# Influence of the Pacing Rate on the Atrioventricular Conduction Time During Aerobic and Anaerobic Exercise: Basic Concepts for a Dromotropically Controlled Rate Responsive Pacemaker

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**MEINE, M., ET AL.: Influence of the Pacing Rate on the Atrioventricular Conduction Time During Aerobic and Anaerobic Exercise: Basic Concepts for a Dromotropically Controlled Rate Responsive Pacemaker.** *The dromotropic pacemaker concept needs a rate responsive algorithm in which the pacing rate is controlled by the atrioventricular conduction time (AVCT). To develop basic concepts for such a rate responsive algorithm, the influence of the pacing rate on the AVCT was investigated. Seven patients (62 $\pm$ 7.8 years) with sick sinus syndrome and intact atrioventricular conduction underwent two cardiopulmonary exercise tests (CPX) on a treadmill. According to the determination of the anaerobic threshold (AT) and the patients maximum capacity in the first incremental CPX the work rate for two exercise levels below and above the AT were chosen for the second constant workload CPX. The calculation of the optimal pacing rate ($HR_{opt}$) was based on the oxygen uptake ($\dot{V}O_2$) during exercise after reaching steady-state conditions. According to the increase of the $\dot{V}O_2$ from 14.8 $\pm$ 2.3 mL/min per kilogram during aerobic work (38.3 $\pm$ 16.0 W) to 19.4 $\pm$ 4.7 mL/min per kilogram during anaerobic work (80.6 $\pm$ 32.3 W), the $HR_{opt}$ was calculated to be 98.6 $\pm$ 6.9 beats/min and 116.4 $\pm$ 4.7 beats/min. Starting from $HR_{opt}$, the pacing rate was increased (overpacing) and decreased (underpacing) by about 5 beats/min every minute. At optimal pacing rate the AVCT decreased significantly from 233.0 $\pm$ 30.5 ms during aerobic work and to 226.4 $\pm$ 27.3 ms during anaerobic work ($P < 0.05$). Whereas overpacing induced a significant prolongation of the AVCT during aerobic work (4.17 $\pm$ 1.78 ms per 10 beats/min) and anaerobic work (3.84 $\pm$ 1.60 ms per 10 beats/min), underpacing yielded a significant shortening of the AVCT by about 4.49 $\pm$ 2.64 ms per 10 beats/min during aerobic work and 4.75 $\pm$ 1.87 ms per 10 beats/min during anaerobic work ($P < 0.01$). The slopes of the regression lines of the relationship between AVCT and pacing rate were not significantly different. Based on the reciprocal relationship of heart rate (HR) and AVCT, basic concepts may be established for a dromotropic rate responsive algorithm. (PACE 1999; 22:1782–1791)*

***atrioventricular conduction, rate responsive pacemaker, sick sinus syndrome***

## Introduction

The improvement of the cardiorespiratory performance in patients with an impaired sinus node function by rate responsive pacing is well established.[1–7] For the estimation of the optimal adapted pacing rate to exercise level, many sensor techniques have been developed (overview[8]), but

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Received October 23,1998; revised January 27, 1999; accepted April 7, 1999.

often this optimal pacing rate still seems to be an unpredictable parameter. The optimal rate for one individual may be suboptimal in another.[9] The difference between pacing rate determined by a sensor and the optimal pacing rate may be greater in activity-controlled pacemakers[10,11] than in systems controlled by physiological signals such as minute ventilation,[12] QT interval,[13,14] or intracardiac impedance.[15]

Ten years ago another concept of electrophysiologically controlled pacing was suggested by Irnich and Conrady.[16] Their concept is based on the physiological reduction of the atrioventricular conduction time (AVCT) while the heart rate (HR) is increased during exercise,[17] however, the AVCT is prolonged by overstimulation.[18] They proposed an algorithm to control the pacing rate in patients with sinus node disease and intact atrioventricular (AV) conduction, which should find the optimal HR at the minimum AVCT. Such a dromotropic control of the chronotropy in patients with impaired sinus node function is the inverse procedure to that used in the AV delay adaptation in patients with AV block and dual chamber pacemakers in which the chronotropy (HR) controls the dromotropy (AV delay). But why are no dromotropically controlled rate responsive pacemakers on the market to date?

In a previous study the correlation of oxygen uptake and AVCT during exercise in patients with sick sinus syndrome (SSS) with or without chronotropic incompetence was shown.[19]

The aims of this study were to correlate the AVCT to the optimal pacing rate during exercise, to analyse the AVCT at pacing rates above and below the optimal HR, and to establish basic concepts for a dromotropically controlled rate responsive algorithm.

