Short-term variability of pulse pressure and systolic and diastolic time in heart transplant recipients

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Received 12 May 1999; accepted in final form 3 January 2000

Chemla, Denis, Eduardo Aptecar, Jean-Louis Hébert, Catherine Coirault, Daniel Loisance, Yves Lecarpentier, and Alain Nitenberg. Short-term variability of pulse pressure and systolic and diastolic time in heart transplant recipients. Am J Physiol Heart Circ Physiol 279: H122–H129, 2000.—In heart transplant recipients (HTR), short-term systolic blood pressure variability is preserved, whereas heart rate variability is almost abolished. Heart period is the sum of left ventricular ejection time (LVET) and diastolic time (DT). In the present time-domain prospective study, we tested the hypothesis that short-term fluctuations in aortic pulse pressure (PP) in HTR were related to fluctuations in LVET. Seventeen male HTR (age 48 ± 6 yr) were studied 16 ± 11 mo after transplantation. Aortic root pressure was obtained over a 15-s period using a micromanometer both at rest (n = 17) and following the cold pressor test (CPT, n = 14). There was a strong positive linear relationship between beat-to-beat LVET and beat-to-beat PP in all patients at rest and in 13 of 14 patients following CPT (each P < 0.01). The slope of this relationship showed little scatter both at rest (0.34 ± 0.07 mmHg/ms) and following CPT (0.35 ± 0.09 mmHg/ms, P = not significant). Given the essentially fixed heart period, DT varied inversely with LVET. As a result, in 13 of 17 HTR at rest and in 12 of 14 HTR following CPT, there was a negative linear relationship between beat-to-beat PP and DT. In conclusion, our short-term time-domain study demonstrated a strong positive linear relationship between LVET and blood pressure variability in male HTR. We also identified a subgroup of HTR in whom there was a mismatch between PP and DT.

In human heart transplant recipients (HTR), the vagally mediated component of respiratory sinus arrhythmia is absent, resulting in a markedly reduced heart rate variability (3, 33, 35). Conversely, the respiratory variations of systolic blood pressure are preserved, and it is thus widely accepted that short-term heart period fluctuations are not mandatory for the maintenance of normal short-term fluctuations of blood pressure (20, 25, 43). Because systolic aortic pressure (SAoP) reflects the combined influence of diastolic aortic pressure (DAoP) and aortic pulse pressure (PP), PP is expected to give a more accurate reflection of pulsatile pressure changes than does SAoP.

PP is mainly determined by stroke volume and total arterial compliance (10, 39). The most widely accepted hypothesis is that short-term fluctuations in PP in HTR are mainly of mechanical origin and reflect respiratory-related changes in stroke volume. Such fluctuations affect PP (13, 20, 34, 41) without the confounding effects of respiratory sinus arrhythmia and baroreflex feedback on heart period and aortic pressures (12, 22, 40–43).

At first glance, blood pressure variability and variability in time intervals may appear to be completely unrelated in HTR. However, one must keep in mind that heart period is the sum of left ventricular ejection time (LVET) and diastolic time (DT) (6, 46). A precise evaluation of beat-to-beat changes in LVET and DT in HTR remains to be documented, as well as the potential link between time-interval variability and blood pressure variability. Given that LVET is strongly related to heart period (5, 6, 15, 23, 46), one might expect the variability of LVET to be markedly decreased in HTR and to be dissociated from the preserved blood pressure variability. On the other hand, heart period is only one of many factors that affect LVET, including loading conditions and inotropic state, and therefore LVET may not necessarily follow heart period in HTR. Given that increased preload tends to prolong ejection duration (5, 8, 23, 38), one might expect blood pressure variability in HTR to be related to beat-to-beat LVET via a common hemodynamic mechanism, namely, the respiratory-related changes in preload. Thus the first aim of the present time-domain study was to document the costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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short-term fluctuations in LVET in HTR and their potential link with beat-to-beat PP. To study a wide pressure range, data were obtained at baseline and following the cold pressor test (CPT) (18, 29).

