Phase I and Phase II Oxygen Uptake Kinetics During Atrioventricular Dyssynchrony in Chronotropically Competent Pacemaker Patients*

Corey R. Tomczak, MSc; Wladyslaw Wojcik, MD; Edward F.G. Busse, MD; and Robert G. Haennel, PhD

**Objective:** To elucidate the effects of atrioventricular (AV) dyssynchrony on phase I and phase II oxygen uptake (V\(\dot{O}_2\)) kinetics in chronotropically competent pacemaker patients during exercise of an intensity comparable to activities of daily living.

**Design:** Blinded patients completed sub-ventilatory threshold (VT) work rate (WR) cycle ergometry exercise in random order during asynchronous AV pacing (AV OFF) and synchronous AV pacing.

**Setting:** Tertiary care hospital in a major city.

**Subjects:** Six chronotropically competent male pacemaker patients (mean ± SD age, 68 ± 10 years) with high-degree AV block and varying cardiac histories.

**Results:** The phase I and phase II V\(\dot{O}_2\) amplitude response and gain (\(\Delta V\dot{O}_2/WR\) ratio) were lower (\(p < 0.05\)) and the time course of phase II was slower (\(p < 0.05\)) during AV OFF; however, the O\(_2\) deficit was similar (\(p > 0.05\)) across pacing modes. The stroke volume index (SVI) was consistently lower (\(p < 0.05\)) during AV OFF pacing and was significantly correlated with the time course of phase II V\(\dot{O}_2\). A significant compensatory amplitude response in heart rate (HR) was observed in addition to a higher (\(p < 0.05\)) \(\Delta HR/V\dot{O}_2\) ratio during AV OFF. Ventilatory responses were consistent with ventilatory-perfusion mismatching and perceived exertion was higher during asynchronous pacing.

**Conclusion:** This study demonstrated that the contribution of SVI affects V\(\dot{O}_2\) kinetics and underscores the importance of the atrial contribution to ventricular filling and, consequently, to metabolic and hemodynamic responses. This study supports the theory of an O\(_2\) transport limitation and further implicates SV as a potential limiting factor during sub-VT exercise intensities that are comparable to those encountered in activities of daily living.

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**Key words:** atrioventricular synchronization; exercise; heart rate kinetics; oxygen uptake kinetics; pacemakers; stroke volume

**Abbreviations:** AV = atrioventricular; AV OFF = asynchronous atrioventricular pacing; AV ON = synchronous atrioventricular pacing; HR = heart rate; Q = cardiac output; RPE = rating of perceived exertion; SV = stroke volume; SVI = stroke volume index; V\(\dot{O}_2\) = oxygen uptake; \(\dot{V}CO_2\) = carbon dioxide output; \(V_e\) = minute ventilation; VT = ventilatory threshold; WR = work rate

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The characterization of oxygen uptake (V\(\dot{O}_2\)) kinetics allows for the quantification of the time course and amplitude responses of metabolic changes associated with varying exercise milieu. In particular, the time course of V\(\dot{O}_2\) is thought to be a valuable index reflecting the adjustment of O\(_2\) transport\(^1\) and utilization.\(^2\) Since V\(\dot{O}_2\) is the product of cardiac output (Q) and the arterial-venous oxygen difference, the relative contribution of Q determinants (ie, heart rate [HR] and stroke volume [SV]) to V\(\dot{O}_2\) are seemingly fundamental in reducing the O\(_2\) deficit and matching metabolic demand during physical activity.

In populations of patients with pacemakers, V\(\dot{O}_2\)
kinetics have been employed to describe O₂ transport limitations associated with chronotropic response patterns and atrioventricular (AV) synchronization. Presumably, many of a pacemaker patient’s activities of daily living occur within energy expenditures that are below the ventilatory threshold (VT). Hence, the importance of maintaining AV synchrony throughout sub-VT exercise is underscored as the normally functioning atrium augments SV by increasing left ventricular filling pressure, thus contributing to a greater ejection fraction to the periphery via the Frank-Starling mechanism.

