Assessment of the Chronotropic/Metabolic Relationship in Patients with the Inos^{2+} CLS Closed Loop Pacemaker

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Summary

The Wilkoff mathematical model of the normal chronotropic response to exercise is commonly used to evaluate the rate response of new pacemakers. The purpose of the present study was to examine the chronotropic responsiveness of the Inos^{2+} CLS pacemaker, and to test the assumptions of the Wilkoff model in our pacemaker population. Twelve patients (seven male, five female; aged 70 ± 9.6 years) implanted 1 month previously with an Inos^{2+} CLS pacemaker performed a treadmill test according to the Chronotropic Assessment Exercise Protocol (CAEP) with simultaneous open circuit spirometry. Heart rate (HR) and oxygen uptake (VO_2) measured in metabolic equivalents (METs) were evaluated at each minute of exercise. Paced HRs were higher than predicted in healthy subjects ($p < 0.001$). Measured METs were lower than predicted ($p < 0.001$) in healthy subjects, however, this did not significantly affect the mathematical prediction of HR. The rate-response behaviour of the pacemaker was assessed using the linear relationship between percent heart rate reserve and percent metabolic reserve and by evaluating the relationship of HR/VO_2 throughout exercise. The reserve slope (0.82), i.e., the slope of the linear relationship, was within the 95% confidence interval of healthy subjects. The y intercept (32.2), i.e., the constant value of the linear relationship, was higher than observed in healthy subjects; a result of high HR at submaximal exercise and a maximum sensor rate programmed less than the age-predicted maximum HR. Setting a zero intercept produced a reserve slope of 1.27 and reduced the variability of individual slopes. The pattern of the HR/VO_2 relationship bore a closer resemblance to that of cardiac patients than of healthy subjects. In conclusion, manipulation of the Wilkoff model appeared to move the results towards normality, therefore methodological differences must be examined carefully when comparing results of different studies. Disparities in the physiological response to exercise may be inevitable between reference and pacemaker populations due to differences in age and disease status.

Key Words

Rate responsive pacemaker, Closed Loop Stimulation (CLS), Chronotropic Assessment Exercise Protocol (CAEP), oxygen uptake

Introduction

The evaluation of the heart rate (HR) response to exercise is important for the assessment of the rate response algorithm of sensor-controlled pacemakers. Rate-responsive pacemakers sense some physiological or non-physiological signal, and translate changes in that signal to a pacing rate that is appropriate for the metabolic demands of the patient. A requirement for new pacing systems is that the rate response of the pacemaker must closely simulate the chronotropic responsiveness of a healthy heart. New pacing systems are commonly evaluated using a mathematical model of the normal chronotropic response to exercise described by Wilkoff et al. [1] in 1989. Wilkoff and his colleagues tested healthy subjects using a maximal treadmill protocol designed specifically for the evaluation of rate-responsive pacemakers: the Chronotropic Assessment Exercise Protocol (CAEP) [1,2]. In order to compare subjects with different heart rates and fitness levels, regression analysis was done using percent heart rate reserve and percent metabolic reserve (in metabolic equivalents, 1 MET = 3.5 ml oxygen uptake per min per kg weight), respectively:

$$\%HRR = \frac{HR - HR_{rest}}{HR_{max} - HR_{rest}} \cdot 100 \qquad (1)$$

$$\%METR = \frac{METs - METs_{rest}}{METs_{peak} - METs_{rest}} \cdot 100$$

A linear relationship was found

$$\%HRR = reserve\ slope \cdot \%METR + y\text{-}intercept \qquad (2)$$

After accepting the slope as 1.0 and the y-intercept as 0, the normal HR at any stage of exercise could be predicted by a mathematical formula. The normal HR response to exercise is now commonly defined by the HR calculated by Wilkoff's formula,

$$HR_{predicted} = HR_{rest} + \frac{(HR_{max} - HR_{rest}) \cdot (METs - METs_{rest})}{METs_{peak} - METs_{rest}} \qquad (3)$$

as well as by an ideal slope of 1.0 when graphing the %HRR / %METR relationship. Wilkoff's model was based on several assumptions: that MET levels calculated from the equations of the American College of Sports Medicine (ACSM) [3] provided an accurate assessment of metabolic exertion at each stage of the CAEP; that the resting MET level was always one; and that the peak HR during exercise could be predicted by the ACSM formula [3]:

$$Age\text{-}predicted\ HR_{max} = (220 - age/years)\ bpm \qquad (4)$$

However, it is generally accepted that both the HR and metabolic response to exercise of young, healthy individuals may be different than what should be expected of older individuals with cardiac dysfunction – the typical patient population who receive pacemakers [4-6]. Wilkoff et al. [1] stated an ideal slope of 1.0 and y-intercept of 0 for the %HRR / %METR regressions. However, others [7-9] submit that the %HRR/ %METR relationship derived from studies of healthy volunteers may not provide sufficient accuracy for assessing the chronotropic response of the average pacemaker patient. Therefore, the purpose of the present study was twofold: to examine the chronotropic responsiveness of the Inos^{2+} CLS pacemaker (Biotronik, Germany) using the generally accepted Wilkoff model and the CAEP exercise protocol, and to test the assumptions of the Wilkoff HR prediction formula in our pacemaker patients.

