Influence of heart rate, respiration and recipient atrial contraction on pulsed wave transmural Doppler flow indices in orthotopic heart transplant recipients

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Aims
The study set out to assess the relative contributions of donor heart rate, respiration and recipient atrial contraction on the mean of pulsed wave transmural Doppler flow indices in orthotopic heart transplant recipients. This would provide information on the theoretical usefulness of pacemaker synchronization of recipient atrial contraction, as well as on the validity of certain strategies used for pulsed wave Doppler analysis of diastolic left ventricular function, which have excluded beats based on recipient atrial contraction timing.

Methods
Thirty two consecutive patients undergoing orthotopic heart transplantation in our centre were prospectively studied. The following Doppler indices were analyzed: peak early diastolic velocity (E) and its area under the Doppler curve (TVIE), diastolic velocity after donor atrial contraction (A) and its area under the curve (TVIA), the total area under the curve (TVI), the isovolumic relaxation period (IVR), the diastolic filling period, the normalized peak filling rate and the pressure half time.

Results
Only 81 out of 347 recordings (23%) allowed analysis of the recipient P wave and thus recipient atrial contraction timing, heart rate and the respiration phase in 22 patients for a total of 1579 beats. The isovolumic relaxation period, E, pressure half time and TVIA are not influenced by donor heart rate. For the isovolumic relaxation period, E, TVI and TVIE, respiration contributes as much as recipient atrial contraction timing to beat-to-beat variation. Pressure half time, the diastolic filling period and peak filling rate were not affected by respiration. TVI was not affected by recipient atrial contraction timing.

Conclusion
With respect to analysis of diastolic function, exclusion of beats based on recipient atrial contraction timing is invalid for the isovolumic relaxation period, E, TVI and TVIE, since these are equally influenced by respiration. Since TVI was not affected by recipient atrial contraction timing, pacemaker synchronization of donor and recipient atria is not expected to be useful in patients with left ventricular diastolic dysfunction.

Key Words: Pulsed wave transmural Doppler, recipient atrial contraction, respiration, heart rate.

Introduction
Several studies have reported on the role of pulsed wave transmural Doppler for the non-invasive diagnosis of acute rejection in orthotopic heart transplant recipients. In a previous study we investigated 32 consecutive cardiac allograft recipients with this technique and concluded that it did not allow the diagnosis of moderate acute rejection. We found that not only recipient atrial contraction, but also respiration may cause considerable beat-to-beat variability in pulsed wave transmural Doppler flow indices of orthotopic heart transplant recipients, and that donor heart rate is an important determinant of the mean values of pulsed wave Doppler flow indices. Based on studies mainly focusing on the timing of recipient atrial contraction, the exclusion of certain beats based on recipient atrial contraction timing was proposed. The present study aims to assess the relative contributions of heart rate, respiration and recipient atrial contraction on the mean values of pulsed wave transmural Doppler flow indices in orthotopic heart transplant recipients.

Patients and methods
All 32 consecutive patients who underwent orthotopic heart transplantation between 1 January and
31 December 1989 were enrolled in a prospective observational study. This study is described in detail elsewhere. Details pertinent to the presented study here are as follows. The Barnard technique of atrial incision was used for preparation of the donor heart. A posterolateral incision is performed in the right atrium, beginning in the inferior caval vein and extending to the base of the right auricle. The superior caval vein is ligated. In this way the donor sinoatrial node is preserved.

Ultrasound recordings, taken for routine monitoring of acute rejection at least 15 times in the first year after transplantation, according to a predefined protocol, were performed within 6 h of endomyocardial biopsy. Additional biopsies and pulsed wave Doppler recordings were performed at other times, in case of clinical suspicion of acute rejection. All patients were in sinus rhythm and PQ intervals were within normal limits.

Pulsed wave Doppler recordings were made and analysed by a single observer, who had no prior knowledge of the results of the endomyocardial biopsies. Studies were performed with a 3.75 or 2.25 MHz combined imaging and Doppler transducer (SSH-160 A, Toshiba America Medical Systems, Austin, CA, U.S.A). Special attention was given to pulsed wave transmitral Doppler recordings from the apical four-chamber view with appropriate gain and filter settings. The sample volume was narrowed to the smallest possible (1 mm) and positioned at the level of the tips of the mitral leaflets in such a way that the highest velocities could be recorded. Doppler strip-chart recordings were made at a paper speed of 100 mm. s⁻¹ in combination with a simultaneous ECG, phonocardiogram and respiratory tracing. Special efforts were made to obtain clear donor and recipient atrial P waves on the ECG. Off-line, on average 20 consecutive beats were analysed with a software program developed in our laboratory using a hand-held digitizer connected to a digitizing tablet (Summa Sketch Plus, Summagraphics, Seymour, CN, U.S.A) and interfaced to a personal computer (M 240, Olivetti U.S.A, Bridgewater, NJ, U.S.A). The pulsed wave transmitral Doppler parameters measured are outlined in Table 1. Pressure half time was calculated to allow comparison with other studies, although the Bernouilli equation should not be used for a non-stenotic mitral valve. Beats which were clearly distorted by recipient atrial contraction were not analysed with respect to pressure half time.

