ENDOCARDIAL VIABILITY RATIO AND ISCHAEMIC DYSFUNCTION OF THE LEFT VENTRICLE DURING HALOTHANE ANAESTHESIA§

J. J. LEHOT, B. LEONE, C. M. FRANCIS, G. R. CUTFIELD AND P. FOËX

Endocardial viability ratio (EVR = diastolic pressure–time index : systolic pressure–time index) has been proposed as a reliable index of oxygen supply : demand ratio of the normal myocardium [1]. This index is used in patients with coronary artery disease [2], but there has been no study relating its reliability in the presence of a constricted coronary artery; an experimental model of constricted coronary artery could provide a means to assess this. Regional dysfunction of the canine myocardium has been shown to be a sensitive index of ischaemia in presence of coronary critical constriction and halothane anaesthesia [3]. This study was designed to compare EVR and regional myocardial dysfunction in the presence of compromised myocardial blood flow in dogs.

MATERIALS AND METHODS

Instrumentation

This study was performed in 13 mongrel dogs weighing 14–30 kg. The dogs were premedicated with morphine sulphate 0.3 mg kg⁻¹ i.m. Anaesthesia was induced with thiopentone 15 mg kg⁻¹ and the trachea intubated. Constant-volume intermittent positive-pressure ventilation was instituted at a rate of 12 b.p.m. and tidal volume 30 ml kg⁻¹, with a mixture of 70% oxygen in nitrogen to which sufficient carbon dioxide was added to maintain end-tidal carbon dioxide concentration at 5.3%. Anaesthesia was maintained during preparation with 0.7–1.5% inspired halothane supplied by a Fluotec vaporizer (Cyprane, Keighley, England) calibrated with a refractometer. In preliminary studies, we determined that this technique had the advantage of speeding up the attainment of stable alveolar anaesthetic concentrations and overcoming any tendency to develop atelectasis. Temperature was measured in mid-

SUMMARY

In normal hearts, the critical value of the endocardial viability ratio (EVR) is thought to be less than 0.5. As myocardial regional dysfunction is a sensitive index of subendocardial ischaemia, the relationship between EVR and regional function has been studied in an experimental model of coronary artery constriction. In 13 dogs anaesthetized with halothane (0.5–2.0% inspired concentration), diastolic and systolic pressure time indices were obtained by planimetry, and their ratio (EVR) correlated with regional function. Halothane alone caused a significant reduction in EVR from 1.38±0.08 to 1.15±0.04 (mean±SEM). In the presence of coronary artery constriction a similar decrease in EVR was observed and was accompanied by post-systolic shortening (PSS), an indicator of regional dysfunction. At high concentrations of halothane, there was an inverse correlation between reduction in EVR and increase in PSS. Mean EVR of approximately 0.9 (mean = 0.92±0.02) was associated with significant worsening of regional function.


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oesophagus and maintained between 37 and 38 °C by a heating element incorporated to the operating table.

The left common carotid artery was exposed and a rigid 7 French-gauge polyethylene catheter inserted and advanced to within 1 cm of the aortic valve for removal of blood samples and measurement of systemic arterial pressure via a Statham pressure transducer. An i.v. cannula was threaded via the femoral vein into the inferior vena cava for infusion of 0.9 % saline at a constant rate of 4 ml kg⁻¹ h⁻¹.

A left thoracotomy was performed, the 5th and 6th ribs excised, and the heart exposed and suspended in a pericardial cradle. A rigid cannula was inserted in the left ventricle via a stab wound in the apical dimple and connected to a Statham pressure transducer.

The left anterior descending coronary artery (LAD) was dissected free distal to the second major diagonal branch. A 3-O woven Dacron suture was placed loosely about the artery and connected to a micrometer-controlled spring-suspended snare that could be tightened or loosened in increments of 2.5 μm. In six animals an electromagnetic flow probe (SEM 230 SE Laboratories) of appropriate diameter was placed around the vessel proximal to the snare and a pneumatic occluder was positioned distal to the probe to obtain zero flow readings.

