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Summary

Objective: To assess independent determinants of beat-to-beat variation in left ventricular performance during atrial fibrillation.

Design: Prospective study.

Setting: University hospital.

Patients: Seven patients with chronic non-valvar atrial fibrillation.

Interventions: Invasive and non-invasive haemodynamic variables were obtained using a non-imaging computerised nuclear probe, a balloon-tipped flow directed catheter, and a non-invasive fingertip blood pressure measurement system linked to a personal computer.

Main outcome measures: Left ventricular ejection fraction, left ventricular volume, ventricular cycle length, pulmonary capillary wedge pressure, and measures for left ventricular afterload (end-systolic pressure / stroke volume) and contractility (end-systolic pressure / end-systolic volume) were calculated on a beat-to-beat basis during 500 consecutive RR intervals. With multiple regression analysis a statistical model of the beat-to-beat variation of ejection fraction was constructed, containing these variables.

Results: Positive independent relations with ejection fraction were found for preceding RR interval, contractility, and end-diastolic volume, whereas inverse relations were found for afterload, preceding end-systolic volume and preceding contractility (all variables p<0.0001). A relatively strong interaction was found between end-diastolic volume and afterload, indicating that ejection fraction was relatively more enhanced by preload in the presence of low afterload.

Conclusions: The varying left ventricular systolic performance during atrial fibrillation is independently influenced by beat-to-beat variations of cycle length, preload, afterload and contractility. Beat-to-beat variations in preload exhibit their effect on ventricular performance mainly in the presence of a low afterload.

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The randomly irregular ventricular response to atrial fibrillation not only causes an irregular but also an unequal pulse. The beat-to-beat variations in ventricular performance have been ascribed to variations in the length of the preceding heart period, beat-to-beat variations in preload by means of the Frank-Starling mechanism, beat-to-beat variations in afterload, and beat-to-beat variations in contractility, acting either by the interval-contractility relationship, or by means of postextrasystolic potentiation, or to a combination of those factors. In a previous study of left ventricular beat-to-beat performance in patients with nonvalvular atrial fibrillation, we have demonstrated that the interval-force relation rather than the Frank-Starling mechanism explained the varying left ventricular systolic performance during atrial fibrillation over the entire range of RR intervals. The contribution of beat-to-beat variation in preload, i.e. the Frank-Starling mechanism, to the varying left ventricular function during atrial fibrillation was limited to short preceding intervals. The contribution of aortic impedance, i.e. afterload, as well as other beat-to-beat regulatory mechanisms, including the positive and negative effects of ejection and the preceding beat contraction history could not be evaluated due to the absence of simultaneous measurement of left ventricular volume and (aortic) pressure measurement on a beat-to-beat basis.

Therefore, the aim of the present study was to assess in what proportion the haemodynamic regulatory mechanisms determine the beat-to-beat variations in left ventricular performance during atrial fibrillation. For this purpose we used a non-imaging computerised nuclear probe allowing beat-to-beat left ventricular volume measurement and invasive and non-invasive haemodynamic monitoring enabling extensive haemodynamic data acquisition on a beat-to-beat basis in a large number of consecutive beats.

METHODS

Patients and study protocol. Seven patients with chronic atrial fibrillation were included (Table 7.1). To avoid blunting of cycle length dependent haemodynamic changes by valvular heart disease, in particular mitral stenosis, only patients with non-valvular atrial fibrillation were studied. Prior to the study, all patients underwent M-mode and Doppler echocardiography. All antiarrhythmic drugs, including digitalis and calcium antagonists were stopped at least 5 drug half-lives before the study. The study was approved by the Institutional Review Board and written informed consent was given by all 7 patients.

