V\text{O}_2 kinetics reveal a central limitation at the onset of subthreshold exercise in heart transplant recipients

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Because the cardiocirculatory response of heart transplant recipients (HTR) to exercise is delayed, we hypothesized that their O2 uptake (V\text{O}_2) kinetics at the onset of subthreshold exercise are slowed because of an impaired early "cardiodynamic" phase 1, rather than an abnormal subsequent "metabolic" phase 2. Thus, we compared the V\text{O}_2 kinetics in 10 HTR submitted to six identical 10-min square-wave exercises set at 75% (36 ± 5 W) of the load at their ventilatory threshold (VT) to those of 10 controls (C) similarly exercising at the same absolute (40 W; C40W group) and relative load (67 ± 14 W; C67W group). Time-averaged heart rate, breath-by-breath V\text{O}_2, and O2 pulse (O2p) data yielded monoexponential time constants of the V\text{O}_2 (s) and O2p increase. Separating phase 1 and 2 data permitted assessment of the phase 1 duration and phase 2 V\text{O}_2 time constant (\tau_{\text{ph2V}}). The V\text{O}_2 time constant was higher in HTR (38.4 ± 7.5) than in C40W (22.9 ± 9.6; P ≤ 0.0002) or C67W (30.8 ± 8.2; P ≤ 0.05), as was the O2p time constant, resulting from a lower phase 1 V\text{O}_2 increase (287 ± 59 vs. 349 ± 66 ml/min; P ≤ 0.05), O2p increase (2.8 ± 0.6 vs. 3.6 ± 1.0 ml/beat; P ≤ 0.0001), and a longer phase 1 duration (36.7 ± 12.3 vs. 26.8 ± 6.0 s; P ≤ 0.05), whereas the \tau_{\text{ph2V}} was similar in HTR and C (31.4 ± 9.6 vs. 29.9 ± 5.6 s; P = 0.85). Thus the HTR have slower subthreshold V\text{O}_2 kinetics due to an abnormal phase 1, suggesting that the heart is unable to increase its output abruptly when exercise begins. We expected a faster \tau_{\text{ph2V}} in HTR because of their prolonged phase 1 duration. Because this was not the case, their muscular metabolism may also be impaired at the onset of subthreshold exercise.

Heart transplantation; pulmonary gas exchange; oxygen consumption; heart rate

As heart transplantation has evolved to an established procedure for the management of end-stage heart failure with extended survival rates, physicians have become more concerned about the patients' quality of life and, therefore, exercise capacity. The latter remains impaired after heart transplantation to ~60% of that of age-matched sedentary controls. The mechanisms of this exercise limitation are only partially elucidated, with some central components due to the transplanted heart's denervation and diastolic impairment (5, 18) and with some peripheral alterations thought to be due to deconditioning, the effects of immunosuppressive therapy (8, 19, 23), and heart failure-induced dysfunctions that would have persisted after transplantation (33).

Among the different mechanisms that may be involved, the role of delayed O2 uptake (V\text{O}_2) transients has been suggested (8, 9, 15, 26, 27). The V\text{O}_2 kinetics at the onset of work depend on numerous factors: phase 1 during the first 15–30 s of work is assumed to result mainly from an abrupt increase in pulmonary blood flow, whereas the following phase 2 depends on the increase in muscular oxidative metabolism (1) and, therefore, is influenced by the type of exercise, age, and fitness (11, 39). The gas exchange kinetics are also influenced by the energetic requirements of work: below the anaerobic threshold (AT) the V\text{O}_2 kinetics reflect the onset of intracellular metabolism and the mechanisms of O2 transfer but remain only slightly affected by the exercise intensity (32, 36). Above the AT, these kinetics slow down with the work level (32), and their behavior is complicated by the superimposition of a slow component (12, 36, 39), which increases V\text{O}_2 above the O2 requirements of subthreshold work, probably because of the recruitment of type II glycolytic fibers (12). Accordingly, the V\text{O}_2 kinetics follow a first-order transfer function only for exercises below the AT (12, 36, 39). Therefore, complexities associated with the V\text{O}_2 slow-component behavior may confound accurate calculation and interpretation of the O2 deficit, as well as the utilization of simple mathematical models to characterize the V\text{O}_2 kinetics (12, 36, 39). Yet most previous studies assessing V\text{O}_2 kinetics in heart-transplanted patients [heart transplant recipients (HTR)] were performed at or above the AT (8, 9, 26).

Patterson et al. (27) reported V\text{O}_2 kinetics below the AT in a limited number of HTR. By the observation of faster V\text{O}_2 kinetics during a second square-wave forcing, when the patients' heart rate (HR) was higher, they suggested that the V\text{O}_2 transients depend on O2 delivery kinetics in HTR. Nevertheless this study concerned patients early (2.3 ± 0.2 mo) after surgery, at a time when the chronotropic response and exercise capacity...
of the HTR are still expected to improve greatly (24). The conclusions of Paterson et al. (27) have been recently questioned by Grassi et al. (15), who studied a larger number of patients at different delays after transplantation and concluded that the slower $V\dot{O}_2$ kinetics of HTR depend on their impaired muscular oxidative capacity and not on a delayed increase in blood flow. Therefore, the issue of the control mechanisms of $V\dot{O}_2$ kinetics in HTR is not yet settled. To our knowledge, the respective contributions of phases 1 and 2 to the rest-to-work $V\dot{O}_2$ transition have never been assessed in HTR.