In HTR, where beat-to-beat fluctuations in DT are concerned, DT is expected to vary inversely with LVET because mathematically the two must add up to the same number (fixed heart period). Decreased DT limits subendocardial perfusion in various pathophysiological settings relevant to coronary heart diseases (6, 15, 16, 26), especially when coronary vasodilation is maximal and coronary pressure is reduced (9, 21, 30), or in cases where arterial load is increased (15, 19). Diastolic abnormalities have also been reported at the early stages of rejection (14) and contribute to the decreased tolerance of exercise (28, 31) and afterload challenge (36) in HTR. It therefore seems important to document DT in HTR, both at rest and during CPT, and this was the second aim of our study.

METHODS

Patients. Seventeen consecutive male heart transplant recipients were enrolled in our prospective study. All patients gave informed consent, and the ethical committee of our institution approved the protocol. Patients were referred for routine evaluation of heart transplant. Coronary arteries were angiographically normal. Right ventricular endomyocardial biopsies performed the day of the investigation did not evidence any signs of rejection. Posttransplantation immunosuppressive therapy included prednisone and cyclosporin for all 17 patients and azathioprine for 8 of these 17. Fourteen patients were given antihypertensive therapy. They were given β-adrenergic blocking agents (n = 8), α-adrenergic blocking agents (n = 9), angiotensin-converting enzyme inhibitors (n = 1), or diuretics (n = 3). Vasoactive drugs were discontinued 24 h before the investigation. Patients were considered normotensive at the time of the investigation, when SAoP was <140 mmHg (n = 9). There were three untreated patients and six patients whose arterial pressure was normally controlled with antihypertensive therapy. The patients whose SAoP was insufficiently controlled despite antihypertensive therapy were considered hypertensive at the time of the investigation (n = 8). The characteristics of the study population are listed in Table 1.

Catheterization technique and protocol. Patients were studied according to our routine protocol (1, 11, 27). All patients were in the fasting state for at least 12 h before the investigation. No premedication was administered. Lidocaine (1%) was used for local anesthesia, and 5,000 units of heparin were administered intravenously. The left heart pigtail catheter was an 8-F single-lumen catheter with a lateral high-fidelity transducer (Cordis/Sentron, Roden, The Netherlands). The percutaneous femoral approach was used: the catheter was advanced from the femoral artery to the aortic root. Right heart catheterization was performed with a thermodilution catheter (Edwards Laboratories) using the femoral vein approach, and cardiac output was determined (average of 3 consecutive measurements) using the thermodilution technique (Cardiac Output Computer model 9520 A, Edwards Laboratories). After a 5-min equilibrium period, pressure data were recorded at baseline over a 15-s period. The catheter was then advanced into the left ventricle, and the left ventricular angiography was performed. After the catheter was withdrawn into the aortic root, and following a 10-min equilibrium period, the CPT was performed (n = 14) by immersing the patient’s hands in ice water for 120 s. Pressure data were then recorded over a 15-s period. The CPT was not performed in three patients for technical reasons. Throughout the protocol, the patient was asked to breath normally. The data were computed on a Toshiba 3,200 SX with customized software (sampling rate: 1,000 Hz). During computation, care was taken not to include premature ventricular beats in the overall 15-s pressure runs under study. A coronary angiography and right ventricular endomyocardial biopsy were performed following CPT.