## Methods

### Patients

Seven patients (five men, two women; age, 62 ± 7.8 years; height, 170 ± 9.5 cm; weight, 75 ± 11.1 kg) with SSS, five with single chamber (AAIR) and two with dual chamber (DDDR) pacemakers (one Dromos SR, Biotronik, Berlin, Germany; four Thera S and two Thera D, Medtronic, Inc., Minneapolis, MN, USA) were involved in this study (Table I). Two patients had coronary artery disease and six patients had mild arterial hypertension. None had angina pectoris or heart failure. Two patients took β-

**Table I.**

Clinical Features of Study Patients

| Case No. | Age [y] | Gender | Height [cm] | Weight [kg] | Diagnosis | Pacemaker Mode | Type | Drug |
|---|---|---|---|---|---|---|---|---|
| 1 | 47 | M | 175 | 77.5 | SA, CAD | DDDR | Thera D Medtronic | Metropolol, ISDN, ASA |
| 2 | 58 | M | 174 | 93.0 | SAB, Hypertension | DDDR | Thera D Medtronic | Enalapril |
| 3 | 71 | M | 167 | 70.5 | SB, CAD, Hypertension | AAIR | Thera S Medtronic | ASA, ISDN Ramipril |
| 4 | 68 | M | 175 | 80.0 | SA, Hypertension | AAIR | Thera S Medtronic | Quadropril, Doxazosin |
| 5 | 64 | F | 155 | 57.0 | BTS, Hypertension | AAIR | Thera SR Medtronic | Nifedipin |
| 6 | 63 | F | 160 | 70.0 | SB, Hypertension | AAIR | Thera S Medtronic | Sotalol, Nifedipin |
| 7 | 63 | M | 182 | 79.0 | SB, Hypertension | AAIR | Dromos SR Biotronik | Amlodipin |

BTS = bradycardia-tachycardia syndrome; CAD = coronary artery disease; F = female; M = male; SA = sinus arrest; SAB = sinoatrial exit block; SB = sinus bradycardia.

blockers. On the day of examination drugs were taken as usual.

Criteria for inclusion in this study were as follows:

1. SSS with or without chronotropic incompetence.
2. A normal PQ interval on the resting ECG (stimulus—R interval $< 240$ ms).
3. 1:1 AV conduction during rapid atrial pacing up to at least 120 beats/min.
4. Normal pulmonary function and diffusion capacity at rest.

### Cardiopulmonary Exercise Testing

In an initial cardiopulmonary exercise test (CPX I) each subject performed a maximum treadmill exercise test using an incremental exercise protocol that was specially constructed in our lab. The aim of this test was to determine peak oxygen consumption ($\dot{V}O_{2peak}$) within 10–12 minutes according to the individually predicted cardiopulmonary exercise capacity. Therefore, the work rate was increased by a uniform amount every two minutes. The increment rate was adapted to the expected performance of the patients. The workload (P [Watt]) was calculated by the speed (v [m/s]) and the elevation ($\alpha$ [°]) of the treadmill and the patients weight (G [N]):

$$P = G * v * \tan\alpha$$

The CPX I was terminated at the patients' maximum capacity. To analyse the patients sinus node function, the rate responsive mode of the pacemaker was switched off. According to the determination of the anaerobic threshold (AT) of this test, a second treadmill exercise test (CPX II) with constant workload at two levels (1) below the AT and (2) above the AT followed on another day of examination. Before exercise testing, the pacemakers were programmed in an AAT mode with a lower rate limit of 60 beats/min without rate adaptation. During exercise, after steady-state conditions were reached, the lower rate limit was set to the calculated optimal pacing rate. Overpacing was induced by an increase of the lower rate limit by about 5 and 10 beats/min every minute. Underpacing was achieved by reduction of the lower rate limit by about 5 beats/min every minute, until the patients' own rhythm occurred.

The optimal pacing rate ($HR_{opt}$) was calculated as described by Wilkoff et al.[20]:

$$HR_{opt} = \frac{(220 - age - HR_{rest}) \times (\dot{V}O_{2stage} - \dot{V}O_{2rest})}{\dot{V}O_{2peak} - \dot{V}O_{2rest}} + HR_{rest}$$

with a maximum predicted HR of 220 minus age. The metabolic reserve, defined as the difference between oxygen uptake at peak exercise ($\dot{V}O_{2peak}$) and oxygen uptake at rest ($\dot{V}O_{2rest}$), was measured during the maximal incremental exercise test (CPX I). At rest the metabolic reserve (MR) and the HR reserve (HRR) were about 100% ($\dot{V}O_{2stage} = \dot{V}O_{2rest}$, $HR_{opt} = HR_{rest}$), at peak exercise the MR and HRR were about 0% ($\dot{V}O_{2stage} = \dot{V}O_{2peak}$, $HR_{opt} = HR_{max}$).

