Pulmonary Vasoconstrictor Response to Soluble Fibrin in Isolated Lungs: Possible Role of Thromboxane Generation

Werner Seeger, Heinz Neuhof, Johannes Hall, and Ladislaus Roka

The blood coagulation system is activated regularly in severe forms of shock, polytrauma, and sepsis. Arising thrombin cleaves the fibrinopeptides A and B from fibrinogen, and it generates monomers of fibrin, which are initially kept in solution by the remaining excess fibrinogen. The effects of soluble fibrin (fibrin monomer/oligomer-fibrinogen complexes) and fibrinopeptides A and B were investigated in blood-free perfused, isolated rabbit lungs. Urea Tris buffer-dissolved fibrin monomers were injected into the pulmonary artery in the presence of circulating excess fibrinogen. In doses above 5 mg, the monomers consistently provoked a sharp rise in pulmonary artery pressure, which was followed by an elevated pressure plateau. Changing to fresh perfusate devoid of soluble fibrin did not restore the pressure to baseline, and a second administration of the soluble fibrin caused a pressor response larger than the first. Only a modest increase in lung weight (< 2 g) was observed, and lung inflation pressure was not altered. The pressor responses were accompanied by a rapid release of thromboxane A, and a more delayed release of prostaglandin I, into the perfusion fluid. A significant correlation between the height of the fibrin-induced pressure rise and the amount of thromboxane release was noted. Inhibition of cyclooxygenase (indomethacin) suppressed the generation of both prostanoids, whereas inhibition of thromboxane synthetase (OKY-046 and imidazole) selectively blocked the liberation of thromboxane. All three inhibitors caused an immediate decline in pulmonary artery pressure, which had been previously elevated due to administration of soluble fibrin, and markedly reduced the pressor response evoked by a subsequent fibrin application in the same lung. Pulmonary artery injection of the fibrinopeptides A and B, up to a dose of 1 mg each, did not affect the pulmonary circulation. We conclude that soluble fibrin monomer/oligomer-fibrinogen complexes, in amounts corresponding to 1–3% of the circulating fibrinogen, cause an acute pulmonary hypertension in rabbit lungs that may be relevant under conditions of an activated coagulation system. A major component of the vasoconstrictor response appears to be mediated by pulmonary thromboxane generation. (Circulation Research 1988;62:651–659)
coagulation factors, that may account for > 5% of the included fibrinogen. Soluble fibrin is not retained in transfusion filters, and as its half-life after intravenous application is known to be 11–16 hours in rabbits and approximately 10 hours in humans, substantial amounts must be expected particularly in the circulation of patients needing multitransfusion. Thus, an investigation of possible vasoactive potencies of soluble fibrin and the fibrinopeptides A and B in the pulmonary circulation appears warranted. In the present study, we used blood-free perfused rabbit lungs to avoid any interference with circulating cells such as thrombocytes and granulocytes. The main finding is that soluble fibrin, in amounts that correspond to only 1–3% of the circulating fibrinogen in rabbits, causes rapid pulmonary hypertension because of vasoconstriction. A major component of this vasoconstrictor response appears to be mediated by pulmonary generation of thromboxane (TX) A₂ generation.

Materials and Methods

Model of Isolated Lungs

The model has been previously described. Briefly, rabbits of either sex (weighing 2.3–2.8 kg) were deeply anesthetized with sodium pentobarbital 60–90 mg/kg body wt and were anticoagulated with heparin 1,000 units/kg body wt. The isolated lungs, suspended freely from a force transducer in a chamber warmed to 38°C, were ventilated with 4% CO₂-17% O₂-79% N₂ (frequency, 45 strokes/min; tidal volume, 30 ml) and were perfused with Krebs-Henseleit buffer (375 ml) with a pulsatile flow of 200 ml/min. The concentration of fibrin monomer was determined by the absorbance at 280 nm. Application of 10 mg fibrin monomer (in <500 μl urea Tris buffer) to 125 ml albumin buffer in the presence of excess fibrinogen (250 mg % wt/vol) allows the formation of soluble fibrin. Des-AB fibrin monomer was generated by clotting bovine fibrinogen dissolved in saline with excess insolubilized bovine thrombin (coupled to agarose, 100–200 mesh). The arising clot was removed, washed several times with saline, dried with filter cloth, and dissolved in urea Tris buffer with subsequent spinning at 5,000g for 10 minutes to remove all agarose-coupled thrombin. The concentration of fibrin monomer was determined photometrically at 280 nm. Application of 10 mg fibrin monomer (in <500 μl urea Tris buffer) to 125 ml albumin buffer in the presence of excess fibrinogen (250 mg % wt/vol) allows the formation of soluble fibrin monomer/oligomer–fibrinogen complexes. This was checked visually by ensuring the absence of aggregation (polymerized) fibrin, at least within the first 2 minutes, after injection of the urea Tris–dissolved fibrin monomers into noncirculating buffer fluid. In contrast, when 10 mg urea Tris–dissolved fibrin monomers were injected into hydroxyethylamyllopectin buffer in the absence of fibrinogen, immediate fibrin polymerization could be visualized. The fibrin monomers dissolved in the urea Tris vehicle and the nonpolymerized fibrin arising after admixture of the monomers to the fibrinogen-containing albumin buffer are referred to as “soluble fibrin” in this study.