Materials and Methods

Patients

The subjects for this study were drawn from the patient population of the Regina General Hospital's pacemaker clinic and consisted of patients who had received an Inos^{2+} CLS pacemaker a minimum of 1 month prior to the study. All patients gave written informed consent prior to entry into the study, and the ethics committees of the University of Regina and the Regina Health District approved the study. The study sample consisted of 12 patients (seven males, five females). The mean age was 70 ± 9.6 years (Table 1). Eight patients were New York Heart Association (NYHA) class 1 and four patients were NYHA class 2. Indications for pacemaker implantation were sinus node dysfunction (four patients), atrioventricular (AV) block (four patients), or both sinus dysfunction and AV block (four patients). Four of the patients had previously diagnosed ischemic heart disease.

Pacemaker

The Inos^{2+} CLS uses a right ventricular impedance sensor to permanently monitor the contractile state of the myocardium and convert this intrinsic information into an appropriate heart rate. The internal impedance sensor of the CLS pacemaker uses beat-to-beat measurements of myocardial contractility, and draws a waveform based on this information using the programmed lower and upper rates as endpoints. This new waveform is compared to a baseline waveform, and the area defining the difference between the two waveforms is used to calculate the appropriate HR increase or decrease. Even in patients with dysfunctional sinus nodes or electrical pathways, neural control mechanisms attempt to control cardiac output by varying inotropy. Therefore, the dynamics of the myocardial

Patient No.	Age (years)	Sex	NYHA	BR (bpm)	MCLR (bpm)	Age-predicted HR_{max} (bpm)	UTR (bpm)	Pacing indication	CAD
1	79	F	1	60	125	141	160	SSS	–
2	82	M	2	45	125	138	160	SSS & AVB	–
3	74	M	1	60	147	146	150	SSS	+
4	68	F	1	60	147	152	150	AVB	–
5	74	M	1	60	139	146	140	SSS	–
6	83	M	1	50	114	147	120	AVB	–
7	59	F	2	50	135	161	150	AVB	–
8	68	F	2	50	125	152	140	AVB	+
9	49	M	1	60	145	171	150	SSS	–
10	74	M	1	60	115	146	120	SSS & AVB	+
11	71	F	2	50	127	149	150	SSS & AVB	–
12	66	M	1	50	110	154	120	SSS & AVB	+

Table 1. Patient characteristics and pacemaker programming. BR = base rate, i.e., programmed lowest pacing rate; age-predicted HR_{max} = (220 – age/years) bpm; MCLR= maximum closed loop rate, i.e. programmed maximum pacing rate; UTR = programmed upper tracking rate; SSS = sick sinus syndrome; AVB = AV block; CAD = coronary artery disease.

contractile force reflect internal information from the circulatory centres. Because the sensor uses the intrinsic regulatory mechanism of the circulatory centres to control the rate response of the pacemaker, this method of rate response is called Closed Loop Stimulation (CLS). As a consequence of the internal feedback loop, this system is expected to provide an appropriate rate response to exercise, as well as to account for each patient's individual disease state and physical condition [10]. Earlier versions of the CLS pacemaker showed rate response highly correlated to control groups in both physical and mental stress situations [10-12].

The pacemaker's lower pacing rate (BR = base rate) ranged from 45 to 60 bpm, which was determined from patient records as the average resting sinus rate before pacemaker implantation. If the normal resting HR could not be determined due to sinus node disease, BR was set at 60 bpm. The pacemaker'ss maximum sensor-driven rate (MCLR = maximum closed loop rate) was set at 70 – 85% of age-predicted HR_{max}, depending on the patient's daily activity, fitness level, and disease status. If the patient had a history of angina brought on by activity, the MCLR was set at a lower rate to stay below the ischemic threshold.

Exercise Test

The CAEP is a maximal treadmill protocol designed specifically for the evaluation of rate-responsive pacemakers [1,2]. This protocol begins at 1.5 METs (1 MET = 3.5 ml O_2/kg/min) and consists of 2-minute stages with small increments ranging from 0.8 to 2.5 METs per stage. This allows most patients to complete several stages of exercise and tests the chronotropic response to submaximal exertion that is close to the range of many activities of daily living [13].