The respiratory gases were analyzed breath by breath using a Vmax 229 ergospirometer (SensorMedics Corp., Yorba Linda, CA, USA) allowing a precise breath-by-breath measurement of oxygen uptake ($\dot{V}O_2$), expired carbon dioxide ($\dot{V}CO_2$) and minute ventilation ($\dot{V}E$). The AT was measured by the V-slope ($\dot{V}O_2/\dot{V}CO_2$) and ventilatory equivalent ($\dot{V}_E/\dot{V}O_2$) method.[21] A steady state was assumed if changes in $\dot{V}O_2$ were lower than 5% for 1 minute.

### ECG Analysis

Two channels of a digital 12-lead surface ECG (Imed/Mesa, Budapest, Hungary/ Benediktbeuern, Germany) were recorded continuously at 1,000 Hz and 12 bit. The AVCT was measured from beat to beat as the interval from the atrial pacing spike to the maximal amplitude of the R wave using a software program developed in our lab (Fig. 1). To assess heart rhythm and ST segment changes a conventional analogous 12-lead surface ECG (MCP-3601, Medicount, Filderstadt, Germany) was recorded on paper with a recording speed of 50 mm/s every last 10 seconds of each minute.

### Statistical Analysis

Results and error bars in graphs are expressed as mean $\pm$ SD. Correlations of HR and AVCT were expressed by Pearson's correlation coefficient. A linear regression was used to characterize the re-

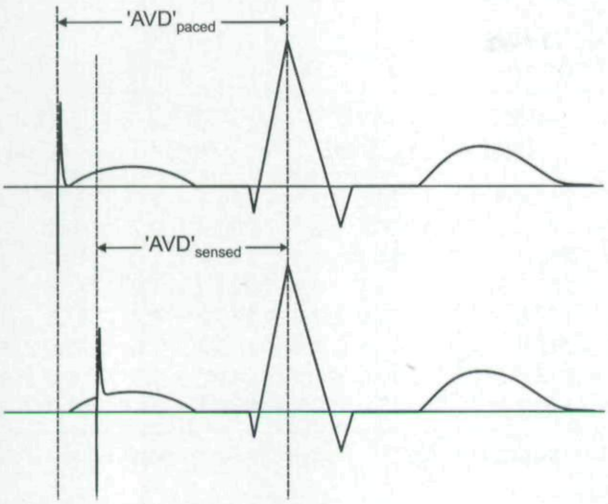


**Figure 1.** *Atrioventricular conduction time (AVCT) measured as spike-R interval in a surface ECG. Although the AV conduction properties were equal, the measured spike-R interval would be longer if the atrium was paced ($AVCT_{paced}$) than if the atrial depolarization was sensed ($AVCT_{sensed}$).*

lationship between pacing rate and AVCT. The slopes of the regression lines between pacing rate and AVCT were compared at the two exercise levels. Differences in mean AVCT values between optimal pacing rate, under- and overpacing were assessed by a paired *t*-test with a two-tailed P value. A P value of 0.05 was considered the limit of significance.

## Results

In the initial CPX (CPX I) all subjects completed a maximum treadmill test attaining a maximum $\dot{V}O_2$ of 25.5 ± 2.9 mL/min per kilogram. The $\dot{V}O_2$ determined at the AT was 16.7 ± 2.6 mL/min per kilogram (65.5% of maximal achieved $\dot{V}O_2$). The HR increased from 68.7 ± 9.3 beats/min at rest to 96.7 ± 10.2 beats/min at the AT and to 124.7 ± 16.5 beats/min at maximum exercise (Table II).

During constant work rate exercise (CPX II) the mean work rate for aerobic work was 38.3 ± 16.0 W and 80.6 ± 32.3 W for anaerobic work. According to a mean $\dot{V}O_2$ of 14.8 ± 2.3 mL/min per kilogram during work below the AT and 19.4 ± 4.7 mL/min per kilogram during work above the AT, the $HR_{opt}$ was calculated to be 98.6 ± 6.9 beats/min and 116.4 ± 6.9 beats/min. The AVCT at $HR_{opt}$ decreased significantly from aerobic (233.0 ± 30.5 ms) to anaerobic (226.4 ± 27.3 ms) exercise level by about 6.64 ± 5.11 ms ($P < 0.05$). Under steady-state conditions an increase in pacing rate above the optimal HR by 5 beats/min and 10 beats/min (overpacing) induced a significant prolongation of the AVCT during aerobic work (+ 5 beats/min: 1.87 ± 1.28 ms and + 10 beats/min: 4.17 ± 1.78 ms, $P < 0.01$) and during anaerobic work (+ 5 beats/min:

