Antagonism of Selectin Function Attenuates Microvascular Platelet Deposition and Platelet-Mediated Myocardial Injury After Transient Ischemia

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OBJECTIVES The goal of this study was to assess whether selectin blockade reduces myocardial platelet deposition and platelet-mediated injury after transient ischemia.

BACKGROUND METHODS Selectins participate in platelet adhesion to reperfused endothelium. Thiopental-anesthetized, open-chest pigs were subjected to mechanical injury of the left anterior descending coronary artery followed by a 48-min occlusion and 2 (n = 20) or 4 (n = 16) h of reperfusion. Fifteen minutes before occlusion, animals were blindly allocated to receive a continuous intravenous infusion of the selectin blocker fucoidan (30 μg/kg/min, plus a 1-mg/kg bolus in the latter group) or saline. In isolated rat hearts infused with thrombin-activated platelets, the effects of fucoidan (30 μg/ml) administered during reperfusion after 40 min of global ischemia were also analyzed.

RESULTS Fucoidan did not prevent the development of cyclic reductions in coronary flow, but reduced the content of 99mTc-labeled platelets in reperfused myocardium after 2 h of reperfusion (23.4 ± 3.3 vs. 42.1 ± 8.3 × 106 platelets/g in treated and untreated animals, p = 0.03) and attenuated the impairment in the coronary flow reserve and reduced infarct size after 4 h (53 ± 2% vs. 73 ± 5% of the ischemic region, respectively, p = 0.003). Treated animals showed a trend toward less neutrophil infiltration early after reperfusion, but not after 4 h. In isolated hearts, fucoidan improved functional recovery and reduced coronary resistance and lactate dehydrogenase release, lacking any beneficial effects if given in the absence of platelets.

CONCLUSIONS The results suggest that selectin-dependent adhesion is a prominent mechanism of platelet deposition in reperfused cardiac microvessels and highlight its potential as a therapeutic target in patients with acute myocardial infarction.

The beneficial effects of prompt restoration of coronary flow in patients with acute myocardial infarction may be limited by insufficient tissue perfusion. Among the factors contributing to this phenomenon (1), platelets deposited in capillaries and venules likely play a prominent role. Supporting this, platelets accumulate preferentially in the most damaged areas of reperfused myocardium (2–5), and studies addressing the effect of these cells after transient ischemia have shown, with some exceptions (6,7), that platelets may hinder blood flow and contractile recovery or increase myocardial injury (8–11).

The mechanisms of platelet deposition in reperfused coronary microvessels are incompletely understood and likely involve both a direct adhesion to the endothelium and binding to adherent leukocytes (12). Interactions between endothelial intracellular adhesion molecule-1 and platelet glycoprotein (GP) IIb/IIIa and between P-selectin expressed on platelets or endothelial cells and their corresponding ligands have been demonstrated after intestinal (13,14), hepatic (15), or cerebral (16) ischemia, but their weight in the heart remains unclear. In this respect, whether GP IIb/IIIa blockade reduces microvascular platelet deposition or myocardial injury after reperfusion independent of its effects on the culprit lesion is controversial (5,17–19). On the other hand, interfering with P-selectin function has long been proposed as a strategy to reduce neutrophil infiltration and subsequent myocardial damage after reperfusion (20–23), but the effects of this approach on microvascular platelet adhesion are unknown.

Accordingly, we aimed to investigate whether selectin blockade reduces microvascular platelet deposition and platelet-mediated myocardial injury after transient ischemia. Experiments were conducted in anesthetized pigs and in isolated rat hearts receiving or not receiving fucoidan, a sulfated polysaccharide that binds P- and L-selectin and has been extensively used as a selectin blocker (22–24).
due to LAD reoclusion. A total of 20 experiments in series Erythrocytes, /H11003 was tightened for 48 min, an occlusion period usually and nine (four receiving fucoidan and five vehicle, p
artery occlusion or to refractory ventricular fibrillation (VF),
dial platelet deposition 2 h after reperfusion, and series were performed: series A was destined to quantify myocar-
which reperfusion was allowed. Two series of experiments
B—in which animals allocated to fucoidan also received a
intracoronary catheter as described (4,5). Then, the snare
after start of the infusion, the LAD was injured with an
reperfusion in vivo (23)—or isotonic saline. Fifteen minutes
that has reduced neutrophil adhesion and infarct size after
Association on research animal use adopted in November
and in accordance with the position of the American Heart
Values are mean /H11006
Table 1. Hematologic Parameters and Results of Coagulation Assays