Two pairs of ultrasonic piezoelectric crystals were placed in the subendocardium, at an angle of 90° to the long axis of the heart, using the technique previously described [3]. One pair was implanted in the area supplied by the LAD coronary artery distal to the isolated segment, the other in the area supplied by the left circumflex coronary artery (LC) to serve as a control segment.

Regional myocardial function

Regional myocardial function was assessed by obtaining continuous measurements of segment length between each pair of crystals, based upon measurement of ultrasonic transit times. A continuous analogue signal of dynamic segment length was provided by a repetitive stimulation rate of 1 kHz. The transit time was calibrated in steps of 1 μs generated by a quartz-controlled oscillator.

The signals were recorded on a Mingograf 81 eight-channel recorder (Elema Schonander, Stockholm, Solna, Sweden) at a paper speed of 100 mm s⁻¹. Figure 1 shows length tracings in relation to

the haemodynamic variables recorded. End-diastole was defined as the time of onset of the sharp upstroke of the first derivative of left ventricular pressure (LV dP/dt) signal, and end-systole as the dicrotic notch on the aortic pressure tracing.

End-diastolic length (EDL), end-systolic length (ESL), maximum length during systole (SLₘₐₓ), minimum length during systole (SLₘᵢₙ), and minimum length during diastole (DLₘᵢₙ) were obtained from the calibrated traces. The following formulae were used for derivatives of lengths:

Systolic shortening

\[
\Delta SL = SLₘₐₓ - SLₘᵢₙ \\
SL(%) = (\Delta SL / SLₘₐₓ) \times 100
\]

Post-systolic shortening

\[
PSS = ESL - DLₘᵢₙ \\
PSS(%) = PSS / (SLₘₐₓ - DLₘᵢₙ)
\]

Global haemodynamics

Arterial and left ventricular pressures were recorded. LV dP/dt was obtained by on-line differentiation. Heart rate was calculated from the R–R interval.
Diastolic pressure time index (DPTI) and systolic pressure time index (SPTI) were measured by planimetry, DPTI as the area under the curve between aortic and left ventricular pressures, and SPTI as the area under the ventricular pressure curve during systole [4] (fig. 1).

EVR was calculated as the ratio DPTI : SPTI in the same heart beat.

Procedure

After completion of the surgical preparation of the animal, a 1-h period of stabilization was allowed and the experiments were initiated at a minimum of 4 h after the administration of thiopentone.

Control recordings were obtained at a halothane concentration of 0.5–0.7 %. The inspired halothane concentration was increased subsequently in steps to 1.0 %, 1.5 % and finally 2.0 %. Each level of inspired halothane concentration was maintained for 10 min and recordings were obtained, since preliminary studies had demonstrated that circulatory stability was always achieved within 7 min. The halothane concentration was then returned to 0.5–0.7 %. All recordings were obtained during a 20-s period of apnoea at end-expiration.

A critical constriction of the LAD coronary artery was then imposed. In the first seven dogs the technique to obtain critical constriction was as previously reported [3]. Briefly, the snare was tightened by increments of 50 μm at 30-s intervals until changes indicative of ischaemia were observed in the LAD segment unaccompanied by such changes in the LC segment. The snare was then loosened by 50–100 μm until the ischaemic changes resolved. After a variable recovery interval, the micrometer was retightened by 12.5-μm increments until early changes of LAD contraction again occurred. The snare was then reloosened by 6.25 μm until these changes resolved, and a 20-min period allowed to elapse. A 90-s period of anoxia with 100 % nitrogen was then imposed. If ischaemic changes in LAD contraction occurred unaccompanied by similar changes in LC contraction, this degree of narrowing was considered a critical constriction. If not, further narrowing was imposed in 6.25–12.5 μm increments until a differential response to hypoxia was obtained.

In the last six dogs, constriction was applied in the same way, but was deemed to be critical if the degree of narrowing applied was such that 95 % of the normal hyperaemic response to a 10-s occlusion of the vessel was abolished. This method was used to avoid the systemic consequences of hypoxaemia. Coronary flow was used to establish the critical nature of constriction and was not measured later, thus avoiding repeated zero flow calibration occlusions which might disturb LAD segment function and exaggerate ischaemic dysfunction. These two methods of producing critical constriction demonstrated the same effects on global and regional myocardial function; thus these two sets of experiments were combined for statistical analysis.

