

## *The Role of Endogenous Prostaglandins in the Pulmonary Circulation*

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THE PURPOSE of this review is to examine the activity of endogenous prostaglandins in the physiology and pathophysiology of the pulmonary vasculature and the ductus arteriosus.

It is important to remember how information about prostaglandins has been obtained, because it is then easier to understand the limitations of our knowledge. Initially, information concerning prostaglandins was derived from observations on the bioactivity of tissue extracts. When the prostaglandins could be synthesized *in vitro* and tested in experimental animals, the activities of different subgroups became apparent. Radioactive labelling facilitated studies of prostaglandin metabolism. Following the discovery that certain drugs inhibited the synthesis of prostaglandins, progress was made in describing the activities of endogenous prostaglandins. Finally, the ability to measure changes in prostaglandin levels in blood and tissues, by bioassay or radioimmunoassay, has been developed. Progress has been limited to some extent by the absence of specific antagonists to the actions of different prostaglandins. The difficulty in distinguishing between the effects of various prostaglandins has been compounded by the fact that the inhibitors of prostaglandin synthesis tend to reduce the formation of all prostaglandins indiscriminately and, in addition, have other pharmacologic actions. Further problems have arisen because actions ascribed to particular prostaglandins may in fact be caused by precursors and related compounds, the endoperoxides and thromboxanes.

### Local Nature of Prostaglandin Function

The discovery, isolation, structure, and biosynthesis of the prostaglandins have been reviewed previously in this journal<sup>1</sup> and are not covered here. The prostaglandins comprise a ubiquitous family of compounds that are not stored in the cells of the body but are synthesized and released on demand. Endogenous prostaglandins usually have their effects near the site of synthesis, rather than acting as circulating agents. They do not act as circulating hormones largely because of the efficient uptake and degradation achieved by the lungs. Inactivation of prostaglandins E<sub>1</sub> and E<sub>2</sub> during one passage through the pulmonary vasculature has been reported to vary between 72 and 95 per cent in several species.<sup>2-5</sup> Prostaglandins of the F series suffer similar inactivation (70 to 98 per cent).<sup>6-8</sup> It has been suggested that the A series prostaglandins could function as circulating hormones because they are not inactivated during passage through the dog lung.<sup>5,9,10</sup> However, infused prostaglandin A<sub>2</sub> loses 23 to 75 per cent of its activity in the isolated guinea pig lung.<sup>11</sup> The physiologic significance of the A series of prostaglandins is still in question.<sup>12-14</sup>

Prostaglandin dehydrogenase is found in many tissues, so that the lungs do not have a monopoly in the degradation of prostaglandins. For instance, in cats, dogs and rabbits, the liver will extract approximately 80 per cent of prostaglandins E<sub>1</sub>, E<sub>2</sub>, and F<sub>2α</sub> presented to it.<sup>15</sup> However, as the entire cardiac output must pass through the pulmonary circulation, the lungs are the most important site of prostaglandin inactivation. In the presence of cardio-pulmonary disease the inactivation of prostaglandins in the lungs may be less efficient,<sup>16</sup> and the prostaglandins could have a systemic effect in such instances.

### Prostaglandins and Vascular Smooth Muscle

A general account of prostaglandins' activities in cells throughout the body is available in an earlier review in this journal.<sup>1</sup> Prostaglandins can affect vascular smooth muscle in several ways, but it is not yet clear how they initiate contraction or

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TABLE 1. Pulmonary Vasculature Responses to Exogenous Prostaglandins\*

Prostaglandin	Hemodynamic Effect		Pulmonary Arterial Strip		Species and Reference
	Vasoconstriction	Vasodilatation	Contraction	Relaxation	
A <sub>1</sub> A <sub>2</sub> A <sub>1</sub> and A <sub>2</sub>	+	+		+	Dog <sup>30, 31</sup> Dog <sup>31</sup> Dog <sup>32</sup>
B <sub>1</sub> B <sub>2</sub> B <sub>1</sub> and B <sub>2</sub>	+		0	0	Dog <sup>33</sup> Dog <sup>33</sup> Dog <sup>32</sup>
D <sub>2</sub>	+				Dog <sup>34</sup>
E <sub>1</sub>	0	+	0 +	+	Dog, <sup>30, 35-37</sup> calf, <sup>38</sup> swine, <sup>39</sup> lamb, <sup>32</sup> man <sup>40</sup> Cat <sup>41</sup> Sheep, <sup>42</sup> dog, <sup>32</sup> chimpanzee, <sup>32</sup> chicken <sup>46</sup> Swine <sup>42</sup> Man, <sup>42</sup> monkey <sup>32</sup>
E <sub>2</sub>	+	+		+	Dog, swine and lamb, <sup>43</sup> calf <sup>44</sup> Calf, <sup>38</sup> guinea pig <sup>45</sup> Calf, <sup>38</sup> chicken <sup>46</sup>
15-me-E <sub>2</sub>	+		+		Dog <sup>47</sup>
F <sub>2</sub>	+		+	0 +	Dog, <sup>35-37, 48, 49</sup> calf, <sup>38, 44</sup> guinea pig, <sup>45</sup> cat, <sup>41, 50, 51</sup> swine, <sup>52</sup> lamb <sup>52</sup> Man, <sup>42</sup> baboon, chimpanzee, monkey, <sup>32</sup> calf, <sup>38</sup> chicken <sup>46</sup> Swine, dog <sup>42</sup> Sheep <sup>42</sup>
F <sub>1α</sub>	+		+		Cat, <sup>51</sup> dog <sup>49</sup> Dog <sup>32</sup>
F <sub>1β</sub>	+	0	+		Cat <sup>51</sup> Dog <sup>49</sup> Dog <sup>32</sup>
F <sub>2β</sub>	+	0	0	0	Cat <sup>51</sup> Dog <sup>49</sup> Dog <sup>32</sup>
15-me-F <sub>2α</sub>	+		+		Dog, <sup>47, 53</sup> man <sup>54</sup> Dog <sup>47</sup>
I <sub>2</sub>			0	0	Rabbit <sup>55</sup>