Physiologic Measurements

One month following pacemaker implantation each patient performed a standard symptom-limited CAEP treadmill test with open circuit spirometry to assess the oxygen uptake (VO_2) response to exercise (TruMax 2400, Parvo Medics, USA). A 1-minute averaging was used to record VO_2, VCO_2, VE, and METs throughout the test. Because it has been suggested that the anaerobic threshold (AT) may be used as an objective measure of chronotropic function in pacemaker patients [14], AT was also calculated from the metabolic data [15]. A continuous lead II ECG was recorded during exercise using the Merlin AM recorder and GEMS software (both from CardioComm Solutions, Canada) and HR was determined by measuring the R-R intervals and calculating a 5-second average at the end of each minute of exercise. All patients were encouraged to exercise to maximum exertion.

Calculated Parameters

The internal impedance sensor of the CLS pacemaker uses beat-to-beat measurement to draw a waveform based on myocardial contractility. This new waveform is compared to a baseline waveform, and the area defining the difference between the two waveforms is used to calculate the appropriate heart rate increase from BR. A continuous sensor self-adjustment guarantees that the HR reaches the full dynamic range between BR and MCLR. Therefore, HR_{rest} = BR and HR_{max} = MCLR were used in equations (1) and (3).

In order to examine the chronotropic responsiveness of the $Inos^{2+}$ CLS pacemaker, we analyzed several parameters. Using t-tests, we compared the observed sensor-driven HR for each minute of exercise to the predicted HR calculated with Wilkoff's formula [1] (see equation (3)) where METs were either measured or predicted from ACSM formulas [5]. Then, we calculated the %HRR and the %METR according to equations (1) so that linear regression analysis could be performed and the reserve slopes and y-intercepts compared to the findings of Wilkoff et al. [1,16]. Data were plotted as %HRR versus %METR at rest, at each minute of exercise, and at peak exercise for the entire group, and for each individual. Reserve slopes and y-intercepts (see equation (2)) were compared to the slope of 0.94 ± 0.12 and y-intercept of 4.58 ± 7.7 that was reported by Wilkoff et al. [1]. In a subsequent analysis, Wilkoff et al. [16] set the y-intercept at 0, and reported the %HRR / %METR slope for the CAEP subjects as 1.058 ± 0.134. To compare the present results to Wilkoff's second analysis, we set the y-intercept of the %HRR / %METR regression line to 0, and recalculated the mean reserve slope.

A final test to determine the appropriateness of the chronotropic response of the $Inos^{2+}$ CLS pacemaker was to calculate anaerobic threshold (AT). The AT was calculated using the V-slope method, which is the point of increase in the slope of the CO_2 uptake without a concomitant increase in the slope of the VO_2 [15]. Time to reach AT and AT as a percent of VO_2 were compared to healthy subjects [17,18] and pacemaker patients [9].

In order to test the assumptions of the formula for predicting HR [1], we used t-tests to compare measured and predicted METs at each stage of the CAEP and calculated confidence intervals around predicted METs. The ACSM [5] cautions that the prediction of VO_2 from a given work rate may have a standard error of estimate SEE = 7%, which is a measure of the accuracy of predictions made with a linear regression analysis. Since SEE can also be interpreted as a Z score of ± 1 [19], and Z ± 2 gives the 95% confidence interval for a p-value = 0.05, the 95% confidence interval was calculated as predicted METs – 14% to predicted METs + 14%.

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS 9.0, USA). Continuous variables were expressed as mean ± standard deviation (SD). Pearson correlation coefficients were computed for variables used in regression analysis. Regression equations were computed between %HRR and %METR using linear regression analysis. Differences between measured and predicted HR and between measured and predicted METs were assessed using paired t-tests. Differences in continuous variables between subjects with low verses normal slopes were assessed using one-way analysis of variances (ANOVA), and differences in categorical variables were assessed using Chi-squared analysis. Significance was set at the 0.05 level of probability for all analyses. 95% confidence intervals were calculated around several variables for purposes of comparison. Selected analyses were plotted in graphical form to visually present significant results.

Results

Exercise Performance

Selected results of the CAEP treadmill test are shown in Table 2. The mean duration of exercise was 10 ± 2.8 min, with measured 4.5 ± 2.4 METs at peak exercise. Patients reached AT in 500 ± 159 s, which was 72% ± 10% of VO_{2max}. Six out of the 12 patients exceeded MCLR during the exercise test, with the pacemaker providing appropriate ventricular tracking. One patient exceeded the upper tracking rate (UTR). When the pacemaker started the Wenkebach pattern, the patient immediately became fatigued and the test was terminated. The data above the UTR were excluded from the final analysis.