TXA₂ and prostaglandin (PG) I₂ were assayed serologically in the buffer fluids as their stable hydrolys products TXB₂ and 6-keto-PGF₁α. Each assay mixture contained a 0.1-ml sample or 5–500 pg of an authentic standard, 0.1 ml antiserum (cross-reactivity with other prostaglandins, each <0.05%), tritium-labeled TXB₂ or tracer 6-keto-PGF₁α and phosphate-gelatin buffer in a total volume of 0.5 ml. Assay mixtures were incubated overnight at 4°C for 16 hours. Antibody-antigen complexes were separated from free antigen by adding charcoal suspension. Tubes were centrifuged for 10 minutes at 1,000g and decanted into liquid scintillation vials. The limit of detection was 5 pg for TXB₂ and 10 pg for 6-keto-PGF₁α and 50% binding occurred at 50 pg for TXB₂ and 170 pg for 6-keto-PGF₁α. This assay did not detect background levels of TXB₂ or 6-keto-PGF₁α in the albumin buffer, whether or not it contained fibrinogen, before perfusion through the lungs. To exclude unspecific effects that might originate from the use of the charcoal separation
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technique, 10 probes with different amounts of TXB
and 6-keto-PGF<sub>1α</sub> were assayed in parallel with the
described technique and with a double antibody
method, using a goat anti-rabbit γ-globulin as precipi-
titating antiserum. Differences between the two tech-
niques never exceeded 10%.

Lactate dehydrogenase (LDH) was measured pho-
tometrically, and potassium was measured by flame
photometry. For histological evaluation, the lungs were
immersed in 10% formalin with simultaneous applica-
tion of formalin to the bronchial tree with a hydro-
sstatic pressure of 15 cm H<sub>2</sub>O. They were stained with
hematoxylin eosin.

Chemicals

OKY-046 was kindly supplied by Ono Pharmaeu-
tical, Osaka, Japan. Indomethacin was obtained from
Merck Sharp & Dohme AG, Munich, Federal Repub-
lic of Germany. Bovine albumin (92% purity, reduced in
free fatty acids <5 μg/g) was purchased from Paesel,
Frankfurt, Federal Republic of Germany, and hydrox-
ezymylopectine from Fresenius Bad Homburg, Fed-
eral Republic of Germany. Bovine fibrinogen (95% pui-
ity) was supplied by Behring, Marburg, Federal Repub-
lic of Germany. Bovine thrombin was obtained from
Hoffman LaRoche, Basel, Switzerland, and the human fibrinopetides A and B from Serva, Heidelberg,
Federal Republic of Germany. Rabbit anti-6-keto-PGF<sub>1α</sub>
and anti-TXB, were purchased from Paesel. (H)-6-
keto-PGF<sub>1α</sub> and (H)-TXB, were supplied by New
England Nuclear, Dreieich, Federal Republic of Ger-
many, and the unlabeled standards by Sigma, Munich,
Federal Republic of Germany. All other biochemicals
were obtained from Merck, Darmstadt, Federal Repub-
lic of Germany, and were used in p.a. quality.

Statistics

All data are given as mean ± SEM. Analysis of
variance followed by multiple comparisons and simple
regression were performed.