Nuclear probe. To measure relative left ventricular volumes on a beat-to-beat basis, a commercially available non-imaging computerised nuclear probe (Nuclear Stethoscope, Bios, Valhalla, NY) was used. Methods are previously described by our group. In short, equilibrium blood pool labelling was obtained by the in vivo
labelling of red blood cells with 20 mCi $^{99m}$Tc. To search for the optimal position of the detector, the technique recommended by the manufacturer was used, by monitoring the continuously displayed values of stroke counts and ejection fraction. At the optimal left ventricular position, the values of stroke counts and ejection fraction were maximal and they were minimal for the background position. The analogue output from the probe, as well as the electrocardiogram, were fed into a personal computer with custom-developed software. This system allowed for continuous real-time display and permanent recording of a simultaneously acquired high temporal resolution radionuclide left ventricular time-activity curve (or background activity level), and an electrocardiographic signal. After final probe positioning, beat-to-beat data were acquired during 500 consecutive beats. Beat-to-beat analysis of the time-activity curve allowed instantaneous assessment of relative left ventricular volume.

**Haemodynamic measurements.** A balloon-tipped flow directed catheter ("Swan-Ganz" catheter) was used to measure pulmonary capillary wedge pressure on a beat-to-beat basis. Directly before the start of the recording of 500 consecutive beats per patient, cardiac output was measured using the thermodilution method.

### Table 7.1. Baseline characteristics of the 7 study patients and mean values ± standard deviations of measured and calculated independent variables determining left ventricular ejection fraction over 500 consecutive cycles arranged by ejection fraction (ranges between brackets)

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
<th>Patient 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64</td>
<td>67</td>
<td>36</td>
<td>61</td>
<td>61</td>
<td>42</td>
</tr>
<tr>
<td>Underlying heart disease</td>
<td>IHD</td>
<td>RHD</td>
<td>lone</td>
<td>lone</td>
<td>IHD</td>
<td>DCM</td>
</tr>
<tr>
<td>Arrhythmia duration (months)</td>
<td>2</td>
<td>168</td>
<td>4</td>
<td>6</td>
<td>56</td>
<td>1.5</td>
</tr>
<tr>
<td>LA diameter, long axis view (mm)</td>
<td>-</td>
<td>47</td>
<td>41</td>
<td>45</td>
<td>50</td>
<td>52</td>
</tr>
<tr>
<td>LV end diastolic diameter (mm)</td>
<td>55</td>
<td>45</td>
<td>50</td>
<td>51</td>
<td>55</td>
<td>70</td>
</tr>
<tr>
<td>LV end systolic diameter (mm)</td>
<td>42</td>
<td>29</td>
<td>38</td>
<td>38</td>
<td>37</td>
<td>58</td>
</tr>
<tr>
<td>Mean RR interval (ms)</td>
<td>427±138</td>
<td>610±131</td>
<td>589±134</td>
<td>776±259</td>
<td>632±147</td>
<td>885±302</td>
</tr>
<tr>
<td>Mean LV ejection fraction (%)</td>
<td>25±15</td>
<td>30±9</td>
<td>31±12</td>
<td>38±12</td>
<td>41±8</td>
<td>42±10</td>
</tr>
<tr>
<td>Range</td>
<td>1-71</td>
<td>7-54</td>
<td>3-61</td>
<td>2-62</td>
<td>8-60</td>
<td>2-67</td>
</tr>
<tr>
<td>Mean LV end diastolic volume (ml)</td>
<td>136±36</td>
<td>215±33</td>
<td>142±24</td>
<td>211±40</td>
<td>136±17</td>
<td>180±27</td>
</tr>
<tr>
<td>Range</td>
<td>52-230</td>
<td>152-335</td>
<td>76-190</td>
<td>112-314</td>
<td>67-164</td>
<td>82-231</td>
</tr>
<tr>
<td>Mean LV end systolic volume (ml)</td>
<td>99±25</td>
<td>148±20</td>
<td>97±18</td>
<td>129±23</td>
<td>80±7</td>
<td>105±24</td>
</tr>
<tr>
<td>Range</td>
<td>41-178</td>
<td>111-221</td>
<td>57-137</td>
<td>73-226</td>
<td>53-98</td>
<td>52-162</td>
</tr>
<tr>
<td>Mean PCWP (mmHg)</td>
<td>21±5</td>
<td>22±3</td>
<td>18±2</td>
<td>9±2</td>
<td>24±6</td>
<td>9±3</td>
</tr>
<tr>
<td>Range</td>
<td>10-35</td>
<td>17-27</td>
<td>13-28</td>
<td>4-33</td>
<td>3-38</td>
<td>4-30</td>
</tr>
<tr>
<td>Mean LV contractility (mmHg/ml)</td>
<td>1.2±0.4</td>
<td>1.0±0.2</td>
<td>1.1±0.2</td>
<td>1.3±0.3</td>
<td>1.2±0.01</td>
<td>1.2±0.4</td>
</tr>
<tr>
<td>Range</td>
<td>0.2-3.1</td>
<td>0.7-1.5</td>
<td>0.7-1.9</td>
<td>0.7-2.4</td>
<td>1.1-12.1</td>
<td>0.2-2.8</td>
</tr>
<tr>
<td>Mean LV aterload (mmHg/ml)</td>
<td>7.3±12.7</td>
<td>2.9±2.6</td>
<td>3.6±4.3</td>
<td>32±5.1</td>
<td>1.9±1.0</td>
<td>18±1.7</td>
</tr>
<tr>
<td>Range</td>
<td>0.5-114.9</td>
<td>1.3-250</td>
<td>1.1-41.6</td>
<td>1.0-52.1</td>
<td>0.8-138</td>
<td>0.5-266</td>
</tr>
</tbody>
</table>