Previous studies have examined the effects of AV synchronization on peak exercise responses; however, these data may not be relevant for elderly pacemaker patients’ daily physical routines. Consequently, Rickli et al studied the effects of AV synchronization on the mean response time (i.e., the combined phase I and II kinetics) of VO₂ during low-level exercise, and, to the best of our knowledge, is the only such study. Moreover, to our knowledge no studies have distinguished between phase I and phase II responses, and no studies have examined these effects in chronotropically competent pacemaker patients. Therefore, the main purpose of this study was to elucidate the effects of AV dysynchrony on phase I and phase II VO₂ kinetics in chronotropically competent pacemaker patients during exercise intensities corresponding to activities of daily living.

MATERIALS AND METHODS

Subjects

Participants in this study included patients (six men; mean [± SD], 68 ± 10 years) in whom a pacemaker (Saphir 3, Clarity 860, Diamond 3 840, or Diamond 2 820 pacemaker; Vitatron Medical BV; Arnhem, The Netherlands) had previously been implanted. All patients were chronotropically competent and had received a diagnosis of high-degree AV block as the primary indication for pacemaker implantation and were assessed as New York Heart Association functional class I or II. Additionally, all patients reported being active and participated in activities such as brisk walking, yard work, and house cleaning a minimum of three times per week. The patients had varied but stable cardiac histories, and none had pulmonary, neurologic, or orthopedic limitations (Table 1). All patients maintained their current medication regimen. This study conformed to the Declaration of Helsinki and was approved by appropriate local university and hospital research ethics boards.

Pacemaker Programming

In order to ensure atrial sensing and ventricular pacing, pacemakers were programmed to VDD, where V indicates ventricular pacing, D indicates atrial and ventricular sensing, and D indicates that cardiac stimulation was either inhibited or triggered during a sensed event. All pacemakers were equipped with the same rate-adaptive AV algorithm and similar programming parameters. The pacemakers employed a fixed AV interval that resulted in no AV adaptation (i.e., 0.0 ms/beat/min; asynchronous AV pacing [AV OFF]) with changes in HR and an adaptive AV interval that adjusted to HR at 0.9 ms/beat/min (i.e., asynchronous AV pacing [AV ON]). Resting impedance cardiography studies were employed to assess the sensed AV interval that yielded the highest SV. This optimized interval was used for subsequent exercise testing.

Exercise Testing

To determine the VT and peak VO₂, patients performed a cycle ergometer test using a ramp protocol with metabolic gas analysis. The protocol involved increments of 10 W/min until volitional fatigue. Patients were instructed to maintain a cadence of approximately 60 revolutions per minute. Resting VO₂ was calculated as the average VO₂ from the last 30 s of the resting period. Gas exchange VT was identified as the VO₂ at which carbon dioxide output (VCO₂) increased disproportionately relative to the rise in VO₂. Peak VO₂ was defined as the highest 30-s VO₂ attained during the exercise test. Work rates (WRs) corresponding to VO₂ at approximately 90% of VT were identified for subsequent sub-VT exercise testing.

Within 1 week of the peak exercise test, patients returned to the laboratory and were randomized into AV OFF or AV ON for sub-VT exercise testing. Resting data were collected over a 2-min period followed by 1 min of unloaded (0 W) cycling. This was followed by an unannounced increase in WR corresponding to approximately 90% of VT that lasted 6 min. The approximate 90% of VT WR was followed by a 5-min period of passive recovery and an additional 20-min period of quiet rest. Patients then were crossed over into the remaining AV setting, and the protocol was repeated. Patients were blinded to their pacemaker setting.

Measurements

Metabolic data were collected using a non-rebreathing flow valve (model 2700; Hans Rudolph Inc; Kansas City, MO) connected with tubing to a heated pneumotachograph flowmeter and mixing chamber (model 3818; Hans Rudolph Inc). Samples of O₂ and CO₂ were collected breath-by-breath and were analyzed (True Max 2400 Metabolic Measurement System; Parvomedics Inc; Salt Lake City, UT). The analyzer was calibrated with known gas concentrations (O₂, 16%; CO₂, 4%), and the pneumotachograph flowmeter was calibrated with a 3.0-L syringe prior to each test. Exercise protocols were programmed into the metabolic system, which was interfaced with an electronically braked cycle ergometer (Ergo-metrics 5008; Roxon Inc; Montreal, QC, Canada).