Results

Administration of a fibrinogen-containing albumin
buffer or injection of urea Tris vehicle did not alter
pulmonary artery pressure. However, the administra-
tion of 5–10 mg soluble fibrin in the presence of
fibrinogen caused a complex pressor response com-
posed of, in sequence, a rapid pressure increase, a small
fall, a slower pressure rise, and a slow fall (Figure 1).
In 17 lungs, the administration of 10 mg soluble fibrin
evoked a maximum pressure rise of 18.85 mm Hg (Table 1). Changing to a fresh perfusate that did not
contain soluble fibrin did not restore the pressure to
baseline, and a second administration of the soluble
fibrin caused a pressure response larger than the first
(Figure 1 and Table 1). Although soluble fibrin
administration did not alter lung inflation pressure, we
considered whether lung fluid accumulation might have
caused the pressor response. In eight lungs, two
sequential administrations of soluble fibrin increased
lung weight by 0.78 ± 0.33 g (Figure 1). In contrast,
elevation of left atrial pressure to 20 cm H<sub>2</sub>O for 30
minutes in five control lungs caused a weight gain of
4.5 ± 0.9 g, but pulmonary arterial pressure did not
increase. Thus, fluid accumulation did not seem a
likely cause of the pressor response to the soluble fibrin.

The fibrin-induced pressor responses were accompa-
nied by a rapid and sustained release into the recircu-
lating perfusate of TXB, and a slower release of
6-keto-PGF<sub>1α</sub> (Figure 2 and Table 2). The magnitude of
the pressor response was significantly correlated with the
level of thromboxane (Figure 3) but not with the level
of 6-keto-PGF<sub>1α</sub>. In the presence of the cyclooxygenase
inhibitor indomethacin, the release of both thromboxane
and 6-keto-PGF<sub>1α</sub> was completely suppressed (Table 2).
The thromboxane synthetase inhibitors imidazole and
OKY-046, however, blocked the thromboxane release
without affecting the liberation of 6-keto-PGF<sub>1α</sub>. After
a fibrin-induced pressor response, changing to a fresh
perfusate containing one of these inhibitors, but no
soluble fibrin, caused a rapid decline in perfusion
pressure to, or below, baseline values (Figure 4). When
in the presence of one of these inhibitors, administration
of the soluble fibrin was repeated the pressor response
was significantly blunted (Figure 4 and Table 1). In the
concentrations used, indomethacin was more effective
than OKY-046, which was more effective than imida-
zolet. In four lungs, 10 mM ε-amino caproic acid, a
noncompetitive plasmin inhibitor, did not inhibit the
response to soluble fibrin.

![Figure 1. Pulmonary artery pressor (PAP) responses induced by repeated injection of 10 mg soluble fibrin (FM) into the pulmonary artery of a Krebs-Henseleit albumin buffer (KHB)-perfused, isolated rabbit lung in the presence of fibrinogen (FBG). Bars, changes of perfusion fluid; arrows, injection of the soluble fibrin. For the second fibrin application, the time scale is stretched to allow better analysis of the pressor response. The evaluation of ΔP I, ΔP II, and ΔP 8' (pressure rise 8 minutes after fibrin application) is shown.](http://circres.ahajournals.org/lookup/doi/10.1161/01.CIR.115.7.653)
The histologic examination of three lungs that had been formalin fixed at the height of the pressor response to 20 mg soluble fibrin showed but few fibers of aggregated fibrin.

Administration of 10 mg urea Tris-dissolved fibrin monomers to four lungs perfused with hydroxyethylamylopectin buffer in the absence of fibrinogen evoked only a very slight pressure peak of 3.2 ± 0.7 mm Hg. Even repetitive application of fibrin (a total of 65 mg) in the absence of circulating fibrinogen caused just a modest cumulative elevation of the pulmonary artery pressure (Figure 5). Administration of 1 mg each of the fibrinopeptides A and B in three lungs provoked no pressor response at all.

**Discussion**

In blood-free perfused rabbit lungs, administration of fibrin monomers induced acute pulmonary hypertension. There are several lines of evidence strongly suggesting that this pressor response is caused by fibrin-induced vasoconstriction rather than by mechanical blockage of the vascular bed due to polymerized fibrin particles. First, there was excess fibrinogen in the recirculating perfusion fluid, enabling the immediate generation of soluble fibrin monomer/oligoferinogen complexes. This was checked in vitro by ensuring the absence of aggregated (polymerized) fibrin after admixture of urea Tris-dissolved fibrin monomers to a fibrinogen-containing albumin buffer. Once formed, fibrin monomer/oligoferinogen complexes are known to remain soluble for hours in the circulation of rabbits and humans.

