Remote preconditioning lessens the deterioration of pulmonary function after repeated coronary artery occlusion and reperfusion in sheep

Un préconditionnement éloigné diminue la détérioration de la fonction pulmonaire après l'occlusion et la reperfusion répétées de l'artère coronaire

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Purpose: We investigated whether remote organ preconditioning (RPC) can preserve pulmonary function following repeated myocardial ischemia/reperfusion in a model mimicking multi-vessel off-pump coronary artery bypass (OPCAB) revascularization.

Methods: Nine sheep (Group-RPC) underwent RPC by three episodes of five-minute occlusion and five-minute reperfusion of the iliac artery. Five sheep (Group-C) were time-matched controls. Afterwards, ten-minute occlusion and reperfusion of the left anterior descending, the first diagonal and the left circumflex coronary arteries were performed consecutively. Hemodynamic and respiratory parameters and arterial blood gases were measured until 120 min after the final coronary reperfusion. Anesthesia was maintained with halothane in oxygen and nitrous oxide. Animals were ventilated with a tidal volume of 15–20 $mL \cdot kg^{-1}$ in a non-rebreathing system, and a respiratory rate 14–16 min, with 5-cm H_2O positive end expiratory pressure after thoracotomy.

Results: Repeated coronary occlusion and reperfusion was associated in this experimental model with an increase in pulmonary vascular resistance (PVR) and pulmonary arterial pressure (PAP) and a decrease in PaO_2 and PaO_2/FIO_2 in Group-C. After 120 min reperfusion, PaO_2 and PaO_2/FIO_2 in Group-RPC were higher (192 ± 69 mmHg and 241 ± 78 *vs* 115 ± 54 mmHg and 129 ± 64, $P < 0.05$), while PVR and PAP were lower than in Group-C. At 120 min of reperfusion, PaO_2 and PaO_2/FIO_2 were inversely correlated with PVR ($P < 0.01$).

Conclusions: RPC by transient occlusion of the iliac artery improves lung gas exchange after repeated coronary artery occlusion and reperfusion mimicking OPCAB surgery, and preserves low PVR in sheep.

Objectif : *Nous avons vérifié si le préconditionnement éloigné d'un organe (PEO) peut préserver la fonction pulmonaire à la suite d'ischémie/reperfusion myocardique répétée chez un modèle imitant la revascularisation d'un pontage aortocoronarien plurivasculaire à cœur battant (PACCB)*

Méthode : *Neuf moutons (Groupe PEO) ont subi un PEO en trois épisodes d'occlusion de cinq minutes suivis de reperfusion de cinq minutes de l'artère iliaque. Cinq moutons (Groupe T) ont constitué le groupe témoin apparié dans le temps. Par la suite, nous avons réalisé successivement l'occlusion et la reperfusion, en dix minutes, des artères coronaires interventriculaire antérieure, première diagonale et circonflexe. Les paramètres hémodynamiques et respiratoires et la gazométrie du sang artériel ont été mesurés jusqu'à 120 min après la reperfusion coronaire finale. L'anesthésie a été maintenue avec de l'halothane dans un mélange d'oxygène et de protoxyde d'azote. Les animaux ont été ventilés selon un volume de 15–20 $mL \cdot kg^{-1}$ avec un système sans réinspiration, et une fréquence respiratoire de 14–16 min selon une pression positive en fin d'expiration de 5 cm de H_2O après la thoracotomie.*

Résultats : *Dans ce modèle expérimental, l'occlusion et la reperfusion coronaires répétées ont été associées à une augmentation de la résistance vasculaire pulmonaire (RVP) et de la tension artérielle pulmonaire (TAP) ainsi qu'à une baisse de la PaO_2 et de la PaO_2/FIO_2 dans le Groupe T. Dans le Groupe PEO, après 120 min de reperfusion, la PaO_2 et la PaO_2/FIO_2 étaient plus élevées (192 ± 69 mmHg et 241 ± 78 vs 115 ± 54 mmHg et 129 ± 64, $P < 0,05$), tandis que la RVP et la TAP étaient plus faibles que dans le Groupe T. À 120 min de reperfusion, la PaO_2 et la PaO_2/FIO_2 étaient en corrélation inverse avec la RVP($P < 0,01$).*