Therefore, the aim of the present study was to compare the $V\dot{O}_2$ kinetics at the onset of subthreshold exercise in long-term stabilized HTR to that of matched sedentary normal controls (C), to examine the respective roles of phases 1 and 2 in these kinetics, and to determine whether the delayed $V\dot{O}_2$ kinetics depend on graft and/or muscular dysfunctions in HTR. We hypothesized that, if delayed $V\dot{O}_2$ kinetics persist for subthreshold exercise late after transplantation, they may also be due to an abnormal “cardiodynamic” phase 1 response and not only to a sluggish “metabolic” phase 2 response. Moreover, we attempted to correlate the phase 1 $V\dot{O}_2$ parameters with cardiac variables (i.e., indexes of diastolic function and chronotropic response), which, if abnormally delayed, may prevent the cardiac output from abruptly increasing at the onset of exercise in HTR.

METHODS

Subjects. Ten male HTR (age 43.3 ± 7.6 yr, weight 77.9 ± 11.4 kg), considered as rehabilitated but not enrolled in a formal retraining program or sporting activities, agreed to participate in the study. It was >6 mo after surgery for all of them (delay since surgery: 32.2 ± 27.1 mo, range: 6.1–87.5 mo). Heart transplantation was performed for ischemic heart disease in three, dilated hypokinetic cardiomyopathy in five, and valvular heart disease in two subjects. They were all under triple-drug immunosuppressive therapy with the cyclosporine dose adapted to ensure whole blood through levels of 150–200 ng/ml. None suffered peripheral vascular disease, and no negative chronotropic drugs were administered. All patients were free of significant graft rejection or accelerated atherosclerosis as disclosed by a recent endomyocardial biopsy and their yearly coronary angiograms. All patients gave informed consent to the study, which had been approved by the local institutional ethics committee. Ten healthy sedentary male subjects (age 44.0 ± 5.2 yr, weight 74.6 ± 11.3 kg) volunteered to serve as C. This C group was similar to the group of patients in terms of age, weight, and fitness level. They all followed the same experimental protocol as the patients. None was taking any medication, and, although they were all professionally and recreationally active, none participated in any regular sporting activity.

Exercise tests. To assess the peak exercise capacity of the patients and C and the position of their ventilatory threshold (VT) taken as an approach of their aerobic-anaerobic transition, both groups were submitted to an incremental, symptom-limited, maximal exercise test while measurements of the gas exchanges were taken. During this test, the work rate was increased by 20-W, 2-min steps up to the point of exhaustion. Thereafter, the $V\dot{O}_2$ kinetics were assessed in each subject by means of six consecutive, identical constant-rate exercise tests. To assess the $V\dot{O}_2$ transients at a level of exercise at which they follow first-order kinetics, the work rate of the constant-rate exercises was set at 75% of the work rate of each patient's individual VT. In the C, two series of six consecutive constant-rate exercise tests were performed: the first series was realized at 75% of the work rate of each subject's individual VT, as in the patients, and the second series was realized at a work rate (2.45 W) that was the closest possible to the mean of the absolute work rates performed by the HTR. Thus we were able to compare HTR and C at same absolute and relative levels of exercise. In HTR and C, the 10-min constant-rate exercise began abruptly after 4 min of rest sitting on the cycle-ergometer, after a brief vocal signal given without warning by the operator. Each series of six subsequent constant-rate exercises was performed on 3 test days, each separated by a maximum of 2 days; the two tests performed the same day were done at least 1 h apart to ensure complete recovery. Before the beginning of exercise, the cycle ergometer (CardiO2 cycle, Medical Graphics, St. Paul, MN) was programmed to electrically drive the flywheel at 60 rotations/min, so as to obviate the need to overcome the flywheel inertia.

Measurements. The minute ventilation (Ve) and gas exchange parameters were measured on a breath-by-breath basis by means of an open-circuit metabolic cart with rapid $O_2$ and $CO_2$ analyzers (CardiO2 apparatus, Medical Graphics) during both the incremental and constant-rate tests. Before each individual exercise test, the pneumotachograph was calibrated with several Stokes given by a 3-liter calibration syringe (Hans Rudolph), and the gas analyzers were calibrated by means of reference gases of known $O_2$ and $CO_2$ concentrations. During the incremental test, the breath-by-breath data were smoothed by a six-point moving averaging algorithm. The breath-by-breath values, acquired during the six successive, identical constant-rate exercises performed by each subject, were not smoothed but were time aligned to the beginning of exercise, interpolated, and time averaged according to the technique described by Whipp et al. (37).

By multiple exercise repetitions, with subsequent time alignment and averaging, the noise was divided by the square root of the number of repetitions (22, 37). Accordingly, as the noise was reduced by a factor of 2.45, the signals were expected to separate adequately the phase 1 and phase 2 data (37). Because our metabolic cart's software calculates the $V\dot{O}_2$ and the $CO_2$ production ($V\dot{CO}_2$) by standard formulas based on measurements of the expiratory gas volume only (3), and without possibilities to measure expired nitrogen, we were not able to correct for the breath-by-breath changes in pulmonary gas stores because of changes in the functional residual capacity. Therefore, we assessed the breath-by-breath gas exchanges at the mouth and not true alveolar exchanges (2). The HR was continuously recorded by a cardiometer included in the metabolic cart.