Second, in the absence of circulating fibrinogen and albumin, that is, in the experiments with hydroxyethylamylopectin buffer fluid, immediate polymerization of the fibrin monomers to insoluble fibrin strands occurred. Therefore, mechanical blockage of the vascular bed must be assumed in these special experiments. However, even the application of a total of 65 mg fibrin within 60 minutes under these conditions provoked only a very modest increase in pulmonary vascular resistance (Figure 5). Thus, the severalfold stronger pressor responses to only 10 mg soluble fibrin (presence of recirculating fibrinogen) must be ascribed to different effects. Third, the elevated pulmonary artery pressure after administration of 10 mg soluble fibrin rapidly declined to baseline levels upon subsequent application of three structurally unrelated inhibitors of arachidonic acid metabolism (indomethacin, imidazole, and OKY-046). In the absence of stimulus-mediated vasoconstriction, these inhibitors provoke at most a very slight (<2 mm Hg) decrease of the pulmonary artery pressure. Moreover, all three inhibitors markedly reduced the pressor response evoked by a subsequent (second) fibrin application. These features are not compatible with pure mechanical vascular occlusion as a responsible factor for the noted pulmonary hypertension but can only be explained by an interference of these agents with soluble fibrin-induced vasoconstriction. Finally, the histological evaluation of lungs fixed at the height of the pressor response showed but few fibers of aggregated fibrin. Compared with the histological evaluation of lungs that were microembolized with inert particles of aggregated albumin, this is clearly insufficient to account for the marked fibrin-induced pressure rise in terms of mechanical obstruction of the vascular bed. Collectively, these findings do not completely exclude the possibility that mechanical blockage of lung vessels may contribute, to a small extent, to the fibrin-induced hypertension.

The administration of soluble fibrin did not increase the concentrations of potassium or LDH above the baseline levels. The histologic examination of three lungs that had been formalin fixed at the height of the pressor response to 20 mg soluble fibrin showed but few fibers of aggregated fibrin.

**Table 1. The Influence of Indomethacin, Imidazole, and OKY-046 on the Pulmonary Artery Pressor Response Induced by Soluble Fibrin**

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Δp total (mm Hg)</th>
<th>Δp I (mm Hg)</th>
<th>Δp II (mm Hg)</th>
<th>Δp III (mm Hg)</th>
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<tbody>
<tr>
<td>Control (n=17)</td>
<td>18.85 ± 1.71</td>
<td>10.45 ± 1.15</td>
<td>11.33 ± 1.03</td>
<td>6.32 ± 0.67</td>
</tr>
<tr>
<td>Indomethacin (35 μM, n=10)</td>
<td>7.57 ± 0.44</td>
<td>39.7 ± 5.2</td>
<td>7.47 ± 0.44</td>
<td>69.4 ± 5.9</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.001*</td>
<td></td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Imidazole (0.88 mM, n=6)</td>
<td>15.33 ± 0.65</td>
<td>62.8 ± 1.7</td>
<td>11.20 ± 0.89</td>
<td>89.7 ± 8.9</td>
</tr>
<tr>
<td></td>
<td>6.30 ± 0.38</td>
<td>48.3 ± 3.1</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>OKY-046 (2 μM, n=6)</td>
<td>8.10 ± 1.50</td>
<td>59.7 ± 6.4</td>
<td>6.25 ± 0.82</td>
<td>89.6 ± 9.0</td>
</tr>
<tr>
<td></td>
<td>2.33 ± 0.46</td>
<td>22.0 ± 2.3</td>
<td>78.0 ± 11.2</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

The table gives the height of the pressure rise (Δp total, Δp I, Δp II, and Δp III; evaluation according to Figure 1) induced by the pulmonary artery injection of 10 mg soluble fibrin in 17 different lungs (Control). Next, two rinsing phases followed in which an inhibitor was admixed to the buffer fluid according to the protocol for Figure 4 (five lungs with indomethacin, six lungs with imidazole, and six lungs with OKY-046).

The injection of soluble fibrin was then repeated one time in each lung in the presence of inhibitor, and the values of the evoked pressor response are given as absolute data in mm Hg (mean ± SEM) as well as in % (mean ± SEM) of the individual preceding control response. In the case of indomethacin only, the fibrin injection was performed twice in the presence of this agent in each isolated lung, and both responses are compared with the initial control response to obtain the % values.

