Ejection Fraction and Heart Rate Correlate with Diastolic Peak Filling Rate at Rest and during Exercise*


We investigated the independent variables correlating with the multigated radionuclide peak filling rate (PFR) at rest and during supine bicycle exercise in 20 normal individuals. Independent variables were systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), ejection fraction (LVEF), time to PFR (TPFR), peak ejection rate (PER) and time to PER (TPER). Fifteen subjects completed at least five stages of exercise at 25 watts each. Correlating independent variables were selected by a forward-backward stepwise multiple linear regression (BMDF2R). A partial correlation statistical program was also used to allow control of critical independent variables. The final regression equations were: a) resting state, \( PFR = -2.5 + 0.03HR + 0.05LVEF + 0.02SBP - 0.05DBP \), and b) exercise state, \( PFR = -3.8 + 0.04HR + 0.08LVEF \). All independent variables mentioned above correlated with PFR (simple correlations designated as zero partials). However, when LVEF and HR were held constant (second order partials), the correlation of PFR with any of the other independent variables disappeared. In summary, the radionuclide global LV PFR is predominantly correlated to LVEF and HR at rest and during exercise. These correlations should be considered when assessing exercise effects of disease states on PFR.

Echocardiography and radionuclide ventriculography (RVG) assess the LV diastolic flow rate during rapid filling. Characteristically, the peak diastolic filling rate (PFR), the time to PFR, and the diastolic filling fraction during rapid filling are computed in RVG studies.

The radionuclide global LV PFR has been found to be subnormal in many patients with coronary artery disease with or without previous myocardial infarction. In addition, the radioisotope LV PFR has been reported to be impaired in 75 percent of patients with hypertrophic cardiomyopathy. Thus, the drug verapamil, which improves symptoms in patients with hypertrophic cardiomyopathy, also improves LV filling in these patients. Finally, echocardiographic and radionuclide investigations have described slowing and reduction of LV diastolic filling in hypertensive patients even in the presence of normal baseline LV contractile state.

Some investigations have assessed the correlation between PFR and other hemodynamic variables. The angiographic study of Hammermeister et al and other RVG studies have reported a good correlation between PFR and the LV ejection fraction (LVEF), while one study reported a lower correlation of PFR with heart rate.

This study was designed to determine the strength of the correlations of RVG PFR with systolic blood pressure, diastolic blood pressure, heart rate, LVEF, peak emptying rate (PER), time to PFR (TPFR) and time to PER (TPER). Multivariate analysis was used to identify significant effects of the independent variables at rest and during exercise. The study collected data at rest and during exercise to insure sufficient data points over a wide range of values for independent variables.

**Material and Methods**

**Subjects**

Thirteen male and seven female normal volunteers were studied. Their mean age was 32 ± 7 years. All were free of symptoms of cardiovascular disease and other medical conditions and none was hypertensive, nor had major risk factors for the development of coronary artery disease. Subjects denied a family history of heart disease. Physical examination and resting electrocardiogram performed on each volunteer gave normal results. The clinical and electrocardiographic response to exercise was normal in all instances. The Institutional Review Committee approved all aspects of the investigation.

**Exercise protocol**

A RVG study was carried out under baseline conditions. The subjects were then instructed on the selected exercise protocol. They performed symptom-limited supine bicycle exercise. Exercise stages were 3 minutes in duration, with work loads set at progressively increasing 25 watts increments. Data collection for RVG variables was obtained during the last 2 minutes of each exercise stage.

**RVG method**

The widely used in vivo red blood cell labeling procedure was used to identify the cardiac blood pools. Twenty MCI of \(^{99m}\) Tc O\(_4\)\(^-\) was utilized for labeling. The same standard field-of-view Anger...
camera fitted with a GAP collimator was employed for studies which were conducted in the LAO projection (45 to 60° angulation) that best presented an unequivocal perpendicular interventricular septum, allowing proper separation of the ventricles. Our RVG method has been used in other investigations. In this investigation the resting studies were performed with 32 frames of 64 by 64 pixels each. In the exercise studies, the cardiac cycle was also divided into 32 frames.

**Data Analysis**

Global analysis of left ventricular function was carried out with user-defined fixed LV region of interest. Ejection fraction and stroke volume functional images were employed to define this region of interest. The end-diastolic (ED) and end-systolic (ES) frames were chosen by the computer as those yielding the maximum or minimum counts per frame, respectively, in the background-corrected LV time activity curve (TAC) generated from this region of interest (ROI). Three background ROIs were automatically formed by the computer. They were positioned along the septal, apical, and lateral sides of the LV ROI respectively. The average left ventricular background was defined as a combination of the ED counts from these ROIs. Although the fixed LV region of interest method consistently underestimates absolute LV ejection fraction values, it produces more reproducible LV ejection fraction than the variable LV region of interest technique.