As part of the patients' routine follow-up, echocardiographic and pulsed Doppler examinations were performed at rest on a monthly basis to record parameters of systolic left ventricular function (ejection fraction) and of diastolic left ventricular function [isovolumetric relaxation time (IVRT), transmval pressure decay half time] as potential indexes of graft rejection (34); these two latter echographic indexes can also be taken to represent, respectively, the amount of the patients' left ventricular relaxation and diastolic compliance impairments, which have been shown to exist in HTR (18, 28). Considering that the main factors of the phase 1 response are hemodynamic, we attempted to correlate the patients' phase 1 amplitude and duration with the previously defined echographic indexes, with the half time of the chronotropic...
Measurements during the incremental exercise. The rest and peak exercise \( \dot{V}O_2 \), \( \dot{V}CO_2 \), and \( \dot{V}E \) were measured by standard, open-circuit ergometric techniques (3). The rest values were 1-min averages of the breath-by-breath values, after stabilization of the \( \dot{V}O_2 \), \( \dot{V}CO_2 \), \( \dot{V}E \), and respiratory exchange ratio (RER = \( \dot{V}CO_2/\dot{V}O_2 \)). The peak values were the averages over the last 30 s of the incremental exercise, with both patients and C being encouraged to push the exercise to the point of exhaustion. The VT was assumed to occur when \( \dot{V}CO_2 \) related to \( \dot{V}O_2 \) changed slope (V-slope method).

Measurements during the constant-rate exercises. \( \dot{V}O_2 \), \( \dot{O}_2 \) pulse (\( \dot{O}_2p = \dot{V}O_2/HR \)), \( \dot{V}CO_2 \), \( \dot{V}E \), and HR were continuously measured during the 4 min of rest, the 10 min of exercise, and the first 5 min of recovery, but only the \( \dot{V}O_2 \), \( \dot{O}_2p \), and HR were analyzed. As representing the rest values, we averaged the measured values over 1 min, with the subjects quietly sitting on the ergometer. All the subjects reached a true steady state during the constant-rate exercises (as the data of the last 3 min of exercise were no longer correlated with time). For the steady-state values, we also averaged the measured data over the last minute of exercise.

The kinetics of the parameters during the overall rest-to-exercise transition were assessed by fitting all of the 10-min time-averaged, breath-by-breath data to a monoeponential model forced to start at the beginning of exercise without a time delay, according to the method described as “model 1” in the work by Whipp et al. (37). Applying the formula \( \Delta Y(t) = \Delta Y(\text{steady state})[1 - e^{-t/\tau}] \), where \( \Delta Y \) may be \( \dot{V}O_2 \), \( \dot{V}CO_2 \), or \( \dot{V}E \); \( \Delta Y(t) \) is the increase in \( Y \) above the prior steady-state value at time \( t \); and \( \Delta Y(\text{steady state}) \) is the steady-state increase in \( Y \), yielded the time constant \( \tau \) for the overall \( \dot{V}O_2 \) and \( \dot{O}_2p \) transition, which characterizes the rest-to-exercise transition regardless of its phases.

Because the slowed HR response to the exercise of HTR has been reported to increase linearly for some authors (8, 9) and exponentially by others (29), we characterized our patients’ HR response by the half time of the HR increase, defined as the time taken from the beginning of exercise for the HR to reach one-half of its increase observed after 10 min of exercise. Because the \( \dot{V}O_2 \) increase during the transition is assumed to follow first-order kinetics, the \( \dot{O}_2 \) deficit was calculated as equal to \( \tau \) for the overall \( \dot{V}O_2 \) transition, as previously defined, multiplied by the increment in \( \dot{V}O_2 \) during the square-wave exercise (\( \dot{V}O_2 \) at steady state – \( \dot{V}O_2 \) at rest) (1, 11, 36).

The end of phase 1 was assumed to occur at the time when a decrease in end-tidal \( P_O2 \) with a simultaneous increase in end-tidal \( P_{CO2} \) appeared, as well as when a sharp decrease in the RER occurred (32, 36, 37). As a rule, this method of separating phase 1 and phase 2 corresponds also to the end of the small initial plateau of the \( \dot{V}O_2 \) (36, 37). To illustrate the components of phase 1 and the phase 1-phase 2 discrimination method, an example of the initial behavior of the RER, the end-tidal \( P_O2 \), \( P_{CO2} \), and its correspondence to the initial \( \dot{V}O_2 \) at the onset of exercise of two representative patients, one with a short and one with a long phase 1, is presented in Fig. 1. The duration of phase 1 was determined as the time between the start of exercise and the phase 1-phase 2 transition, assessed with the preceding criteria by agreement between two observers (Q. Zhao, E. Epailly) unaware of the other’s results. The phase 1 amplitude for \( \dot{V}O_2 \), \( \dot{O}_2p \), and HR was calculated as the average of all the values throughout phase 1 as in the work by Sietsema et al. (32). The exercise increase in \( \dot{V}O_2 \), \( \dot{O}_2p \), and HR was calculated for phase 1 or the steady state as the corresponding \( \dot{V}O_2 \), \( \dot{O}_2p \), or HR values minus the corresponding average rest values. The phase 2 \( \dot{V}O_2 \) was calculated after fitting the time-averaged breath-by-breath \( \dot{V}O_2 \) data to the same monoeponential formula as described previously, but with the fitting time starting at the phase 1-phase 2 transition point. This corresponds to “model 3” in the work by Whipp et al. (37).

Statistical analysis. Values are expressed as means ± SD. The monoeponential fitting of the \( \dot{V}O_2 \), HR, and \( \dot{O}_2p \) data was performed by multiple iterations and the least squares technique by using commercially available software (Prism Graphpad software, San Diego, CA). Owing to the small populations studied, nonparametric tests were used to perform comparisons. The incremental exercise and kinetic measurements performed in HTR were compared with those of the C by means of the Mann-Whitney U test for unpaired values; the steady-state exercise values were compared with the rest values.
values within each group by means of the Mann-Whitney U test for paired values; and the rest and steady-state exercise values were compared between the HTR and the C groups, working at similar absolute and relative loads to the HTR, by means of the Kruskal-Wallis test followed by Dunn's procedure. A P ≤ 0.05 was taken to represent a significant difference.