A standard 12-lead ECG was monitored and recorded contin-
nously throughout peak and sub-VT testing (Merlin AM hardware; CardioComm Solutions, Inc; Victoria, BC, Canada). For sub-VT testing, beat-to-beat HR was measured from the onset of ventricular stimulation at 100 mm/s (GEMS software; CardioComm Solutions, Inc; Vancouver, BC, Canada). Data were transferred to a personal computer for further analysis using a custom program (Annoexport; CardioComm Solutions, Inc).

SV was determined using impedance cardiography (Minnesota Impedance Cardiograph, model 304B; Surcom Inc; Minneapolis, MN), a phonocardiogram (model 21050A; Hewlett Packard; Palo Alto, CA) and a three-lead ECG. The phonocardiogram was integrated with the impedance cardiograph for the purposes of identifying S1 and S2 heart sounds so as to landmark respective B and X points of dZ/dt waveforms. The impedance cardiograph calculated SV during 7-s sampling periods at the end of each minute throughout sub-VT exercise using the Bernstein equation. Impedance cardiography has been widely used and validated as a noninvasive measure in patients with ventricular dysfunction and pacemakers with < 5% random error, and its results have been demonstrated to correlate with values obtained by thermodilution.

Analysis

Breath-by-breath VO<sub>2</sub> was filtered for outliers, which were defined as any value that was > 2 SDs for the 10-s preceding and following questionable data points. Data points were interpolated to 1-s intervals and were averaged into 5-s time bins so as to reduce noise and enhance the underlying characteristics of physiologic phenomena. Phase II VO<sub>2</sub> kinetics were analyzed for sub-VT exercise using a first-order (monoexponential) model of the form

Y<sub>01</sub> = Y<sub>01</sub> + A · [1 - e<sup>-(t - TD/τ)</sup>] (1)

where Y was VO<sub>2</sub> at any given time (t), b was the baseline value of VO<sub>2</sub>, A was the amplitude change in VO<sub>2</sub> above b, τ was the time constant or time for VO<sub>2</sub> to reach 63% of A, and TD was the time delay or displacement from time 0 of the extrapolation curve to b. Curve fits were modeled employing least-squares nonlinear regression where the best fit was defined by the minimization of the residual sum of squares. The data were fit from the phase I-phase II interface to 6 min of exercise. The amplitude change during phase I was calculated as the difference between b and the end of phase I. The end of phase I was determined as the point at which a decrease in VO<sub>2</sub> or VO<sub>2</sub>/HR ratio coincided with the ending of the initial plateau in VO<sub>2</sub>, VO<sub>2</sub>, and minute ventilation (VE). Phase II onset was the point of increase in VO<sub>2</sub> following the end of phase I.

The O<sub>2</sub> deficit was estimated by fitting phase I and II VO<sub>2</sub> using equation 1 with τ starting at a TD of 0 s. The O<sub>2</sub> deficit was then calculated as follows:

\[ \Delta V_{O_2} = V_{O_2} \times \tau \] (2)

where \( \Delta V_{O_2} \) was the amplitude change in VO<sub>2</sub> above b.

Beat-by-beat HR data were filtered for outliers, which were defined as any value that was > 2 SDs for the 10-s preceding and following questionable data points. As was done with VO<sub>2</sub>, data points were interpolated to 1-s intervals and were averaged into 5-s time bins so as to reduce noise and enhance the underlying characteristics of physiologic phenomena. Data were modeled with equation 1 while employing the same fitting criteria as described for VO<sub>2</sub>.

The SV index (SVI) was calculated using the Mosteller equation for body surface area, and the data were described for rest, pretransition cycling (0 W), exercise onset to 3 min (corresponding to the phase II response), and steady-state exercise (3 to 6 min). Ventilatory responses during steady-state sub-VT exercise were calculated as VE and the ventilatory equivalent of CO<sub>2</sub> (VE/VO<sub>2</sub> ratio). Subjective ratings of perceived exertion (RPEs) were determined in the last 10 s of each minute throughout sub-VT exercise period using a 20-point Borg scale and were averaged to yield an overall exercise score.