High-fidelity recordings at the aortic root level and cardiac output. SAoP and DAoP were measured automatically, and PP was calculated (PP = SAoP − DAoP). Mean aortic pressure was calculated as the total area under the pressure curve divided by heart period. Our high-precision (1 ms) analysis enabled subtle beat-to-beat changes in time intervals to be measured. Heart period was measured as the time between two consecutive aortic pressure upstrokes. LVET was measured from the foot of the pressure upstroke to the trough of the incisura. As previously recommended (15, 16), DT was measured from the foot of the pressure upstroke to the trough of the incisura. As previously recommended (15, 16), DTc was calculated using the standard formula (46). Heart rate-corrected DT (DTc) was calculated as T minus LVETc, where T is heart period. The intra- and interobserver reproducibility of time-interval measurements was 99% and 97% respectively. Heart rate-corrected LVET (LVETc) was calculated using the standard formula (46). Heart rate-corrected DT (DTc) was calculated as T minus LVETc. We also calculated the systolic pressure-time index (SPTI) and the diastolic pressure-time index (DPTI), i.e., the pressure-time integral during systole and diastole, respectively. The DPTI-to-SPTI ratio (DPTI/SPTI) was also calculated, given that this ratio has been proposed as a reliable index of subendocardial perfusion (7, 9, 19). Stroke volume (SV) was calculated by dividing cardiac output by heart rate.

Data analysis and statistics. Pressure values and time parameters were averaged out over the 15-s period under study. Results are expressed as means ± SD. We investigated whether changes in DT and LVET from one beat to the next were in phase (i.e., both time intervals increased or both
respectively, each PP were linearly related to LVET (r = 0.96, P < 0.001) and following the cold pressor test (CPT) (B, n = 14).

RESULTS

Systolic time and diastolic time at rest. A strong relationship was found between heart period and DT (n = 17; r = 0.96, P < 0.001) (Fig. 1A). Both SAoP and PP were linearly related to LVET (r = 0.73 and 0.76 respectively, each P < 0.01), but not to heart period (r = 0.26 and 0.43, respectively) or DT (r = 0.04 and 0.23, respectively). Heart period was similar in normotensive and hypertensive HTR. Compared with their rate-corrected values, LVET was prolonged and DT was shortened in hypertensive HTR (Table 2).

Both the increased aortic pressure and the prolonged LVET resulted in a markedly higher SPTI (~35%) in hypertensive than in normotensive HTR (Table 2). The DPTI was moderately higher (~20%) in hypertensive HTR than in normotensive subjects. The proportionally larger increases in SPTI compared with DPTI resulted in a lower DPTI/SPTI in hypertensive HTR compared with normotensive subjects (Table 2).

Beat-to-beat fluctuations of time intervals at rest. Over the 15-s period under study, 20 ± 2 consecutive beats were analyzed (range: 16–23 beats). Beat-to-beat fluctuations in time intervals (calculated as CV; n = 17) were 0.7 ± 0.2, 2.4 ± 1.1, and 1.3 ± 0.4% for heart period, LVET, and DT, respectively. In 13 of 17 patients, in >50% of the beats under study (69 ± 11%, range: 55–89%), spontaneous changes in LVET and DT were out of phase, i.e., one time interval increased while the other decreased. In these patients, given that heart period was essentially fixed, DT fluctuations from one beat to the next were therefore about equal in magnitude and opposite in sign in comparison with LVET fluctuations. In the remaining 4 of the 17 patients, LVET and DT were out of phase in 50% (n = 3) and 45% (n = 1) of the beats.

Beat-to-beat relationship between time intervals and aortic pressure at rest. In all patients, there was a strong positive linear relationship between beat-to-beat LVET and beat-to-beat PP (n = 17, each P < 0.001 except in 1 of 17 HTR, where P < 0.01) (Table 3). Similar results were observed when SAoP was considered instead of PP, although the correlation was weaker (Table 3). The slope of the PP-LVET relationship showed little scatter among patients (means ± SD; 0.34 ± 0.07 mmHg/ms; n = 17) (Fig. 2). There was a negative relationship between beat-to-beat PP and beat-to-beat DT in 13 of 17 patients (P < 0.05 to P < 0.001) (Table 3). A typical example is shown in Fig. 3B. This finding was explained by both the positive relationship between beat-to-beat PP and LVET and the virtually fixed beat-to-beat heart period. Thus the higher the beat-to-beat pulsatile stress, the shorter the heart period during sinus rhythm.