\* The + sign denotes constriction or dilatation, depending on the column. The 0 sign in both columns indicates that the prostaglandin in question had no effect.

relaxation. They can act on smooth muscle by altering the intracellular concentrations of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP); by changing membrane conductance; and more indirectly, by inhibiting the release of sympathetic neurotransmitters from autonomic nerve terminals. Prostaglandins can alter cyclic nucleotide concentrations by stimulating adenylate cyclase or guanylate cyclase, and may also do so by acting on phosphodiesterase and ATP-regulating enzymes.<sup>18</sup> Although an increase in cAMP tends to be associated with relaxation of vascular smooth muscle and an increase in cGMP may be

associated with contraction,<sup>5</sup> the ratio of cAMP to cGMP is probably more important than the absolute level of either alone.<sup>19</sup> There may even be more than one intracellular pool of cAMP.<sup>20</sup>

Prostaglandins also alter membrane conductance in smooth muscle. Prostaglandin E<sub>1</sub> in low doses can cause hypopolarization of cell membranes and thus enhance the responses of systemic vascular strips to angiotensin and serotonin.<sup>21</sup> Larger doses cause depolarisation in the absence of other stimuli.<sup>21</sup> Studies using <sup>45</sup>Ca to examine the action of prostaglandin F<sub>2α</sub> on strips of systemic artery and vein suggest that the prostaglandin enhances the permea-

TABLE 2. Pulmonary Vascular Responses to Exogenous Prostaglandin-like Substances\*

Prostaglandin-like Substance	Hemodynamic Effect		Pulmonary Arterial Strip		Species and Reference
	Vasoconstriction	Vasodilatation	Contraction	Relaxation	
Arachidonic acid Dihomo- $\gamma$ -linolenic acid Linoleic acid	+ + 0	  0	   	   	Goat <sup>56</sup> , dog <sup>57, 58</sup> Dog <sup>59</sup> Dog <sup>57</sup>
PG H <sub>2</sub> PG H <sub>2</sub> analog I PG H <sub>2</sub> analog I and PG H <sub>2</sub> analog II	+ +  	   	   +	   	Dog <sup>60</sup> Dog <sup>60</sup> , sheep <sup>61</sup>  Guinea pig, man <sup>62</sup>
Thromboxane B <sub>2</sub> Endoperoxides (U 44069, U 46619, A20 Compound)	+  +	   	   	   	Cat, <sup>63</sup> guinea pig <sup>62</sup>  Dog <sup>64</sup>

\* The + sign denotes pulmonary vasoconstriction or contraction of a pulmonary arterial strip, depending on the column. The 0

sign in both columns indicates that the control fatty acid had no hemodynamic effect on the pulmonary vasculature.

bility of the smooth muscle membrane to calcium.<sup>22</sup> Alternatively, prostaglandin F<sub>2 $\alpha$</sub>  may facilitate calcium transport within the cell.

While the actions of prostaglandins are not mediated by sympathetic stimulation,<sup>23</sup> there is good evidence that such stimulation can lead to the formation of prostaglandins of the E series, which in turn inhibit the release of norepinephrine from the nerve terminals.<sup>24</sup> It is not clear whether the prostaglandins are synthesized in smooth muscle cells, the nerve terminals themselves, or other tissues.<sup>25</sup> The feedback inhibition of sympathetic neurotransmitter release seems to occur through interference with the availability of calcium, which is necessary for that release.<sup>24,26</sup> The study of the interaction between prostaglandins and sympathetic neurotransmission has led to numerous reports, many of which are mentioned in references 27-29.

#### Actions of Prostaglandins on Pulmonary Vessels

The effects of prostaglandins, their precursors, and the thromboxanes on the pulmonary vasculatures of various species are summarized in tables 1 and 2. The experimental findings vary with species, animal preparation employed, dose of prostaglandin used, mode of administration (bolus or infusion), and effects of the prostaglandin on other variables such as cardiac output. However, most studies have examined the responses elicited by prostaglandins of the E and F series, and in general, it is true that prostaglandin E<sub>1</sub> causes vasodilatation, while prostaglandin F<sub>2 $\alpha$</sub>  stimulates vasoconstriction. The pressor effect of prostaglandin F<sub>2 $\alpha$</sub>  has been demonstrated when the lung is perfused with dextran and is therefore independent of the formed elements of the blood.<sup>32</sup> All the precursors of prostaglandins studied so far induce pulmonary vasoconstriction.