*By analysis of variance, the % values are compared with the % values obtained by a second pulmonary artery injection of soluble fibrin in the absence of any inhibitor in eight different isolated lungs. In these eight control experiments, the second 10-mg fibrin application evoked a pressure rise of 139 ± 16% (Δp total), 171 ± 16% (Δp I), 118 ± 7% (Δp II), and 128 ± 10% (Δp III) compared with the preceding response to the same dose of inhibitor.
dominant part of the pressor response must, however, be ascribed to pulmonary vasoconstriction elicited by soluble fibrin monomer/oligomer-fibrinogen complexes. Most probably, this vasoconstrictor response was evoked by the soluble fibrin itself, and not by fibrin degradation products. There was no circulating plasminogen that could be cleaved by urokinase-like or tissue-type plasminogen activators, and ε-amino caproic acid, a noncompetitive potent plasmin inhibitor, was found to be ineffective. Moreover, the instantaneous onset of the pressor response after application of the soluble fibrin argues against a preceding sequence of proteolytic cleavage. Although in the present study, bovine fibrin monomer was used throughout, parallel experiments with application of urea Tris-dissolved bovine and rabbit fibrin monomers in intact rabbits showed no difference with respect to their potencies in raising pulmonary artery pressure.

The fibrin-induced vasoconstriction was accompanied by a rapid and continuous release of thromboxane into the recirculating buffer fluid, significantly correlating with the degree of the pressure rise. In the presence of a cyclooxygenase inhibitor and of two structurally unrelated thromboxane synthetase inhibitors (OKY-046 and imidazole), the fibrin-induced pulmonary hypertension was significantly suppressed. The effects of OKY-046 and imidazole were found to be selective. The thromboxane generation was nearly completely blocked, whereas the release of PGI₂ was not diminished. This is in accordance with studies in tracheal strips, alveolar macrophages, and different blood cells, which characterize these agents as specific inhibitors of thromboxane synthetase.

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>1 minute TXB₂ (pg/ml)</th>
<th>3 minutes TXB₂ (pg/ml)</th>
<th>5 minutes TXB₂ (pg/ml)</th>
<th>8 minutes TXB₂ (pg/ml)</th>
<th>1 minute 6-keto-PGF₁α (pg/ml)</th>
<th>3 minutes 6-keto-PGF₁α (pg/ml)</th>
<th>5 minutes 6-keto-PGF₁α (pg/ml)</th>
<th>8 minutes 6-keto-PGF₁α (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control* (n = 6)</td>
<td>555 ± 76</td>
<td>387 ± 145</td>
<td>509 ± 84</td>
<td>508 ± 168</td>
<td>300 ± 67</td>
<td>620 ± 250</td>
<td>205 ± 58</td>
<td>805 ± 297</td>
</tr>
<tr>
<td>Indomethacin† (35 μM, n = 6)</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
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<tr>
<td>IMI/OKY-046 (0.88 mM/2 μM, n = 6)</td>
<td>&lt;50‡</td>
<td>626 ± 133</td>
<td>1,037 ± 251</td>
<td>1,458 ± 325</td>
<td>50</td>
<td>1,718 ± 329</td>
<td></td>
<td></td>
</tr>
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</table>

The table gives the levels of TXB₂ and 6-keto-PGF₁α in the recirculating perfusion fluid 1, 3, 5, and 8 minutes after application of 10 mg soluble fibrin (absolute data, mean ± SEM). In control phases, in which only 250 mg fibrinogen and urea Tris buffer (vehicle for fibrin monomer) were applied, the TXB₂ and the 6-keto-PGF₁α levels ranged below 100 and 200 pg/ml, respectively, at each time after onset of perfusion (n = 4, data not given in the table).