Statistical Analysis

Statistical analysis was performed using a statistical software package (SPSS, version 10.0; SPSS; Chicago, IL), and comparisons were made using two-tailed, dependent, paired t tests for all physiologic variables. Subjective RPE scores were analyzed using the Wilcoxon signed rank test. Relationships between variables were assessed with correlation-regression analysis. The data are presented as the mean ± SD, and p < 0.05 was considered to be statistically significant.

RESULTS

Patient characteristics and peak exercise testing results are presented in Table 1. During peak exercise, the mean WR at approximately 90% of VT was 38 ± 7 W. For sub-VT exercise, the mean percentages of ventricular pacing during AV OFF and AV ON modes were 89 ± 11% and 91 ± 14%, respectively. The percentages of ventricular pacing in the

<table>
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<tr>
<th>Patient No.</th>
<th>Age, yr</th>
<th>Height, m</th>
<th>Mass, kg</th>
<th>BMI</th>
<th>Cardiac History</th>
<th>VT WR, W</th>
<th>VT VO&lt;sub&gt;2&lt;/sub&gt;, mL/min</th>
<th>Peak WR, W</th>
<th>Peak VO&lt;sub&gt;2&lt;/sub&gt;, mL/min</th>
<th>Peak VO&lt;sub&gt;2&lt;/sub&gt;, mL/kg/min</th>
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<td>37</td>
<td>CM, PHTN</td>
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<td></td>
<td>10</td>
<td>187</td>
<td>16</td>
<td>320</td>
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</table>

**Table 1—Patient Characteristics and Peak Exercise Responses**

*BMI = body mass index; CAD = coronary artery disease; ANG = angina (ie, suspected CAD); HTN = hypertension; MI = myocardial infarction; CM = cardiomyopathy; PHTN = pulmonary hypertension.
AV OFF and AV ON modes throughout sub-VT exercise were 95 ± 13% and 92 ± 20%, respectively. To confirm the absence of a slow-component (phase III) rise in VO₂, which typically is present in exercise above the VT, the VO₂ response slope between 3 and 6 min was calculated. The VO₂ slope was not significantly different from a reference slope of 0 for either the AV OFF and AV ON tests, indicating the absence of a phase III rise in VO₂. Additionally, the mean steady-state VO₂ for both AV OFF and AV ON pacing was 87 ± 10% of the estimated VT determined from peak exercise testing, further confirming that the prescribed exercise intensities were below the VT. In addition, the mean metabolic equivalents during sub-VT exercise were within energy expenditures comparable to those during activities of daily living (AV OFF, 3.0 ± 0.4 metabolic equivalents; AV ON, 3.1 ± 0.4 metabolic equivalents).

**VO₂ Kinetics**

Baseline VO₂ during pretransition (0 W) was 14% higher (p < 0.05) during AV OFF (Table 2). The amplitude change in phase I VO₂ was 67% lower (p < 0.05) during AV OFF (60 ± 53 mL/min) compared with AV ON (173 ± 87 mL/min). Additionally, the phase I VO₂ gain (ΔVO₂/WR) was 67% lower (p < 0.05) during AV OFF (1.7 ± 1.6 mL/min/W) compared with AV ON (4.5 ± 2.4 mL/min/W).

Figure 1 illustrates VO₂ responses and phase II monoexponential curve fits during AV OFF and AV ON throughout sub-VT exercise. The amplitude change in phase II VO₂ was 18% lower (p < 0.05) during AV OFF (Table 2), and the phase II VO₂ gain (ΔVO₂/WR) was 18% lower (p < 0.05) during AV OFF (10.8 ± 1.7 mL/min/W) compared with AV ON (13.2 ± 1.9 mL/min/W). There were no differences in steady-state VO₂ across pacing modes. While phase II τ VO₂ was 15% slower (p < 0.05) during AV OFF (Table 2), the estimated O₂ deficit was similar (p > 0.05) across pacing modes (AV OFF, 563 ± 305 mL; AV ON, 567 ± 283 mL).