The left ventricular TAC was corrected for loss of counts occurring in the last diastolic points due to differences in the number of cardiac cycles contributing counts to these frames (from sinus arrhythmia). This correction consisted of finding which frame after end-systole had maximum total count per frame, then multiplying each value of the time activity curve from that point to ED by the ratio of the maximum total count to the total count of that frame. This was done because the Fourier transform (to be described subsequently) assumes the data to be periodic and difficulties arise (Gibbs phenomenon) during temporal filtering if discontinuities occur in the data. In this study, there was continuous ECG monitoring during resting and exercise conditions. In no instance were extrasystoles present.

The background was first subtracted from the ventricular time activity curve, then subjected to low-pass filtering in the frequency domain. The design of the filter was based upon knowledge of the average signal and noise power spectrums of LV TACs. It has been observed that the LV TAC signal is lost in the Poisson noise of the count data around the fifth to sixth harmonic. If more terms than this are kept, the signal-to-noise content of the LV TAC is decreased; if fewer terms are kept, the shape of the curve is not faithfully reproduced. The low-pass filter used in this study was a compromise between these two limitations. It allowed the first two harmonics to pass unattenuated, then attenuated the rest using the down slope of a Gaussian function. This function was designed to roll-off so that about 50 percent of the fifth harmonic was passed and very little of the eighth or higher harmonics were passed. This form of filter was used instead of a sharp cut-off at the fourth or fifth harmonic to avoid the Gibbs phenomenon problems that sharp cut-off filters produce. The filtered curve was transformed back to the temporal domain for calculation of the first derivative (instead of calculating it in the frequency domain from its harmonics) since this method is easily normalized. The normalized first derivative of the filtered TAC was calculated according to the following equation:

\[ PFR = \frac{PER}{TFPR} \]

**Figure 1.** Schematic of method used to derive systolic and diastolic events and timing intervals. Upper left: background-corrected left ventricular time activity curve. Upper right: filtered time activity curve using Fourier transform (FFT). Lower left: first derivative curve used in the measurements. PER = peak ejection rate. TPER = time to peak ejection rate. PFR = peak filling rate. TFPR = time to peak filling rate.
residual variance in PFR. From previous published it is known that there are no nonlinear components in the relationships between PFR and the selected potential independent variables described above.

**Multivariate Analysis**

We used the forward-backward stepwise multiple linear regression analysis (BMDP2R, UCLA Press, 1983) to identify the determinants of PFR. The potential independent variables used in the program were systolic blood pressure, diastolic blood pressure, HR, LVEF, PER, TPFR, and TPER. These independent variables (along with PFR, the dependent variable), were entered into the regression equation, one at a time according to their ability to reduce the residual variance in PFR. From previous published data, it is known that there are no nonlinear components in the relationships between PFR and the selected potential independent variables described above.

**Partial Correlations**

We had noted that by this stepwise multiple regression program, PER initially appeared as an important correlate of PFR but it was removed from the regression equation after LVEF was entered. Therefore, we carried the analysis a step further by examining partial correlations using the statistical program SPSS. Again, the dependent variable was PFR. The independent variables were systolic blood pressure, diastolic blood pressure, HR, LVEF, PER, TPFR, and TPER.

Statistical analyses were performed using BMDP and SPSS 170 statistical software on HARRIS 500 and CYBER computer systems. All data are expressed as mean ± one SD. T-tests and analyses of variance were performed where appropriate. Simple bivariate relationships were available from the BMDP2R and the SPSS partial correlation programs described above.

**Results**

Table 1 shows the values of independent and dependent variables at rest and during exercise. N is the number of data points at rest and during exercise.