Table 2. Aortic pressure, time intervals, and pressure area at baseline in normotensive and hypertensive HTR

<table>
<thead>
<tr>
<th></th>
<th>Normotensive HTR</th>
<th>Hypertensive HTR</th>
<th>Hypertensive vs. Normotensive HTR, P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 9)</td>
<td>(n = 8)</td>
<td></td>
</tr>
<tr>
<td>SAoP, mmHg</td>
<td>125 ± 9</td>
<td>160 ± 14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DAoP, mmHg</td>
<td>82 ± 7</td>
<td>98 ± 7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MAoP, mmHg</td>
<td>101 ± 7</td>
<td>125 ± 8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T, ms</td>
<td>754 ± 49</td>
<td>772 ± 80</td>
<td>NS</td>
</tr>
<tr>
<td>LVET, ms</td>
<td>273 ± 18</td>
<td>295 ± 13</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVETc, ms</td>
<td>277 ± 9</td>
<td>280 ± 14</td>
<td>NS</td>
</tr>
<tr>
<td>DT, ms</td>
<td>481 ± 37</td>
<td>476 ± 77</td>
<td>NS</td>
</tr>
<tr>
<td>DTC, ms</td>
<td>477 ± 40</td>
<td>492 ± 66</td>
<td>NS</td>
</tr>
<tr>
<td>SPTI, mmHg · s</td>
<td>30.4 ± 3.1</td>
<td>41.5 ± 4.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DPTI, mmHg · s</td>
<td>45.5 ± 5.3</td>
<td>54.6 ± 8.4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>DPTI/SPTI</td>
<td>1.51 ± 0.16</td>
<td>1.32 ± 0.19</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Values are means ± SD. Normotensive HTR, patients whose systolic aortic pressure was <140 mmHg at the time of the study; hypertensive HTR, patients whose systolic aortic pressure was ≥140 mmHg at the time of the study; SPTI, systolic pressure-time interval; DPTI, diastolic pressure-time interval. There was no significant difference between LVET and DT values and their corresponding rate-corrected values (LVETc and DTc) in normotensive HTR, whereas these values differed significantly (P < 0.05) in hypertensive HTR.
Table 3. Correlation between beat-to-beat PP and beat-to-beat time intervals and between beat-to-beat SAoP and beat-to-beat time intervals at baseline