**Table II.**

Results of Incremental Exercise Testing (CPX I)

| | Rest | | Anaerobic Threshold | | | Peak Exercise | | |
|---|---|---|---|---|---|---|---|---|
| Case No. | HR [bpm] | $\dot{V}O_2$ [mL/min/kg] | HR [bpm] | $\dot{V}O_2$ [ml/min/kg] | P [Watt] | HR [bpm] | $\dot{V}O_2$ [ml/min/kg] | P [Watt] |
| 1 | 70 | 4.2 | 113 | 18.5 | 55 | 139 | 24.9 | 119 |
| 2 | 72 | 4.0 | 98 | 13.6 | 79 | 126 | 21.6 | 156 |
| 3 | 87 | 4.0 | 103 | 15.5 | 61 | 139 | 25.4 | 121 |
| 4 | 66 | 4.8 | 97 | 15.7 | 68 | 123 | 26.6 | 135 |
| 5 | 60 | 3.9 | 97 | 14.4 | 29 | 129 | 22.0 | 72 |
| 6 | 66 | 5.8 | 81 | 20.8 | 41 | 90 | 28.9 | 68 |
| 7 | 60 | 4.1 | 88 | 18.6 | 65 | 127 | 28.8 | 127 |
| **mean** | **68.7** | **4.4** | **96.7** | **16.7** | **56.9** | **124.7** | **25.5** | **114.0** |
| **± SD** | **9.3** | **0.7** | **10.2** | **2.6** | **17.0** | **16.5** | **2.9** | **32.5** |

HR = heart rate; $\dot{V}O_2$ = oxygen consumption; P = work load; bpm = beats per minute

**Table III A.**

Patients Results During Aerobic Work (CPX II)

| Case No. | P [Watt] | $\dot{V}O_2$ [mL/kg/min] | $HR_{opt}$ [beats/min] | $AVCT_{-10}$ [ms] | $AVCT_{-5}$ [ms] | $AVCT_0$ [ms] | $AVCT_{+5}$ [ms] | $AVCT_{+10}$ [ms] |
|---|---|---|---|---|---|---|---|---|
| 1 | 24 | 14.7 | 100 | 214.9 ± 2.3 | 216.2 ± 1.1 | 222.5 ± 1.9 | 225.1 ± 1.6 | 227.7 ± 1.4 |
| 2 | 55 | 13.0 | 100 | 268.8 ± 1.7 | 272.4 ± 2.1 | 276.4 ± 2.1 | 280.7 ± 2.7 | 283.2 ± 2.8 |
| 3 | 45 | 16.5 | 110 | 241.2 ± 1.4 | 242.4 ± 1.1 | 244.4 ± 1.0 | 245.7 ± 1.0 | 248.2 ± 1.3 |
| 4 | 46 | 14.3 | 100 | 218.0 ± 1.4 | 218.7 ± 1.5 | 219.4 ± 1.6 | 220.3 ± 1.2 | 221.8 ± 1.0 |
| 5 | 17 | 13.7 | 100 | 176.5 ± 1.1 | 177.8 ± 1.6 | 178.6 ± 2.4 | 179.2 ± 1.3 | 181.0 ± 1.2 |
| 6 | 25 | 12.4 | 90 | 246.1 ± 1.9 | 247.6 ± 1.9 | 249.2 ± 1.4 | 250.4 ± 1.6 | 252.0 ± 1.7 |
| 7 | 56 | 19.0 | 90 | 234.1 ± 1.9 | 236.6 ± 2.0 | 240.5 ± 2.4 | 242.7 ± 1.9 | 246.3 ± 2.1 |
| **means** | **38.3 ± 16.0** | **14.8 ± 2.3** | **98.6 ± 6.9** | **228.5 ± 29.2** | **230.3 ± 29.9** | **233.0 ± 30.5** | **234.9 ± 31.4** | **237.2 ± 31.7** |

CPX = cardiopulmonary exercise test; $\dot{V}O_2$ = oxygen uptake; $HR_{opt}$ = optimal pacing rate; AVCT = atrioventricular conduction time.

1.28 ± 0.60 ms and + 10 beats/min: 3.84 ± 1.60 ms, $P < 0.01$). A reduction of the pacing rate below the optimal HR (underpacing) yielded a significant shortening of the AVCT by about 2.76 ± 2.06 ms per −5 beats/min and 4.49 ± 2.64 ms per −10 beats/min for aerobic work ($P < 0.01$) and 1.87 ± 0.85 ms per −5 beats/min and 4.75 ± 1.87 ms per −10 beats/min for anaerobic work ($P < 0.01$). A significant correlation coefficient of pacing rate and AVCT was found both during aerobic ($r = 0.9853$, $P < 0.05$) and anaerobic work ($r = 0.9923$, $P < 0.05$). The slopes of both regression lines were not significantly different from one another but differed significantly from zero (0.42 ± 0.04 ms per beats/min and 0.41 ± 0.03 ms per beats/min; $P < 0.01$). The y-intercepts showed a significant difference (191.2 ± 4.2 ms and 179.2 ± 3.4 ms; $P < 0.01$), (Table III, Fig. 2).