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Conclusion : *Le PEO par occlusion transitoire de l'artère iliaque améliore les échanges gazeux pulmonaires après l'occlusion et la reperfusion répétée de l'artère coronaire simulant un PACCB et il maintien une faible RVP.*

FOLLOWING cardiac surgery, pulmonary dysfunction rate ranges from < 2% (adult respiratory distress syndrome) to 64% (postoperative atelectasis),[1] and is one of the major contributors to postoperative morbidity and mortality. Off-pump coronary artery bypass (OPCAB) surgery may have the potential advantage of reducing postoperative pulmonary dysfunction compared with conventional coronary artery bypass grafting (CABG) using extra-corporeal circulation. Manipulation of the heart during exposure of the obtuse marginal or the right CABG during OPCAB might, however, cause valvular regurgitation and jeopardize hemodynamics and pulmonary function. Also, patients with severe left ventricular dysfunction (ejection fraction < 30%) will occasionally experience a rise in pulmonary arterial pressure (PAP) during OPCAB[2] due to further ischemic deterioration of the ventricle. The rise in pulmonary artery pressure is followed by a drop in systolic pressure and a significant decrease in myocardial contractility,[2] compromising the safe completion of the procedures without cardiopulmonary bypass (CPB). Respiratory insufficiency accounts for one tenth (4/39) of the causes of early postoperative death in 2,052 patients receiving OPCAB surgery as reported by Tasdemir *et al.*[3] A transesophageal echocardiographic study showed that a five-minute coronary occlusion was associated with significantly elevated left ventricular wall motion score and concomitant significantly increased pulmonary artery pressure in patients undergoing OPCAB surgery.[4] Other laboratory findings have shown that coronary artery occlusion caused pulmonary damage that was worsened by coronary reperfusion.[5] All this suggests that although OPCAB surgery allows avoiding the deleterious pulmonary effects of CPB, there still might be pulmonary dysfunction caused by the OPCAB procedure.[6,7] Therefore, techniques to reduce pulmonary dysfunction may enhance the safety of coronary artery bypass surgery even when extracorporeal circulation is avoided.

It has been reported that brief ischemia of remote organs (remote preconditioning, RPC), such as mesentery[8] or gastrocnemius muscle,[9] can reduce myocardial infarct size following prolonged ischemia and improve myocardial function. This RPC is much more attractive than the classical cardiac ischemic preconditioning since it avoids aortic cross clamping with its inherent risk of cerebral emboli. Moreover, in the case of beating heart OPCAB surgery, aortic cross clamping is, of course, impossible. It was shown recently that cardiac ischemic preconditioning protects pulmonary function in heart valve surgery.[10] The effect of RPC on pulmonary function has not yet been fully explored. We postulated that RPC could improve lung gas exchange following myocardial ischemia/reperfusion. We tested this hypothesis using a clinically relevant animal model of OPCAB surgery in which RPC was achieved by three episodes of brief iliac artery occlusion and reperfusion, and myocardial ischemia and reperfusion was achieved by consecutive occlusion/reperfusion of three main coronary arteries.

Methods

Animal preparation

All animals received humane care in compliance with the European Convention on Animal Care. The animal Ethics Committee of the Katholieke Universiteit Leuven approved the study. Fourteen adult sheep weighing between 53–65 kg were used in this study. Nine sheep were pretreated by RPC, and, five control sheep were used. The sheep were fasted for 48 hr, but access to water was allowed until 20–24 hr before anesthesia.