<table>
<thead>
<tr>
<th></th>
<th>Series A</th>
<th>Series B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fucoidan (n = 10)</td>
<td>Vehicle (n = 10)</td>
</tr>
<tr>
<td></td>
<td>Initial</td>
<td>Final</td>
</tr>
<tr>
<td>Erythrocytes, × 10^12/μl</td>
<td>4.3 ± 0.3</td>
<td>4.2 ± 0.2</td>
</tr>
<tr>
<td>Leukocytes, × 10^9/μl</td>
<td>15.2 ± 1.1</td>
<td>10.5 ± 1.1</td>
</tr>
<tr>
<td>Platelets, × 10^12/μl</td>
<td>442 ± 20</td>
<td>358 ± 21*</td>
</tr>
<tr>
<td>Mean platelet volume, fl</td>
<td>7.7 ± 0.3</td>
<td>7.5 ± 0.3</td>
</tr>
<tr>
<td>Prothrombin time, %</td>
<td>111 ± 3</td>
<td>111 ± 2</td>
</tr>
<tr>
<td>Activated partial thromboplastin time, s</td>
<td>24 ± 2</td>
<td>25 ± 2</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. *p < 0.001 for the effect of treatment.

Abbreviations and Acronyms
- CFR = cyclic flow reduction
- GP = glycoprotein
- LAD = left anterior descending coronary artery
- LDH = lactate dehydrogenase
- LVEDP = left ventricular end-diastolic pressure
- MPO = myeloperoxidase
- VF = ventricular fibrillation

METHODS

Animal preparation. After obtaining institutional approval, and in accordance with the position of the American Heart Association on research animal use adopted in November 1984, 49 pigs of either gender (35 ± 1 kg) were sedated with 10-mg/kg intramuscular azaperone, anesthetized with thiopental (10-mg/kg intravenous bolus and continuous infusion), intubated, and ventilated with room air. After sternotomy, the left anterior descending coronary artery (LAD) was dissected in its midssegment and surrounded by a snare. A Doppler flow probe (Transonic Systems, Ithaca, New York) was placed immediately distal to the snare, and a Millar (Houston, Texas) micromanometer-tipped catheter advanced into the left ventricle.

Study protocol. Animals were randomly and blindly allo-
cated to receive a continuous intravenous infusion of 30 µg/kg/min fucoidan (Sigma, St. Louis, Missouri)—a dose that has reduced neutrophil adhesion and infarct size after reperfusion in vivo (23)—or isotonic saline. Fifteen minutes after start of the infusion, the LAD was injured with an intracoronary catheter as described (4,5). Then, the snare was tightened for 48 min, an occlusion period usually causing incomplete infarctions in this model (4,25), after which reperfusion was allowed. Two series of experiments were performed: series A was destined to quantify myocardial platelet deposition 2 h after reperfusion, and series B—in which animals allocated to fucoidan also received a 1-mg/kg bolus—to assess infarct size 4 h after reperfusion.

A total of four animals were excluded due to left main artery occlusion or to refractory ventricular fibrillation (VF), and nine (four receiving fucoidan and five vehicle, p = NS) due to LAD reoclusion. A total of 20 experiments in series A (10 per group) and 16 in series B (8 per group) remained valid.

Study monitoring. Hematologic determinations and bleeding time were serially measured (5). One electrocardiographic lead, aortic pressure, coronary blood flow, and left ventricular pressure were amplified, digitized (ML795-PowerLab, AD Instruments, Mountain View, California), and recorded. When VF occurred, 10 to 20 J internal shocks were applied.

Myocardial platelet content. The previous day, autolo-
gous platelets were labeled with 99mTc-hexamethyl-
propyleneamineoxime as described (4,5) and immediately reinjected in animals from series A. After excising the heart, the aortic root was perfused (4) to wash the coronary vasculature, and the heart sliced. The radioactivity of fragments obtained from the reperfused anteroseptal region (2.9 ± 0.1 g) and from the inferior region (3.8 ± 0.2 g), along with that of 1-ml blood, was counted, and myocardial platelet content calculated as described previously (4,5).