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>PP vs. LVET</th>
<th>PP vs. DT</th>
<th>PP vs. T</th>
<th>SAoP vs. LVET</th>
<th>SAoP vs. DT</th>
<th>SAoP vs. T</th>
<th>No. of Consecutive Beats Analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.93</td>
<td>−0.78</td>
<td>0.45*</td>
<td>0.85</td>
<td>−0.80</td>
<td>0.30‡</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>0.78</td>
<td>0.20‡</td>
<td>0.35‡</td>
<td>0.67†</td>
<td>0.07‡</td>
<td>0.41‡</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>0.88</td>
<td>−0.92</td>
<td>0.01‡</td>
<td>0.88</td>
<td>−0.92</td>
<td>0.00‡</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>0.86</td>
<td>−0.49*</td>
<td>0.53*</td>
<td>0.83</td>
<td>−0.44‡</td>
<td>0.56*</td>
<td>19</td>
</tr>
<tr>
<td>5</td>
<td>0.78</td>
<td>−0.66</td>
<td>0.21‡</td>
<td>0.56†</td>
<td>−0.62†</td>
<td>0.02‡</td>
<td>23</td>
</tr>
<tr>
<td>6</td>
<td>0.83</td>
<td>0.60</td>
<td>0.33‡</td>
<td>0.68</td>
<td>−0.39‡</td>
<td>0.39‡</td>
<td>22</td>
</tr>
<tr>
<td>7</td>
<td>0.92</td>
<td>−0.73</td>
<td>0.49*</td>
<td>0.84</td>
<td>−0.66†</td>
<td>0.43‡</td>
<td>18</td>
</tr>
<tr>
<td>8</td>
<td>0.64†</td>
<td>0.13‡</td>
<td>0.48*</td>
<td>0.52*</td>
<td>−0.02‡</td>
<td>0.46*</td>
<td>20</td>
</tr>
<tr>
<td>9</td>
<td>0.95</td>
<td>−0.89</td>
<td>−0.49*</td>
<td>0.91</td>
<td>−0.90</td>
<td>−0.60*</td>
<td>16</td>
</tr>
<tr>
<td>10</td>
<td>0.82</td>
<td>−0.26‡</td>
<td>0.35‡</td>
<td>0.64†</td>
<td>−0.31‡</td>
<td>0.17‡</td>
<td>21</td>
</tr>
<tr>
<td>11</td>
<td>0.78</td>
<td>−0.51*</td>
<td>0.00‡</td>
<td>0.78</td>
<td>−0.64†</td>
<td>−0.16‡</td>
<td>19</td>
</tr>
<tr>
<td>12</td>
<td>0.86</td>
<td>−0.53*</td>
<td>0.64†</td>
<td>0.81</td>
<td>−0.37‡</td>
<td>0.71</td>
<td>21</td>
</tr>
<tr>
<td>13</td>
<td>0.91</td>
<td>−0.69</td>
<td>0.28‡</td>
<td>0.83</td>
<td>−0.70</td>
<td>0.15‡</td>
<td>19</td>
</tr>
<tr>
<td>14</td>
<td>0.83</td>
<td>−0.30‡</td>
<td>0.52‡</td>
<td>0.63†</td>
<td>−0.21‡</td>
<td>0.28‡</td>
<td>18</td>
</tr>
<tr>
<td>15</td>
<td>0.95</td>
<td>−0.51*</td>
<td>0.85</td>
<td>0.79</td>
<td>−0.23‡</td>
<td>0.89</td>
<td>18</td>
</tr>
<tr>
<td>16</td>
<td>0.96</td>
<td>−0.92</td>
<td>0.63‡</td>
<td>0.83</td>
<td>−0.75</td>
<td>0.62‡</td>
<td>19</td>
</tr>
<tr>
<td>17</td>
<td>0.90</td>
<td>−0.71</td>
<td>0.56‡</td>
<td>0.57†</td>
<td>−0.67‡</td>
<td>0.11‡</td>
<td>21</td>
</tr>
</tbody>
</table>

Data are correlation coefficients (r) analyzed over a 15-s period. PP, aortic pulse pressure. P < 0.001 for each patient unless otherwise indicated: *P < 0.05; †P < 0.01; or ‡P = NS.

beat-to-beat diastolic duration in these patients. As expected, no systematic relationship was found between beat-to-beat SAoP and beat-to-beat heart period (Table 3). Finally, there was no difference between normotensive and hypertensive patients with regard to the CV of PP, DT, LVET, and heart period.

Effects of CPT on time intervals. The effects of CPT are summarized in Table 4 (n = 14). Heart period was related to DT (r = 0.93, P < 0.001) and LVET (r = 0.66, P < 0.05) (Fig. 1B). Compared with baseline values, heart period decreased while LVET increased, resulting in disproportionate decreases in DT. After CPT, the shortened DT compensated for the increases in aortic pressure such that DPTI remained unchanged. Conversely, both the increased aortic pressure and increased LVET resulted in an increased SPTI (P < 0.001) and thus a lower DPTI/SPTI (P < 0.001) (Table 4).

Over the 15-s study period, 20 ± 2 consecutive beats were analyzed (range: 15–22 beats). After CPT, beat-to-beat fluctuations in time intervals (calculated as CV; n = 14) were 0.9 ± 0.5% [P = not significant (NS) vs. baseline], 2.6 ± 1.4% (P = NS vs. baseline), and 2.1 ± 1.3% (P = 0.05 vs. baseline) for heart period, LVET, and DT, respectively. In 11 of 14 patients, in >50% of the beats under study (71 ± 13%, range: 55–93%), spontaneous changes in LVET and DT were out of phase. In the remaining 3 of the 14 patients, LVET and DT were out of phase in only 42, 47, and 48% of the beats, respectively.