DCM = dilating cardiomyopathy, IHD = ischaemic heart disease, LA = left atrial, lone = 'lone' arrhythmia, LV = left ventricular, PCWP = pulmonary wedge pressure, RHD = rheumatic heart disease.
The mean value of three measurements was used to calculate the individual factor which allows the conversion of measured counts to ml. This factor equals the ratio of cardiac output and the product of stroke counts and heart rate. Peripheral blood pressure was assumed to change similar to aortic pressure. To measure peripheral blood pressure a non-invasive fingertip blood pressure measurement system (Finapres, Ohmeda TM 2300, Inglewood, CO) was used which enables accurate measurement of systolic and diastolic blood pressure on a beat-to-beat basis compared to intra-arterial measurement. In essence, the method is based on a control loop, consisting of an inflatable finger cuff equipped with an infrared photoplethysmographic device to measure the finger artery blood volume under the cuff. The system is set to maintain a null transmural pressure. Changes in arterial blood volume due to pressure changes, detected by plethysmography, are counteracted by means of a fast electropneumatic servo system, which modulates the cuff pressure.

**Data processing.** The obtained data were simultaneously fed into a personal computer, enabling accurate, beat-to-beat calculation (and storage) of ejection fraction, left ventricular volume, left ventricular cycle length, pulmonary capillary
wedge pressure and peripheral blood pressure in a large number of consecutive beats (Figure 7.1). Using these pressure and volume data, left ventricular afterload of the index interval was defined as the ratio of end-systolic pressure and stroke volume (ESP/SV), and left ventricular contractility of the index interval as the ratio of end-systolic pressure and end-systolic volume (ESP/ESV). In this way, left ventricular afterload and left ventricular contractility values of the index interval, preceding and pre-preceding interval were calculated on a beat to beat basis. Pulmonary capillary wedge pressure (PCWP) and end-diastolic volume (EDV) were used as parameters for left ventricular preload of the index interval.

**Statistical analysis.** The validity of a multivariate model of left ventricular beat-to-beat performance in atrial fibrillation described previously by our group, was tested using the same non-invasive haemodynamic variables measured in the present patients, i.e. preceding RR interval, pre-preceding RR interval, end-diastolic volume, and preceding end-systolic volume. A measure of the fit of a model to the data, in this study left ventricular ejection fraction, is the model correlation ($R^2$).

To estimate univariate associations with the dependent variable left ventricular ejection fraction the independent factors from our previous model were analysed together with the following newly measured and calculated factors: pulmonary capillary wedge pressure, afterload, contractility of the index cycle, contractility of the preceding cycle, and contractility of the pre-preceding cycle. The significant variables describing ejection fraction in our previous model were filled in with the obtained haemodynamic factors of the present study showing significant univariate associations with ejection fraction (P<0.05), to assess independent determinants of ejection fraction in a mixed effects model. In this model the variation between the patients was added as an additive variation term. Using a backward selection method variables with a t-test parameter <10 were deleted from the model. Clinically relevant potential one-way interaction terms were evaluated in addition. The independent variables were introduced as centred terms, by subtracting the mean.