## Discussion

### Dromotropic Response

The results of this study showed the relationship between HR and AVCT in patients with SSS during a constant work rate test on two exercise levels. During exercise at below and above the AT, a high positive linear correlation of pacing rate and AVCT was observed.

This cardiopulmonary exercise test with a computerized beat-to-beat ECG analysis of seven

**Table III B.**

Patients Results During Anaerobic Work (CPX II)

| Case No. | P [Watt] | $\dot{V}O_2$ [mL/kg/min] | $HR_{opt}$ [beats/min] | $AVCT_{-10}$ [ms] | $AVCT_{-5}$ [ms] | $AVCT_0$ [ms] | $AVCT_{+5}$ [ms] | $AVCT_{+10}$ [ms] |
|---|---|---|---|---|---|---|---|---|
| 1 | 58 | 16.9 | 115 | 214.8 ± 1.7 | 216.5 ± 1.6 | 219.8 ± 1.0 | 220.9 ± 1.0 | 222.1 ± 0.9 |
| 2 | 110 | 17.5 | 115 | 255.5 ± 3.1 | 260.2 ± 2.7 | 262.6 ± 2.1 | 264.4 ± 2.0 | 267.6 ± 2.0 |
| 3 | 110 | 21.6 | 130 | 231.0 ± 2.5 | 235.6 ± 0.9 | 237.2 ± 1.6 | 237.7 ± 0.8 | 242.2 ± 1.5 |
| 4 | 90 | 18.0 | 115 | 214.2 ± 1.4 | 215.2 ± 1.4 | 216.0 ± 1.5 | 217.1 ± 1.7 | 218.9 ± 1.7 |
| 5 | 35 | 18.0 | 120 | 173.4 ± 3.1 | 175.3 ± 1.3 | 176.3 ± 1.4 | 177.2 ± 1.1 | 178.2 ± 1.3 |
| 6 | 50 | 14.9 | 110 | 241.3 ± 2.1 | 243.8 ± 2.0 | 245.8 ± 1.6 | 247.1 ± 1.6 | 249.4 ± 1.3 |
| 7 | 111 | 29.2 | 110 | 221.0 ± 2.4 | 224.8 ± 2.4 | 226.8 ± 2.5 | 229.1 ± 2.2 | 233.0 ± 2.4 |
| **means** | **80.6 ± 32.3** | **19.4 ± 4.7** | **116.4 ± 6.9** | **221.6 ± 26.0** | **224.5 ± 26.9** | **226.4 ± 27.3** | **227.7 ± 27.5** | **230.2 ± 28.3** |

$AVCT_0$ = atrioventricular conduction time at optimal pacing rate; $AVCT_{+5,+10}$ = AVCT at overpacing with 5 beats/min and 10 beats/min above the optimal pacing rate; $AVCT_{-5,-10}$ = AVCT at underpacing with 5 beat/min and 10 beats/min below the optimal pacng rate; $HR_{opt}$ = optimal pacing rate; see Table III A for remainder of definitions.