The prevailing oxygen tension has recently been

shown to have an important influence on the activities of exogenous prostaglandins in the pulmonary vasculature. The increase in pulmonary perfusion pressure caused by prostaglandin F<sub>2 $\alpha$</sub>  in the isolated cat lung is potentiated by hypoxia.<sup>50</sup> This finding has been confirmed in the intact anesthetized dog.<sup>65</sup> Prostaglandin E<sub>1</sub> (2  $\mu$ g/kg/min) was demonstrated to have no effect on pulmonary arterial pressure or resistance at a systemic arterial oxygen tension of 100 mm Hg, while the same infusion of prostaglandin E<sub>1</sub>, at an oxygen tension of 44 mm Hg, reduced pulmonary arterial pressure by 7 mm Hg and pulmonary vascular resistance by 3.1 mm Hg/l/min (42 per cent). The potentiating effect of hypoxia on the pulmonary vasodilation caused by prostaglandin E<sub>1</sub> can be inferred from data given in two other reports.<sup>66,67</sup> These reports complement the finding that the relaxation of the isolated lamb ductus arteriosus by prostaglandin E<sub>1</sub> and E<sub>2</sub> is also more marked in a low-oxygen environment,<sup>68</sup> though this has recently been disputed.<sup>69</sup>

A recent study of the activity of prostaglandin E<sub>1</sub> (1  $\mu$ g/kg/min) on the pulmonary vasculature of the conscious dog did not confirm the potentiating effect of hypoxia.<sup>70</sup> When systemic arterial oxygen tension was 80 mm Hg, infusion of prostaglandin E<sub>1</sub> reduced the pulmonary arterial pressure by 2 mm Hg and pulmonary vascular resistance by 76 dynes/cm/sec<sup>-5</sup>. At an oxygen tension of 37 mm Hg the same infusion reduced pulmonary arterial pressure by 0.6 mm Hg and pulmonary vascular resistance by 74 dynes/cm/sec<sup>-5</sup>. While the reduction in pulmonary arterial pressure caused by prostaglandin E<sub>1</sub> at low oxygen tension was shown in statistical terms to be less than the reduction at high oxygen tension, a difference of 1 mm Hg is not biologically significant. The disparity between the work quoted earlier and this study<sup>70</sup> is probably related to the poor pulmonary

vascular pressor response to hypoxia recorded prior to prostaglandin E<sub>1</sub> infusion. The absence of anesthesia does not explain the difference in the pressor responses, as marked pulmonary vasoconstriction has been reported to occur in conscious dogs.<sup>71</sup> The answer may lie in the poor reactivity of the pulmonary vasculature of dogs living in certain low-altitude areas.<sup>72</sup>

A recent paper may help to explain the effect of changes in oxygen tension.<sup>73</sup> Low oxygen tensions were found to reduce membrane polarization and high oxygen tensions caused hyperpolarization of the membrane of the invertebrate, *Aplysia californica*. This association was mediated through alteration in the activity of the sodium-potassium pump. If such observations can be extrapolated to the pulmonary vascular smooth muscle cell membrane in the mammal, they supply a possible explanation for the observed interaction between vasoactive substances and oxygen tension. Whatever the underlying mechanism, the changes induced by variation of the oxygen tension in the reactivity of the pulmonary vasculature to prostaglandins and other vasoactive agents are of particular interest with regard to patients with pulmonary disease or those receiving oxygen therapy.

#### RELEASE OF PROSTAGLANDINS FROM THE LUNGS

Anaphylaxis was the first stimulus found to elicit the production of prostaglandins from the lungs.<sup>7,74</sup> Prostaglandins E<sub>2</sub> and F<sub>2α</sub> were identified by bioassay in Krebs' solution used to perfuse isolated guinea pig lungs. It is interesting that the rabbit aorta-contracting substance described in those experiments has been shown to consist mainly of thromboxane A<sub>2</sub>.<sup>75</sup> Other prostaglandin-like substances (thromboxane B<sub>2</sub> and 6-oxo-PGF<sub>1α</sub>), released during anaphylaxis, have been identified more recently.<sup>76</sup> Trauma to guinea pig lungs can also induce prostaglandin formation.<sup>77</sup> Pulmonary edema provoked by intravenous injection of alloxan is associated with release of a metabolite of prostaglandin F<sub>2α</sub> into the lymph and blood.<sup>78</sup> Prostaglandins have not, however, been identified in the effluent from lungs made edematous by increased hydrostatic pressure.<sup>79</sup> Release of the E series of prostaglandins has been demonstrated after positive-pressure ventilation of isolated guinea pig,<sup>80</sup> rat,<sup>80</sup> and dog<sup>81</sup> lungs. A teleologic explanation would be that local production of a dilator prostaglandin in response to "stretching" of the airways leads to local vasodilatation and matching of ventilation and perfusion. Production of prostaglandins stimulated by hypoxia, hyperoxia, endotoxin, and emboli is considered in greater detail below. Piper and Vane postulated that the common factor necessary for the formation of prostaglandins was distortion of the cell membrane, and suggested that the action of the

released prostaglandin might be to oppose the initial stimulus and restore the status quo, or alternatively, to allow the cell to adapt to the stimulus.<sup>77</sup> This concept that prostaglandins might maintain homeostasis has been reiterated recently.<sup>82</sup>