**RESULTS**

The same results as before were found when the non-invasive parameters describing a previous multiple regression model of left ventricular ejection fraction were obtained from the present patients and were fitted into the previous model. The model correlation ($R^2$) was now 0.70, comparable to the value found previously (0.73). After adding the newly studied parameters, pulmonary capillary wedge pressure, left ventricular afterload, left ventricular contractility of the index beat, contractility of the preceding beat, and contractility of the pre-preceding beat, the final model used the following equation:
EF = Constant + \sum_{i=1}^{7} P_i + \beta_1(pRR-pRR) + \beta_2(pEDV-pEDV) + \beta_3(pESV-pESV) + \\
\beta_4(ESP/SV-ESP/SV) + \beta_5(ESP/ESV-ESP/ESV) + \beta_6(pESP/pESV-pESP/pESV) + \\
\beta_7(EDV-EDV)(ESP/SV-ESP/SV)

where EF = left ventricular ejection fraction; P_1 to P_7 = effects for the 7 patients; \beta_1 to \beta_7 = regression coefficients for the independent variables and their interaction terms, which determine left ventricular ejection fraction; pRR = preceding RR-interval; EDV = end-diastolic volume; pESV = preceding end-systolic volume; ESP/SV = ratio of end-systolic pressure and stroke volume; ESP/ESV and pESP/pESV = ratio of end-systolic pressure and end-systolic volume of the index beat, and of the preceding cycle, respectively. In addition, the model shows one interaction term. The model correlation (R^2) in the new model was 0.87.

Baseline characteristics of the 7 study patients, individual echocardiographic dimensions, ejection fraction and haemodynamic measurements as well as their ranges during 500 consecutive cardiac cycles are shown in table 7.1. Table 7.2 summarises the results of the univariate correlation analysis. Pulmonary capillary wedge pressure was the only parameter which had only weak correlation with ejection fraction in the univariate analysis (p>0.01). All other tested parameters had significant univariate correlations with ejection fraction (p<0.01). The strongest univariate correlations were present between ejection fraction and preceding RR interval, end-diastolic volume, contractility, and afterload (all t-test parameters > 10).

<table>
<thead>
<tr>
<th>Variable, Contractility</th>
<th>T</th>
</tr>
</thead>
<tbody>
<tr>
<td>pRR</td>
<td>41.12</td>
</tr>
<tr>
<td>ppRR</td>
<td>4.67</td>
</tr>
<tr>
<td>EDV</td>
<td>21.74</td>
</tr>
<tr>
<td>PCWP</td>
<td>-2.37</td>
</tr>
<tr>
<td>pESV</td>
<td>-5.53</td>
</tr>
<tr>
<td>Afterload</td>
<td>-31.53</td>
</tr>
<tr>
<td>Contractility</td>
<td>28.18</td>
</tr>
<tr>
<td>p-Contractility</td>
<td>8.48</td>
</tr>
<tr>
<td>pp-Contractility</td>
<td>9.75</td>
</tr>
</tbody>
</table>

pRR = preceding RR interval; ppRR = pre-preceding RR interval; EDV = end-diastolic volume; PCWP = pulmonary capillary wedge pressure; pESV = preceding end-systolic volume; Afterload = end-systolic pressure/stroke volume; Contractility = end-systolic pressure/end-systolic volume; p-Contractility = preceding end-systolic pressure/preceding end-systolic volume; pp-Contractility = pre-preceding end-systolic pressure/pre-preceding end-systolic volume.
FIGURE 7.2 Relation between preceding RR interval and left ventricular (LV) ejection fraction in one of the patients, illustrating the positive relation between preceding RR interval and LV ejection fraction. There is a curvilinear relationship with ejection fraction remaining rather constant at long RR intervals.

