induced rest sinus bradycardia is not caused by increased parasympathetic activity or decreased sympathetic activity, but is related to intrinsic adaptations. Indeed, atropine and propranolol caused parallel shifts in the sinus automaticity of athletes and nonathletes—that is, the incremental and decremental changes were identical. Increased parasympathetic activity would cause greater heart rate responses post-atropine and a reduction in sympathetic activity would cause lesser heart rate responses post-propranolol in athletes than in nonathletes.

The maximal SNRT/SCL of athletes was significantly longer than that of nonathletes after both parasympathetic and double-autonomic blockade, compatible with nonautonomic adaptation. This longer recovery time may reflect greater overdrive suppression, longer retrograde and anterograde sinoatrial conduction times or both. In view of the effects on AV node conduction, it is tempting to speculate about the substantial impact of these sinoatrial conductive components.

**Atrioventricular node conduction in athletes.** In the present study, the effects of autonomic blockade on the WC and anterograde ERP of the AV node were equal to the effects on SCL. The differences in these electrophysiologic measurements between athletes and untrained individuals were very similar in magnitude at baseline, after atropine and after propranolol, again discordant with the view of an imbalance in autonomic activity. These findings are consistent with the experiments conducted by Yamaya et al. (20), who used pharmacologic blockade in horses with AV node conduction abnormalities. Similar to the findings in horses, our data indicate that prolonged and intensive training did not disrupt the normal balance of the autonomic nervous system, and that the longer SCL and refractory period of the AV node were essentially caused by significant intrinsic electrophysiologic modifications. These findings also confirmed our previous observations (3) suggesting that the longer AV node refractory period of athletes could be
mediated mainly by nonautonomic factors, most likely induced by athletic training.

Possible mechanisms. The physiologic mechanisms by which endurance training may induce these intrinsic changes in the specialized conduction system of the heart are unknown and may be multifactorial. An altered ionic balance across the membrane (21), as well as biochemical and mechanical effects induced by dilation and hypertrophy (14,15), have been proposed as possible mechanisms. Clinical and research data indicate that active and passive changes in the mechanical environment of the heart are capable of influencing both the initiation and spread of cardiac excitation through pathways that are intrinsic to the heart—a phenomenon known as “mechanoelectric feedback” (22). One unifying explanation for the controversy about autonomic versus nonautonomic determinants of electrophysiologic adaptations in athletes could be that short-term physical training programs, such as those used in prospective studies (13,18), could induce autonomic adaptations, with a reduction in sympathetic activity and an increase in parasympathetic activity. Long-term aerobic training, accompanied by anatomic changes such as atrial and ventricular dilation, would create the mechanoelectric feedback necessary to induce intrinsic electrophysiologic adaptations, as demonstrated in the present and other cross-sectional studies (3,14,15). Interestingly, rats (23) and dogs (24) whose hearts were denervated before training did not develop intrinsic and rest bradycardia, respectively. Thus, it is likely that a functioning autonomic system is necessary for the development of electrophysiologic adaptations.

Possible clinical relevance. In the present study, we evaluated a group of well-trained athletes with rest bradycardia, but without conduction abnormalities. Thus, the demonstration of intrinsic electrophysiologic adaptations can be generalized only to other athletes with similar characteristics. However, taken together with our previous observations in another group of endurance athletes (3), we believe that intrinsic adaptations represent the electrophysiologic substrate that may facilitate the appearance of more advanced conduction abnormalities. The demonstration by Zepilli et al. (11) of a reversal in conduction abnormalities of athletes by sympathetic or vagolytic maneuvers may simply represent normal parasympathetic activity superimposed on altered intrinsic electrophysiology.

Study limitations. In this study, we assumed that the differences between athletes and untrained individuals represent physiologic adaptations in response to training. Because this is a cross-sectional study, an alternative explanation could be that the intrinsic changes represent inherited characteristics that may facilitate success or trainability. However, this is unlikely, based on the observations of previous prospective studies on sinus bradycardia (13,18) and conduction abnormalities of athletes (11). The use of pharmacologic blockade as a tool for the evaluation of autonomic and nonautonomic influences on electrophysiologic variables also has its limitations. The possible sympathomimetic effect of atropine (25), as well as its attenuated antagonism (26), could have confounded our findings. However, both of these actions, if anything, would have resulted in overestimation of parasympathetic activity, particularly in favor of the athletes (9), which we did not find in our study.

Conclusions. Our controlled intracavitary electrophysiologic studies under pharmacologic blockade demonstrate that endurance athletes with rest bradycardia and a normal ECG present with sinus automaticity and AV node conduction changes that are related to intrinsic physiology, rather than to autonomic influences.

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REFERENCES