Once a satisfactory and stable critical constriction had been obtained, and after a 20-min rest period, recordings were obtained as in the previous phase.

Statistics

The data were digitalized manually. Results were analysed for statistical significance using two-way analysis of variance followed by Duncan’s multiple range test utilizing an SAS program—a commercially available statistical analysis program (SAS Institute, Cary, NC, U.S.A.). Chi-square test and linear regression were used when appropriate. \( P < 0.05 \) was considered significant. Results are expressed as mean ± SEM.

RESULTS

Global haemodynamics and EVR (table I)

Heart rate did not change significantly, whilst systolic arterial pressure, diastolic arterial pressure, DPTI, SPTI and EVR decreased significantly with increased halothane concentration, but the response was the same in the presence or absence of critical constriction.

Myocardial regional function (table I)

Before critical constriction, end-diastolic length increased and systolic shortening decreased significantly in both segments with increasing halothane concentrations.

With critical constriction of the LAD coronary artery, systolic shortening in the ischaemic segment was significantly more depressed at all but one halothane concentrations. However, the non-ischaemic segment (LC segment) was significantly less depressed than before constriction at 2.0 % halothane concentration.
**TABLE I.** Haemodynamic and regional function effects (mean ± SEM) of increasing halothane concentration before and during constriction of the left anterior descending coronary artery in dogs (n = 13). Statistical significance (analysis of variance and Duncan's test): comparison with preconstriction or constriction control (0.5–0.7%): *P < 0.05, **P < 0.01; comparison with same inspired concentration preconstriction: ††P < 0.05, ‡‡P < 0.01.

<table>
<thead>
<tr>
<th>HR (beat min⁻¹)</th>
<th>0.5–0.7</th>
<th>1.0</th>
<th>1.5</th>
<th>2.0</th>
<th>0.5–0.7</th>
<th>1.0</th>
<th>1.5</th>
<th>2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAP (mm Hg)</td>
<td>102.5 ± 3.0</td>
<td>89.7 ± 3.1**</td>
<td>77.1 ± 3.0**</td>
<td>60.9 ± 3.4**</td>
<td>98.3 ± 4.1</td>
<td>86.7 ± 3.4**</td>
<td>76.3 ± 4.1**</td>
<td>62.5 ± 5.4**</td>
</tr>
<tr>
<td>DAP (mm Hg)</td>
<td>74.8 ± 3.3</td>
<td>63.2 ± 3.6**</td>
<td>52.1 ± 3.3**</td>
<td>39.8 ± 2.9**</td>
<td>70.8 ± 4.5</td>
<td>60.5 ± 3.0**</td>
<td>52.5 ± 3.9**</td>
<td>42.0 ± 3.7**</td>
</tr>
<tr>
<td>DPTI (mm Hg s)</td>
<td>26.0 ± 1.2</td>
<td>22.2 ± 1.0**</td>
<td>18.0 ± 0.7**</td>
<td>13.4 ± 0.8**</td>
<td>24.8 ± 1.8</td>
<td>20.5 ± 1.1**</td>
<td>17.6 ± 1.5**</td>
<td>12.7 ± 1.2**</td>
</tr>
<tr>
<td>SPTI (mm Hg s)</td>
<td>19.2 ± 1.0</td>
<td>17.2 ± 0.5*</td>
<td>15.2 ± 0.5**</td>
<td>11.6 ± 0.7**</td>
<td>19.0 ± 0.9</td>
<td>17.2 ± 0.7*</td>
<td>15.0 ± 0.8**</td>
<td>12.0 ± 1.1**</td>
</tr>
<tr>
<td>EVR</td>
<td>1.38 ± 0.08</td>
<td>1.30 ± 0.06</td>
<td>1.19 ± 0.04**</td>
<td>1.15 ± 0.04**</td>
<td>1.30 ± 0.07</td>
<td>1.20 ± 0.05*</td>
<td>1.16 ± 0.05*</td>
<td>1.06 ± 0.04**</td>
</tr>
<tr>
<td>LAD</td>
<td>11.68 ± 0.67</td>
<td>11.75 ± 0.70</td>
<td>11.92 ± 0.76</td>
<td>12.18 ± 0.81**</td>
<td>11.51 ± 0.59</td>
<td>11.65 ± 0.62</td>
<td>11.89 ± 0.68*</td>
<td>12.27 ± 0.74**</td>
</tr>
<tr>
<td>ΔSL (%)</td>
<td>21.3 ± 1.3</td>
<td>18.1 ± 1.1**</td>
<td>15.3 ± 1.1**</td>
<td>11.7 ± 1.2**</td>
<td>19.0 ± 1.5†</td>
<td>16.3 ± 1.4*</td>
<td>12.1 ± 1.4** ††</td>
<td>7.5 ± 1.0** ††</td>
</tr>
<tr>
<td>PSS (%)</td>
<td>0.5 ± 0.5</td>
<td>0.1 ± 0.6</td>
<td>2.2 ± 1.3</td>
<td>11.8 ± 5.5*</td>
<td>4.5 ± 2.6</td>
<td>7.8 ± 3.3</td>
<td>26.2 ± 9.9†</td>
<td>61.4 ± 19.3** ††</td>
</tr>
<tr>
<td>LC</td>
<td>9.38 ± 0.44</td>
<td>9.55 ± 0.42</td>
<td>9.71 ± 0.44**</td>
<td>9.90 ± 0.43**</td>
<td>9.38 ± 0.46</td>
<td>9.42 ± 0.47</td>
<td>9.61 ± 0.46*</td>
<td>9.89 ± 0.46**</td>
</tr>
<tr>
<td>ΔSL (%)</td>
<td>14.7 ± 1.4</td>
<td>13.7 ± 1.1</td>
<td>11.8 ± 1.1**</td>
<td>9.7 ± 0.9**</td>
<td>13.2 ± 1.3</td>
<td>11.6 ± 1.1</td>
<td>10.5 ± 0.9**</td>
<td>10.4 ± 0.9** ††</td>
</tr>
<tr>
<td>PSS (%)</td>
<td>6.8 ± 6.1</td>
<td>7.0 ± 4.6</td>
<td>11.7 ± 5.5*</td>
<td>13.2 ± 4.7*</td>
<td>10.1 ± 5.1</td>
<td>18.1 ± 10.3</td>
<td>25.7 ± 9.6** ††</td>
<td>23.1 ± 10.6</td>
</tr>
</tbody>
</table>