Anesthesia and surgical procedure

The sheep were given *im* ketamine 15–20 $mg \cdot kg^{-1}$. Anesthesia was induced with halothane (1–4 vol%) in oxygen and maintained after endotracheal intubation with halothane (1.5–2.0 vol%) in a mixture of oxygen and nitrous oxide. The animals were ventilated mechanically (Engström model 200, Engström, Sweden) at a respiratory rate of 14–16 $\cdot min^{-1}$, an in- to expiratory cycle ratio of 1:2, and the tidal volume (15–20 $mL \cdot kg^{-1}$) was individually adjusted to maintain arterial carbon dioxide tension ($PaCO_2$) between 35 to 45 mmHg. The tidal volume and respiratory rate for individual animals was not further adjusted during the experiment after baseline normal $PaCO_2$ was achieved. Sigh breaths were given to treat increasing airway pressures. Angiocatheters (18 G and 20 G) were inserted respectively into a peripheral vein and a left ear artery for *iv* infusion and for arterial blood pressure monitoring and arterial blood sampling. A catheter was introduced into the right atrium through the jugular vein for continuous monitoring of central venous pressure. The electrocardiogram was monitored continuously. Fentanyl (0.1 mg, Janssen, Beerse, Belgium) was given before surgery and was further

administered in boluses during thoracotomy. Physiological saline was given intravenously at a constant rate of 6 $mL \cdot kg^{-1} \cdot min^{-1}$ throughout the procedure. Heparin (400 $IU \cdot kg^{-1}$ *iv*) was administered before any vascular occlusion.

After a left thoracotomy was performed in the third intercostal space and the fourth rib was removed, a positive end-expiratory pressure of 5 cm H_2O was established. A 20-mm ultrasonic flow probe connected to a flow meter (Transonic System, Ithaca, NY, USA) was placed around the pulmonary artery for cardiac output (CO) measurement. Three fluid-filled pressure catheters were placed to measure left atrial, pulmonary artery, and aortic pressures. Suture snares were put respectively around the left anterior descending coronary artery distal to the first diagonal branch, the first diagonal branch itself and the left circumflex coronary artery. The left external iliac artery was exposed for RPC. All the hemodynamic variables were continuously recorded on a heat-writing recorder (Nihon-Kohden, Tokyo, Japan) after signal conditioning with a carrier-amplifier (Triton Technology, San Diego, CA, USA). All signals were digitized on-line at 200 Hz with an analogue to digital converter equipped in the Conduct-PC hardware (CardioDynamics, Leiden, the Netherlands) and recorded on a computer. Blood gas variables were obtained from an automated blood gas analyzer (ABL3, Radiometer, Copenhagen, Denmark). The pulmonary vascular resistance (PVR) was calculated as: PVR = 80*(PAP-LAP)/CO from PAP, left atrial pressure (LAP) and CO.

Experimental protocol

Fourteen sheep were randomly assigned by using sealed envelopes to a control group (Group-C, $n = 5$) and a RPC group (Group-RPC, $n = 9$). Blood gases, respiratory and basic hemodynamic variables were recorded after induction of anesthesia. During instrumentation, basic hemodynamic variables did not change, and baseline data were recorded ten minutes after completion of the surgical instrumentation. RPC was subsequently achieved by three episodes of five-minute occlusion followed by five-minute reperfusion of the iliac artery, and data after preconditioning were recorded ten minutes after the final reperfusion of the iliac artery, or time-matched in Group-C which did not undergo iliac artery occlusion and reperfusion.

Subsequently, animals in both groups were subjected to repeated coronary occlusion and reperfusion. Firstly, the left anterior descending coronary artery was occluded for ten minutes. Ten minutes after left anterior descending coronary reperfusion, the first diagonal branch was occluded for ten minutes followed by reperfusion, ten minutes afterwards, the circumflex was occluded for ten minutes and then reperfused. Arterial blood samples were taken, and hemodynamic and respiratory variables recorded every 30 min after circumflex reperfusion until 120 min. Successful coronary occlusion was checked, by observing the immediate colour change of the tissues perfused by the corresponding arteries. Reperfusion was checked by the return of the bright red colour of the tissues. After the completion of the experiment, suture snares were checked to see if they completely circled coronary arteries, to ensure that occlusion of the corresponding coronary arteries was complete in each animal.