FIGURE 7.3 Relation between left ventricular (LV) end-diastolic volume and LV ejection fraction in the same patient, illustrating the positive relation between LV end-diastolic volume and LV ejection fraction.

FIGURE 7.4 Example of the relation between left ventricular (LV) contractility of the index cycle (ESP/ESV indicates the ratio of end-systolic pressure and end-systolic volume) and LV ejection fraction in the same patient, illustrating the positive relation between LV contractility and LV ejection fraction.

FIGURE 7.5 Example of the relation between left ventricular (LV) afterload of the index cycle (ESP/SV indicates the ratio of end-systolic pressure and stroke volume) and LV ejection fraction, illustrating the negative relation between LV afterload and LV ejection fraction.
The relations between these independent variables and the dependent variable left ventricular ejection fraction are illustrated in figures 7.2 to 7.5. Figure 7.2 illustrates the positive relation between preceding RR interval and ejection fraction in one of the patients. Figure 7.3 illustrates the positive relation between end-diastolic volume and ejection fraction in the same patient. Figure 7.4 shows an example of the positive relation between contractility of the index cycle (ESP/ESV) and left ventricular ejection fraction, and figure 7.5 shows an example of the inverse relation between afterload (ESP/SV) of the index cycle and left ventricular ejection fraction.

**Multiple regression analysis.** Table 7.3 summarises the factors to which ejection fraction was significantly related in the multiple regression analysis. Preceding RR interval, left ventricular end-diastolic volume, and left ventricular contractility of the index beat showed an independent positive relationship with ejection fraction, whereas preceding end-systolic volume, left ventricular afterload of the index beat and contractility of the preceding beat showed an independent inverse relation with ejection fraction.

**TABLE 7.3** Independent variables and their association with left ventricular ejection fraction with multiple regression analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression Coefficient</th>
<th>SE of Regression Coefficient</th>
<th>T</th>
</tr>
</thead>
<tbody>
<tr>
<td>pRR</td>
<td>0.0092</td>
<td>0.00057</td>
<td>16.13</td>
</tr>
<tr>
<td>EDV</td>
<td>0.1771</td>
<td>0.00508</td>
<td>34.80</td>
</tr>
<tr>
<td>pESV</td>
<td>-0.2664</td>
<td>0.00724</td>
<td>-36.82</td>
</tr>
<tr>
<td>afterload</td>
<td>-1.0475</td>
<td>0.05173</td>
<td>-20.25</td>
</tr>
<tr>
<td>contractility</td>
<td>21.9391</td>
<td>0.46395</td>
<td>47.29</td>
</tr>
<tr>
<td>p-contractility</td>
<td>-14.9105</td>
<td>0.52436</td>
<td>-28.44</td>
</tr>
<tr>
<td>EDV * afterload</td>
<td>-0.0081</td>
<td>0.00071</td>
<td>-11.52</td>
</tr>
<tr>
<td>Intercept</td>
<td>37.1621</td>
<td>0.22925</td>
<td>162.10</td>
</tr>
</tbody>
</table>

*p 0.0001 for all comparisons.
PpRR indicates preceding RR interval; EDV, end-diastolic volume; pESV, preceding end-systolic volume; afterload, end-systolic pressure / stroke volume; contractility, end-systolic pressure / end-systolic volume; p-contractility, preceding end-systolic pressure / preceding end-systolic volume.

**Effects of interactions on left ventricular ejection fraction.** There was one separate statistically significant one-way interaction term which met the criteria to stay in the final model (Table 7.3). Figure 7.6 illustrates the influence of the interaction between left ventricular end-diastolic volume and afterload of the index beat. For a given end-diastolic volume, the ejection fraction was relatively less enhanced if the afterload was high, whereas with low afterload, end-diastolic volume affected the ejection fraction more.
DISCUSSION

The present study describes a statistical model of the beat-to-beat variation of ejection fraction in atrial fibrillation. In this multivariate model of the beat-to-beat changes of ejection fraction, beat-to-beat variation of contractility, preceding contractility, as well as preload and afterload, determined ejection fraction of the index beat. Considering the t-test parameters of the multiple regression analysis, the most important parameter appeared to be contractility of the index cycle. The present model filled in the previously described model, and the addition of measures of preload, afterload and contractility strongly improved the strength of the model.