Patient No.	Exercise duration (min)	Maximum exercise (METs)	Measured HR_{max} (bpm)	MCLR (bpm)	AT (% of $VO_{2\,max}$)	Time to reach AT (s)
1	10	3.5	125	125	76	558
2	10	2.4	121	125	72	348
3	9	3.4	137	147	62	450
4	9	3.9	150*	147	71	258
5	14	5.8	150*	139	81	810
6	9	4.3	117*	114	69	468
7	12	5.1	134	135	70	390
8	6	1.5	125	125	85	468
9	17	11.2	163*	145	49	768
10	7	4.0	114	115	85	438
11	10	4.7	150*	127	76	570
12	10	4.4	129*	110	72	480

*Table 2. Exercise Test Results. * = Pacing up to the programmed maximum pacing rate (MCLR = maximum closed loop rate), then tracked the intrinsic atrial rate providing atrioventricular synchronous ventricular pacing up to HR_{max}. AT = anaerobic threshold.*

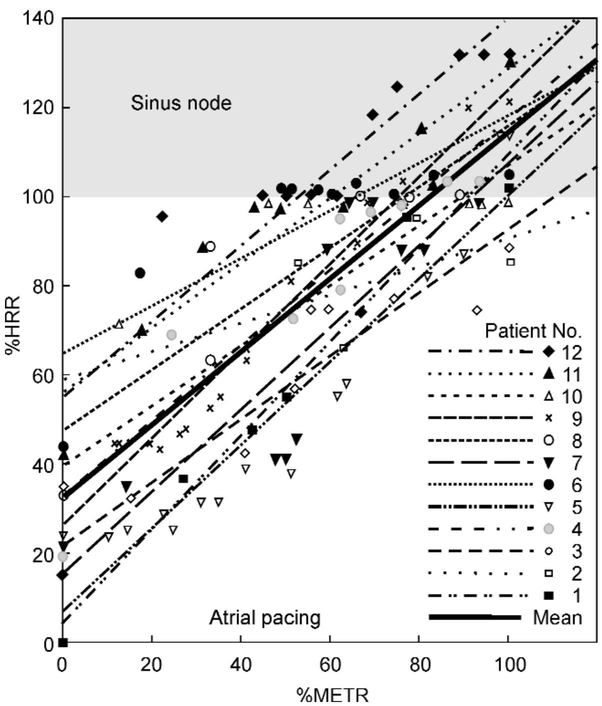

Figure 1. Plot of the linear regression of %HRR and %METR during the chronotropic assessment exercise protocol (CAEP). Each solid line represents an individual patient, with the solid line representing the mean. The mean slope of the relationship was 0.82 ± 0.56. The mean y-intercept was 32.2 ± 3.4. The linear regression equation is: %HRR = 0.82 %METR + 32.2, with a correlation coefficient between %HRR and %METR of r = 0.8 (p < 0.001).

Reserve Slopes

Regression of %HRR and %METR produced an equation of %HRR = 0.82 • %METR + 32.2, with a correlation coefficient r = 0.8 ($p < 0.001$). Individual slopes for the 12 study patients (Figure 1) ranged from 0.32 to 1.05, with a mean of 0.82 ± 0.56. The mean y-intercept was 32.2 ± 3.4. The mean slope fell within the 95% confidence interval (0.70 to 1.18) of the healthy subjects who performed the CAEP protocol in Wilkoff et al's original study [1]. The mean y-intercept was greater than 2 SD above the mean for normal subjects (-10.82 to 19.98). The linear regression for %HRR versus %METR produced an equation of %HRR = 0.82 (%METR) + 32.2, with a correlation coefficient between %HRR and %METR of r = 0.8 ($p < 0.001$).

Among the 12 study patients, four had a reserve slope less than 2 SD below the mean for the 221 normal subjects previously reported [1] (0.94 – 2 • 0.12 = 0.7), but none had a slope greater than 2 SD above the mean of the normal subjects (0.94 + 2 • 0.12 = 1.18). ANOVA showed no difference in age, exercise duration, MCLR, or base rate between the four subjects with a low slope and the remaining patients. Chi-squared analysis showed no differences in NYHA class, sex, or presence of heart disease between the low slope versus the normal slope patients. By mathematically forcing the y-intercept through the origin (Figure 2) to com-

