Alterations in the Contractile Response of Bovine Intrapulmonary Arteries Due to Pneumonia

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It is an important issue how lung vascular injury due to pulmonary diseases alters the mechanical function of the vascular bed, because the vessels in this bed contribute not only to the efficiency of gas exchange but also to the metabolism of many hormones and autacoids [2, 7]. The relationship between lung injury and functional alterations in the pulmonary vessels has often been investigated in experimental pulmonary injuries caused by chemical substances [1, 3, 4, 6]. These studies are limited to small experimental animals such as rats and hamsters. There have been few reports delineating how spontaneous pulmonary diseases affect the function of pulmonary vessels in domestic animals. The purpose of the present study, therefore, is to examine the effect of pneumonia on the contractile responses of bovine intrapulmonary arteries.

The lungs were dissected from four pneumonic and three healthy adult Japanese black cattle at a local slaughter house. Pneumonia was determined macroscopically after thoracotomy. Intrapulmonary arteries were isolated from a healthy region and a diseased region with evident purulence of the pneumonia-affected lung. Arteries isolated from the healthy region or those isolated from healthy cattle were used as control. If the whole lung was affected by pneumonia, arteries were used as test. The ring preparations, 1 to 2 mm in width, were made with care to preserve the endothelial layer. The preparations were suspended in an organ bath and equilibrated for 60 min with a resting tension of 1 g in normal solution of the following composition (mM): NaCl 136.9, KCl 5.4, CaCl₂

1.5, MgCl₂ 1.0, NaHCO₃ 24.0 and glucose 5.5. The solution was aerated with 95% O₂ and 5% CO₂ at 37°C and pH 7.4. The tension was measured isometrically using a force-displacement transducer and recorded on a pen-writing oscillograph.

Data are expressed as means $\pm$ s.e. Statistical difference was evaluated by Student's *t*-test. A difference was considered to be significant at $P < 0.05$.

The contractions induced by the addition of K⁺, which causes membrane depolarization and thereby activates the voltage-dependent Ca²⁺ channels [8], are shown in Fig. 1. Figure 1A shows the developed tension in gram, while Fig. 1B shows the relative tension which was normalized as a percentage of the contraction due to 60 mM K⁺ in each preparation. There was no significant difference between the developed tensions in control arteries and pneumonic arteries when the administered K⁺ was less than 30 mM. However, at 60 mM K⁺, the maximal tension of the pneumonic arteries was reduced to $54.6 \pm 4.2\%$ of that in control arteries. This suggests that the contractility, or the Ca²⁺-sensitivity, was depressed by the pneumonia. When the response was normalized, the log dose-response curve for the pneumonic arteries was shifted to the left compared to the control curve (Fig. 1B). The EC₅₀ value in the pneumonic arteries was 21.2 ± 1.5 mM ($n=8$), which is smaller than that in control arteries, 35.6 ± 0.6 mM ($n=8$). Thus, it seems that the sensitivity to K⁺ increased in the injured arteries. Although we do not know whether the increased sensitivity to K⁺ resulted from partial depolarization of the pneumonic arteries or a greater Ca²⁺ influx at a given depolarization in injured arteries than in intact ones, it is possible that the decreased contractility

Fig. 1. (A) Dose-response relationship for the K⁺-induced contractions of intrapulmonary arteries isolated from intact lung tissue (control ●) and pneumonic lung tissue (■). (B) The ordinate is expressed as a percentage of that to each 60 mM KCl-induced contraction. KCl was added cumulatively to the medium, as indicated on the abscissa. * $P < 0.05$ (vs. control)

Fig. 2. Dose-response relationship for Ang II and PGF 2α -induced contractions of intrapulmonary arteries from intact lung tissue (control ●, ○) and pneumonic lung tissue (■, □). The filled symbol and open symbol represent Ang II and PGF 2α , respectively. Ang II and PGF 2α were added cumulatively to the medium, as indicated on the abscissa. * $P < 0.05$ (vs. control)

and the increased sensitivity may offset each other in a way that the contractile force due to less than 30 mM K⁺ becomes similar.

The autacoid receptor-mediated contractions were then compared. Angiotensin II (Ang II; Peptide Foundation) and prostaglandin F 2α (PGF 2α ; Upjohn) caused contractions in intact pulmonary arteries. In contrast to K⁺-induced response, the responses to both substances were greatly inhibited in arteries affected by pneumonia (Fig. 2). The tension responses in gram to 1×10^{-7} M Ang II and 1×10^{-5} M PGF 2α were reduced to $8.7 \pm 0.9\%$ and $17.3 \pm 2.8\%$ of the response in control arteries, respectively. Even if the contraction was expressed as the relative contraction of the 60 mM K⁺-induced one, the responses to Ang II and PGF 2α were significantly depressed in pneumonic arteries. These results suggest that the suppression of receptor-mediated contractions was not solely due to a reduction in the contractility of pneumonia-

affected arteries.

To evaluate whether endothelial injury modified the contractile response, we observed the contractile responses to K⁺, Ang II and PGF 2α in healthy arteries with the endothelium removed by abrasion. Removal of the endothelium did not significantly affect the contractile responses to these substances (data not shown), indicating that endothelial injury by pneumonia was not involved in the decline in responses. The decreased responses to Ang II and PGF 2α in the pneumonic arteries are possibly due to inhibition of their receptor systems in smooth muscle cells. This speculation is consistent with the finding of Greenlees *et al.* [5] that pneumonia due to *Pasteurella* inoculation blunted the β -adrenoceptor-mediated hemodynamic response of bovine pulmonary circulation. Therefore, pneumonia may primarily impair the receptor-coupled function of pulmonary vessels, regardless of its relevance to contraction or to relaxation. This study showed that pneumonia impairs the contractility and, more severely, the receptor-coupled contractions of the arteries. It must be clarified how these impairments are related to the secondary diseases of pneumonia.

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