Reactive hyperemic response. At baseline, 15, 60, and 180 min after reperfusion, the LAD was occluded for 25 s immediately proximal to the occlusion site in series B. Peak flow was the maximum mean flow after these occlusions, expressed as a percentage of the respective baseline values.

Infarct size and neutrophil infiltration. In series B, the heart was excised 4 h after reperfusion and sliced. The area at risk (in vivo fluorescein) and infarct size (triphenyltetra-
chorium chloride reaction) were calculated as described (4,5,25).

Myeloperoxidase (MPO) activity, an index of neutrophil infiltration, was determined as described earlier (4,5) in samples (1.3 ± 0.1 g) from reperfused and control myocardium. Myeloperoxidase activity was also analyzed in eight additional pigs allocated to fucoidan or vehicle and receiving the same protocol as in series A, but only 1 h of reperfusion. One slice was processed for histologic analysis, stained with hematoxylin-eosin, and examined with an Olympus (Tokyo, Japan) IMT2 microscope. Neutrophil infiltration was scored from 0 to 3 as previously described (5).

Experiments in isolated rat hearts. Porcine platelets were isolated and resuspended in modified Tyrode buffer as described earlier (11). After activation with 0.1-U/ml hu-
man thrombin, platelets were treated or not treated with 30-μg/ml fucoidan—a concentration that has preserved ventricular function in blood-reperfused isolated hearts (22)—for 5 min at 37°C (final concentration, 4 × 10^10 platelets/l). We previously assessed that platelet incubation with this concentration of thrombin induces a marked increase in P-selectin expression but not aggregation (11), which is unaffected by subsequent incubation with fucoidan.

Hearts from pentobarbital-anesthetized male Sprague-Dawley rats (n = 16) were placed in a Langerdoff apparatus, perfused at 10 ml/min with modified Krebs-Henseleit bicarbonate buffer (11,25). After equilibration, hearts were subjected to 40 min of no-flow ischemia followed by 60 min of reperfusion. Thrombin-activated platelets were infused into the coronary flow at a constant rate of 0.5 ml/min. Hearts were infused with 10^8 untreated platelets during the last 5 min of equilibration and with 10^8 platelets, treated or not treated with fucoidan, during the first 5 min of reperfusion. Eight additional hearts subjected to the same protocol received or did not receive fucoidan for 5 min before ischemia in the absence of platelets. Left ventricular end-diastolic pressure (LVEDP), developed pressure, perfusion pressure, and lactate dehydrogenase (LDH) release were measured (11,25).

**Statistical analysis.** Statistical analysis was performed using SPSS software. Values are expressed as mean ± SEM. Paired t tests and repeated measures analysis of variance were used to assess changes in physiologic parameters and their modification by treatment as well as differences between reperfused and control myocardium within the same animal. Independent, prespecified intergroup comparisons were performed by Student t tests, with the exception of those involving histologic scores, which were subjected to the Mann-Whitney U test. Values of p < 0.05 were considered significant.

**RESULTS**

**Hematologic determinations and bleeding time.** Blood cell counts and coagulation parameters experienced minor changes and were unaffected by treatment allocation, with the exception of platelet count, which was reduced by about 20% by fucoidan (Table 1). Bleeding time increased slightly in controls and showed a rapid and sustained prolongation after start of fucoidan (Fig. 1).

**Hemodynamic data, ventricular arrhythmias, and coronary blood flow.** Heart rate and mean aortic pressure were within the normal range at baseline and increased (p < 0.01) during the experiment (Table 2). Left ventricular end-diastolic pressure increased after coronary occlusion (p < 0.01) and remained stable thereafter, without between-group differences. Treated and untreated animals had a similar incidence of VF during coronary occlusion (22% in both arms) and immediately after reperfusion (33% vs. 39%, p = NS). Baseline blood flow at the LAD averaged 16 ± 2 ml/min. The total number of cyclic flow reductions (CFRs) during the reperfusion period in treated and untreated animals was, respectively, 6 ± 2 versus 11 ± 2 in series A and 6 ± 2 versus 14 ± 6 in series B (p = 0.089 for comparison between both arms in pooled data). Approximately one-half of CFRs occurred during the first hour of reperfusion.