The transmitral flow velocity pattern was classified as 'summation filling pattern' if there was only one peak in diastole after the P wave. In such Doppler recordings, indices such as E, TVIE, TVIA, and pressure half time could not be measured because clear E and A waves could not be identified. The single velocity peak was considered as A. All other parameters were measured both in summation filling patterns and in non-summation filling patterns.

Whenever the recipient atrial P wave could be identified (and not extrapolated according to the P wave frequency) on the ECG, its appearance was related to four phases of the cardiac cycle: early and late systole and early and late diastole. Early systole was defined as the first half of systole, and late systole as the second half of systole ending at the start of mitral inflow, thus including the isovolumic relaxation period. Isovolumic relaxation period was measured as the interval between the aortic component of the second heart sound on the phonocardiogram (A2; which was verified by the M-mode echocardiogram of aortic valve closure) and the start of mitral inflow. Early diastole was defined as the period between the start of mitral inflow and the onset of the donor P wave, late diastole as the period between the donor P wave and the end of mitral inflow. The pulsed wave transmitral Doppler flow signal was related to the respiratory phase, according to Fig. 1. In this way four respiratory phases were defined: inspiration, end-inspiration, expiration and end-expiration. Only signals which were clearly in one of those four phases were used. Beats which were in a relatively long period of apnoea were disregarded for the analysis of respiration.

Orthotopic heart transplant recipients

End-inspiration

Expiration

Inspiration

End-expiration

Figure 1 The four predefined phases of the respiratory cycle are shown (each phase demarcated between little arrows).

Statistical analysis

An unbalanced repeated measures analysis of variance model with structured covariance matrices was used. Thus the independent relative contribution of donor heart rate, the timing of recipient atrial contraction and the respiration phase on the transmitral pulsed wave Doppler flow indices were assessed. To allow comparison with previous studies, univariate analysis of only recipient atrial contraction timing in the four phases of the cardiac cycle was performed (without heart rate and respiration). A Student t-test was used for the comparison between donor and recipient atrial heart rates.

Results

Only 81 records (23%) in 22 patients from the 347 records of the original study (with a total of 32 patients) allowed analysis of recipient atrial contraction timing and respiration phase. In this subgroup, median time after transplantation was 42 (range 6–333) days. A total number of 1579 heart beats were available for analysis. A summation filling pattern with analysable recipient atrial contraction timing and respiratory phase was observed in 304 (19%) beats. Donor atrial heart rate was 90 ± 10 beats min⁻¹, and recipient atrial heart rate 85 ± 11 beats min⁻¹ (P<0.001).

The number and proportional distribution of recipient atrial contraction timing in four parts of the cardiac cycle (indicated by symbols) are shown. The mean ± SD and number of beats analysed in each part of the cardiac cycle are indicated. Due to summation filling patterns, undetermined recipient atrial contraction timing and respiratory phase, it was not possible to analyse any index for a total of 1579 beats.

The results of the repeated measures analysis of variance for nine Doppler flow indices and their number (n) analysed are shown in nine histograms (Fig. 2). For each Doppler index they represent the relative contributions of heart rate, respiratory phase and timing of recipient atrial contraction according to the linear model Y=ax+b+c. Factor Y represents the mean value of a particular pulsed wave Doppler index for all beats analysed in the repeated measures model. n is the total

Table 2 Relative distribution of phases of recipient atrial contraction (RAC) and respiration

<table>
<thead>
<tr>
<th>Number of beats</th>
<th>Proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAC early systole</td>
<td>275</td>
</tr>
<tr>
<td>RAC late systole</td>
<td>191</td>
</tr>
<tr>
<td>RAC early diastole</td>
<td>491</td>
</tr>
<tr>
<td>RAC late diastole</td>
<td>223</td>
</tr>
<tr>
<td>RAC undetermined</td>
<td>399</td>
</tr>
<tr>
<td>Inspiration</td>
<td>434</td>
</tr>
<tr>
<td>End inspiration</td>
<td>113</td>
</tr>
<tr>
<td>Expiration</td>
<td>424</td>
</tr>
<tr>
<td>End expiration</td>
<td>180</td>
</tr>
<tr>
<td>Resp. undetermined</td>
<td>428</td>
</tr>
</tbody>
</table>