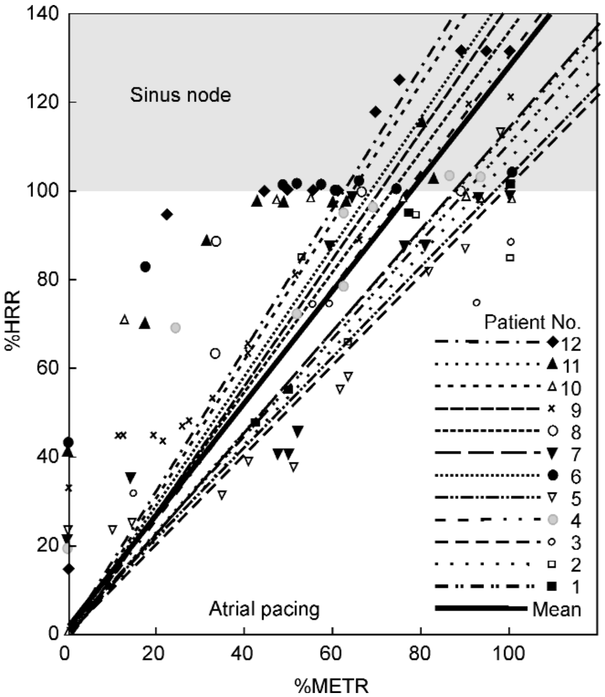

Figure 2. Reserve slopes of %METR and %HRR during the chronotropic assessment exercise protocol (CAEP) with the y-intercept set at zero. Each solid line represents an individual patient, with the solid line representing the mean. The mean slope was 1.274 ± 0.36, with a correlation coefficient between %HRR and %METR of r = 0.954 (p < 0.001).

pare to Wilkoff et al's subsequent analysis of their subjects [16], we obtained a mean slope of 1.274 ± 0.36, with a correlation coefficient of r = 0.954 ($p < 0.001$).

Predicted versus Measured Values

The comparison of both measured versus predicted METs and HR were not computed at stage 7 or 8 since only two patients completed stage 7 and one patient completed stage 8. Overall, measured METs were significantly lower than METs predicted by ACSM [5] formulas (3.3 ± 1.6 METs verses 4.1 ± 2.1 METs, respectively; t-value = -6.06, $p < 0.001$ (degrees of freedom = 58 from MET values for each patient for each stage of exercise). The overall mean measured value 3.3 METs fell below the 95% confidence interval of the predicted value (3.5 – 4.7 METs). There was no order effect of testing, i.e., no trend or differences were seen from patient 1 to patient 12. When analyzed by stage, significant differences were found at stages 3, 4, and 5, but not at stages 1, 2, or 6 (Figure 3). Sensor-driven HR was significantly higher throughout the exercise test than predicted HR (112 ± 22 bpm versus 95 ± 24 bpm, respectively), t -value = 14.2, $p < 0.001$ (degrees of freedom = 121). When analyzed by stage, significant differences were found at stages 1, 2, 3, and

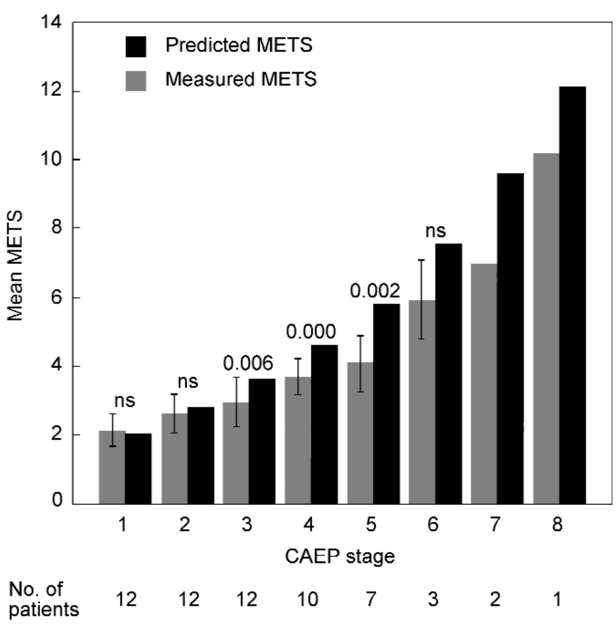

Figure 3. Measured and predicted METs at each stage of the chronotropic assessment exercise protocol (CAEP). Measured METs were significantly smaller than predicted METs at stages 3, 4, and 5. Note that differences were not computed at stage 7 or 8 since only two patients completed stage 7 and one patient completed stage 8.

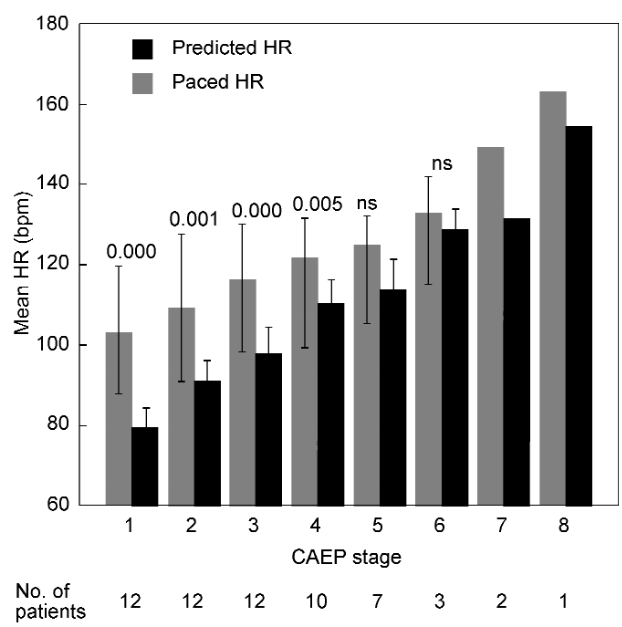

Figure 4. Paced and predicted heart rates at each stage of the chronotropic assessment exercise protocol (CAEP). Paced rates were significantly higher than predicted at stages 1, 2, 3, and 4. Note that differences were not computed at stage 7 or 8 since only two patients completed stage 7 and one patient completed stage 8.