Effect of contractility on ejection fraction. The finding that left ventricular beat-to-beat variation of contractility during atrial fibrillation is strongly related to beat-to-beat variation of left ventricular ejection fraction is in agreement with results of previous studies. In addition, ejection fraction was related to contractility of the preceding cycle. This observation confirms earlier reports which demonstrate the possibility of cardiac performance to be dependent on the mechanical events of more than one preceding beat. In the univariate analysis left ventricular ejection fraction was positively influenced by preceding contractility. However, the multivariate analysis showed an inverse relation between left ventricular ejection fraction and preceding contractility. The positive univariate relation between ejection fraction and preceding contractility is apparently described by other parameters in the multivariate model, so that in the multivariate model the true negative relation is exposed. The positive univariate relation between preceding contractility and ejection fraction may be explained by the model described by Hardman et al, in which the effect of postextrasystolic potentiation decays over a number of beats.
The positive relation between contractility of the preceding beat and ejection fraction was however not demonstrated in the present multivariate model. Possibly, this is caused by the presence of measures of contractility of the index beat, which show a relatively strong effect on left ventricular ejection fraction compared to contractility of the preceding cycle.

The origin of the remaining negative multivariate relation between contractility of the preceding cycle and left ventricular ejection fraction is more difficult to establish, although it may be found in the same model by Hardman et al. A short pre-preceding cycle will be poorly mechanically restituted, and is followed by a weak contraction. The following ejection will be strengthened due to postextrasystolic potentiation. However, the scope of the present model does not allow such conclusions. In order to elucidate the origin of the complicated relation between left ventricular ejection fraction and preceding contractility a study needs to be performed into the relative dependency of left ventricular contractility, preceding contractility, and cycle length fluctuations.

**Effect of pre- and afterload parameters on ejection fraction.** The positive relation which existed between left ventricular end-diastolic volume and ejection fraction confirms findings of previous studies in which the effect of the Frank-Starling mechanism on ejection fraction in patients with non-valvular atrial fibrillation was demonstrated. In a previous study by our group this contribution of the Frank-Starling mechanism to the varying ejection fraction was however limited to situations of short preceding cycle lengths and long pre-preceding cycle lengths. The interactions between end-diastolic volume and preceding and pre-preceding RR-interval were however not demonstrable in the present model and were described by the remaining interaction between end-diastolic volume and afterload.

The interaction between left ventricular end-diastolic volume and afterload indicates that ejection fraction was relatively more influenced by variations in preload in the presence of a low afterload, compared to the influence of preload in the presence of a high afterload. This suggests that the role of the Frank-Starling mechanism in the determination of ejection fraction in patients with atrial fibrillation is restricted to situations in which afterload is low, which may be the situation in the presence of a short pre-preceding RR interval. After a short pre-preceding interval only a small amount of blood volume will be ejected and the rise in aortic pressure will be small. As a consequence, the runoff in the aorta will be considerable and aortic impedance (i.e. afterload) during the next beat will be relatively low, resulting in an increased ejection fraction.

**Effect of cycle length fluctuations on left ventricular ejection fraction.** After the addition of the abovementioned determinants of contractility and afterload to our
previous model,\textsuperscript{9} the influence of the preceding RR interval on left ventricular ejection fraction, measured by its t-test parameter, tended to be less in the present multivariate model. In addition, the relation between pre-preceding RR interval and ejection fraction did not even reach a t-test parameter high enough to remain in the final model. Part of the relation between preceding RR-interval and ejection fraction and the entire relation between pre-preceding RR-interval and ejection fraction were apparently described by other parameters, which had not been included in our previous model. In our opinion, this related to the predominating effect of the interval-force relation determining the variable left ventricular performance in atrial fibrillation. In the presence of a long preceding RR interval, mechanical restitution will be complete and the following ejection will be strengthened, whereas in the presence of a short pre-preceding RR interval contractility of the index beat will be high ("postextrasystolic potentiation").\textsuperscript{8,24,25} These cycle length fluctuations influence ejection fraction indirectly by their effect on contractility, but also by their effect on afterload. Taking contractility and afterload into account when assessing the origin of the fluctuations of ejection fraction in atrial fibrillation, this strongly replaces the influence of random cycle length fluctuations.