**HR Kinetics**

Figure 1 illustrates the HR responses and monoexponential curve fits during AV OFF and AV ON throughout sub-VT exercise. Baseline HR in the 0 W pretransition was similar (p > 0.05) across pacing modes. However, the amplitude change in HR was 28% higher (p < 0.05) during AV OFF (Table 2), and the change in HR for a given VO₂ (ΔHR/VO₂) was 41% higher (AV OFF, 50 ± 24 beats/L; AV ON, 27 ± 14 beats/L; p < 0.05). Despite a similar baseline and a greater amplitude change in HR during AV OFF, the steady-state HR was similar (p = 0.204) across pacing modes. Furthermore, τ HR was similar (p > 0.05) for the two conditions (Table 2).

**SVI Responses**

Figure 2 illustrates SVI responses across pacing modes throughout sub-VT exercise. The mean resting SVI was similar (p > 0.05) during AV OFF (44.0 ± 4.9 mL/beat/m²) compared with AV ON (42.0 ± 4.2 mL/beat/m²). However, the SVI demonstrated a transient increase and was 26% lower (p < 0.05) in the 0-W pretransition during AV OFF (37.4 ± 4.2 mL/beat/m²) compared with an increase during AV ON (50.6 ± 3.8 mL/beat/m²). The mean SVI response from exercise onset to 3 min of exercise was 7% lower (p < 0.05) during AV OFF (48.9 ± 6.0 mL/beat/m²) compared with AV ON (52.9 ± 6.8 mL/beat/m²). Additionally, the mean steady-state SVI remained 10% lower (p < 0.05) during AV OFF (47.4 ± 6.0 mL/beat/m²; AV ON, 54.4 ± 6.1 mL/beat/m²). The SVI response from exercise onset to 3 min was negatively correlated with phase II τ VO₂ where τ VO₂ = -1.0 (SVI) + 120.7 (r = 0.59; p < 0.05) [Fig 3].

**Ventilatory Responses**

Patients demonstrated a similar (p > 0.05) mean V̇E response across the AV OFF and AV ON modes (23.5 ± 4.8 vs 23.8 ± 4.5 L/min, respectively). However, the mean V̇E/VO₂ ratio response was 3% higher (p < 0.05) during AV OFF (28.2 ± 4.0) compared with AV ON (27.3 ± 3.7 L/min).

**Subjective Responses**

Figure 4 illustrates averaged subjective RPE scores across the two pacing modes throughout sub-VT exercise. Patients demonstrated significantly higher RPE scores during AV OFF at each minute of sub-VT exercise. The averaged RPE scores were 17% higher (p < 0.05) during AV OFF (9.9 ± 1.0) compared with those during AV ON (8.2 ± 0.7).

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**Table 2—Kinetic Parameters for Phase II VO₂ and HR**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>VO₂, mL/min</th>
<th>HR, beats/min</th>
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<tbody>
<tr>
<td>AV OFF</td>
<td>AV ON</td>
<td>AV OFF</td>
</tr>
<tr>
<td>Y(b)</td>
<td>540 ± 119</td>
<td>472 ± 170†</td>
</tr>
<tr>
<td>A</td>
<td>417 ± 100</td>
<td>510 ± 122†</td>
</tr>
<tr>
<td>SS</td>
<td>957 ± 91</td>
<td>982 ± 125</td>
</tr>
<tr>
<td>τ (s)</td>
<td>77 ± 26</td>
<td>64 ± 18†</td>
</tr>
</tbody>
</table>

*Values are given as the means ± SD for the entire study group. Y(b) = baseline value; A = amplitude change; SS = steady-state (asymptotic) values; τ = time constant for phase II VO₂ kinetics and HR kinetics.†Significantly different vs AV OFF (p < 0.05).
The main purpose of this study was to describe phase I and II \( \dot{V}O_2 \) kinetic responses during synchrony (AV ON) and dyssynchrony (AV OFF) in chronotropically competent pacemaker patients at exercise intensities that were comparable to activities of daily living. In the present study, we normalized the prescribed steady-state WR to approximately 90% of the VT for each patient, whereas similar studies \(^5,^19\) have employed absolute exercise intensities. By employing quantified relative exercise intensities, our methodology controlled for variations in amplitude and time-course responses among patients with varying exercise capacities \(^20\) (Table 1) and further ensured sub-VT responses. Ensuring a sub-VT response was important, as metabolic acidosis is one mechanism that is known to alter kinetic responses.\(^2\)