RESULTS

Incremental exercise. During the 20-W, 2-min incremental maximal test, the HTR reached 126 ± 21 W, whereas the C reached 206 ± 54 W (P ≤ 0.0004). The rest, the peak values, and values recorded at the VT are presented in Table 1. The resting values are similar in HTR and C, except that the HR is higher in HTR, as expected. At the VT, the work rate and, therefore, the gas exchange values are lower in HTR, but the RER is similar [P = 0.59, not significant (NS)], the Ve is only insignificantly lower (P = 0.12, NS), and the HR is insignificantly higher (P = 0.27, NS). The VT is reached for a similar percentage of the peak VO₂ in both groups: 55 ± 11% in HTR and 51 ± 6% in C (P = 0.85, NS). As expected, the peak VO₂ of our HTR is ~60% that of our C (P = 0.0004). The peak exercise RER appears similar in both groups and appears indicative of maximal exercise (P = 0.94, NS), whereas the peak Ve and HR are only insignificantly lower in HTR than in C (P = 0.35 and 0.17, respectively).

Constant-rate exercise. Because the HTR exercised at 75% of the work rate of their individual VT, four patients exercised at 30 W and six at 40 W, corresponding to a mean work rate of 36 ± 5 W. Therefore, all the C exercised at 40 W to serve as controls at a similar absolute work rate. We label this latter group of measurements as C40W. Similarly to the HTR, all C also performed a set of constant-rate exercises at 75% of the work rate of their individual VT, corresponding to an average of 67 ± 14 W. We label this group of measurements as C67W. The resting and steady-state exercise values are presented in Table 2. At rest, all the gas exchange values are similar, and the RER values remain within the range of usual resting values in all three groups of measurements. The resting HR is higher in HTR, but with only a slightly and insignificantly lower O₂p (Table 2). During steady-state exercise, all the ventilation and gas exchange parameters are similar in HTR and C at the same absolute work rate (HTR vs. C40W; Table 2). At these loads, the patients’ HR tends to be only insignificantly higher and the O₂p slightly lower than that in C. On the other hand, the C67W group of measurements is higher for the ventilation, gas exchanges, and O₂p, because of the higher work rate performed. Because during steady-state exercise the RER values remain <1 for the three groups of measurements, we assume that the subjects really exercised below their VT.

VO₂ and HR kinetics. The τ values of the rest-to-constant-rate-exercise transition are presented in Table 3. At a similar absolute work rate (HTR and C40W),

Table 1. Results of incremental maximal exercise in heart transplant recipients and controls with values recorded at rest, ventilatory threshold, and maximal effort

<table>
<thead>
<tr>
<th></th>
<th>HTR (n = 12)</th>
<th>C (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Work rate, W</td>
<td>126 ± 21</td>
<td>206 ± 54</td>
</tr>
<tr>
<td>VO₂, ml/min STPD</td>
<td>315 ± 55</td>
<td>299 ± 67</td>
</tr>
<tr>
<td>VO₂/kg, ml·min⁻¹·kg⁻¹ STPD</td>
<td>4.1 ± 0.7</td>
<td>4.3 ± 0.8</td>
</tr>
<tr>
<td>VO₂, ml/min STPD</td>
<td>272 ± 58</td>
<td>251 ± 46</td>
</tr>
<tr>
<td>RER</td>
<td>0.86 ± 0.09</td>
<td>0.85 ± 0.08</td>
</tr>
<tr>
<td>Ve, l/min BTPS</td>
<td>11.6 ± 2.6</td>
<td>10.2 ± 2.9</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>105.4 ± 13.5</td>
<td>73.0 ± 8.6</td>
</tr>
</tbody>
</table>

Table 2. Rest and steady-state values during the constant-rate exercises in heart transplant recipients and controls

<table>
<thead>
<tr>
<th>Group</th>
<th>VO₂, ml/min STPD</th>
<th>VO₂, ml/min STPD</th>
<th>RER</th>
<th>Ve, l/min BTPS</th>
<th>HR, beats/min</th>
<th>O₂p, ml/beat STPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTR</td>
<td>301 ± 56</td>
<td>243 ± 47</td>
<td>0.81 ± 0.07</td>
<td>10.2 ± 1.7</td>
<td>98.9 ± 14.7</td>
<td>3.1 ± 0.6</td>
</tr>
<tr>
<td>C40W</td>
<td>298 ± 45</td>
<td>260 ± 43</td>
<td>0.87 ± 0.04</td>
<td>10.4 ± 1.8</td>
<td>80.7 ± 9.1</td>
<td>3.7 ± 0.4</td>
</tr>
<tr>
<td>C67W</td>
<td>289 ± 45</td>
<td>237 ± 34</td>
<td>0.82 ± 0.03</td>
<td>9.8 ± 2.3</td>
<td>74.4 ± 14.2</td>
<td>3.9 ± 0.5</td>
</tr>
<tr>
<td>Steady state</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTR</td>
<td>893 ± 77*</td>
<td>797 ± 81*</td>
<td>0.89 ± 0.07</td>
<td>26.0 ± 2.7</td>
<td>111.3 ± 14.7</td>
<td>8.1 ± 1.0*</td>
</tr>
<tr>
<td>C40W</td>
<td>914 ± 70*</td>
<td>857 ± 78*</td>
<td>0.94 ± 0.03</td>
<td>24.9 ± 3.0</td>
<td>105.3 ± 18.2</td>
<td>8.9 ± 1.6*</td>
</tr>
<tr>
<td>C67W</td>
<td>1,191 ± 252*</td>
<td>1,105 ± 258*</td>
<td>0.92 ± 0.04</td>
<td>31.5 ± 9.6</td>
<td>103.7 ± 11.9</td>
<td>11.5 ± 2.1*</td>
</tr>
</tbody>
</table>