Effects of CPT on the beat-to-beat relationship between aortic pressure and time intervals. No systematic relationship was found between beat-to-beat PP and beat-to-beat heart period (n = 14). Conversely, in 13 of 14 patients, a strong positive relationship was found between beat-to-beat LVET and beat-to-beat PP (r ranging from 0.65 to 0.98, each P < 0.001). Similar overall results were observed when systolic aortic pressure was considered instead of PP, although the correlation was weaker. The slope of the PP-LVET relationship showed little scatter among patients (0.35 ± 0.09 mmHg/ms, n = 14; P = NS vs. baseline) (Fig. 4). CPT induced a parallel, upward shift in this relationship such that beat-to-beat PP increased whatever the LVET. A typical example is given in Fig. 3A. The negative relationship between beat-to-beat PP and beat-to-beat DT previously documented at baseline was still found in 12 of the 14 patients (P < 0.05 to P <
such that the higher the pulsatile stress, the shorter the DT (Fig. 3B).

**DISCUSSION**

The present study showed that, in male HTR, there was a strong linear relationship between beat-to-beat LVET and beat-to-beat aortic PP in the absence of heart period variability. Similar results were obtained at baseline and following CPT, and the slopes of the various PP-LVET relationships showed very little scatter. Short-term recordings (15 s) were studied in the time domain, so it was essentially respiratory-related changes in arterial pressure that were analyzed. The present observation links cardiac hemodynamics with blood pressure variability in HTR and is consistent with the major role of respiratory-related changes in stroke volume in aortic pressure variability in HTR. In clinical settings associated with chronic (hypertensive HTR) or acute (CPT) increases in aortic pressure, we documented a mismatch between increased arterial load and unchanged or decreased DT, and this contributed to the lower DPTI/SPTI. We also identified a subgroup of HTR in whom the higher the beat-to-beat PP, the shorter the beat-to-beat DT. The decreased DT together with increased arterial load might be consid-

![](Figure3.png)

**Fig. 3.** Typical beat-to-beat relationships between time intervals and aortic pulse pressure at baseline (○) and following CPT (●) in 1 patient. A: strong positive relationship between LVET and aortic pulse pressure at baseline ($r = 0.96, P < 0.001$) and following CPT ($r = 0.95, P < 0.001$). Note the upward shift in this relationship following CPT. B: strong negative relationship between DT and aortic pulse pressure at baseline ($r = -0.95, P < 0.001$) and following CPT ($r = 0.99, P < 0.001$). C: weak relationship between heart period and arterial pulse pressure at baseline ($r = 0.63, P < 0.01$) and lack of relationship between heart period and arterial pulse pressure following CPT ($r = 0.08, P$ not significant).
erred a deleterious hemodynamic pattern where graft perfusion is concerned.

Relationship between beat-to-beat LVET and PP. In spontaneously breathing subjects, short-term fluctuations in blood pressure mainly reflect the respiratory-related changes in stroke volume, thus leading to inspiratory decreases and expiratory increases in blood pressure (41). In HTR, respiratory variations of systemic pressure are preserved, whereas heart rate variability is markedly reduced. Previous studies performed in healthy subjects or in patients with various forms of cardiac diseases have shown that both chronic and acute increases (or decreases) in stroke volume are associated with increases (or decreases) in LVET (5, 8, 23, 38). Although a cause-and-effect relationship cannot be proved in the present study, beat-to-beat changes in LVET could reflect respiratory-related changes in stroke volume, which would affect PP (13, 20, 34, 41), without the confounding effects of respiratory sinus arrhythmia and baroreflex feedback on heart period and aortic pressures (12, 22, 40–43). This hypothesis is reinforced by our finding that LVET was very closely related to PP. Indeed, numerous studies have suggested that beat-to-beat PP reflects the respiratory-related changes in stroke volume more accurately than does beat-to-beat SaOP (13, 20, 34). Because PP is mainly determined by stroke volume and total arterial compliance (10, 39), the role of arterial compliance needs to be discussed. Respiratory-related changes in intrathoracic pressure may modify aortic compliance and thus PP. Conversely, sympathetic mediated changes in aortic compliance are unlikely to be involved in our short-term results because compliance fluctuates slowly with fluctuations in sympathetic tone. Finally, beat-to-beat changes in the extent of wave reflection may also contribute to the relationship between LVET and PP (19), a point that deserves further study.