**Myocardial platelet content.** Platelet content averaged 12.5 ± 1.1 × 10^9/g in the control zone, without intergroup differences, and 32.7 ± 4.8 × 10^9/g in the reperfused zone (p < 0.001 with respect to the value in the control region). Platelet deposition in the reperfused zone did not correlate with the number of CFRs (r = 0.14) and was significantly reduced by fucoidan (Fig. 2).

**Reactive hyperemic response.** At baseline, peak hyperemic response after a brief LAD occlusion was 206 ± 21% of the preocclusion value in animals allocated to fucoidan and 279 ± 41% in controls (p = 0.14). The hyperemic response was severely blunted in both groups after reperfusion, but treated animals had a significantly better recovery of microvascular function (Fig. 3).

**Infarct size and neutrophil infiltration.** The area at risk averaged 8.4 ± 0.9% of biventricular mass in animals receiving fucoidan and 9.2 ± 1.5% in controls (p = NS). Infarct size was significantly reduced by fucoidan (53 ± 2% of the ischemic region vs. 73 ± 5% in controls, p = 0.003).

In all series, MPO activity values in reperfused myocardium were significantly higher than in the control zone (Table 3). There was a trend toward less MPO activity in reperfused myocardium in animals receiving fucoidan after 1 (p = 0.18) and 2 (p = 0.2) h of reperfusion, especially in the subepicardial zone. At 4 h, the values were much higher and comparable in both groups. Histologic scores for neutrophil infiltration in treated and untreated animals were, respectively, 0.5 ± 0.3 versus 1.4 ± 0.2 in series A (p = 0.04) and 2.3 ± 0.4 versus 1.7 ± 0.5 in series B (p = NS). Only two arteriolar microemboli were seen, in one treated animal from series B.

**Studies in isolated rat hearts.** The absence of microaggregates in the platelet suspensions was assessed by flow...
compared with hearts infused with untreated activated platelets, those receiving fucoidan during the initial minutes of reperfusion had similar hypercontracture, as assessed by the early peak in LVEDP, but showed improved contractile recovery as well as reduced coronary resistance (Fig. 4) and released less LDH (51 ± 8 vs. 81 ± 6 U/gdw, p = 0.008) throughout the reperfusion period (Fig. 5). If administered in the absence of platelets, fucoidan lacked any beneficial effects on these functional parameters or on LDH release (81 ± 5 vs. 79 ± 6 U/gdw, respectively, p = NS).

**DISCUSSION**

In the present study, selectin antagonism with fucoidan in a model of transient, thrombotic coronary occlusion in swine improved the coronary flow reserve and reduced the magnitude of platelet deposition and the extent of necrosis in reperfused myocardium, with these effects being paralleled by a diminished neutrophil infiltration only early after reflow. Fucoidan was also protective when administered after global ischemia in isolated rat hearts infused with activated platelets, but not if given before ischemia without platelets.

Platelet deposition in coronary microvasculature and reperfusion injury. Because platelets participate in the "no-reflow" phenomenon (1–5,8–11), attempts have been made to increase myocardial salvage after reperfusion by inhibiting platelet function. Cyclooxygenase inhibitors have failed to attenuate myocardial platelet accumulation (2–4), and studies have differed on the effects of GP IIb/IIIa blockers on microvascular function after reperfusion (17,18).

Recently in our laboratory, GP IIb/IIIa blockade stabilized the culprit lesion but did not reduce microvascular platelet accumulation or infarct size after transient coronary occlusion. Fucoidan was also protective when administered after global ischemia in isolated rat hearts infused with activated platelets, but not if given before ischemia without platelets.