Constant WR exercise elicits a three-phase rise in \( \dot{V}O_2 \).\(^{21,22}\) Briefly, phase I kinetics reflect a transit delay of metabolites and are the result of immediate increases in \( Q \) and pulmonary blood flow.\(^2\) Phase II kinetics are distinguished by an exponential increase in \( \dot{V}O_2 \) that is related to \( Q \) and is temporally associated with changes in phosphocreatine within exer-
cising muscles, thus reflecting \( O_2 \) delivery\(^{23} \) and energy metabolism.\(^{21,24} \) Phase III kinetics occur when steady state is achieved during sub-VT exercise. Although the steady-state \( V_{O_2} \) is typically achieved between 3 and 4 min of sub-VT exercise, the adenosine triphosphate turnover rate reaches steady-state instantaneously, resulting in an \( O_2 \) deficit that is composed mostly of reductions in high-energy phosphates and \( O_2 \) stores.\(^{25} \)

The main finding of this study was that phase II \( \tau \) \( V_{O_2} \) kinetics are slowed (Table 2, Fig 1) during dysynchrony, which is consistent with previous observations\(^5 \) for the mean response time of \( V_{O_2} \) (combined phase I and II kinetics). The data from the present study imply that a greater degree of AV synchrony was maintained during AV ON compared with AV OFF, thus resulting in observed differences in the rate of \( O_2 \) delivery. Presumably, the mechanism by which \( V_{O_2} \) kinetics were slowed during AV OFF was through a reduction in left ventricular end-diastolic filling\(^8,26 \) and hence, a relatively smaller ejection fraction. This is evidenced by the attenuated SVI response during AV OFF (Fig 2) and is further supported by the inverse relationship between SVI and phase II \( \tau V_{O_2} \) (Fig 3). Consistent with our observations, others\(^8,27,28 \) have demonstrated that synchronous AV pacing results in a higher exercise SV compared to asynchronous pacing, without affecting SV at rest.\(^{29} \) This observation has implications for pacemaker programming during resting states and further emphasizes the value of cardiopulmonary exercise testing when available.

The \( \Delta V_{O_2} \) gain (\( \Delta V_{O_2}/WR \)) reflects \( O_2 \) transport and utilization for work performed, and is contingent on WR and cardiovascular disease status.\(^{30} \) Given that exercise intensities were normalized to approximately 90% of the VT, differences in the \( V_{O_2} \) gain across pacing modes can be used to interpret differences in \( O_2 \) transport and thus in cardiovascular efficiency. It is likely that the lower \( V_{O_2} \) gain during phase I was due to a lower SVI response during AV OFF. Consequently, this resulted in a lower amplitude change and \( V_{O_2} \) gain during phase I kinetics, which is indicative of a smaller cardiodynamic response or “bolus surge” as a result of increasing HR because of parasympathetic withdrawal at exercise onset. In effect, poor AV coordination due to abrupt HR changes in response to increases in WR resulted in a reduction in ventricular end-diastolic filling, pressure, and contractile force, and thus a lower SVI via an attenuated Frank-Starling response. Consistent with phase I kinetics, a lower amplitude change was observed during phase II kinetics. We theorize that, once again, the lower SVI response pattern contributed to less \( O_2 \) utilization for a given WR because of limited \( O_2 \) transport to working tissue. This is further substantiated by the lower \( V_{O_2} \) gain and the slower \( \tau V_{O_2} \) observed during AV OFF (Table 2, Fig 1). Similarly, other investigators\(^1,31 \) have demonstrated that various perturbations can affect \( O_2 \) transport during phase II \( V_{O_2} \); however, to the best of our knowledge, this is the first study to ascertain a relationship between SVI and phase II \( \tau V_{O_2} \) (Fig 3).