Values are means ± SD. During the constant-rate exercises, the HTR exercised at 36 ± 5 W, the controls of the C40W group of measurements all exercised at 40 W, and the controls of the C67W group of measurements exercised at 67 ± 14 W. HTR vs. C at rest or steady-state exercise: *P < 0.05, †P < 0.01, ‡P < 0.001. Rest vs. exercise values within each group: *P < 0.05, †P < 0.01, ‡P < 0.001.
when the overall data of the 10-min square-wave forcing are considered regardless of its phases [as in model 1 in the work by Whipp et al. (37)], we observed a higher $\tau$ for the monoexponentially fitted $\dot{V}_O_2$ data in HTR than in C. Accordingly, the calculated $O_2$ deficit is higher in HTR than in C (Table 3) at the same absolute work rate. The $\tau$ of the monoexponentially fitted $O_2p$ data is also greater in HTR than in C at the same work rate (Table 3). The half time of the HR increase is much greater in HTR than in C because of the at least partially denervated state of the transplanted heart. Interestingly, the dispersion of these half times is large in the HTR (range: 16–266 s), with some patients having a HR response almost as fast as that of the C. The patients’ individual HR responses and the corresponding $\dot{V}_O_2$ are depicted in Fig. 2 and are sorted by increasing phase 1 durations.

At a similar relative work rate (HTR vs. C67W), the HTR still exhibited a slightly but significantly higher $\tau$ than the C ($38.4 \pm 7.5$ vs. $30.8 \pm 6.8$ s; $P < 0.05$) for the monoexponential fits of the entire 10-min $\dot{V}_O_2$ data. At these work rates, the $O_2$ deficit is only insignificantly higher in C, despite their higher work rate ($378 \pm 87$ vs. $232 \pm 90$ ml STPD).

### Table 3. Kinetic parameters in heart transplant recipients and C40W at the same absolute level of exercise

<table>
<thead>
<tr>
<th>Parameters</th>
<th>HTR</th>
<th>C40W</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\tau_{\dot{V}_O_2}$, s</td>
<td>$38.4 \pm 7.5$</td>
<td>$22.9 \pm 9.6$</td>
<td>0.002</td>
</tr>
<tr>
<td>$O_2$ deficit, ml STPD</td>
<td>$379 \pm 87$</td>
<td>$232 \pm 90$</td>
<td>0.004</td>
</tr>
<tr>
<td>$\tau_{O_2p}$, s</td>
<td>$32.2 \pm 8.3$</td>
<td>$22.4 \pm 13.6$</td>
<td>0.02</td>
</tr>
<tr>
<td>$t_{1/2HR}$, s</td>
<td>$85 \pm 76$</td>
<td>$14 \pm 8$</td>
<td>0.0001</td>
</tr>
<tr>
<td>Phase 1 duration, s</td>
<td>$36.7 \pm 12.3$</td>
<td>$26.8 \pm 6.0$</td>
<td>0.05</td>
</tr>
<tr>
<td>Phase 1 amplitude of $\dot{V}_O_2$ increment, ml/min STPD</td>
<td>$287 \pm 59$</td>
<td>$349 \pm 66$</td>
<td>0.05</td>
</tr>
<tr>
<td>Phase 1 amplitude of $O_2$ pulse increment, ml/beats STPD</td>
<td>$2.8 \pm 0.6$</td>
<td>$3.6 \pm 1.0$</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Values are means $\pm$ SD; $P$ values are HTR vs. C. $\tau_{\dot{V}_O_2}$, time constant of the monoexponentially fitted overall $\dot{V}_O_2$ data; $\tau_{O_2p}$, time constant of the monoexponentially fitted overall $O_2$ pulse data; $t_{1/2HR}$, half time of the heart rate increase during the 10-min exercises; $\tau_{p2\dot{V}_O_2}$, time constant of the monoexponentially fitted phase 2 $\dot{V}_O_2$ data; $\tau_{p2O_2p}$, time constant of the monoexponentially fitted phase 2 $O_2$ pulse data; NS, not significant.

![Fig. 2. Individual recordings of heart rate (ΔHR) and $\dot{V}_O_2$ variations (Δ$\dot{V}_O_2$) during exercise. Patients are sorted by increasing phase 1 durations to exemplify relationships between chronotropic response and phase 1 characteristics.](http://jap.physiology.org/)
474 ± 230 ml in HTR and C67W, respectively; P = 0.47, NS).

The comparison of the HTR and C exercise transitions at the same absolute work rate shows that the differences concern essentially the phase 1 rather than the phase 2 response (Fig. 3, Table 3). The phase 1 duration is significantly longer and the VO₂ and O₂p increases during phase 1 are significantly smaller in HTR (Table 3). On the other hand, as shown in Table 3 and Fig. 4, the \( t \) values of monoexponential fits of the phase 2 VO₂ \( (t_{ph2VO₂}) \) or O₂p data that start at the end of phase 1 [as in model 3 in the work by Whipp et al. (37)] are similar in HTR and C at the same absolute work rate.

Whereas no significant correlations were found with the phase 1 amplitude values, we found an inverse correlation between the phase 1 duration and the peak VO₂ \( (r = -0.67, P = 0.04; \text{Fig. 5}) \). We also observed a slight but significant direct correlation between the phase 1 duration and the IVRT \( (r = 0.63, P = 0.05; \text{Fig. 5}) \) but not with the transmitral pressure decay half time \( (r = 0.32, P = 0.36) \) or with the ejection fraction \( (r = -0.07, P = 0.84) \). The phase 1 duration is correlated to the HR half time \( (r = 0.81, P = 0.005; \text{Fig. 6}) \) and is inversely correlated to the HR variation during phase 1 \( (r = -0.72, P = 0.02; \text{Fig. 6}) \). The delay since the operation only tends to be inversely related to the phase 1 duration \( (r = -0.58, P = 0.08) \).