**FIG. 2.** Comparison of post-systolic shortening (PSS), according to the value of endocardial viability ratio (EVR) (mean ± SEM) at the three higher halothane concentrations. *P value refers to unpaired Student's t test.

**TABLE II.** Number of observations according to the value of endocardial viability ratio (EVR) and the presence of post-systolic shortening in ischaemic LAD segment (n = 56, x² = 9.87, df = 1, P < 0.01).

<table>
<thead>
<tr>
<th>EVR</th>
<th>PSS</th>
<th>No PSS PSS present</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.25</td>
<td>14</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>1–1.25</td>
<td>14</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>&gt;1.25</td>
<td><strong>4</strong></td>
<td><strong>22</strong></td>
<td><strong>10</strong></td>
</tr>
</tbody>
</table>

*PSS in the LC segment was significant at the two higher halothane concentrations, but was less than 2.5% (P < 0.01) (Table II). As there was essentially no PSS in the ischaemic LAD segment, PSS was more common when EVR was less than 1.25 (P < 0.01) (Table II). In the LAD segment, with critical constriction, PSS up to 61.4% ±19.3% of total systolic shortening occurred at halothane concentrations of 2.0%.
with the lowest halothane concentration, we compared values of PSS in the three higher halothane concentrations based upon the values of EVR. PSS was lower when EVR was greater than 1.25:0.08 ± 0.04 mm, compared with 0.50 ± 0.10 mm (P < 0.025) for EVR less than 1.25. This difference in PSS increased when comparing the extreme values of EVR (fig. 2). Similarly, EVR was greater (1.21 ± 0.04) when PSS was absent than when it was present (1.08 ± 0.04) (P < 0.025).