The number and the proportions of beats according to recipient atrial contraction timing in the cardiac cycle and according to the position of beats in the respiratory cycle. The total number of beats analysed for recipient atrial contraction timing, heart rate and respiratory phase was 1579.
Table 3 Timing of recipient atrial contraction

<table>
<thead>
<tr>
<th></th>
<th>Early systole (\text{*})</th>
<th>Late systole (\text{†})</th>
<th>Early diastole (\text{‡})</th>
<th>Late diastole (\text{§})</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(E) (ms \text{s}^{-1})</td>
<td>0.86 ± 0.22 (n=275)</td>
<td>0.96 ± 0.24 (n=275)</td>
<td>0.92 ± 0.22 (n=490)</td>
<td>0.83 ± 0.20 (n=222)</td>
<td>(&lt;0.0001)</td>
</tr>
<tr>
<td>(A) (ms \text{s}^{-1})</td>
<td>0.51 ± 0.19 (n=275)</td>
<td>0.50 ± 0.21 (n=275)</td>
<td>0.50 ± 0.24 (n=490)</td>
<td>0.54 ± 0.18 (n=222)</td>
<td>(&lt;0.0001)</td>
</tr>
<tr>
<td>PHT (ms)</td>
<td>44 ± 11 (n=275)</td>
<td>39 ± 11 (n=275)</td>
<td>41 ± 14 (n=490)</td>
<td>46 ± 15 (n=222)</td>
<td>(=0.0001)</td>
</tr>
<tr>
<td>IVR (ms)</td>
<td>69 ± 21 (n=266)</td>
<td>63 ± 18 (n=266)</td>
<td>70 ± 20 (n=468)</td>
<td>72 ± 21 (n=212)</td>
<td>(&lt;0.0001)</td>
</tr>
<tr>
<td>TVI (cm)</td>
<td>14.5 ± 3.6 (n=275)</td>
<td>14.7 ± 3.9 (n=275)</td>
<td>15.2 ± 3.5 (n=490)</td>
<td>15.0 ± 3.5 (n=222)</td>
<td>(&lt;0.0001)</td>
</tr>
<tr>
<td>TVIE (cm)</td>
<td>12.1 ± 3.2 (n=189)</td>
<td>12.6 ± 3.3 (n=189)</td>
<td>12.7 ± 3.4 (n=468)</td>
<td>11.4 ± 3.3 (n=473)</td>
<td>(&lt;0.0001)</td>
</tr>
<tr>
<td>TVIA (cm)</td>
<td>3.8 ± 1.5 (n=189)</td>
<td>3.6 ± 1.4 (n=189)</td>
<td>3.6 ± 2.0 (n=468)</td>
<td>4.6 ± 1.7 (n=473)</td>
<td>(&lt;0.0001)</td>
</tr>
<tr>
<td>PFR (SV. \text{s}^{-1})</td>
<td>5.8 ± 1.0 (n=275)</td>
<td>6.3 ± 1.1 (n=275)</td>
<td>5.9 ± 1.2 (n=490)</td>
<td>5.5 ± 1.0 (n=222)</td>
<td>(&lt;0.0001)</td>
</tr>
<tr>
<td>DFP (ms)</td>
<td>311 ± 77 (n=275)</td>
<td>324 ± 88 (n=275)</td>
<td>318 ± 79 (n=490)</td>
<td>321 ± 77 (n=222)</td>
<td>(&lt;0.0001)</td>
</tr>
</tbody>
</table>

Nine Doppler indices were examined in four different phases (labelled \text{*}, \text{†}, \text{‡}, \text{§}) of the cardiac cycle by one-way analysis of variance. See Table 1 for abbreviations of the Doppler indices. Means ± SD, the number of beats (\(n\)), and the \(P\) values for comparison between different phases are shown.

Discussion

Although the effects of recipient atrial contraction, heart rate and respiration on pulsed wave transmitral Doppler flow indices have been reported separately \[6,5,11\] in several studies, none of them have described the relative importance of each of these factors when interacting in orthotopic heart transplant recipients.