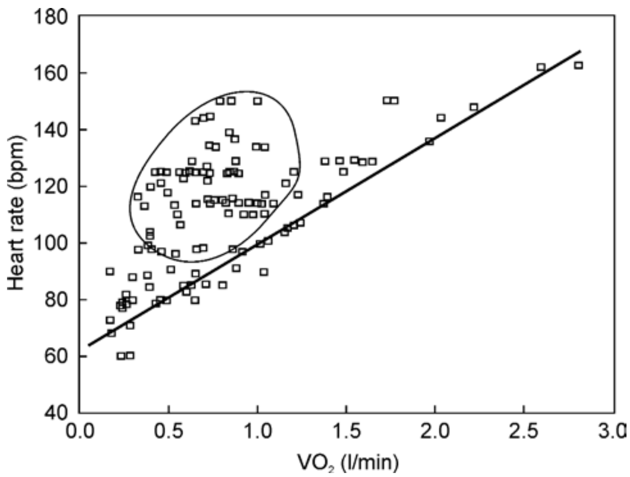

Figure 5. The relationship between heart rate and oxygen uptake (VO_2) in pacemaker subjects is higher (circled area) than that expected of normal subjects (line), and resembles the response seen in cardiac patients [6]. Only one subject exhibited a normal response – a linear relationship, represented by the straight line. VO_2 is given for STPD, i.e., standard conditions of temperature (0°Celcius), pressure (760 mmHg), dry (no water vapor in gas).

4, but not at stages 5 or 6 (Figure 4). Although measured METs were significantly lower than predicted METs, the difference in predicted HR using measured or predicted METs was not significant.

To further assess the pacemaker's rate response to exercise for our 12 study patients, the HR/VO_2 relationship throughout the exercise test was graphed (Figure 5). The cluster of points (shown circled), display a higher HR relative to the VO_2 than that expected of normal subjects (represented by the straight line).

Discussion

The purpose of this study was to assess the rate response of the Inos^{2+} CLS pacemaker during CAEP exercise testing, and to test the assumptions of the Wilkoff [1] mathematical model of chronotropic response in our pacemaker patients. Our findings demonstrated that the Inos^{2+} CLS provided paced HRs that appropriately adapted for steadily increasing metabolic requirements during exercise, despite the finding that paced HRs were significantly higher than predicted HRs during the first 8 min of exercise. Measured METs were significantly lower than predicted after 4 min of the CAEP, but the choice of measured or predicted METs in the HR prediction formula did not result in any significant differences in HR prediction.

Predicted versus Measured METs

The patients in our study exercised for 10 ± 2.8 min, with a peak exercise of 4.5 ± 2.4 METs. These results are similar to the exercise capacity recorded in two similar studies of pacemaker patients [7,9] but are lower than those observed in younger subjects [1] and the healthy elderly [18]. The group of young, healthy subjects studied by Wilkoff et al. [1] reached a maximum of 11.3 ± 2.4 METs during the CAEP. In a study by Page et al. [18] healthy elderly subjects exercised for 14.7 ± 2.9 min, and reached a VO_2 peak of 28.7 ml/kg/min (8.2 METs). Both of these studies of healthy individuals reported MET values much higher than achieved by the paced patients in our study. Comparable to the results of the current study, Carmouche et al. [9] reported a treadmill duration of 10.6 min in pacemaker patients, but VO_2 was reported in ml/min without information on patients' weight, thus precluding comparison with our data. Similarly, Kay [7] measured maximal VO_2 of pacemaker patients using the CAEP protocol as 13.2 ± 4.1 ml/kg/min (3.7 ± 1.2 METs). However, the pacemaker patients in a study by Freedman et al. [20] more closely resembled healthy subjects, reaching stage 8 of the CAEP, with maximum METs of 12.1 predicted by formulas. Possible explanations of the lower peak METs achieved by the patients in our study could be the advanced age of our patients [6], or the setting of MCLR at less than the age-predicted maximum HR [9].