When individual EVR and PSS values in the LAD ischaemic segment were correlated, there was a significant negative linear correlation (r = -0.41, slope = -0.89 ± 0.28, n = 52, P < 0.01). Moreover, when halothane concentration was increased from 1.5 to 2.0%, there was a correlation between increase in PSS and decrease in EVR (r = -0.65, slope = -1.35 ± 0.48, n = 13, P < 0.02) (fig. 3); the regression line passed through the origin of the axes.

Several haemodynamic parameters, including the rate–pressure product (HR x SAP), were compared when EVR was less than or equal to 1.00 and greater than 1.25 (table III). These parameters were not significantly different in the two sets, but the lower values of EVR were associated with significantly lower SPTI (P < 0.05) and DPTI (P < 0.001). Despite the significant difference in DPTI, there was no correlation between reduction in DPTI and PSS. There was also no correlation between EVR and systolic shortening.

**DISCUSSION**

Determination of EVR has been suggested as a method to monitor ischaemia of the inner layers of the myocardium which are particularly susceptible to ischaemia [5]. In their original study, Buckberg and co-workers [6] observed that the inner:outer myocardial flow ratio began to decrease when the DPTI:SPTI ratio decreased below a range of 0.5–0.8. Griggs and Chen [7] showed, in dogs with experimental aortic incompetence, that the subendocardial lactate:pyruvate ratio began to increase when aortic and left ventricular pressures gave a ratio equivalent to a DPTI:SPTI ratio of 0.4. In healthy men studied by Barnard and co-workers [8], ST depression on sudden maximal exercise was not seen until EVR was less than 0.45, and no ST changes were seen with EVR greater than this value. Thus Hoffman and Buckberg [1] suggested that a more correct figure to choose for the critical value below which the inner:outer flow ratio begins to decrease is 0.4–0.5. However, in 35 patients, Philips and co-workers [9] showed that, in the early period after cardiopulmonary by-pass for correction of valvular or coronary artery disease, EVR had prognostic value: when EVR was less than 0.7, the patients needed cardiac assistance using intra-aortic balloon counterpulsation, and the five patients with EVR less than 0.55 died. There is no experimental study relating the reliability of EVR in presence of critical coronary constriction and anaesthesia.

PSS has been observed to be a marker of regional ischaemia [3]. Reductions in systolic shortening and systolic thickening have also been
utilized as markers of regional function and ischaemia by various groups [10-13]. However, all of these investigators used a model utilizing a constant level of anaesthesia and thus a constant degree of myocardial depression. In this study, as in that of Lowenstein and colleagues [3], the anaesthetic depth was varied in order to examine its effects on compromised myocardium and regional myocardial function. As seen during the control period when coronary arteries are undisturbed, increases in halothane concentration cause myocardial depression and thus decrease systolic shortening and, by inference, systolic thickening. However, as Lowenstein's group [3] observed, it is only after critical constriction had been applied that substantial PSS occurred in response to deepening halothane anaesthesia and was far more suggestive of ischaemic dysfunction than the significant but relatively modest worsening of regional shortening. Therefore, in the context of varying depth of anaesthesia, PSS is a more sensitive indicator of myocardial ischaemia than is the reduction of systolic shortening. PSS may occur when the excitation-contraction coupling is disturbed by other interventions such as exposure to the combined effect of verapamil and halogenated anaesthetics [14,15] or the addition of nitrous oxide to halothane [16]. However, none of these combinations was used in the present study.

Using PSS as a marker of ischaemia, it can be seen that EVR less than 1.0 was associated with a large amount of PSS while EVR greater than 1.25 was associated with little or no PSS (fig. 2). An EVR of greater than 1.25 is seldom associated with PSS (table II). However, an EVR of less than 1.0 appears to be a good predictor of ischaemia in the presence of critical coronary artery stenosis. The significant inverse correlations between PSS and EVR ($r = 0.41, P < 0.01$) and between changes in EVR and changes in PSS at high halothane concentrations ($r = -0.65, P < 0.02$) (fig. 3) confirm the predictive value of EVR for myocardial ischaemia.