Numerous mechanisms tend to prolong or shorten LVET, so other explanations cannot be excluded. Changes in the speed at which stroke volume is ejected are unlikely to be involved in the PP-LVET relationship, because faster ejection rates are associated with increased PP but decreased LVET (5). Although the low-frequency harmonic spectral power in systolic blood pressure is significantly decreased in HTR (20), we cannot exclude the possibility that primary increases in peripheral arterial tone contribute to SaOP increases, thus leading to prolonged LVET (37). However, this mechanism is likely to play a minor role in our results given that only short-term recordings were analyzed.

The increase in aortic pressure following CPT was associated with a decrease in heart period, a paradoxical shortening of LVET, and, thus, a disproportionate decrease in DT. This could be explained by the inability of the denervated, grafted heart to respond adequately to inotropic and chronotropic stimulation by shortening electromechanical systole (17, 24), therefore unmasking the prominent influence of increased preload on LVET. Similarly, in reducing the effects of catecholamines on the myocardium, β-blockade has been shown to induce a disproportionate lengthening of LVET during exercise and, thus, a shorter diastolic time, in hypertensive patients (16). Shaver et al. (37) also reported that LVET lengthens when arterial pressure is elevated (through metoxamine infusion), whereas heart rate is held constant by atrial pacing.

As observed in patients at rest, a strong positive relationship between short-term variability of LVET and aortic PP was also found in all patients following CPT. The slopes of the various PP-LVET relationships showed very little scatter in both cases. This point remains to be explained. The CPT causes an elevation in mean arterial pressure and total peripheral resistance via increased sympathetic vasomotor control (18, 29). It can therefore be said that acute changes in arterial pressure, total peripheral resistance, and sympathetic drive did not appear to modify the slope of the relationship between LVET and aortic PP variability.

DT in HTR. The duration of LV subendocardial wall perfusion is mainly dependent on DT (9, 21). Decreased DT limits subendocardial perfusion in various pathophysiological settings relevant to coronary heart diseases, especially in cases where arterial load is increased (15, 19, 21).

In HTR, a close linear relationship between heart period and DT was found at rest, indicating that heart period was the main determinant of DT (Fig. 1). This close relationship is consistent with previous findings in normal subjects and in patients with various forms of cardiac diseases (6, 15, 16, 26). When heart period was taken into account, the HTR whose systolic aortic pressure was <140 mmHg had a normal DT, whereas hypertensive HTR had a decreased DT. This finding was explained by both the similar heart period in the two subgroups and the prolonged LVET in hypertensive versus normotensive HTR.

Our results also indicated that unchanged or decreased DT together with increased arterial load contributed to the imbalance between myocardial O2 supply and demand in hypertensive HTR and in all HTR during CPT (Table 4). DT may well play a critical role in coronary perfusion abnormalities in HTR whose hypertension is insufficiently controlled by medical therapy and in all HTR during stress.

We observed small beat-to-beat fluctuations in DT in HTR, whereas heart rate variability was almost abolished. The most likely explanation is that HTR start with a fixed heart period (lack of autonomic modulation of the sinoatrial node) and, because LVET fluctuates (probably subsequent to fluctuations in stroke volume), DT necessarily varies inversely with LVET because mathematically the two must add up to the same number. Primary changes in DT may also play a role, albeit minor, in light of the suggestion by Bernardi et al. (4) that spontaneous changes in DT may adapt to changes in LV filling in the absence of autonomic modulation of heart rate in HTR. In 13 of 17 HTR at rest and in 12 of 14 HTR following CPT, beat-to-beat analysis indicated that the longer the duration of LV ejection, the higher the aortic PP and the shorter the
DT. This may lead to cyclic mismatch between arterial load and the subendocardial perfusion duration in normal daily life.