Anaerobic Threshold

All patients reached AT within a mean of 500 ± 159 s, which was 72% ± 10% of VO_{2max}. This compared favourably with 532 ± 50 s and 75% of VO_{2max} reported by Carmouche et al. [9], but was higher than reported in other studies of normal subjects. Page et al. [18] found that healthy elderly subjects reached AT at 65% of VO_{2max} during CAEP exercise testing. Wasserman et al. [17] state that the mean AT can be expected to be between 55 and 65% of VO_{2max} for individuals aged 40 to 70 years, with the ratio of AT/VO_{2max} increasing with age, and higher in women than in men. For the mean age of our study group (70 years), we calculated the 95% confidence intervals of AT/VO_{2max} as being 47 to 69% for men, and 54 to 76% for women. Therefore, the AT/VO_{2max} ratio of 72% from our study was within SD of the mean of healthy 70-year-old subjects.

Reserve Slopes

Wilkoff et al. [1] stated an ideal slope of 1.0 and y-intercept of 0 for the %HRR versus %METR regressions. This was a generalization based on pooled results from both the CAEP and the Bruce treadmill protocols and was used to derive the HR prediction formula. The actual slope and intercept for the 221 subjects using the CAEP protocol in the original paper [1] were 0.94 and 4.58 respectively. In a subsequent abstract published in 1990 [16] after a second analysis using more subjects (n = 303), the slope for the CAEP was reported as 1.058 with the y-intercept set at 0. The methodological differences in these two important papers may have caused some confusion with later investigators.

Although the majority of investigators have used the Wilkoff mathematical model, their method of use differs. Most subsequent investigators have compared their results to the theoretically ideal slope of one [14,18,20-22], although Freedman et al. [20] also compared their reserve slopes to the actual slopes of Wilkoff's second analysis [16]. Some have forced their regressions through the origin [18,20,21], while others have allowed a y-intercept [7,22]. Of the two studies we found that allowed a y-intercept, Kay [7] studied ten paced patients during CAEP exercise, but used a normalization method where resting HR and METs were set at zero, and maximal HR and METs were set at one. This mathematical manipulation of the data is similar, but not identical to Wilkoff's model, so although their mean reserve slope was similar to ours (0.81 ± 0.25), it would not be entirely accurate to compare the two. Swain et al. [22] also allowed a y-intercept but tested a young, healthy population (age 26 ± 1 years) using a bicycle protocol. They found a slope of 1.03 ± 0.01, with a y-intercept of 1.5 ± 0.6.

Predicted versus Measured HR

One reason for a high y-intercept and low slope in the present study is that most patients exhibited a HR that was higher than predicted for up to stage 3 (6 – 8 min) of the CAEP ($p < 0.001$). Our results are similar to those of Kay [7], who reported paced HRs that were significantly higher than expected during the first and fourth quartiles of exercise. Since the slope of the %HRR / %METR was within acceptable limits (95% confidence interval of Wilkoff's reference population), we considered the idea that a HR prediction formula derived from healthy subjects may not be appropriate for our pacemaker population.

There are inherent differences between the young, healthy subjects that are routinely used to derive 'norms' for reference populations and a typical pacemaker population, which impact on the physiological response to exercise. The mean age of our patients was 70 years, which is comparable to similar studies of pacemaker subjects [7,14,20,21], but older than most reference [1,16] and healthy [22] populations, with the exception of the group of healthy elderly (70-year-old) individuals studied by Page et al. [18]. It is well known that as one ages, the maximum HR and VO_2 decreases [5,6]. Generally, the older one is, the more sedentary one becomes [23], and heart diseases that develop as one ages become more severe [24]. In addition to the effect of age on maximum HR, Cooper [4] stated that the more sedentary the individual, the lower the peak HR. Wasserman [6] reported that subjects with heart disease experience a higher HR relative to VO_2 at maximal exercise than healthy individuals [6]. In pacemaker patients, Carmouche et al. found that setting the upper rate limit at age-predicted HR_{max} improved exercise performance (both duration and VO_2 achieved) at both high and low exercise workloads [9], and Freedman et al. [20] reported lower reserve slopes when HR_{max} sensor rate was less than age-predicted HR_{max}. However, pacemaker patients rarely reach their maximum age-predicted HR. Instead, pacemakers have a programmed upper rate which is set at a percentage of the age-predicted maximum HR of the patient. The MCLR of the pacemaker in our study was set at 70 – 85% of patients' age-predicted HR_{max}. In half of our patient group, the sinus node took over and exceeded the MCLR of the pacemaker. However, the average peak HR of 134 bpm was still less than the age-predicted HR_{max} of 150 bpm, and less than the peak HR of 154 bpm attained by the healthy elderly subjects in the study by Page et al. [18].