*The Control group includes the levels obtained during the first fibrin application in six separate isolated lungs.
†The Indomethacin and IMI/OKY-046 groups give the values during a second fibrin application in the presence of indomethacin (n = 6), imidazole (n = 3), or OKY-046 (n = 3). The values obtained in the presence of both thromboxane synthetase inhibitors are given together.
‡After the fibrin application in the presence of imidazole, there was one TXB₂ value after 3 minutes (62 pg/ml) and two values after 5 minutes (52 pg/ml and 69 pg/ml) that exceeded the detection limit of 50 pg/ml. All other values ranged below 50 pg/ml.
inhibitors of thromboxane synthetase. Thus, even if unspecific effects of indomethacin, such as inhibition of phospholipase in higher concentrations, are considered, the inhibitory potencies of these three structurally unrelated agents collectively indicate a major role of thromboxane in the vasoconstrictor response to soluble fibrin. Moreover, from a previous study, it is known that the stable TXA₂-mimicking substance U46619 provokes an acute pressure rise in the isolated lung model when applied in the same range of concentration in which TXB₂ is detected in the perfusion fluid after administration of soluble fibrin, thus supporting a significant role of the detected thromboxane. Its vasoconstrictive potency apparently surpasses the vasodilatory effect of PGI₂, which was released more gradually than thromboxane after soluble fibrin application. This is in accordance with the pattern of prostanoid generation induced by various other stimuli that exert thromboxane-mediated pulmonary vasoconstriction accompanied by PGI₂ generation, such as staphylococcal α-toxin; the calcium ionophore A23187, and granulocyte-derived hydrogen peroxide. Since the soluble fibrin-induced pressure rise was not completely blocked by cyclooxygenase inhibition, noncyclooxygenase metabolites of arachidonic acid with vasoactive potency may additionally be involved; these agents were, however, not addressed in the present study.

The intravenous route of application and the marked PGI₂ generation suggest a major role of endothelial cells in the pulmonary response to soluble fibrin. The cellular source of thromboxane in blood- and plasma-free perfused lungs has, however, not yet been established. Alveolar, interstitial, or even resident intravascular macrophages may be of major importance in this connection. Surface binding of soluble fibrin on cells of the reticuloendothelial system, peritoneal macrophages and polymorphonuclear leukocytes,
and platelets has been demonstrated; however, no information is available concerning the interaction of soluble fibrin with lung vascular or perivascular cells. The absence of LDH- and potassium-release after fibrin administration indicates the absence of overt cellular damage, which is found, for example, after application of Pseudomonas aeruginosa cytotoxin in the isolated lung model. This is in accordance with studies in endothelial cell monolayers, in which morphological changes and disorganization were not noted during a period of 2 hours after application of fibrin. In contrast to soluble fibrin, no vasoactive potency in blood-free perfused lungs could be demonstrated for the fibrinopeptides A and B, even when used in very high concentrations. This observation conflicts with a previous study in which a significant pulmonary hypertension was noted after the application of far smaller doses of bovine fibrinopeptides in intact rabbits, dogs, and lambs. An explanation for this discrepancy may be the absence of circulating inflammatory cells in the present study, because fibrinopeptide B, for example, is known to possess marked chemotactic activity for neutrophils and thus may exert effects in intact animals through stimulation of these cells.

As already mentioned, numerous studies have documented the fact that fibrin may exist in a soluble form in the circulation, generally complexed with fibrinogen. Under pathophysiological circumstances, plasma soluble fibrin was measured to represent from 2 to > 10% of the total circulating fibrinogen, and the percentage of soluble fibrin in different stored blood components may surpass 5% of the included fibrinogen. The amounts of soluble fibrin applied in the present study correspond to approximately 1–3% of the circulating fibrinogen of rabbits. Soluble fibrin must thus be considered a pulmonary vasoconstrictor agent in situations of disseminated intravascular coagulation and multitransfusion and may be relevant for the understanding of lung injury encountered under these circumstances. Soluble fibrin exerted its effect in blood-free perfused lungs (i.e., without enlisting the aid of circulating inflammatory cells such as granulocytes); however, it is also effective in the same dose range in intact rabbits. Soluble fibrin monomer/oligomer–fibrinogen complexes thus enlarge the list of vasoactive potencies ascribed to coagulation products.

Acknowledgments

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References


FIGURE 5. Pulmonary artery pressor (PAP) responses evoked by repetitive injection of fibrin monomers (FM) into the pulmonary artery of lungs perfused with Krebs-Henseleit hydroxyethylamyloluein buffer (KHHB) in the absence of fibrinogen. Bars, changes of perfusion fluid; arrows, injection of fibrin. IND, indomethacin.
Protective effect of thromboxane synthetase inhibition on lung fluid balance. 


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Physiol Rev 1984;54:577–592


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