Clinical implications. In earlier reports the effects of beat-to-beat variations of cycle length, contractility, preload an afterload on the variation of the pulse during atrial fibrillation have been described.\textsuperscript{8,9,10} These mechanisms are probably responsible for the adverse haemodynamics produced by the irregularity of the pulse in atrial fibrillation.\textsuperscript{26,27} The mutual proportions in which these mechanisms contribute to the beat-to-beat left ventricular systolic performance in patients with nonvalvar atrial fibrillation as measured by left ventricular ejection fraction are demonstrated in the present study. In order to optimise haemodynamics in patients with atrial fibrillation the origin of the beat-to-beat variations of contractility, preload and afterload, i.e. random cycle length fluctuations, may be a starting-point for therapeutic options, as was demonstrated for transcatheter ablation of the atrioventricular junction and pacemaker implant resulting in a regular ventricular rhythm.\textsuperscript{28} Another starting-point for therapeutic options in these patients may be optimisation of left ventricular afterload without reduction of preload and contractility. The latter option however remains to be investigated.

Limitations. First, although patients with valvar heart disease were excluded from this study, patients were still relatively heterogeneous with respect to underlying heart disease. The latter, in combination with the small number of patients, precluded subgroup analysis. Moreover, this was not the primary target of the present study. Secondly, the description of contractility and afterload by ESP/ESV and ESP/SV depends on the accuracy of the approximation of end-systolic aortic
pressure by non-invasive measurement of peripheral blood pressure. Although the values of ESP equal that of intra-arterial blood pressure measurement,\textsuperscript{18} they differ significantly from aortic systolic pressure on physiologic grounds. However, the beat-to-beat variability of ESP will equal that of aortic systolic pressure. Therefore, the approximation of aortic systolic pressure by ESP would change the values of the regression coefficients of the multiple regression analysis for afterload, contractility of the index cycle, and contractility of the preceding cycle, but not the value of the t-test parameter.

**Conclusions.** The varying left ventricular systolic performance measured by left ventricular ejection fraction in atrial fibrillation is dominated by variations of contractility, probably caused by the interval-force relation. Beat-to-beat variations in preload and afterload play a more modest role. The presence of pre- and afterload variations may result from random cycle length fluctuations as well. Beat-to-beat variations in preload, consistent with the Frank-Starling mechanism, exhibit their effect on ventricular performance mainly in the presence of a reduced afterload.

**References**


Letter to the editor about chapter 7

Beat to beat left ventricular performance in spontaneous atrial fibrillation does not depend on afterload

Accepted for publication in Heart

Professor Mark I.M. Noble
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The recent article in Heart on this subject by Muntinga et al.¹ confirms, using non-invasive techniques, the findings obtained more directly by Brookes et al.² that beat to beat left ventricular performance in spontaneous atrial fibrillation depends on beat to beat variation in cycle length, left ventricular end-diastolic volume (EDV), and contractility. Their contention that afterload is another independent determinant rests on their Figure 7.5 (page 75) in which ejection fraction is plotted against ESP/SV where ESP is end-systolic pressure and SV is stroke volume. However, ejection fraction is SV/EDV, so they have SV on both axes, which is invalid. A plot of a variable, in this case SV, against its reciprocal 1/SV will lead inevitably to an inverse hyperbolic relationship as a mathematical necessity. In this case it is accompanied by a small amount of scatter caused by the other variables, but the main relationship shown is a mathematical artefact and not an actual dependence of ejection fraction on afterload.

Figure 7.3 is also incorrect because SV/EDV is plotted against EDV (EDV appearing on both axes), but in this case a plot of SV against EDV would have resulted in a positive relationship and the same conclusion.