Von Euler, who gave prostaglandins their name in 1935, suggested in 1946 that alveolar hypoxia caused pulmonary vasoconstriction.<sup>84</sup> Vasoconstriction in response to hypoxia is an important factor controlling the balance between ventilation and perfusion in the lung. The clinical importance of local hypoxic pulmonary vasoconstriction has been demonstrated by the effect of infused prostaglandin E<sub>1</sub> in dogs with lobar pneumococcal pneumonia.<sup>85</sup> When the hypoxic vasoconstriction was prevented by infusion of prostaglandin E<sub>1</sub> (10 μg/min) there was a 54 per cent decrease in systemic arterial oxygen tension in five anesthetized dogs breathing 100 per cent oxygen.

The mechanism responsible for hypoxic pulmonary vasoconstriction remains unknown. One school of thought considers that hypoxia may have a direct effect on the smooth muscle of the pulmonary arterioles, thereby causing contraction.<sup>86</sup> However, the smooth muscle of the systemic arterioles tends to relax when hypoxic. In order to explain the different behaviors of the pulmonary vasculature it has been postulated that a mediator substance, such as histamine, 5-hydroxytryptamine, dopamine, or norepinephrine, released from the mast cells or neuroepithelial bodies as a result of hypoxia, might stimulate pulmonary vasoconstriction. The different hypotheses have recently been reviewed.<sup>87,88</sup>

It has been suggested that an endogenous constrictor prostaglandin should be considered for the role of mediator of the pressor response to hypoxia.<sup>89,90</sup> Prostaglandin-like activity has been found in the venous effluent from isolated perfused cat lungs subjected to hypoxia.<sup>90</sup> However the pressor response to hypoxia was absent or very poor (1 mm Hg) in many of these experiments, and the prostaglandin-like activity was not always demonstrated, even when greater pressor responses were obtained. Aspirin, used to inhibit prostaglandin synthesis, increased the control resistance prior to hypoxia, and the absolute level of resistance obtained during hypoxia was unchanged. These shortcomings led other researchers to question whether the experiments established a role for prostaglandin-like substances in hypoxic pulmonary vasoconstriction.<sup>91</sup> In reply to this criticism, further studies in anesthetized cats showed that aspirin did slightly decrease the pressor response to hypoxia, though the use of another inhibitor of prostaglandin synthesis, indomethacin, increased the response.<sup>92</sup> These results failed to elucidate whether prostaglandins play a part in mediating the pressor response to hypoxia.

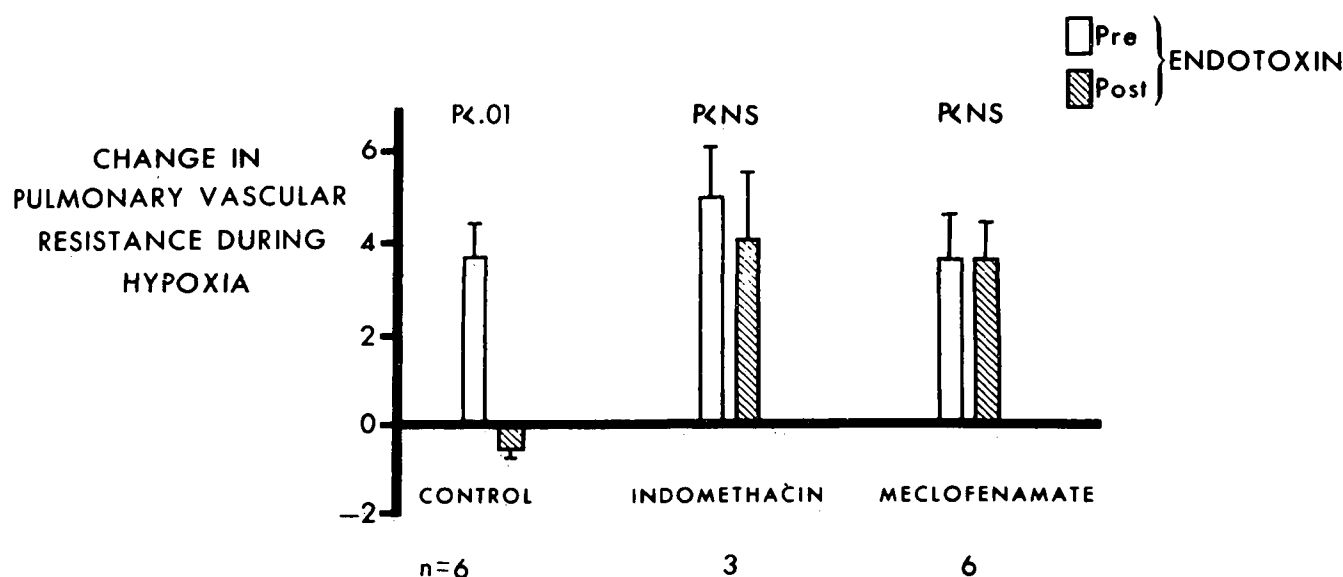


FIG. 1. The increase in pulmonary vascular resistance (mmHg/l/min) produced by airway hypoxia no longer occurs following endotoxin (control). Inhibition of prostaglandin synthetase by either indomethacin or meclofenamate protects the hypoxic pressor response from this action by endotoxin. (Reproduced from J Lab Clin Med 88:975-983, 1977, by permission of the C. V. Mosby Company and the author).