**DISCUSSION**

In accordance with our working hypothesis, we found delayed VO₂ kinetics in HTR even long after the operation, leading to an increased O₂ deficit at the onset of moderate subthreshold exercise. When partitioned in the initial cardiodynamic phase 1 and in the subse-
Fig. 5. Correlation of phase 1 duration with peak VO₂ (A) and with echo-Doppler isovolumic relaxation time (IVRT; B) in the 10 heart transplant patients. Peak VO₂ is inversely correlated with the phase 1 duration, suggesting that a slow phase 1 may have a negative impact on exercise capacity. Phase 1 duration is directly correlated with echo-Doppler IVRT estimations, suggesting that a slowed ventricular relaxation may lengthen phase 1.

Fig. 6. Correlation of phase 1 duration with parameters of chronotropic response to rectangular exercise in the 10 heart transplant patients. A: phase 1 duration is positively correlated with the half time of heart rate increase during constant-rate exercise, suggesting that a rapid heart rate response may shorten the phase 1 duration. B: phase 1 duration is negatively correlated with amplitude of heart rate response during phase 1, suggesting that appearance of a heart rate increase during early exercise may shorten phase 1 duration.

quent metabolic phase 2, it appears that most of the delayed VO₂ kinetics are due to a less pronounced and longer phase 1 rather than to a slowed phase 2. Because this phase 1 response depends essentially on the capacity of the cardiovascular system to abruptly increase the pulmonary blood flow and, therefore, cardiac output at the beginning of exercise, our findings represent an element of central exercise limitation that operates even at moderate subthreshold work rates. Moreover, we found that the phase 1 duration correlates with the IVRT, taken as an index of ventricular relaxation, and inversely with indexes of rapidity and importance of the chronotropic response at the onset of exercise. By slowing the cardiac output kinetics to various extents, the degrees of chronotropic incompetence and relaxation abnormalities may combine their deleterious effects on VO₂ kinetics, thus explaining in part the wide differences in the early gas exchange response to exercise from one patient to another.

Maximal and steady-state submaximal exercise. In our patients, we observed a peak exercise capacity (8, 18, 19, 24), a VO₂ at the VT, and a maximal HR (24) within the range of what has been previously shown in long-term HTR. Yet the HR dispersion at maximal exercise was higher in HTR than in C, suggesting that the chronotropic incompetence varies widely among patients. Because the peak RER is similar in both groups and clearly >1, we assume that we adequately assessed peak exercise capacity in our subjects. During the constant-rate exercises, the steady-state RERS remained <1 in all HTR and C, indicating that they exercised below their VT. There is no clear explanation for the slightly higher RER in the C40W group at rest than in the HTR and the C67W groups. This C40W group of measurements might have been done in a slightly more stressful environment owing to the higher HR observed. However, this should not affect our conclusions.

Overall VO₂ kinetics. When the rest-to-subthreshold-exercise increase in VO₂, O₂p, and HR are considered regardless of the transition phases, we found higher τ values in HTR than in C exercising at the same absolute (Table 3) and relative levels. Only a few studies have compared the VO₂ kinetics in HTR and C, either in terms of half times (8, 9, 15, 26) or τ values (27). Our C kinetics agree with the previously published values in normal subjects (32, 37). On the other hand, our HTR VO₂ τ is shorter than that previously reported. This may be explained as follows:

1) The VO₂ kinetics are affected by work rate. Below the VT, the VO₂ τ is almost independent of work rate (32), but above the VT it increases greatly as a function of work rate (32, 36). In previous studies on VO₂ kinetics in HTR, one was designed to assess the transition below the VT (27). Others were either slightly (9, 26) or far (8) above it.

2) Above the VT, the steady state no longer holds and the VO₂ increases further with a slow component (12, 36, 39). At these work-rate levels, because the VO₂ does not follow first-order kinetics, monoexponential fitting of the data is not accurate, and the half-time estimates increase with the duration of exercise. This is the case in the studies by Cerretelli et al. (8, 9), Meyer et al. (26), and probably of some patients in the study by Grassi et al. (15) when working at 50 W. In this latter study, the VO₂ kinetics were also slower in HTR at 25 W, a work rate below the VT in both HTR and C; nevertheless, at such low exercise levels, close to 80% of the VO₂ increase occurs during phase 1 (32), potentially obscur-
ing the phase 2 V\textsubscript{O}_2 kinetics in some subjects, especially in the normal C.

3) The large difference between the values of Paterson et al. (27) (77 ± 26 s) and ours (38.4 ± 7.5 s) might be explained by the fact that for their patients it was <3 mo (2.3 ± 0.2 mo) after surgery, whereas for our HTR it was >6 mo after transplantation. Increases in the exercise capacity within the first 6 mo have been consistently reported (5, 24) because of improvements in the cardiocirculatory response to exercise (5, 24) and the retraining effect of daily activities (19). These mechanisms might have speeded up V\textsubscript{O}2 kinetics within the first 6 mo after the operation by shortening the phase 1, as well as by accelerating the phase 2, response. For time periods later than 6 mo, Grassi et al. (15) showed that the lapse of time after surgery does not affect the V\textsubscript{O}2 kinetics any more. As previously suggested (15), because the τ of the V\textsubscript{O}2 increase is higher in our patients than in the C at similar absolute and relative work rates, the long-term HTR keep slightly but significantly delayed V\textsubscript{O}2 kinetics, despite an improvement with time in their exercise capacity, and, accordingly, accumulate a higher O\textsubscript{2} deficit at the onset of subthreshold exercise.