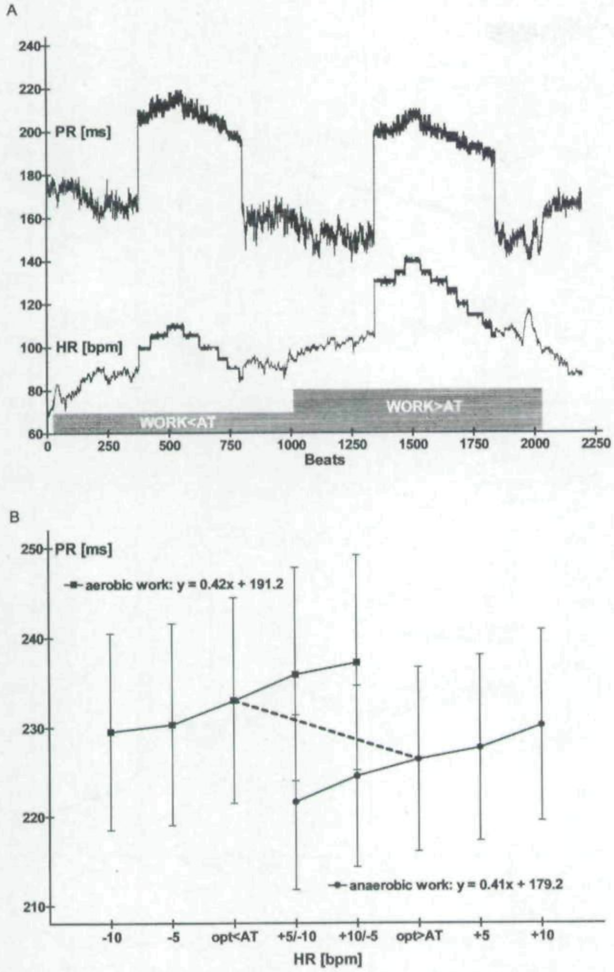


**Figure 2.** *(A) Beat-to-beat ECG analysis of one patient (case 2) during steady-state exercise at 55 W (< AT) and 110 W (> AT). Dashed lines represent heart rate (HR) and spike-R interval (P-R) during patients' sinus rhythm. The pacing rate and the paced P-R interval are shown in solid lines. At the beginning of low and high level exercise, an increase of the heart rate and a decrease of the spike-R interval were measured. During atrial pacing the abrupt increase of the spike-R interval was caused by the difference between the* $AVCT_{sensed}$ *and* $AVCT_{paced}$*. Overpacing induced a prolongation of the P-R interval and underpacing induced a reduction of the P-R interval until patients' sinus rhythm occurred. (B) Mean AVCT of all patients measured as the interval between atrial spike and R wave (P-R interval) as a function of pacing rate (HR) during aerobic work and anaerobic work ± SE. The dotted line connects the* $AVCT_0$ *at optimal pacing rate below the AT (opt < AT) and the* $AVCT_0$ *at optimal pacing rate above the AT (opt > AT). AT = anaerobic threshold; AVCT = atrioventricular conduction time.*

pacemaker patients supported the statement of Irnich and Conrady[16] that overpacing induced a prolongation of the AVCT but did not confirm the assumption that the AVCT was constant or even prolonged by reduction of the pacing rate (underpacing). The minimum of the AVCT postulated at the optimal HR[16] could not be demonstrated. A reduction in pacing rate induced a shortening of the AVCT in all the study patients without exception. A rate responsive algorithm looking for the minimum AVCT would always find the programmed lower rate limit or the patients' own sinus rate.

The different behavior of the AV conduction during optimal, over-, and underpacing apparently was based on the slow inward calcium current that mediated not only the plateau but also the up stroke of the action potential in the sinus and AV nodes.[22] The probability of calcium channel opening was increased by catecholamines[23] and reduced by a decrease in pacing interval.[24] The more calcium channels were opened, the faster was the up stroke of the action potential and consequently the intercellular conduction. In short, during exercise under steady-state conditions (= constant autonomic tone) a decrease in pacing rate caused a higher probability of calcium channel opening and therefore a faster AV conduction.

## Chronotropic Response

During incremental CPX I, the patients' own HR was 96.7 ± 10.2 beats/min at the AT and 114.0 ± 32.5 beats/min at peak exercise. According to the predicted maximum HR of 158 beats/min ($HR_{max}$ = 220—age) the chronotropic response appeared to be inadequate. Thus this study of patients with SSS and chronotropic incompetence had the typical indication for atrial rate responsive pacing.[25–27] If there were no AV conduction disturbances these patients could be treated with a dromotropically controlled rate responsive pacemaker. The estimation of the optimal pacing rate was based on the measurement of the oxygen consumption ($\dot{V}O_2$) and the calculation of the metabolic reserve.[20] The following parameters were inserted in Wilkoff's formula: (1) the oxygen consumption during the patients' own chronotropically incompetent sinus rhythm ($\dot{V}O_{2stage}$), (2) the maximum oxygen consumption measured in the incremental CPX ($\dot{V}O_{2peak}$), (3) the maximum HR calculated as 220 minus age ($HR_{max}$), and (4) the HR and oxygen consumption measured at rest ($HR_{rest}$, $\dot{V}O_{2rest}$). The estimated $HR_{opt}$, based on the calculation of the MR and HRR, was slightly underestimated for two reasons: (1) the $\dot{V}O_{2stage}$ was lower without rate response in comparison to the $\dot{V}O_2$ with optimal pacing, and (2) the lower the $HR_{rest}$ (lower rate limit) at the starting position the lower was the calculated $HR_{opt}$. This slight underestimation of the $HR_{opt}$ would not influence the correlation between the pacing rate and the AVCT. Furthermore the dromotropic pacemaker would control the HR independent of oxygen consumption.

**Intact AV Conduction**

Even the $AVCT_{paced}$ (measured as the interval between atrial pacemaker spike and maximum amplitude of the R wave) in our study patients with SSS was long. An intact AV conduction could be assumed because of the determination of the Wenckebach point beyond a HR of about 120 beats/min and the exercise induced shortening of the AV conduction time at optimal pacing rate of about 3.7 ms per 10 beats/min, similar to the results of Daubert et al.,[17] who demonstrated a mean AVCT reduction of 3.8 ms per 10 beats/min during incremental bicycle exercise in healthy subjects.