Other workers found that the inhibition of prostaglandin synthesis by indomethacin, meclofenamate, or aspirin potentiates, rather than inhibits, the pulmonary pressor response to hypoxia in the anesthetized dog,<sup>93-95</sup> isolated perfused rat lungs,<sup>95,96</sup> anesthetized neonatal goat,<sup>97</sup> and awake cattle.<sup>95</sup> Polyphloretin phosphate, an inhibitor of peripheral prostaglandin action, has also been found to enhance hypoxic pulmonary vasoconstriction in the anesthetized dog.<sup>98</sup> Drugs such as indomethacin may alter the response of vascular smooth muscle to vasoactive substances by a direct effect on the contractile mechanism.<sup>99</sup> Inhibitors of prostaglandin synthesis also prevent the formation of the precursor cyclic endoperoxides and their non-prostanoid metabolites, the thromboxanes.<sup>100</sup> Thus, the evidence quoted from experiments using blockers of prostaglandin synthesis or action has yet to be confirmed. It does suggest, however, that a dilator prostaglandin, endoperoxide, or thromboxane produced during hypoxic pulmonary vasoconstriction may reduce the severity of the pulmonary hypertension. It is clear that prostaglandins cannot mediate the pressor response to hypoxia.

Contrary to the general concept that prostaglandins play a homeostatic role and tend to modulate the effects of other vasoactive agents, a recent report suggests that a prostaglandin might mediate part of the pulmonary vasodilatation seen when 100 per cent oxygen is inhaled.<sup>101</sup> Indomethacin reduced the reduction in pulmonary vascular resistance caused by ventilation with 100 per cent oxygen in the anesthetized neonatal pig and the isolated pig lung. The vasodilatation caused by prostaglandin E<sub>1</sub> in the iso-

lated preparation was unaltered by indomethacin. We have not been able to confirm this effect of indomethacin on hyperoxic pulmonary vasodilatation in the anesthetized adult dog,<sup>‡</sup> but the dose we used (2 mg/kg) was lower than that used in the neonatal pigs (5-10 mg/kg). Again, the interpretation of the indirect evidence of prostaglandin involvement requires considerable caution.

One of the clinical manifestations of endotoxin shock is systemic arterial desaturation. Experimentally, it has been shown that even a minute intravenous dose of endotoxin (15 µg/kg), too small to cause systemic hypotension, will abolish the pulmonary pressor response to hypoxia in the dog and therefore upset the balance of ventilation and perfusion in the lung.<sup>102</sup> Endotoxin is known to stimulate the formation of prostaglandins in the dog,<sup>103,104</sup> mouse,<sup>105</sup> and calf.<sup>106</sup> Recent work has shown that when the synthesis of prostaglandins is inhibited, the pressor response to hypoxia in the anesthetized dog is protected against the effects of endotoxin (fig. 1).<sup>107</sup> This suggests that endotoxin may oppose pulmonary vasoconstriction by inducing the production of a dilator prostaglandin. It appears that the prostaglandin comes from vessels or tissues rather than platelets<sup>107</sup> or leukocytes.<sup>§</sup> Species variation is evident in the response to endotoxin. In cattle intravenous endotoxin stimulates the production of a constrictor prostaglandin (F series) and causes pulmonary hypertension, which can be pre-

‡ Weir EK, Grover, RF: Unpublished observations.

§ Mlczech J, Weir EK, Grover RF, et al: Pulmonary vascular effects of endotoxin in leukopenic dogs (in manuscript).

vented by pretreatment with indomethacin.<sup>106</sup> Endotoxin also causes pulmonary hypertension in cats; this hypertension is greatly reduced by pretreatment with indomethacin<sup>108</sup> or flurbiprofen.<sup>109</sup> If the response to endotoxin in man follows that of the dog, calf, or cat, the pulmonary vascular effect would be deleterious and an improvement in systematic arterial oxygen saturation might be expected from the use of prostaglandin synthetase inhibitors such as indomethacin.

The actions of prostaglandin-like substances, produced as a result of endotoxin stimulation, may have further clinical significance in management of patients who have hepatic dysfunction. Such patients have been found to have increased levels of circulating endotoxin.<sup>110,111</sup> Vasodilatation of the pulmonary microvasculature and reduced systemic arterial oxygen tensions have been found in patients with hepatic cirrhosis<sup>112</sup> and also following portacaval anastomosis in man.<sup>113</sup> Failure of the pulmonary pressor response to hypoxia has been reported to occur in the former group.<sup>112</sup> If endotoxin in the portal circulation is not removed by the liver it will circulate to the lungs. Alternatively, if production of prostaglandins is induced by endotoxin in the splanchnic region the compromised liver may fail to remove them from circulation in the usual manner,<sup>114</sup> thus allowing them to reach the lungs, prevent hypoxic vasoconstriction, and cause the observed vasodilatation. This hypothesis remains to be proven, but if it is correct, an inhibitor of prostaglandin synthesis should restore the pulmonary pressor response to hypoxia and the normal balance of ventilation and perfusion. Again if the hypothesis is correct, a somewhat tenuous extrapolation would suggest that some form of portacaval bypass might be beneficial in patients with primary pulmonary hypertension. The dilatation of the pulmonary vessels and the inhibition of platelet aggregation induced by prostaglandins of the E series could be helpful.