Contrary to previous observations,\(^5 \) \( O_2 \) deficit was not affected by AV dysynchrony, despite slower phase II \( V_{O_2} \) kinetics. The similar \( O_2 \) deficits can be attributed to (1) the higher \( V_{O_2} \) pretransition baseline during AV OFF and (2) the similar steady-state asymptotes across pacing modes (Table 2, Fig 1). Contrasting the present study, Rickli et al\(^5 \) had patients perform treadmill exercise at a constant WR of 35 W with exercise onset starting from rest.\(^{19} \) Exercise onset from an elevated baseline has been shown to speed \( V_{O_2} \) kinetics\(^{32} \); however, other investigators\(^{23} \) have demonstrated a similar phase II \( \tau V_{O_2} \) response between rest and 0-W pretransition cycling to steady-state exercise in healthy subjects. In the present study, it would appear that the elevated pretransition \( V_{O_2} \) observed during AV OFF mitigated the effects of a slowed kinetic response, thus resulting in comparable \( O_2 \) deficits across pacing modes. This observation may be important for activities of daily living or for those patients participating in cardiac rehabilitation exercise programs, as even a brief “warm-up” appears to reduce \( O_2 \) deficit in the presence of AV dysynchrony.

The \( \tau \) HR responses were similar across pacing modes; however, the amplitude response was greater during AV OFF (Table 2, Fig 1). It has been hypothesized that AV dysynchrony may stimulate sympathetic activity via baroreflexes as a result of lower SV and arterial pressure responses.\(^{31} \) Accord-
ingly, the greater amplitude of the HR response that we observed may be attributed to the attenuated SVI as a physiologic attempt was made to maintain systemic BP and appropriate Q to working tissue.\textsuperscript{34} The elevated HR response may be interpreted further as a marker of cardiovascular inefficiency and is supported by the higher HR/\textit{Vo}_2 ratio response during AV OFF, thus illustrating a greater dependence on HR rather than SV to increase Q.

Typical of ventilatory-perfusion mismatching and associated with AV dyssynchrony are symptoms such as lethargy, dyspnea, shortness of breath, syncope, and reduced functional capacity.\textsuperscript{23} Consistent with our findings, others have observed that AV dyssynchrony also results in a compensatory increase in HR\textsuperscript{34} and contributes to an altered \textit{Ve}/\textit{Vco}_2 ratio response.\textsuperscript{5,35} The altered \textit{Ve}/\textit{Vco}_2 ratio response observed in the present study may be due to a reduction in the pressure gradient across the pulmonary vascular bed, thus resulting in disproportionate alveolar ventilation and perfusion coupling. It is likely that this phenomenon would have been caused by an increase in pulmonary wedge pressure due to valvular regurgitation and elevated atrial pressure\textsuperscript{36} because of delayed AV valve closure.\textsuperscript{37} This theory is in agreement with those of others\textsuperscript{38} who have demonstrated strong correlations between pulmonary wedge pressure assessed by Swan-Ganz catheter and AV synchronization. The patients in the present study also demonstrated higher subjective RPE scores during AV OFF, which is consistent with the clinical presentation of AV dyssynchrony and is similar to previous observations.\textsuperscript{39}

\textbf{Limitations}

There were some limitations to this study. The patients in our sample had varied cardiac histories, thus limiting our ability to generalize our observations. However, cardiac disease beyond the typical indications for pacemaker therapy is common, and thus we think that our study group is representative of those patients who are encountered in clinical settings. Another limitation was that pacemaker interrogation reports indicated that AV synchronized pacing and ventricular pacing were not maintained 100\% of the time in all of the patients throughout exercise testing. Expectedly during the analysis of the ECG HR data for kinetic modeling and upon closer inspection of pacemaker interrogation reports, it was noted that most of the loss of AV synchronized pacing was due to premature ventricular contractions. Accordingly, these erroneous data were eliminated so as to ensure that only paced cardiac cycles were included in the analyses.

\textbf{Conclusion}

This study demonstrated that AV dyssynchrony affects phase I and phase II \textit{Vo}_2 kinetics. In particular, the phase I and phase II gain and amplitude response are lower during AV dyssynchrony, suggesting a blunted \textit{O}_2 transport response resulting in less \textit{O}_2 availability during increases in metabolic demand. This study further established that phase II $\tau$ \textit{Vo}_2 is slowed during AV dyssynchrony and that this may be related to SVI at exercise onset, thus implicating the SV response as a potential limiting factor for \textit{O}_2 transport during sub-VT exercise. Ventilatory-perfusion mismatching typical of AV dyssynchrony was also evident in our study group as well as higher subjective perceived exertion. The data from the present study underscore the seemingly important contribution of SV to metabolic and hemodynamic kinetic responses during exercise comparable to activities of daily living.

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