The critical value of EVR appears to be much greater than previously proposed values of 0.4 and 0.7 [7,9]. This may not be surprising. Whilst Sarnoff and colleagues [17] showed a close relationship between the tension-time index (SPTI) and myocardial oxygen consumption in a canine model, others showed that this index only predicts myocardial oxygen consumption with wide individual variability [18], because changes in contractility and ventricular dimensions are not correctly reflected. In the current study, SPTI may have correlated poorly with oxygen consumption because contractility decreased and end-diastolic dimensions increased. Indeed, the 21% decrease of SPTI on increasing the halothane concentration from 0.5% to 1.5% is smaller than the 26% decrease of myocardial oxygen consumption observed by Smith and colleagues [19]. However, the 31% decrease in coronary blood flow observed by these authors is similar to the decrease of DPTI before critical constriction in the present study.

However, critical constriction reduces coronary blood flow by approximately 20% and makes it proportional to the driving pressure [20]. Since critical constriction is not accompanied by significant haemodynamic alterations, DPTI remains unchanged and overestimates oxygen supply. Moreover, the values of DPTI are comparable only for the same impairment of the coronary arteries and the same oxygen content of arterial blood [4]. The overestimation of DPTI is probably more important than the overestimation of SPTI. If DPTI overestimates oxygen supply in the presence of coronary artery stenosis, the critical value for EVR is bound to be higher for the compromised heart than for the normal heart. It is therefore not surprising that the critical value of EVR ($0.92 \pm 0.02$) was found to be much higher than previously reported.

In our study, EVR was calculated by planimetry, but EVR can be monitored if peripheral

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**Fig. 4.** DPTI and SPTI as calculated by Philips' formula [9]. Note that DPTI is overestimated and SPTI underestimated, as compared with measurement by planimetry. IVR = isovolumic ventricular relaxation; IVC = isovolumic ventricular contraction; $Ts$ and $Td$ = duration of systole and diastole, respectively, as available in absence of recording of left ventricular pressure; LVP = left ventricular pressure; SAP = systemic arterial pressure; PCWP = pulmonary capillary wedge pressure which approximates left ventricular end-diastolic pressure.
arterial and pulmonary capillary wedge pressures are measured (fig. 4) instead of aortic and left ventricular pressures [9, 21]. The following formula can be used:

\[
EVR = \frac{DPTI}{SPTI} = \frac{(DP - PCWP) \times Td}{SP \times Ts}
\]

where \(DP = \text{mean systemic diastolic pressure; PCWP = pulmonary capillary wedge pressure; SP = mean systemic arterial pressure; } Td = \text{diastolic time}; Ts = \text{systolic time.}

A commercially available computer can be used to calculate the EVR from the arterial and pulmonary artery pressures on a beat-by-beat basis using the above formula [21].

Using planimetry for EVR calculation introduces a difference between our experimental EVR measurement and estimation of EVR clinically. If the measurement of SPTI is compared in Philips’ formula [9] and in our measurements, the area under the ventricular pressure curve during isovolumic ventricular contraction (approximately 7% of SPTI) is not taken into account by Philips’ formula (fig. 4). This area is included in the measurement of DPTI in Philips’ formula, in addition to the area under the ventricular pressure curve during isovolumic relaxation, and thus DPTI is overestimated by approximately 10%. As a result, the critical value of EVR estimated by Philips’ formula should be almost 18% larger than our reported value,—approximately 1.08.

This study demonstrates an inverse relationship between EVR and regional myocardial dysfunction (PSS) in an area supplied by a critically constricted coronary artery, and shows that the critical value of EVR (0.96) is markedly higher than previously proposed and that EVR is a better indicator of ischaemia than conventional haemodynamics or rate-pressure product, both of which failed to predict the occurrence of EVR equal to or less than 1.0 (table III). If EVR is used to assess subendocardial viability, values of approximately 1.0–1.25 should be considered as the threshold for ischaemia in the presence of a critically stenosed coronary artery. However, as pointed out by Kaplan [21], the critical value of EVR cannot be predicted in patients with various degrees of coronary disease, and the changes in EVR may prove useful in assessing the adequacy of the oxygen balance in a given patient. Because EVR is easier to obtain than any measurement of regional wall motion, it may prove a valuable indicator of subendocardial ischaemia once it is accepted that the threshold value is much higher than previously reported.

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