Embolization of the lungs induces release of prostaglandins in the venous effluent.<sup>115-117</sup> Inhibition of prostaglandin synthesis by indomethacin blocked the increase in tracheal pressure observed when barium sulfate microemboli were injected intravenously in anesthetized open-chested dogs.<sup>118</sup> The increase in pulmonary arterial pressure caused in this preparation was not affected by indomethacin. However, meclofenamate, a more potent inhibitor of prostaglandin synthesis, and polyphlorethin phosphate, a blocker of peripheral prostaglandin action, markedly reduced the pulmonary hypertension (both pressure and resistance) produced by glass-bead microemboli in the anesthetized dog.<sup>119</sup> In addition, they attenuated the alveolar hypoventilation normally observed after the embolization. Similarly, a recent study has shown that indomethacin reduces the pul-

monary hypertension and hypoxemia produced by an infusion of Intralipid in sheep.<sup>120</sup> Thus, prostaglandin-like substances may be responsible for part of the pulmonary hypertension and bronchoconstriction that follow pulmonary embolism.

Prostaglandin-like substances are known to be released during pulmonary microembolism with platelet aggregates, even in the absence of glass beads or barium particles.<sup>117</sup> Aspirin reduces the pulmonary hypertension induced by platelet emboli in the lungs.<sup>121,122</sup> The reduction in pulmonary hypertension could be due to a decrease in synthesis of a constrictor prostaglandin, or in part to inhibition of endoperoxide and thromboxane production,<sup>100</sup> with a consequent reduction in platelet release. While platelets are responsible for some of the pulmonary hypertension that follows embolism,<sup>117,123,124</sup> it has been demonstrated that they cannot be the only source of prostaglandins. Emboli injected into the isolated lungs of guinea pigs and rats perfused with Krebs' solution induced prostaglandin E<sub>2</sub> formation.<sup>115</sup> As an artificial perfusate was used, these prostaglandins must have come from the lungs. In summary, it can be said that microembolization leads to the release of prostaglandins from the lungs themselves. Inhibition of prostaglandin synthesis, or the removal of platelets, reduces the pulmonary hypertensive response to emboli. Prostaglandins or their precursors may be involved in the part played by platelets in the production of embolic pulmonary hypertension.

Prostaglandins in both E and F series have been demonstrated in the pulmonary lymph of dogs in which intravascular coagulation and inhibition of fibrinolysis were induced.<sup>125</sup> Aggregation or lysis of platelets by a platelet-specific antiserum in dogs causes pulmonary vasoconstriction, followed by a period when the pulmonary vasculature is unresponsive to hypoxia.<sup>126</sup> The observation that these effects can be prevented by prior treatment with an inhibitor of prostaglandin synthesis, meclofenamate, suggests that there may be an initial production of a constrictor prostaglandin and subsequently a dilator prostaglandin. The circulating platelet count is dramatically reduced in the presence or absence of meclofenamate, so that meclofenamate does not protect the platelets from the action of the antiserum. These experiments demonstrate that the interaction of platelets and prostaglandins, or their precursors, can have an important influence on pulmonary circulation control.

Is this interaction of clinical relevance outside the context of pulmonary embolization? Hypobaric hypoxia reduces the numbers of circulating platelets in man,<sup>127</sup> cattle,<sup>128</sup> mice,<sup>129</sup> and rats,<sup>130</sup> and there is evidence that the platelets may be sequestered in the lungs.<sup>127</sup> However, neither platelets nor prostaglandins are essential for the pulmonary pressor re-

sponse to hypoxia.<sup>95,131</sup> The intravascular aggregation of platelets does produce a transient increase in the permeability of the pulmonary vasculature.<sup>132</sup> It might be thought that the sequestration of platelets in the lungs and the release of factors increasing pulmonary vascular permeability during hypobaric hypoxia would explain the pathophysiology of high-altitude pulmonary edema. However, a study of normal subjects taken to an altitude of 4,350 meters showed that pretreatment with the antiplatelet drug, sulfinpyrazone, did not prevent the decrease in platelet count.<sup>133</sup> Other investigators did not find a change in platelet count or platelet function at high altitude, but did obtain evidence of a coagulopathy.<sup>134</sup>

The probable actions of endogenous prostaglandins on the pulmonary vasculature, based on the evidence given above, are summarized in table 3. Prostaglandins are produced in the lungs in response to a variety of stimuli, such as anaphylaxis, trauma, or positive-pressure respiration. Under normal conditions they appear to modulate hypoxic pulmonary vasoconstriction and fulfil a physiologic function. Endotoxin can stimulate the formation of prostaglandins, which will temporarily inhibit the pressor response to hypoxia and may be responsible for the loss of this response in patients with hepatic cirrhosis. Prostaglandins from the lungs and possibly from the platelets are partially responsible for the pulmonary hypertension associated with microembolism. Thus, prostaglandins may be shown to be mediators involved in the pathophysiology of embolism and cirrhosis. The aggregation or lysis of platelets by an antiserum renders the pulmonary vasculature unresponsive to hypoxia, an effect that can be prevented by meclofenamate and could be due to the formation of a dilator prostaglandin-like substance. It is evident that the roles played by prostaglandins, endoperoxides, and thromboxanes in many normal and pathologic mechanisms in the pulmonary vasculature have still to be clarified. Once selective inhibitors, not only of the different prostaglandins, but also of endoperoxides and thromboxanes, have been developed, the task will be easier.<sup>135</sup>