The high interindividual variability of the AVCT of pacemaker patients based mainly on the different site of the atrial pacing lead. The greater the distance of the pacing lead from the atrial septum the longer was the interatrial conduction time[28] and consequently the AV delay.[29] In this study the coefficient of variation of the AVCT at optimal pacing rate was 13.1% and 12.1% during aerobic and anaerobic work, respectively. There was no correlation between the absolute AVCT and the extent of its shortening during exercise (Table III). Therefore the interindividual variability of the AV conduction had to be taken into account for programming a dromotropic rate responsive algorithm.

In a previous study we demonstrated the correlation of the AVCT and oxygen consumption in patients with SSS while the rate responsive algorithm was switched off.[19] Patients with chronotropic competence and patients with an impaired sinus node function showed a shortening of the AVCT instantaneously with an increase in oxygen uptake. The observation that there was a lack of physiological adaptation of the AVCT in

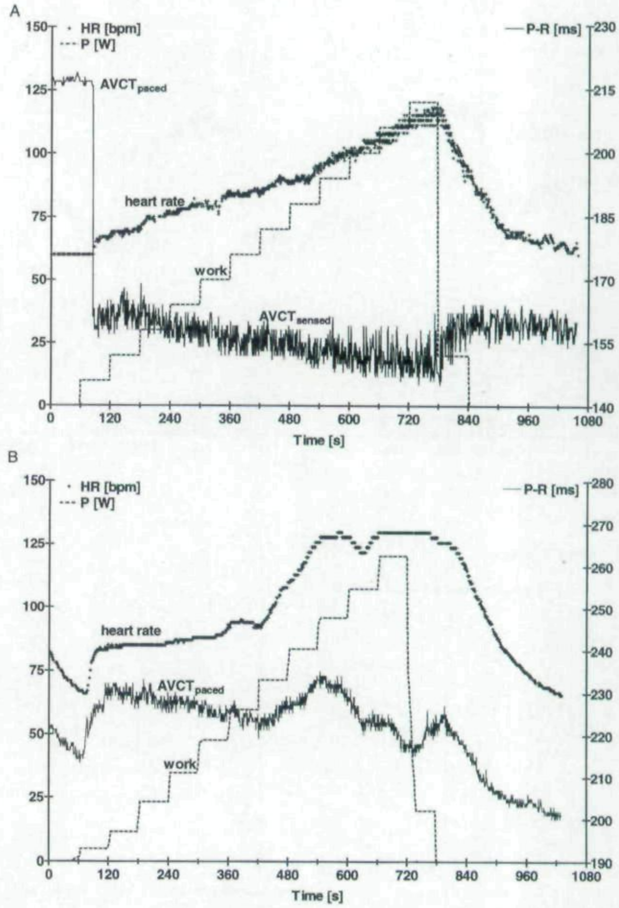


*Figure 3. Incremental cardiopulmonary exercise test on a treadmill of a 68-year-old man with a Medtronic Kappa400 AAIR pacemaker and intact AV conduction. The left ordinates represent the heart rate (HR `+') and the work load (P `—`), the right ordinates represent the spike-R interval (P-R `—`). (A) While the pacemaker was programmed in an AAT mode without rate adaptation exercise induced an increase of the heart rate and a decrease of the AV conduction time (AVCT). Notice the difference between paced P-R interval ($AVCT_{paced}$) at the lower rate limit and the sensed P-R interval ($AVCT_{sensed}$) at sinus rhythm. (B) In the AAIR mode with `rate profile optimization$^{TM}$' the fast chronotropic response (HR +) of the activity sensor led during warming up (time 60–120 seconds) already to a prolongation of the AVCT (overpacing). A further increase in work rate induced a decrease in the P-R interval while the pacing rate was unchanged until the minute ventilation sensor led to a further overpacing with a prolongation of the P-R interval. At the upper rate limit of 130 beats/min a further increase of work rate induced again a reduction of the P-R interval. AV = atrioventricular; AAT = atrial triggered pacing mode.*

patients with SSS[30] seemed to be the typical phenomenon of sensor induced overpacing (Fig. 3). This nonphysiological overpacing (e.g., caused by activity controlled pacemakers[31]) induced a nonphysiological AVCT that might lead to the so called AAIR pacemaker syndrome.[32]

### Basic Concepts for the Dromotropic Pacemaker

To enable the development of a dromotropic rate responsive algorithm the following aspects had to be confirmed:

1. The AVCT at optimal pacing rate shows a reciprocal relationship with the metabolic requirements during exercise. The reference line for AVCT and $HR_{opt}$ ($AVCT_0/HR_{opt}$) has a negative slope that varies individually.
2. During constant autonomic tone at low and high level exercise the regression lines of the relationship between AVCT and the pacing rate ($AVCT_X$/HR) are different but parallel to one another (positive slopes).
3. The optimal pacing rate adapted to the metabolic requirement is the point of interception of the reference line with the regression line $AVCT_X$/HR corresponding to the exercise level.
4. An automatic slope adaptation of the reference line has to take into consideration a change in the behavior of the AV conduction.
5. For a stable dromotropic control of pacing rate, the intraindividual AVCT variability has to be taken into account. The first standard deviation of the AVCT during constant work rate and constant pacing rate ranges from 0.8 to 3.1 ms.

### Practical Implementation

In practice, to implement a dromotropic rate responsive algorithm we must have the knowledge about the individual AV conduction properties of the particular patient. The AVCT reference line can be obtained during an exercise test. During rest the pacemaker is programmed to pace with the desired pacing rate ($HR_{rest}$) and the AVCT is measured ($AVCT_{rest}$). This procedure is repeated at the maximum exercise rate yielding $HR_{max}$ and $AVCT_{max}$. Based on the linear relationship between AVCT, metabolic demand,[19] and HR[17] the AVCT reference line results in the connection of these two points ($HR_{rest}$ /$AVCT_{rest}$) and ($HR_{max}$ /$AVCT_{max}$) with a negative slope. Every HR is assigned to one AVCT on the AVCT reference line and the aim of the dromotropic algorithm is to find the AVCT on the reference line by changing the pacing rate. For example, when the sympathetic tone increases, or the metabolic rate, respectively, the AVCT decreases below the reference line. To get an AVCT on the reference line the pacing rate has to be increased that consecutively induces a prolongation of the AVCT itself. In addition to this closed loop control with negative feedback we have to consider the physiological variability of the AVCT to get a stable dromotropical control of the HR.

A dromotropic algorithm can easily be implemented to a single (atrial) chamber pacemaker that will register the AVCT through the atrial lead by atrial sensed far-field ventricular signals[33] (single-lead ADIR pacemaker).

The importance of the normal sequence of ventricular activation in cardiac pacing even if the AVCT was prolonged, [34–36] and the contradiction to the statement that patients with SSS had a high risk of developing AV conduction disturbances,[37,38] led to a change in attitude towards treatment of the SSS. Furthermore, the physiological relationship between AVCT, metabolic demand, and pacing rate in patients with SSS has correctly been investigated by a close co-operation of clinicians, physiologists, and control engineers'[19,39] so that it should now be possible to develop the dromotropic pacemaker.

## Conclusion

In patients with SSS and intact AV conduction, an increase in sympathetic tone induced a shortening of the AVCT, whereas an artificial increase in HR induced a prolongation of the AVCT and vice versa. During constant autonomic nervous tone the relationship between HR and AVCT remained the same at low level and at high level exercise (mean slope = 0.414 ms per 1 beat/min; Fig. 4). Based on this reciprocal relation it should be possible to regulate the HR by the AVCT in a closed loop control with a negative feedback.

From the system-physiological viewpoint the dromotropic pacemaker concept is able to restore the physiological cardiovascular control so that the amount of adverse effects of rate adaptive pacing[40] would be reduced in patients with SSS.

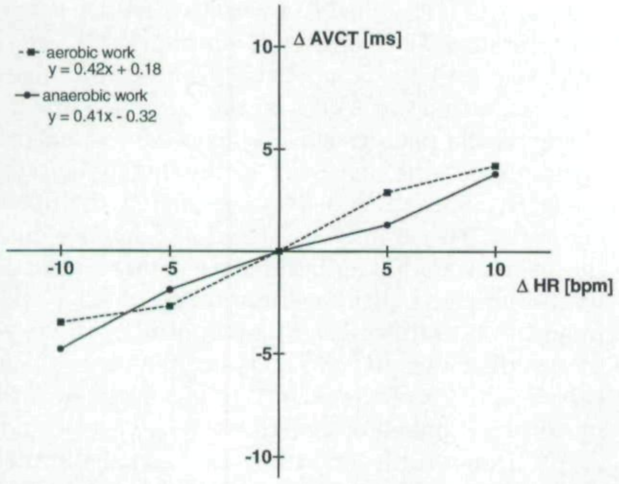


**Figure 4.** *Changes in atrioventricular conduction time (Δ AVCT) as function of changes in pacing rate (Δ HR) during aerobic and anaerobic work (difference from the optimal pacing rate and the corresponding measured AVCT). A negative Δ HR means underpacing and a positive Δ HR overpacing. The slopes of the regression lines are not significantly different. HR = heart rate.*

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