V\textsubscript{O}2 kinetics during phases 1 and 2. This study is the first to examine the respective contributions of phases 1 and 2 to the V\textsubscript{O}2 kinetics in HTR. Grassi et al. (14) already examined in HTR the phase 1 ventilatory response, but they did not report V\textsubscript{O}2 during this phase. As we separated the V\textsubscript{O}2 transition into its two phases, we observed that the delayed overall V\textsubscript{O}2 kinetics of HTR depend on an abnormal phase 1 response, in amplitude as well as in duration, whereas the phase 2 kinetics are similar in HTR and C. We found that the patients' phase 1 duration is negatively correlated with their peak V\textsubscript{O}2, whereas neither the phase 1 duration nor its amplitude is correlated with the peak V\textsubscript{O}2 in C. Because we were not able to correct for the acute changes in functional residual capacity, these changes may have affected the breath-by-breath V\textsubscript{O}2 pattern during phase 1 (2). Nevertheless, the artifacts due to lung gas stores changes should be of the same magnitude in patients and C, because both groups have been assessed with the use of the same technology and protocol. Should the differences in phase 1 gas exchanges that we observed be due only to lung gas stores changes, then a systematic difference between the HTR and C functional residual capacity changes would have occurred during phase 1. This is not likely the case because Grassi et al. (14) observed that the changes in inspiratory and expiratory air flows are the same during phase 1 in HTR as well as in matched C.

The importance of the V\textsubscript{O}2 response during phase 1 can be taken as a noninvasive marker of the abrupt circulatory adjustments at the beginning of exercise. Krogh and Lindhard (21) already hypothesized in their pioneering work that the increase in V\textsubscript{O}2 that follows the initiation of exercise must be due to an abrupt increase in cardiac output. Afterwards, several lines of evidence confirmed that the major determinant of the V\textsubscript{O}2 increase during phase 1 is the initial increase in pulmonary blood flow, either by indirect arguments (36) or by direct comparisons of the kinetics of V\textsubscript{O}2 and cardiac output increase (40). Moreover, phase 1 has been found to be blunted in diseases that prevent the pulmonary blood flow from increasing with exercise (30, 31). The duration of phase 1 represents also the circulatory delay taken by the desaturated muscular blood to reach the lung exchanger (1, 36). For instance, this duration has been found to be longer than normal in pulmonary vascular disease, in which the increase in pulmonary blood flow is abnormally low at the onset of exercise (30). Accordingly, our results suggest that the HTR are unable to increase their cardiac output abruptly at the onset of exercise. At present, one group only measured the cardiac output kinetics in HTR by using Kubicek's impedance method (9, 26). Although the validity of Kubicek's impedance method has been questioned (35), this group found neither blunted cardiac output kinetics in HTR nor a significant effect of these kinetics on the V\textsubscript{O}2 response (9, 26). The fact that the phase 1 duration is inversely correlated with the peak V\textsubscript{O}2 in HTR suggests that the abnormal phase 1 may contribute to limit their maximal exercise capacity. On the other hand, the phase 2 V\textsubscript{O}2 increase reflects, at the lung exchanger level, the increase in muscular V\textsubscript{O}2 (1). McCrery et al. (25) showed that the subthreshold phase 2 V\textsubscript{O}2 kinetics reflect the kinetics of muscular phosphocreatine decrease. Nevertheless, as shown by Barstow et al. (1), phases 1 and 2 are not independent processes: in the face of unchanged muscular V\textsubscript{O}2 kinetics, phase 2 should be speeded up when phase 1 is altered by delayed blood flow kinetics (1, 7). Thus our similar phase 2 τ values in HTR and C may in fact reflect slower than normal muscular V\textsubscript{O}2 kinetics in patients. This agrees with the impaired muscular oxidative capacity that we and others have reported after heart transplantation (18, 23).

The issue of whether muscular V\textsubscript{O}2 is limited at the beginning of exercise, either by O\textsubscript{2} delivery or by intramuscular mechanisms beyond the capillary level, is not yet completely clarified and might be affected by the subject's fitness or pathological situations. On the one hand, Grassi et al. (16) observed in well-trained cyclists that the initial increase in muscular blood flow is accompanied by a temporary decrease in muscular arteriovenous O\textsubscript{2} difference, showing that muscular V\textsubscript{O}2 temporarily lags behind local O\textsubscript{2} delivery. On the other hand, several authors reported delayed V\textsubscript{O}2 kinetics with interventions that blunt the cardiac output response to exercise (39).

By assessing the V\textsubscript{O}2 kinetics with increasing levels of carboxyhemoglobin in sedentary subjects, Koike et al. (20) showed that the O\textsubscript{2} delivery can limit the phase 2 V\textsubscript{O}2 kinetics at the diffusion level, even at the onset of subthreshold exercise. Cochran and Hughson (10) suggested that, if the muscular O\textsubscript{2} utilization determines the V\textsubscript{O}2 kinetics in the normal situation, then the balance between O\textsubscript{2} delivery and O\textsubscript{2} utilization is very delicate during the unsteady state after exercise onset. Thus even subtle changes in O\textsubscript{2} transport, diffusion gradients, or blood flow requirements in the nonwork-
ing tissues would cause the \( V\dot{O}_2 \) increase to follow \( O_2 \) delivery.