In the study of Brookes et al, the left ventricular systolic pressure (directly measured with catheter-tip manometer) varied rather little during atrial fibrillation, which the authors attributed to clamping of the arterial systolic pressure by peripheral mechanisms. This finding and the invalidity of using ESP/SV (above) raises the question, “What is the afterload in the intact mammal?” I prefer not to use the term because there are so many different indices that purport to be “afterload”; I prefer to use the measured variable. Many workers in the field would accept using left ventricular systolic pressure. However, the term was invented to describe the constant force or stress in an isolated strip of muscle when shortening during contraction in a particular experimental set-up. The only corresponding variable variable in the intact human is systolic wall stress, but this declines during ejection that there is no single value. However inspection of directly measured left ventricular pressure-volume loops during spontaneous atrial fibrillation (2) shows that, most of the time, contraction takes place over similar mid-systolic values implying the same wall stress.
Of course, left ventricular performance will depend on "afterload" (If that can be defined) if "afterload" changes, but my conclusion is that in spontaneous atrial fibrillation there are no important changes.

References


Response

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In his letter, Professor Noble concludes, based on a recent study by Brookes et al,¹ that in chronic atrial fibrillation there are no important beat to beat changes of left ventricular afterload measured by left ventricular systolic pressure. Based on figure 7.5 of our article he concludes that the relation between afterload as calculated by the ratio of end systolic pressure (ESP) and stroke volume (SV), and ejection fraction is a mathematical artefact, instead of a physiological relationship.² He rejects left ventricular afterload as an important measure of left ventricular performance. The conclusion that afterload, preload and contractility are independent determinants of left ventricular ejection fraction however rests on a multivariate model of left ventricular ejection fraction.

In our study we non-invasively measured peripheral blood pressure, which we assumed to change, parallel with aortic pressure.² We calculated left ventricular volumes in millilitres from results of measurements with a "Nuclear Stethoscope" and a "Swan Ganz" catheter. Left ventricular afterload was then calculated as the fraction of ESP and SV. The validity of the ESP to SV relationship as a measure of effective arterial elastance was tested by Sunagawa et al.³ The arterial system properties then consist of three elements: peripheral resistance, arterial compliance and characteristic impedance of the arterial system. In table 7.1 of our article we demonstrate that this measure of afterload varies significantly from beat to beat in each investigated patient. The argumentation that a limited variation of end systolic pressure in patients with atrial fibrillation (in our patient group the average ESP was 126 and the average standard deviation of ESP was 13 mmHg) is measured because arterial pressure is damped by baroreceptor and other reflex mechanisms.
confirms in our opinion the observation that afterload, which unites the above mentioned properties of the arterial system changes from beat to beat.

In experimental models of the intact cardiovascular system a unique relationship exists in the left ventricle between SV and ESP when preload and contractility remain constant.\textsuperscript{4,5} In this situation, afterload determines the exact value for SV and ESP. SV is therefore inevitably both a measure of left ventricular performance, and a measure of left ventricular afterload. Indeed, this results in a mathematical relationship between ejection fraction and afterload. The other measured factors, end diastolic volume and ESP, also influence the measure of interdependence between ejection fraction and afterload, and can determine the value of this relationship. The conclusion in our article that ejection fraction in patients with atrial fibrillation is dependent on afterload (apart from the dependency on preload and contractility) is based on the multivariate analysis. Figure 7.5 is added to illustrate the univariate relation between ejection fraction and afterload. It further illustrates that SV importantly determines the direction and nature of the relation between ejection fraction and afterload. The multivariate analysis is also the basis for the conclusion that ejection fraction is dependent on preload. The univariate relation between ejection fraction and preload is illustrated with figure 7.3. If this relation had only a mathematical nature, a negative hyperbolic relation would have been found (1/EDV versus EDV) instead of a linear positive relation. SV apparently determines the direction of this relation. This finding can physiologically be explained by the Frank-Starling mechanism.\textsuperscript{6} The differences between figures 7.3 and 7.5 contribute in our opinion largely to their importance to the present article.

We agree with Professor Noble that a mathematical relationship exists between ejection fraction and the described measures of afterload and preload, but we do not share his opinion that we may not use these measures in a model to describe left ventricular beat to beat performance.

References