**Resting Data**

To better understand the relationships between PFR, LVEF, and HR at rest, the 20 individuals were arbitrarily divided into three groups based on their resting LVEF. These groups were: 1) LVEF ≤60 percent, (n = 9), 2) LVEF 61–70 percent, (n = 6), and 3) LVEF 71–76 percent, (n = 5). We postulated that by dividing the groups along well-defined resting LVEF intervals, it may be possible to account for effects of

### Table 1—Ancillary Descriptive Statistics (means ± 1 SD)

<table>
<thead>
<tr>
<th></th>
<th>REST</th>
<th>n</th>
<th>EXERCISE*</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood</td>
<td>116 ± 8.9</td>
<td>18</td>
<td>157 ± 22.9</td>
<td>94</td>
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<tr>
<td>pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Diastolic blood</td>
<td>77 ± 7.2</td>
<td>18</td>
<td>83 ± 10.5</td>
<td>94</td>
</tr>
<tr>
<td>pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>HR, BPM</td>
<td>62 ± 8.0</td>
<td>20</td>
<td>117 ± 26.4</td>
<td>108</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>62 ± 9.5</td>
<td>20</td>
<td>73 ± 9.7</td>
<td>108</td>
</tr>
<tr>
<td>PER, EDV/sec</td>
<td>3.37 ± 0.56</td>
<td>20</td>
<td>6.1 ± 1.65</td>
<td>108</td>
</tr>
<tr>
<td>TPFR, msec</td>
<td>151 ± 20.4</td>
<td>20</td>
<td>117 ± 25.4</td>
<td>108</td>
</tr>
<tr>
<td>PER, EDV/sec</td>
<td>3.05 ± 0.6</td>
<td>20</td>
<td>4.8 ± 1.28</td>
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</tr>
<tr>
<td>TPFR, msec</td>
<td>166 ± 24.5</td>
<td>20</td>
<td>110 ± 29.3</td>
<td>108</td>
</tr>
</tbody>
</table>

*Exercise stages = Rest + 3 stages 20 subjects
Rest + 4 stages 18 subjects
Rest + 5 stages 15 subjects
Rest + 6 stages 10 subjects
Rest + 7 stages 6 subjects
Rest + 8 stages 1 subject

Exercise duration = 17.8 ± 3.6 min (n = 108)

### Table 2—Resting Data

<table>
<thead>
<tr>
<th></th>
<th>Mean PFR</th>
<th>Range</th>
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<tbody>
<tr>
<td>Group (total n = 20)</td>
<td>3.37 ± 0.56 EDV/</td>
<td>2.5-4.5</td>
</tr>
<tr>
<td>1 (n = 9)</td>
<td>3.07 ± 0.417 EDV/</td>
<td>2.5-3.9</td>
</tr>
<tr>
<td>2 (n = 6)</td>
<td>3.27 ± 0.383 EDV/</td>
<td>2.8-3.9</td>
</tr>
<tr>
<td>3 (n = 5)</td>
<td>4.04 ± 0.39 EDV/</td>
<td>3.5-4.5</td>
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**t-Tests**

<table>
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<tr>
<th></th>
<th>Results</th>
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<tbody>
<tr>
<td>Group 1 vs Group 2</td>
<td>NS</td>
</tr>
<tr>
<td>Group 1 vs Group 3</td>
<td>p = 0.001</td>
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<tr>
<td>Group 2 vs Group 3</td>
<td>p = 0.01</td>
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</table>
LVEF and heart rate on resting PFR. As can be seen in Table 2, the PFR values were statistically significantly higher in group 3 individuals as compared to those in groups 1 or 2. However, as indicated in Table 3, the mean heart rates for the three groups were not statistically different (by analysis of variance). Also in Table 3, the simple univariate correlations between PFR and heart rate for groups 1, 2, and 3 were 0.43, 0.45 and 0.60, respectively. However, when all PFR values were correlated with heart rate (n = 20 individuals), no correlation was noted (r = 0.12). This indicates that the variances for the regressions of PFR versus HR are smaller over each of the three EF intervals than they are over the entire LVEF range of values.

Results of stepwise regression for resting data are shown in Table 4. LVEF, heart rate, SBP and DBP were successively entered into the regression equation at the second, third, and fourth iterations. No variable was removed in the stepwise regression procedure. For the resting data, the final regression equation in the model was PFR = -2.5 + 0.03 HR + 0.05 LVEF + 0.02 SBP - 0.02 DBP.

Exercise Data

Figure 2 shows the progressive increases of LVPFR during the first five stages of exercise. As can be seen, 15 of the twenty individuals completed the five stages. The LVEF means at rest ± SD were: rest, 62 ± 10 percent; stage one, 69 ± 9 percent; stage two, 69 ± 7 percent; stage three, 71 ± 10 percent; stage four, 74 ± 10 percent; and stage five, 77 ± 10 percent. The LV pixel number at ED (a relative measurement of ED volume) were: rest, 197 ± SD 52; stage one, 174 ± 44; stage two, 174 ± 41; stage three, 177 ± 43; stage four, 179 ± 47; and stage five, 178 ± 36.