**Table 2. Hemodynamic Data**

<table>
<thead>
<tr>
<th></th>
<th>Before CO</th>
<th>15 min CO</th>
<th>48 min CO</th>
<th>30 min R</th>
<th>2 h R</th>
<th>4 h R</th>
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<tr>
<td>Heart rate, beats/min</td>
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<td></td>
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<tr>
<td>Vehicle</td>
<td>76 ± 10</td>
<td>76 ± 9</td>
<td>79 ± 10</td>
<td>86 ± 8</td>
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<tr>
<td>Fucoidan</td>
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<td>82 ± 5</td>
<td>83 ± 4</td>
<td>88 ± 4</td>
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<td></td>
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<td></td>
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<tr>
<td>Vehicle</td>
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<td>97 ± 6</td>
<td>101 ± 5</td>
<td>103 ± 5</td>
<td>106 ± 7</td>
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<tr>
<td>Fucoidan</td>
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<td>94 ± 5</td>
<td>95 ± 5</td>
<td>99 ± 5</td>
<td>103 ± 5</td>
<td>—</td>
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<tr>
<td>LVEDP, mm Hg</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Vehicle</td>
<td>8 ± 1</td>
<td>14 ± 3</td>
<td>15 ± 4</td>
<td>13 ± 3</td>
<td>14 ± 2</td>
<td>—</td>
</tr>
<tr>
<td>Fucoidan</td>
<td>6 ± 2</td>
<td>13 ± 2</td>
<td>11 ± 1</td>
<td>16 ± 4</td>
<td>15 ± 3</td>
<td>—</td>
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<td><strong>Series B (n = 8 per group)</strong></td>
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<td>Heart rate, beats/min</td>
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<tr>
<td>Vehicle</td>
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<td>101 ± 9</td>
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<tr>
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<td>96 ± 5</td>
<td>94 ± 7</td>
<td>96 ± 7</td>
<td>102 ± 6</td>
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<tr>
<td>Vehicle</td>
<td>81 ± 8</td>
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<td>83 ± 8</td>
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<td>Fucoidan</td>
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<td>LVEDP, mm Hg</td>
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<tr>
<td>Vehicle</td>
<td>6 ± 1</td>
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<td>19 ± 4</td>
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<td>16 ± 4</td>
<td>20 ± 3</td>
<td>10 ± 3</td>
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</table>

Values are mean ± SEM. No significant intergroup differences were observed.

CO = coronary occlusion; LVEDP = left ventricular end-diastolic pressure; R = reperfusion.

cytometry. Compared with hearts infused with untreated activated platelets, those receiving fucoidan during the initial minutes of reperfusion had similar hypercontracture, as assessed by the early peak in LVEDP, but showed improved contractile recovery as well as reduced coronary resistance (Fig. 4) and released less LDH (51 ± 8 vs. 81 ± 6 U/gdw, p = 0.008) throughout the reperfusion period (Fig. 5). If administered in the absence of platelets, fucoidan lacked any beneficial effects on these functional parameters or on LDH release (81 ± 5 vs. 79 ± 6 U/gdw, respectively, p = NS).

**Figure 2.** Myocardial platelet content after 2 h of reperfusion.

**Figure 3.** Peak hyperemic response at the left anterior descending coronary artery. p value: effect of fucoidan (repeated measures analysis of variance).
sion in swine (5) nor protect against platelet-mediated injury in isolated reperfused rat hearts (11). Not at variance with these results, the main benefit of these agents in patients with acute myocardial infarction receiving reperfusion therapy has been a reduced incidence of recurrent ischemic events (26).

In the present study, the selectin-binding polysaccharide fucoidan, at doses inhibiting selectin function and lacking anticoagulant effects (22–24), prolonged bleeding time but had a modest effect on the thrombus burden at the epicardial artery, as it did not reduce reocclusion rate and lessened the number of CFRs by only one-half. However, fucoidan significantly attenuated microvascular platelet deposition and myocardial injury.

Fucoidan not being a specific P-selectin antagonist, it is not possible to ascertain to what extent its effects on platelet deposition were due to the inhibition of a direct, P-selectin-mediated interaction between platelets and endothelial cells (14–16) or to a reduced leukocyte recruitment—by antagonizing P- and L-selectin—and subsequent platelet binding to adherent leukocytes (12). The small effect of fucoidan on MPO activity and its protective effect in isolated hearts perfused without leukocytes suggest that the role of endothelium-dependent platelet adhesion is significant.

Our results also stress the importance of activation status in determining the influence of platelets on reperfused myocardium (11), which could help explain the discrepancy in results of previous studies (7–10). The lack of correlation between myocardial platelet content and the number of CFRs, and the paucity of microemboli found at histologic analysis concur with previous observations (4,5) indicating that spontaneous microembolization in this model is rare and suggest that the protective effects of fucoidan were independent of this phenomenon.

