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

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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 perfuse 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 (125 ml) with a pulsatile flow of 200 ml/min was used. Each perfusion system consisted of two different perfusion systems, it was possible to perform repetitive perfusion phases in the same isolated lung, each with fresh perfusion fluid. In the standard protocol (Figures 1-3 and 5), each perfusion phase lasted 10 minutes. The physical variables, including pressure, ventilation pressure, and weight of the isolated lung, were registered continuously by pressure transducers and a force transducer. The reproducibility of these physical measurements showed a standard deviation of <3%. Only those lungs were selected that, after a steady-state period of at least 45 minutes with numerous changes of perfusion fluid, were completely blanched and showed no spontaneous edema formation or changes of ventilation and perfusion pressure. Light microscopic examination of these lungs revealed virtually no adherence of erythrocytes, platelets, and leukocytes to the vascular wall, and no evidence of interstitial edema or alveolar flooding was noted.

Fibrin monomers, dissolved in <500 µl urea (3 M) Tris (50 mM) buffer, or the fibrinopeptides A and B, dissolved in <500 µl saline, were injected directly into the pulmonary artery (injection time 10 seconds; indicated by arrows in Figures 1, 2, 4, and 5). Inhibitors were added to the perfusion fluid at the stated final concentrations before recirculation. Appropriate doses of the different inhibitors were determined by use of dose-response curves obtained from previous investigations: 1 µM indomethacin (cyclooxygenase inhibitor) in hydroxyethylamylpectin buffer and 35 µM indomethacin in albumin buffer due to the albumin binding.

Preparation of Fibrin Monomer

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. It was checked visually by ensuring the absence of aggregated (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 hydroxyethylamylpectin 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 hydrolysis 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 unpecific 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$_{\alpha_2}$ were assayed in parallel with the described technique and with a double antibody method, using a goat anti-rabbit $\gamma$-globulin as precipitating antiserum. Differences between the two techniques never exceeded 10%.

Lactate dehydrogenase (LDH) was measured photometrically, and potassium was measured by flame photometry. For histological evaluation, the lungs were immersed in 10% formalin with simultaneous application of formalin to the bronchial tree with a hydrostatic pressure of 15 cm H$_2$O. They were stained with hematoxylin eosi.

**Chemicals**

OKY-046 was kindly supplied by Ono Pharmaceutical, Osaka, Japan. Indomethacin was obtained from Merck Sharp & Dohme AG, Munich, Federal Republic of Germany. Bovine albumin (92% purity, reduced in free fatty acids $<5 \mu$g/g) was purchased from Paesel, Frankfurt, Federal Republic of Germany, and hydroxyethylamyllose from Fresenius Bad Homburg, Federal Republic of Germany. Bovine fibrinogen (95% purity) was supplied by Behring, Marburg, Federal Republic of Germany. Bovine thrombin was obtained from Hoffmann LaRoche, Basel, Switzerland, and the human fibrinopeptides A and B from Serva, Heidelberg, Federal Republic of Germany. Rabbit anti-6-keto-PGF$_{\alpha_2}$ and anti-TXB were purchased from Paesel. (3-H)-6-keto-PGF$_{\alpha_2}$ and (3-H)-TXB, were supplied by New England Nuclear, Dreieich, Federal Republic of Germany, and the unlabeled standards by Sigma, Munich, Federal Republic of Germany. All other biochemicals were obtained from Merck, Darmstadt, Federal Republic 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 administration of 5–10 mg soluble fibrin in the presence of fibrinogen caused a complex pressor response composed 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$_2$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 accompanied by a rapid and sustained release into the recirculating perfusate of TXB, and a slower release of 6-keto-PGF$_{\alpha_2}$ (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$_{\alpha_2}$. In the presence of the cyclooxygenase inhibitor indomethacin, the release of both thromboxane and 6-keto-PGF$_{\alpha_2}$ 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$_{\alpha_2}$. 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 imidazole. In four lungs, 10 mM $\varepsilon$-amino caproic acid, a noncompetitive plasmin inhibitor, did not inhibit the response to soluble fibrin.
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.

Administration of 10 mg urea Tris-dissolved fibrin monomers to four lungs perfused with hydroxyethylamyllopectin 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 present in the recirculating perfusion fluid, enabling the immediate generation of soluble fibrin monomer/oligomer–fibrinogen complexes. This was checked in vitro by ensuring the absence of aggregated fibrin after admixture of urea Tris-dissolved fibrin monomers to a fibrinogen-containing albumin buffer. Once formed, fibrin monomer/oligomer–fibrinogen 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 pre-
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KHAB

PAP

40
32
24
18
12
6
0

FBQ

FM 5mg

FBG

FM 10mg

IND 35pm

FBG

FM 10mg

FIGURE 2. Pulmonary artery pressor (PAP) responses and prostanoid release evoked by the administration of 5 and 10 mg soluble fibrin (FM) in the presence of fibrinogen (FBG). Subsequently, indomethacin (IND) was admixed to the perfusate. It caused a rapid decline of the elevated pulmonary artery pressure and nearly completely blocked pressor response and prostanoid release upon a subsequent fibrin application. Bars, changes of perfusion fluid; arrows, injection of fibrin.

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

Table 2. Thromboxane and PGI2 Release After Application of Soluble Fibrin in the Absence or Presence of Inhibitors

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>1 minute</th>
<th>3 minutes</th>
<th>5 minutes</th>
<th>8 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TXB2 (pg/ml)</td>
<td>6-keto-PGF1α (pg/ml)</td>
<td>TXB2 (pg/ml)</td>
<td>6-keto-PGF1α (pg/ml)</td>
</tr>
<tr>
<td>Control* (n = 6)</td>
<td>555 ± 76</td>
<td>387 ± 145</td>
<td>509 ± 84</td>
<td>508 ± 168</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>
</tr>
<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>
</tr>
</tbody>
</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.
PRESSOR RESPONSE AND THROMBOXANE RELEASE AFTER 10 mg FIBRIN MONOMERS

FIGURE 3. Correlation between the pulmonary artery pressor (PAP) responses ($\Delta p$ II given, see Figure 1) and the maximum levels of TXB2, released into the perfusate after application of 10 mg soluble fibrin in six different isolated lungs. The corresponding correlation coefficient for the total height of the fibrin-induced pressor responses instead of $\Delta p$ II was $r = 0.90$.

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 alpha-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**

We thank Mrs. K. Klapper, Mrs. Ch. Ernst, and Mr. H. Michnacz for excellent technical assistance. We are grateful to Prof. Dr. H. Bleyl and Mrs. H. Peichl for their help with the production of insulobilized thrombin and to Mr. P. Müller for skilfull graphical illustration.

**References**


**KEYWORDS** • soluble fibrin • fibrin monomer • thrombin • thromboxane A2 • prostaglandin I2 • pulmonary vascular resistance • pulmonary artery pressor response
Pulmonary vasoconstrictor response to soluble fibrin in isolated lungs: possible role of thromboxane generation.
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Circ Res. 1988;62:651-659
doi: 10.1161/01.RES.62.4.651

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