For the 20 individuals, 108 exercise data points were used in the stepwise regression. The final equation of the model for the exercise data was PFR = -3.8 + 0.04 HR + 0.08 EF. This equation was quantitatively similar in those ten individuals who completed six exercise stages and the five individuals who had LVEF at rest greater than 70 percent.

We could not understand why PER became a nonsignificant independent variable after the first step in the stepwise regression procedure. To clarify this lack of correlation, we performed partial correlation analyses. It was found that when HR and LVEF were held constant (controlled variables), all other variables became nonsignificantly correlated with PFR.

Discussion

This investigation demonstrates that over a wide range of heart rates, PFR is well correlated with LVEF and HR. This was proven by using multivariate stepwise regression and partial correlation analyses. These statistical programs were applied to data acquired at rest and during incremental symptom-limited supine bicycle exercise in normal volunteers.

It is very likely that our results depend importantly upon three factors: 1) we selected a relatively high number of normal individuals compared to previous investigations, 2) heart rate varied widely from the resting to the exercise levels (while the range of variation of the other determining variable, LVEF, was less), 3) we used statistical analyses which were concordant in their results. The results of this investigation also showed that even at rest HR (and to lesser degree systolic blood pressure and diastolic blood pressure) and LVEF are importantly correlated with PFR.

Some physiologic and methodologic issues require discussion. Oldershaw et al. recently investigated diastolic physiologic mechanisms during exercise. In their study, the isovolumic relaxation time remained unaltered during exercise in normal individuals. Since stroke volume was expected to have increased slightly and left ventricular filling time (from mitral valve opening to ED) shortened down to 100 msec at a rate of 150 beats/min during exercise, a progressive rise in PFR must have occurred. Thus, one would anticipate a close correlation during exercise between PFR and HR as HR progressively increases, as documented in our investigation. However, other variables also change during exercise: systolic blood pressure, LVEF and PER all increase, while TPFR and TPER decrease. It was necessary, therefore, to study all potential independent determinants of PFR by such statistical methods as stepwise regression and partial

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<table>
<thead>
<tr>
<th>Table 3—Resting Data</th>
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<tbody>
<tr>
<td>Simple Univariate Correlations</td>
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<tr>
<td>Patients</td>
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<tr>
<td>LVEF≤60% (n = 9)</td>
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<tr>
<td>LVEF 61-70% (n = 6)</td>
</tr>
<tr>
<td>LVEF≥71% (n = 5)</td>
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*The correlation between heart rate and PFR for all 20 patients combined was 0.12; between PFR and PER, 0.76. There were no differences between the mean heart rates for the three groups having LVEF of ≤60%, 61-70% and ≥71% (ANOVA), but analysis of variance revealed significant differences between the mean LVEF for each group.

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<table>
<thead>
<tr>
<th>Table 4—Resting Data</th>
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<tbody>
<tr>
<td>Final equation, PFR = -2.5 + 0.03 HR + 0.05 LVEF + 0.02 SBP - 0.02 DBP</td>
</tr>
<tr>
<td>Step*</td>
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<tr>
<td>0</td>
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<td>1</td>
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<td>2</td>
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<td>3</td>
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<td>4</td>
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*Stepwise regression, n = 18
†Dependent variable = PFR
‡Independent variables = SBP, DBP, HR, LVEF, PER, TPFR, TPER

Diastolic Peak Filling Rate at Rest and Exercise (Blanco et al.)
correlation. In agreement with previous observations, PER correlated PFR as strongly as LVEF did. Nevertheless, as LVEF was entered into the final regression equation (derived from stepwise regression), PER was eliminated. Similarly, when LVEF and HR were controlled, systolic blood pressure, diastolic blood pressure, PER, TPFR and TPER no longer correlated with PFR.

Other recent observations made during atrial pacing in normal individuals and patients with heart disease support our conclusion on the close correlation between HR and PFR. Magorien et al. found that a change in the atrial pacing frequency of 25-45 beats/min did not result in changes in LVEF, but augmented radionuclide PFR by 60 and 80 percent, respectively. Similarly, Vita et al. and Heller et al. also reported significant increases in PFR with the tachycardia of atrial pacing. In fact, in the study of Vita et al., the increase in PFR correspondent to increases in HR was quantitatively identical to that noted in the study of Magorien et al. (ie, PFR increased from 2.5 ± SD 1.04 EDV/sec to 4.1 ± 1.3 EDV/sec for an increase in HR of 40 beats/min). Incidentally, this increase in PFR corresponds to a change of 0.04 PFR units/heart beat. This factor appears in our final regression equation of exercise state.