**Involvement of neutrophils.** Treatment with fucoidan was associated with a reduced neutrophil infiltration in the

<table>
<thead>
<tr>
<th>Time After Reperfusion</th>
<th>Control Zone</th>
<th>Subendocardial Region</th>
<th>Subepicardial Region</th>
<th>Overall</th>
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<tr>
<td>1 h (n = 8)</td>
<td>0.15 ± 0.05</td>
<td>0.04 ± 0.02</td>
<td>0.57 ± 0.17</td>
<td>0.39 ± 0.18</td>
</tr>
<tr>
<td>2 h (n = 20)</td>
<td>0.14 ± 0.05</td>
<td>0.11 ± 0.02</td>
<td>——</td>
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<tr>
<td>4 h (n = 16)</td>
<td>0.43 ± 0.20</td>
<td>0.33 ± 0.25</td>
<td>3.02 ± 1.13</td>
<td>1.76 ± 0.59</td>
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</tbody>
</table>

Values are mean ± SEM. Separate sampling from the subendocardial and subepicardial zones within the ischemic region was not performed in the 2-h group. No significant intergroup differences were observed.

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**Figure 4.** Left ventricular end-diastolic pressure (LVEDP), developed pressure (LVdevP), and perfusion pressure (PP) throughout the experiments in isolated rat hearts. P value: effect of fucoidan (repeated measures analysis of variance). Solid circles = control (n = 8); open circles = fucoidan (n = 8).

**Figure 5.** Lactate dehydrogenase (LDH) release after reperfusion in isolated hearts. P value: effect of fucoidan (repeated measures analysis of variance).
area at risk early after reflow, especially in the subepicardial region, but not at 4 h. This is consistent with a predominant involvement of selectins in the early inflammatory response, which may be perpetuated later on by alternative mechanisms (27). Significant neutrophil infiltration in reperfused tissues despite selectin inhibition has been reported previously (19,23).

Although not always successfully (28), selectin antagonists have long been used to reduce neutrophil recruitment and subsequent myocardial damage after ischemia (20–23). In addition, platelets and neutrophils act synergistically, by a mechanism involving P-selectin, in provoking postischemic cardiac dysfunction (10). Accordingly, it is possible that part of the benefit of fucoidan in our experiments in swine was mediated by an effect on neutrophils. Although neutrophil infiltration was comparable in both groups 4 h after reperfusion, toxic substances causing myocardial injury might have been released by intravascular neutrophils in the earlier phases (27). However, the results of the experiments in isolated hearts indicate that part of the protective effect of fucoidan was independent of neutrophils and was platelet-mediated.

Methodologic considerations and limitations. The decrease in blood platelet count after fucoidan administration concurs with previous reports (29). Because fucoidan does not affect platelet P-selectin expression in vitro (data not shown) nor mean platelet volume, it is unlikely that this phenomenon was caused by an enhanced activation or by the formation of platelet aggregates.

Platelet content in the control region in series A seems high. This could have been due to some activation during the experimental protocol (11) or occurring postmortem. However, if this background activity had been lower, the reduction in the estimated platelet content with fucoidan would probably have been greater. In series B, the size of the area at risk was somewhat smaller than in previous studies in the same model (5,25). However, infarcts (as a percentage of the ischemic zone) were relatively large, making it difficult that the results would have been different with a more proximal occlusion. Although myocardial perfusion was not directly measured, microvascular function was indirectly assessed in both models.

Fucoidan could have not been so beneficial in swine if administered only during the reperfusion period. However, the results of the experiments in isolated hearts, along with previous reports of a protective effect of P-selectin antagonism during reperfusion (20–23), suggest that it acted mainly in this period. Finally, it cannot be completely excluded that fucoidan had worked, in part, through mechanisms other than interacting with selectins, although its lack of effect when given alone and the fact that it did not influence hemodynamics, coagulation parameters, or platelet activation status work against this possibility.

Clinical implications. Improving myocardial perfusion is crucial in the management of patients with acute myocardial infarction. The present study highlights the deleterious influence of activated platelets and suggests that selectins contribute significantly to platelet deposition in reperfused coronary microvessels. Moreover, the results suggest that part of the protective effect of antagonizing these adhesion molecules described previously (20–23) might have been platelet-mediated and stress the role of selectin-mediated platelet adhesion as a potential therapeutic target. However, as the encouraging results of strategies blocking other cell adhesion receptors in animal studies have apparently not been paralleled by a reduction in infarct size in patients with acute myocardial infarction (27,30), the potential clinical benefit of inhibition of selectin-mediated platelet adhesion has yet to be proved.

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REFERENCES