Presence of recipient atrial contraction

In contrast to the total group of heart transplant recipients, the patients in the subgroup with visible recipient P waves reported here were mainly found early post-operation (median time after transplantation 42 days vs 180 days for the total group in our previous study). The interval in the population studied by Triposkiadis et al.\[13\] after heart transplantation was longer (mean 15 ± 9 months), whereas in the study by Valantine et al.\[6\] there was an early (mean 2.5 months) and a late group (mean 3 years) after transplantation. The presence of visible recipient P waves is dependent on several factors, of which the actual presence of electrical recipient atrial activity, the ECG leads used, the electrical conductivity of the tissues surrounding the heart.
Orthotopic heart transplant recipients 1667

Figure 2 In nine histograms for each of nine Doppler flow indices, the number of beats is shown (n), as well as the calculated mean (MEAN) of the mathematical model. The absolute contributions to this calculated mean are represented by the constant (CONST) of the model, the heart rate (HR), and the different phases of respiration and timing of recipient atrial contraction. The asterix (*) denotes a statistically significant contribution. E-INSP=end-inspiration, EXP=expiration, E-EXP=end-expiration. RAC-LS=recipient atrial contraction in late systole, RAC-ED=recipient atrial contraction in early diastole, RAC-LD=recipient atrial contraction in late diastole. Inspiration and recipient atrial contraction in early systole are both arbitrarily set at 0 in this model, and therefore are omitted from the histograms. IVR=isovolumic relaxation period; PHT=pressure half time; DFP=diastolic filling period; PFR=peak filling rate.

and the size of the recipient atrial cuff are likely to be of primary importance. By using non-standard sternal leads, P waves with a larger amplitude could be obtained in comparison with the standard ECG leads. The distribution of recipient atrial contraction over the phases of the cardiac cycle (Table 2) cannot be readily compared to the other studies since it was undermined in 25%, which is attributable to our strict definition that only visible identifiable recipient P waves would be analysed. This approach effectively avoids effects due to recipient atrial arrhythmia, which is quite common after orthotopic heart transplantation12-16.

Univariate analysis on the timing of recipient atrial contraction was performed to allow comparison of our findings with previous studies.

Effect of timing of recipient atrial contraction on transmitral Doppler parameters

The effects of recipient atrial contraction timing on the isovolumic relaxation period, pressure half time and E were similar, as reported by Valantine et al.49. During recipient atrial contraction in late diastole TVIA (but not A) as in previous studies4,5 was increased. The difference between A and TVIA is caused by the relatively large proportion of summation filling patterns, of which the peak was defined as A, whereas TVIA was exclusively present in non-summation filling patterns. In contrast to the study by Triposkiadis et al.19 the extreme
low values for A and TVIA during recipient atrial contraction in early diastole were neither observed in the study by Valantine et al.\textsuperscript{[4]} nor in the present study. Also, TVI was not affected by recipient atrial contraction timing. The latter finding, in combination with the effect of recipient atrial contraction timing on peak filling rate might indicate that recipient atrial contraction timing merely causes shifts in left ventricular filling rate rather than affecting total filling volume and thereby (forward) stroke volume and cardiac output. The patients in the present study had a much more restrictive filling pattern than those in the studies by Valantine and Triposkiadis as measured by E to A ratio, isovolumic relaxation period, pressure half time and peak filling rate. Therefore only a fraction of left ventricular filling took place in late diastole. In extreme cases the left ventricle might even become unfillable in late diastole\textsuperscript{[17]}. This might explain the lack of increase of TVI during recipient atrial contraction in late diastole in the population of the present study, contrary to the study by Triposkiadis et al. Therefore the suggested (but not proved) haemodynamic benefit by Triposkiadis\textsuperscript{[23] of pacemaker synchronization of donor and recipient atrial contractions to increase TVI and thereby cardiac output at rest is not likely to be expected in the patient population in the present study.

**Heart rate**

In orthotopic heart transplant recipients, donor sinus rhythm is increased as a result of denervation, an augmented adrenergic sensitivity in the presence of normal mean plasma noradrenaline levels with normal 24 h variability\textsuperscript{[18,19]} and elevated levels of calcitonin gene related peptide\textsuperscript{[19]}. There is also some evidence that cardiac sympathetic nerve activity partly normalizes after transplantation. Thus after more than 2 years the heart rate response during exercise may become normal\textsuperscript{[20]}. Donor heart ischaemic time has been shown to act as a transient deleterious factor on postoperative sinus node function up to 3 months after transplantation\textsuperscript{[12]}. After this time a consistent postoperative heart rate of <70 beats.min\textsuperscript{-1} indicates donor sinus node dysfunction with a relatively lower probability of recovery to normal donor sinus rhythm and a greater probability of (pre)syncope\textsuperscript{[13]}. According to this definition none of the patients in the present study had evidence of sinus node dysfunction at any time.