The correlations between PFR and HR during exercise and atrial pacing have common characteristics. In both states there is, of course, heart rate augmentation (tachycardia). Additionally, exercise is accompanied by an enhanced inotropic state since catecholamines are released into the blood. Similarly, recent canine and human data demonstrate that there is also an enhanced inotropic state during atrial pacing. However, differences do exist between exercise and atrial pacing. During exercise, stroke volume rises slightly while end-diastolic volume does not change, or increases only slightly during supine exercise. During atrial pacing, however, stroke volume and end-diastolic volume both decline. Regardless of these similarities and differences, PFR is closely correlated with HR during exercise and atrial pacing. Neither this investigation, nor investigations using atrial pacing, have proven a cause-effect relation between increases in HR and PFR because a concomitant effect of enhanced contractile state has not been excluded. Thus, it may well be that the correlation between the LVEF and HR may simply be a function of the volume curve becoming more symmetric at higher heart rates with resulting higher peak filling rates. The LVEF increased initially as our healthy individuals began exercise but it tended to plateau thereafter, while the PFR continued to increase (Fig 2). On the other hand, other factors which affect the PFR would not appear to explain our results: end-diastolic volume changes little during exercise as shown in this investigation by the small initial decline of LV pixel size in our subjects (LV pixel size remained unchanged through stages two to five). Likewise, left atrial pressure and end-systolic volume did not increase during exercise. Finally, we cannot exclude a change in LV relaxation during exercise, but little is known of the relationship between LV relaxation and PFR.

In the clinical setting, it might be possible to correct for changes (if any) in LVEF and HR during exercise and atrial pacing, such that expected PFR at a given HR (from data obtained in normal individuals) could be compared to PFR at the same HR in patients with impaired LV diastolic performance. This appears to be an area of great potential for clinical research. For instance, Liu et al. have shown that during exercise, the pulmonary blood volume ratio (which is correlated with LV filling pressure) is a diastolic index which is more sensitive to changes in LV function than LVEF (a systolic index of ventricular performance). Similar conclusions were reported in the study of Reduto et al. and, more recently, by Poliner et al.

Methodologic issues concerning our investigation center on: 1) high temporal resolution of the LV volume curves required in exercise studies, 2) possible alteration.
tion of the shape of the LV TAC (and of its timing events) by the Fourier filtering method employed, and 3) perturbations created by extrasystolic and post-extrasystolic cycles, as well as the loss of counts near ED in the presence of sinus arrhythmia.

Radionuclide first-pass PFR mildly correlates with echocardiographic indices. Similarly, radionuclide gated PFR correlates with angiographic PFR. In fact, the radionuclide and angiographic LV TAC remarkably resemble each other. The reproducibility of interstudy PFR determinations has been reported as excellent. Our observations support these previous results. Similarly, our studies were framed so that they would possess the high temporal resolution demanded by exercise investigations, as specified by Bacharach et al. Finally, with exercise the HR increases, thus decreasing the RR interval. Since the RR interval was divided into 32 frames in our method, the temporal resolution of the study increased with exercise. Similarly, fewer harmonics may be needed to fit the shape of the LV TAC accurately since its complexity decreases with exercise.

No individual in this research series had extrasystoles or post-extrasystolic cycles during data collection. Count loss at ED due to sinus arrhythmia was corrected where appropriate, in the manner previously described. Parenthetically, sinus arrhythmia lessens during exercise.

In summary, our research has demonstrated that LVEF and HR are importantly correlated to PFR at rest and during exercise. Systolic blood pressure and diastolic blood pressure (LV loading) are less well correlated with PFR at rest, while they are not correlated with PFR during exercise. Normograms (in normal individuals) of PFR versus LVEF and HR as suggested by Mirsky may allow one to study PFR during exercise in populations with heart disease. This would appear to be a fruitful area for research since functional LV diastolic abnormalities may become evident during exercise before they express themselves in the resting state and before systolic contractile abnormalities are noted.

Addendum

The authors of this manuscript will make available to any interested reader the detailed statistical calculations employed in this investigation to ascertain the nature of the major correlates of the peak early diastolic filling rate.

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