### Prostaglandins and the Ductus Arteriosus

Nearly 40 years ago, experiments in guinea pigs suggested that there might be an association between constriction of the ductus arteriosus and an increase in arterial oxygen tension.<sup>136-138</sup> This association was confirmed by Born *et al.* in 1956.<sup>139</sup> However, the mechanism underlying the observation has not been understood until recently. It was considered that oxygen might stimulate the release of an endogenous hormone, or might "accelerate some rate-limiting enzyme reaction related to contraction."<sup>140</sup> The con-

TABLE 3. Postulated Actions of Endogenous Prostaglandins on the Pulmonary Vasculature

Stimulus	Prostaglandin Action
Hypoxia	Reduces hypoxic pulmonary hypertension
Endotoxin	Stimulates pulmonary hypertension in cattle and cats Renders pulmonary vasculature unresponsive to hypoxic vasoconstriction in dogs and (?) in patients with hepatic cirrhosis
Platelet antiserum	Initial pulmonary vasoconstriction Subsequent lack of constriction in response to hypoxia
Pulmonary microembolism	Increases pulmonary hypertension and hypoxemia

cept that oxygen might suppress the formation or activity of an endogenous dilator substance, such as prostaglandin E, is relatively recent.<sup>141</sup> If an endogenous prostaglandin is responsible for keeping the ductus arteriosus open, then inhibition of prostaglandin synthesis will lead to closure. It also follows that an exogenous dilator prostaglandin might maintain patency after birth. Both associations have now been demonstrated in man and other animals.

Administration of any of the prostaglandin synthetase inhibitors indomethacin, acetylsalicylic acid, and sodium salicylate causes constriction or closure of the ductus arteriosus in fetal lambs,<sup>68,141,142</sup> rats,<sup>143,144</sup> and rabbits.<sup>144</sup> Similarly, either indomethacin or another inhibitor, eicosa-tetraenoic acid, will induce contraction of the isolated ductus arteriosus of the lamb.<sup>68,145</sup> Construction of the patent ductus arteriosus by indomethacin has been inadvertently demonstrated in an infant with pulmonary atresia.<sup>146</sup>

Closure of the patent ductus arteriosus, as judged by clinical and echocardiographic criteria, has been achieved in premature infants by inhibition of prostaglandin synthesis.<sup>147,148</sup> Acetylsalicylic acid, administered by orogastric tube, closed the ductus of one infant, constricted it in another, but had no effect in a third. Indomethacin (0.1–0.3 mg/kg) was effective after one to three doses in 14 of 15 premature infants in one report.<sup>147</sup> A single dose of 5 mg/kg per rectum, or 2.5 mg/kg by nasogastric tube, was effective in all six infants in the other report.<sup>148</sup> The ability to close the patent ductus in these premature infants with respiratory distress by medical means is a great advance, in view of the definite association of mortality with thoracotomy and ligation in this group.<sup>149,150</sup>

Indomethacin has been shown to increase the pulmonary vascular pressor response to hypoxia in neonatal animals.<sup>97</sup> The increase in the pulmonary

vascular resistance response to hypoxia was 38 per cent in anesthetized, newborn, full-term goats and 55 per cent in premature goats. The respiratory distress syndrome and associated alveolar hypoxia are common in premature neonates with large left-to-right shunts. Consequently, pulmonary hypertension is a theoretical risk when these infants are given indomethacin in order to close the ductus arteriosus. Indomethacin has been shown angiographically to close the ductus arteriosus in one such baby, and the pulmonary vascular resistance did not increase in that instance.<sup>¶</sup> It may be that the pulmonary vasculature of the premature infant will be found to be unresponsive to hypoxia, as demonstrated in the fetal lamb,<sup>151</sup> or that in this particular case there was insufficient atelectasis and alveolar hypoxia to stimulate vasoconstriction.

The use of indomethacin to inhibit premature labor<sup>152,153</sup> raises the possibility of intrauterine closure of the ductus arteriosus and also the possibility of pulmonary hypertension. Neonatal rats delivered at term by cesarian section from pregnant rats that had been given indomethacin 12 or 18 hours earlier showed significant constriction of the duct at birth, together with transient cyanosis and acidosis.<sup>143</sup> Constriction of the duct was not elicited by indomethacin earlier in fetal development.<sup>144</sup> Pulmonary arterial hypertension has been observed in fetal lambs given acetylsalicylic acid by gastric tube.<sup>141</sup> In this study and another study of fetal lambs, inhibitors of prostaglandin synthesis caused constriction of the ductus arteriosus.<sup>68,141</sup> These experiments in animals indicate that intrauterine closure of the duct and pulmonary hypertension may occur as a result of the inhibition of prostaglandin synthesis.