Therefore, it appears that the widely accepted relationships between age and HR_{max} and between HR and VO_2 during exercise may not hold true for older pacemaker patients. The use of the age-predicted HR_{max} may not result in an accurate prediction of peak HR for paced patients, and in turn, will artificially decrease the calculated %HRR (equation (1)). Our use of MCLR for HR_{max} in the denominator of the %HRR formula instead of age-predicted HR_{max} resulted in a smaller denominator, and thus a larger %HRR. This may explain the higher y-intercept and lower slope seen in the %HRR / %METR regression in this study when compared to that of healthy reference subjects [1].

The HR/VO_2 Relationship

Graphing the HR/VO_2 relationship revealed a similar pattern to that seen in cardiac patients and described by Wasserman et al. [6] (Figure 5). Although a linear relationship between HR and VO_2 during exercise has been demonstrated in studies of healthy populations [17,25], studies of patients with heart disease [6,26] have demonstrated that the increase in HR as a function of VO_2 in nearly all heart diseases is steeper than normal, with cardiac patients exhibiting a higher HR relative to VO_2 than normal, older, or respiratory subjects. When individual cases were identified on our HR/VO_2 graph, the circled area did not contain only those patients who had heart disease, but rather contained points from all patients except one. Patient 9 was the youngest and fittest of the group, displaying a linear HR/VO_2 response to exercise. These results suggest that the HR response to exercise of pacemaker patients may be closer to that of cardiac patients than to normal subjects. This assumption is supported by Kay [7], who states "standards for the HR/VO_2 relation that are derived from studies of normal volunteers are unlikely to provide sufficient accuracy for assessing the chronotropic response of individuals with a permanent pacemaker and widely varying degrees of cardiac disease."

Testing the Assumptions of the Wilkoff Formulas

When testing the assumptions of the Wilkoff [1] mathematical model of chronotropic response in our pacemaker patients, we investigated two possible sources of error in the HR prediction formula. The first source of error involved the assumption that maximum HR can be calculated by the formula (220 – age) [5]. This is discussed in detail in the preceding section. The second source of error involved the prediction of METs from ACSM equations. The ACSM [5] states that these metabolic equations have a standard error of the estimate of 7%, which translates to a ± 14% variance of predicted METs from actual METs. We hypothesized that this may be enough to significantly affect the prediction of HR at any stage of the CAEP. However, while we found that measured METs were significantly lower than predicted METs at moderate levels of exertion (stages 3 – 5 of the CAEP), the choice of predicted or measured METs in the HR prediction formula did not make a significant difference in predicted HR. However, we have also discussed how the metabolic response to exercise of paced patients is different than that of healthy individuals. Consequently, our conclusion is that Wilkoff's formula for predicted HR during exercise, which uses both predicted METs per CAEP stage and age-predicted HR_{max}, which are both based on a healthy reference population, maybe not accurately project expected HR for an older individual with heart disease.

Limitations

The use of the pacemaker's programmed settings for MCLR in place of age-predicted HR_{max} in the formulas may have affected the results. The accuracy of the use of age-predicted HR_{max} in an older or paced population has been questioned by others [9,18,20], and may have been responsible for the lower than predicted METs and higher %HRR in our patient group. It is uncertain whether similar results would be observed if the MCLR were to be set closer to each patient's age-predicted HR_{max}. Evaluating the rate responsiveness of a pacemaker from rest to maximal exercise requires that the patient exercise to maximal capacity. Although our study patients were encouraged to exercise as long as they could, and all reached anaerobic threshold, we cannot be positive that all were motivated enough to achieve their maximal exercise work load. The present study proposes inherent differences between a normal population and a pacemaker population that, in turn, implies that the Wilkoff model of normal chronotropic response to exercise may not be appropriate for pacemaker assessment. Although this hypothesis is supported by other authors [7,18,20], our sample of 12 patients is too small to permit generalizations of our results to the larger population of all pacemaker patients.

Conclusion

The results of this study show that the $Inos^{2+}$ CLS produced physiological pacing rates that were appropriate for metabolic needs during exercise. The HR response to exercise was higher than expected, but linearity of the HR/metabolic relationship was within the confidence intervals of healthy reference subjects. Manipulation of the Wilkoff mathematical model increased the mean slope and reduced the variability of individual slopes, thus appearing to move the results towards normality. Therefore, methodological differences must be examined carefully when comparing results of different studies. This study also illuminated some of the methodological obstacles that must be considered when using the Wilkoff mathematical formulas to evaluate pacemaker performance. A significant difference between measured and predicted METs failed to make a difference in the prediction of HR in our patient group. Nonetheless, we advise the use of measured METs whenever possible. Pacemaker settings as well as inherent differences between a pacemaker population and a healthy reference population such as age, fitness level, presence and etiology of disease, may affect the HR response to metabolic demand. The HR/VO_2 relationship of patients in our study more closely resembled a cardiac population than a normal population. Therefore, application of the Wilkoff mathematical model, which is based on a young healthy population, needs careful scrutiny before conclusions are drawn when testing new pacemaker systems.

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