In accordance with earlier studies, recipient atrial heart rate was lower than donor atrial heart rate, which was similar in other studies\textsuperscript{[4,5]}. Isovolumic relaxation period, E, pressure half time, and TVIA are heart rate independent Doppler indices. Patients with higher heart rates had both a significantly higher A and a non-significant increase in TVIA, which is in accordance with a dog model of Doppler derived diastolic function, in which pacing, atropine or isoproterenol was used\textsuperscript{[21]}. The changes in A in this model are presumed to be a normal non-specific response to increasing heart rates. However, in contrast to the dog model in the present study TVI(E) was significantly decreased and summation filling patterns appeared at a much lower (donor) heart rate (mean 101 ± 7 beats. min\textsuperscript{-1} with normal PQ intervals\textsuperscript{[22]}. In the dog model the largest diastolic transmitral gradient and left atrial pressures were observed in summation filling patterns, in which atrial contraction occurs before mitral valve opening. Therefore we hypothesize that, apart from the factors already mentioned, diastolic dysfunction may be another important primary determinant of donor heart rate in the (still almost completely) denervated heart early after orthotopic heart transplantation. If a larger transmitral gradient is required because of diastolic dysfunction (e.g. by left ventricular hypertrophy and/or fibrosis, or cellular infiltration, all common after transplantation\textsuperscript{[22]}) the denervated heart may adapt by increasing the heart rate with the early onset of summation filling patterns presumably through a local mechanoreceptor response via cardiac stretch receptors which modulate heart rate\textsuperscript{[14]}.

**Recipient atrial contraction and respiration**

For most parameters, heart rate was a more important contributor to the estimated mean of the model in comparison with respiration and recipient atrial contraction timing. The relative contributions of recipient atrial contraction timing and respiration are similar for E, isovolumic relaxation period, TVI and TVIE. For diastolic filling period, pressure half time and peak filling rate there was no significant beat-to-beat variation induced by respiration, and for TVIA and A recipient atrial contraction timing had a slightly greater effect in comparison with respiration. In most of the recordings only mild or no pericardial effusion was present. There was therefore no exaggerated respiratory variation.

Valantine et al.\textsuperscript{[15]} have proposed omitting beats in which recipient atrial contraction (according to the presence of the recipient P wave) occurred in late systole for the measurement of isovolumic relaxation period, pressure half time and E, and beats in which recipient atrial contraction occurred in diastole for the measurement of A. This approach neglects the role of respiration. From the histograms it can be observed that this approach is correct for respiration independent indices diastolic filling period, pressure half time and peak filling rate.

**Study limitations**

Simultaneous cardiac catheterization was not performed. Therefore the effect of recipient atrial contraction timing on left ventricular filling could not be determined directly. Also the haemodynamic meaning of summation filling patterns could have been evaluated directly by measuring the transmural pressure gradient.
during cardiac catheterization. The nature of this study, however, did not allow this approach. Clear recipient atrial P waves, which allowed analysis of recipient atrial contraction timing, could be observed in only a small minority (23%) of consecutive patients relatively early after orthotopic heart transplantation (median 42 days). Whether this implies a loss of electrical or mechanical performance of the recipient atrium for the remaining 77% cannot be answered.

**Clinical implications**

Isovolumic relaxation period, E, pressure half time (and TVIA), the most commonly used pulsed wave transmirtal Doppler indices for assessment of left ventricular diastolic function are (donor) heart rate independent. Recipient atrial contraction timing is an important source of beat-to-beat variation in patients after orthotopic heart transplantation, but respiration is of equal importance for E and isovolumic relaxation period. Therefore the recommendation to omit beats from the analysis according to recipient atrial contraction timing is unnecessary for these indices if both inspiratory and expiratory beats are used for the analysis of transmitral Doppler indices. However, beat-to-beat variability can be reduced only if end-tidal volume apnoeic beats are used for the analysis.

The early appearance of a summation filling pattern with increased donor heart rate in comparison with the non-summation filling patterns may represent an adaptation of the denervated heart (possibly due to a local mechanoreceptor response) to provide an increased transmitral diastolic pressure gradient in case of diastolic dysfunction.

Pacemaker synchronization of donor and recipient atrial contraction is not likely to be beneficial (at least not in resting conditions) in patients with diastolic dysfunction as in the present study.

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**References**