Such considerations, together with methodology differences, might explain the differences between our results and those of others, as well as the apparent contradictions between the data reported by Paterson et al. (27) and Grassi et al. (15). Our group has shown that HTR have a decreased muscular capillary density (23); thus their phase 2 \( V\dot{O}_2 \) kinetics might be more sensitive to \( O_2 \) transport, especially if the chronotropic response is blunted (24). This explains the observation of Paterson et al. of a slower than normal phase 2 \( V\dot{O}_2 \) response in patients early after surgery that speeds up to near normal values during a second square-wave exercise when the HR response is faster (27). The data of Paterson et al. suggest also that the phase 2 of exercise does not differ in HTR and C during the second square-wave exercise when \( O_2 \) delivery is no longer limited. This agrees with our similar phase 2 kinetics in HTR and C. The fact that the half times of the \( V\dot{O}_2 \) increase failed to shorten at the time of a second square-wave forcing, despite slightly faster cardiac output kinetics in the study by Grassi et al. (15), may be explained by the fact that several of their patients must have exercised close to their VT, as suggested by their lactate and RER data. A transient anaerobic lactic \( O_2 \) deficit may have occurred at the onset of the second square-wave forcing (11), thus masking the effects of the improved \( O_2 \) delivery during that second exercise. Therefore, we believe that the observations by Grassi et al. (15) still concur with those of Paterson et al. (27) and our conclusions.

Potential mechanisms of the delayed \( V\dot{O}_2 \) transition in HTR. Because the patients’ cardiodynamic phase 1 is abnormal, we attempted to correlate its duration and \( V\dot{O}_2 \) or \( O_2p \) amplitude with parameters of graft function to characterize some of its mechanisms. We found the phase 1 duration to be correlated with the IVRT, as a marker of the graft relaxation, and with the half time of the HR response, as an index of the chronotropic response kinetics.

Despite a normal systolic function, the transplanted heart is characterized by slowed relaxation (28) and decreased compliance (18), which both worsen during acute rejection (34). These diastolic abnormalities may affect the phase 1 kinetics by preventing the cardiac output from increasing abruptly at the beginning of exercise, as suggested by our correlation between the IVRT and the phase 1 duration. However, because this result offers indirect evidence at most, and the stroke volume has been observed to increase after exercise onset in HTR (9, 26), the impact of the impaired graft relaxation should be investigated further.

The correlations between the phase 1 duration and the parameters of chronotropic response that we found in our patients suggest more firmly the existence of a relationship between the phase 1 \( V\dot{O}_2 \) kinetics and the rapidity of HR increase after the onset of exercise in the HTR. Although the mean HR kinetics are consistent with previous reports (29), we found a wider range of HR half times (16–266 s). This opens the question of the occurrence of partial orthosympathetic reinnervation in some patients. Some HTR have a HR response almost as fast as normal, whereas others exhibit a widely delayed response (Fig. 2). Several lines of evidence suggest that orthosympathetic reinnervation (38) and a characteristic variability of the R-R interval (4) can occur with time in the transplanted cardiac graft but with no clear beneficial consequences for the peak exercise capacity (5, 24). The observation of a rapid HR response accompanied by a short phase 1 in certain of our patients could reflect partial reinnervation. Nevertheless, this important issue should be investigated further.

Potential clinical consequences of the delayed \( V\dot{O}_2 \) kinetics. Because the delay in the \( V\dot{O}_2 \) increase at the beginning of subthreshold exercise concerns essentially the early cardiodynamic phase 1, which depends on graft characteristics, we speculate that this delay might be only partially shortened by retraining but might be sensitive to chronotropic interventions. The patients might tolerate differently the onset of exercise, depending on their own \( V\dot{O}_2 \), \( \tau \), chronotropic response, and ventricular diastolic function. The impaired ventricular relaxation of the graft depends on numerous factors (28, 34), including some pericardial constraint due to surgery and the effects of hypertension, denervation, and interstitial fibrosis presumably due to rejection and cyclosporine therapy. At present, the effects that these factors may have on retraining are unknown, but they are unlikely to occur. The chronotropic response to exercise of the graft depends on atrial stretch, the rise of circulating catecholamines (29), atrial \( \beta \)-receptor sensitivity (13), and reinnervation (38). Although training is unlikely to affect reinnervation, the catecholamine response and receptor sensitivity may be increased by regular exercise, thus improving the chronotropic response (19). Moreover, those patients who have a slow \( V\dot{O}_2 \) response would benefit from gradual increases in exercise levels and from techniques aimed at accelerating the HR before the exercise, if they are willing to engage in sports.

Conclusion. Our study shows that the \( V\dot{O}_2 \) transition remains delayed at the onset of moderate subthreshold exercise in long-term stabilized HTR, leading to an increased \( O_2 \) deficit, but to a smaller extent than early after surgery. It also shows that this slowed \( V\dot{O}_2 \) transition is due to an abnormally low and delayed early cardiodynamic phase 1. This indicates that the graft is less able than normal to abruptly increase its output at the onset of exercise, even if moderate. Our data also suggest that the abnormal phase 1 might result from an impaired relaxation of the graft and from a delayed chronotropic response to exercise. Therefore, the abnormal response of the graft during exercise transitions introduces a central factor of limitation that operates even at moderate subthreshold exercise levels. Nevertheless, as the patients’ phase 2 \( V\dot{O}_2 \) kinetics should have appeared faster with respect to their lower phase 1 but were found to be similar to that of normal
subjects, an impairment of the muscular metabolism may also operate in HTR at the onset of exercise. As a consequence of the phase 1 limitation, which appears to be inherent in the transplanted graft function, exercise training may only partially improve the transitory gas exchange kinetics at the onset of moderate exercise but should have a greater impact on exercise-to-exercise than on rest-to-exercise transients. Therefore, a progressive onset of work should be better tolerated by the HTR than an abrupt onset.

This study was supported in part by the Institut National de la Santé et de la Recherche Médicale network “Activité physique muscule et handicap.”

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Received 22 September 1997; accepted in final form 22 November 1999.

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