What is the significance of closure of the ductus arteriosus *in utero*? Intrauterine obstruction of the ductus arteriosus in dogs is compatible with life until the time of birth, but at that time all the pups die.<sup>154</sup> Pathologic studies show thrombosis of the pulmonary artery, dilatation and hypertrophy of the right ventricle, and enlargement of the liver. Two long-term survivors have been reported from a group of 20 lambs subjected to intrauterine ligation of the ductus arteriosus.<sup>155</sup> Intrauterine cardiac failure has been reported in two cases where premature closure has occurred in man.<sup>156,157</sup> Inhibition of prostaglandin synthesis may have been responsible, as the mother had received salicylates for ten days in one instance.<sup>157</sup> Death occurred at 42 weeks of gestation in the other case.<sup>156</sup> Two further cases of intrauterine cardiac failure associated with duct closure are mentioned in another report.<sup>144</sup> When indomethacin was used to inhibit premature labor in 50 women, 12 premature babies

were born in spite of therapy. One was stillborn (1,100 g) and four died within 48 hours of birth (mean weight 1,075 g). No ill effect was observed in the remaining 45 infants.<sup>152</sup> The simultaneous use of a beta stimulating drug,<sup>153</sup> which also inhibits labor, has the theoretical advantage of inducing pulmonary vasodilatation and opposing the pulmonary hypertension produced by indomethacin.<sup>158</sup> While further observation may demonstrate that indomethacin does contribute to neonatal death in those cases where it fails to inhibit labor, "at this early stage of gestation there is also little to lose since the alternative is a fetus with little or no chance at all to survive."<sup>153</sup>

Inhibition of prostaglandin synthesis will cause closure of the ductus, but it is also of clinical importance that infusion of the E series of prostaglandins will keep the duct open. Infants who have congenital lesions that obstruct outflow on the right side of the heart may depend on the ductus arteriosus for most of their pulmonary blood flow. Examples of these conditions are pulmonary atresia, tetralogy of Fallot with severe valvular or infundibular stenosis, and severe pulmonary valvular stenosis with an intact septum or single ventricle. The reversed shunt through a ductus arteriosus is also vital for perfusion of the lower half of the body in the presence of an interrupted aortic arch.

Studies *in vitro* have shown that prostaglandins E<sub>1</sub> and E<sub>2</sub> will relax the ductus arteriosus of fetal lambs.<sup>68,145,159</sup> This ability to induce relaxation in strips of the ductus was most apparent at low oxygen tensions.<sup>145</sup> Prostaglandin E<sub>1</sub> also caused relaxation in strips of the ductus taken from fetal calves.<sup>160</sup> Prostaglandin E<sub>2</sub> produced an initial contraction followed by more marked relaxation. Strips of human ductus reacted similarly. Experiments *in vivo* using the whole-body-freezing technique have demonstrated that subcutaneous injection of prostaglandin E<sub>1</sub> will reopen the closing ductus in newborn rats and rabbits.<sup>161</sup> Angiography in neonatal piglets shows that prostaglandins E<sub>1</sub>, E<sub>2</sub>, A<sub>1</sub>, and A<sub>2</sub> can open and dilate the ductus.<sup>162</sup> Alteration of the percentage of oxygen in the inspired gas was not discerned to affect the activity of the prostaglandins in that study.

Prostaglandin F<sub>2α</sub> causes constriction in strips of the ductus arteriosus taken from fetal lambs<sup>68</sup> and fetal calves.<sup>161,163</sup> An increase in oxygen tension has a synergistic effect in stimulating constriction in the fetal calves.<sup>161</sup> This is opposite to the interaction between prostaglandin F<sub>2α</sub> and oxygen tension in the pulmonary vasculature. In the intact anesthetized dog the pulmonary pressor effect of prostaglandin F<sub>2α</sub> is greatest at low oxygen tensions.<sup>65</sup> The relationship between prostaglandin E<sub>1</sub> and oxygen tension seems to be the same in both the pulmonary vasculature and the ductus arteriosus. The ability of the E series

¶ Joffe HS, Weir EK: Unpublished observations.



of prostaglandins to open and dilate the ductus arteriosus is just beginning to be exploited clinically.<sup>68-146,164,165</sup> These reports describe seven infants with obstruction to pulmonary blood flow, all of whom showed marked improvement in systemic oxygen saturation on infusion of prostaglandin E<sub>1</sub> or E<sub>2</sub>. Hyperpyrexia and episodes of apnea have been reported to occur during infusion of prostaglandin E<sub>2</sub> but have not so far been reported with prostaglandin E<sub>1</sub>. Transient apnea has also been found to be more common with prostaglandin E<sub>2</sub> than with prostaglandin E<sub>1</sub> in neonatal pigs.<sup>162</sup> Using prostaglandin E<sub>1</sub>, we observed rapid improvement in two deeply cyanosed infants with pulmonary atresia, who were dependent on a patent ductus arteriosus for pulmonary blood flow.<sup>\*\*</sup> Hyperpyrexia and apnea did not arise during infusion. Although the number of patients involved is small and the underlying anatomic problem remains, the short-term benefit of prostaglandin E infusion is dramatic, and allows time for catheterization and operation.

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