Implications. Our results are consistent with the mechanical role of respiratory-related changes in stroke volume in PP variability. Furthermore, mean power of the ejection left ventricle critically depends on the duration of LV ejection. Thus the strong relationship observed between LVET and PP suggests a powerful link between LV energetics and blood pressure variability in HTR. The implications of our results in terms of the variability of the ventricular-arterial coupled system have yet to be studied.

The long-term survival of human transplant recipients is compromised by cardiac allograft vasculopathy, i.e., an accelerated graft coronary artery disease that is essentially immune mediated (44). Coronary perfusion may be also impaired by hemodynamic factors limiting subendocardial perfusion. Overall, decreased DT together with increased arterial load might be considered a deleterious hemodynamic pattern where graft perfusion is concerned.

During stress, it has been suggested that a decrease in diastolic perfusion time could not be balanced by a proportional increase in coronary blood flow in cases where there is failure to achieve maximal coronary vasodilation (15). This is likely to occur in HTR with fixed coronary artery stenosis or in HTR soon after grafting, in whom the CPT fails to dilate epicardial coronary arteries (2). After acute elevation of LV afterload (e.g., exercise), increased filling pressure and decreased ejection performance have been reported in HTR. These changes have been linked to several factors, including inadequate heart rate response (31), decreased isovolumic relaxation rate (28), and a decreased preload reserve (36). The disproportionate decrease in DT may also play a part in increasing filling pressure, a point that deserves further study.

Study limitations. One of the limitations of our study is that only male patients were analyzed. Further study is needed to confirm our findings in female HTR. DT is shorter in healthy women than in men at any heart rate level (5, 23, 46). The shorter DT contributes to the lower DPTI/SPTI consistently observed in healthy women >50 yr of age compared with men (19). Given the higher mortality in women undergoing heart transplantation, it might be important to incorporate heart rate and DT in the risk factors used in univariate and multivariate analyses of survival (45).

A second limitation is that only short-term recordings (15 s) were analyzed in the time domain, so only the respiratory-related changes in arterial pressure were covered. A third limitation is that recent studies have reported that, in some experimental conditions, a reduction in DT was not necessarily associated with changes in myocardial perfusion (32) and that there was a substantive systolic component in nutritive myocardial perfusion. These findings call into question the validity of time intervals for assessing O2 supply and demand. A fourth limitation is that neither respiration nor beat-to-beat stroke volume were monitored in our study, so further study is needed to confirm our hypotheses. A fifth limitation is that the study was not controlled, so the specific influences of both intact autonomic control of heart rate and hypertension on the PP-LVET relationship remain to be investigated.

In summary, a positive linear relationship was found between beat-to-beat LVET and aortic PP in male HTR in the absence of heart period variability. The slope of the PP-LVET regression lines showed very little scatter both at baseline and following CPT. This finding demonstrates a strong link between cardiac hemodynamics and blood pressure variability in HTR and is consistent with the major role of respiratory-related changes in stroke volume in PP variability. On average, in men with grafted hearts, DT was mainly related to heart period. In hypertensive HTR at rest and in all patients during CPT, prolonged LVET and unchanged or shortened DT contributed to the lower DPTI/SPTI. We also identified a subgroup of HTR in whom there was a continuous beat-to-beat mismatch between DT and PP at rest. Overall, the hemodynamic pattern of decreased DT together with increased arterial load may be considered deleterious from the viewpoint of graft perfusion.

We thank the nurses from the Service de Physiologie et d’Explorations Fonctionnelles, Hôpital Bichat. We also thank Sheila Carrodus for helpful discussions.

This study was funded in part by grants from Assistance Publique-Hôpitaux de Paris (PHRC AOM96174).

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