Statistical analysis

The significance of differences within the same group was determined by repeated measures ANOVA, with Dunnett's multiple comparison test and Tukey's multiple comparison test as appropriate. Statistical significance between the two groups was determined using unpaired Student's t test with Welch's correction. All data are presented as mean ± standard deviation (SD) and $P < 0.05$ was considered significant. Power calculations comparing the two groups were performed for the observed values obtained after 120 min of reperfusion (the final measurement) for the major outcomes concerning pulmonary function: this gives for PAP ß = 0.83, PVR ß = 0.91, PAP-LAP ß = 0.92, PaO_2 ß = 0.77, PaO_2/FIO_2 ß = 0.85. The power calculations were performed using the online power calculators from the UCLA Department of Statistics (http://calculators.stat.ucla.edu/powercalc/).

Results

Animals in Group-RPC and Group-C did not differ significantly in body weight (58.3 ± 5.9 kg *vs* 60.0 ± 3.4 kg), anesthetic doses used, fractional inspired oxygen (FIO_2) and peak airway pressure throughout the procedure (Table I). As shown in Table II, hemodynamic variables were comparable in both groups at baseline. RPC immediately decreased the PVR. Mean PAP and PVR in Group-C increased gradually during reperfusion and after 120 min of reperfusion were higher than the corresponding baseline values. RPC prevented this increase in mean PAP and PVR. An increase of the transpulmonary pressure gradient, calculated as the pressure difference between the mean PAP and LAP, was observed in Group-C after reperfusion. This transpulmonary pressure gradient was higher in the control group than that in Group-RPC after 90 and 120 min of reperfusion. Repeated coronary occlusion and reperfusion was associated with a decrease in systemic arterial pressure and CO in both

TABLE I Anesthetic gas and ventilatory variables

	Baseline	*Preconditioned*	*30' reperfusion*	*90' reperfusion*	*120' reperfusion*
Halothane (vol%)					
Group-RPC	2.0 ± 0.4	1.9 ± 0.4	1.9 ± 0.5	1.9 ± 0.5	1.9 ± 0.5
Group-C	1.8 ± 0.3	1.8 ± 0.3	1.8 ± 0.3	1.8 ± 0.3	1.8 ± 0.3
F_IO_2					
Group-RPC	0.83 ± 0.1	0.82 ± 0.1	0.76 ± 0.1	0.79 ± 0.1	0.80 ± 0.1
Group-C	0.83 ± 0.1	0.81 ± 0.1	0.87 ± 0.1	0.87 ± 0.1	0.88 ± 0.1
P-Paw (cm H_2O)					
Group-RPC	22.2 ± 9.3	24.4 ± 3.2	26.4 ± 4.4	26.4 ± 4.4	27.2 ± 4.1
Group-C	23.0 ± 2.4	23.8 ± 2.5	24.5 ± 3.3	24.5 ± 3.3	26.5 ± 2.4

Values are means ± standard deviations. No significant differences between the groups were observed. F_IO_2 = fractional inspired oxygen; P-Paw = peak airway pressure.

TABLE II Hemodynamic variables

	Baseline	*Preconditioned*	*30' reperfusion*	*90' reperfusion*	*120' reperfusion*
HR (beats·min^{-1})					
Group-RPC	97 ± 21	91 ± 19	92 ± 19	90 ± 20	87 ± 20
Group-C	93 ± 18	92 ± 16	92 ± 16	96 ± 19	90 ± 16
MAP (mmHg)					
Group-RPC	77.3 ± 8.6	74.1 ± 7.8	56.8 ± 10.7*	56.3 ± 12.9*	53.2 ± 9.8*†
Group-C	77.9 ± 14.4	81.1 ± 16.0	47.3 ± 16.8*	51.9 ± 13.7*	38.1± 8.4*
PAP (mmHg)					
Group-RPC	23.9 ± 6.3	19.6 ± 5.2	21.3 ± 5.5	20.7 ± 4.2	20.4 ± 4.2†
Group-C	23.2 ± 4.1	24.0 ± 4.9	23.2 ± 4.6	25.6 ± 5.4	27.6 ± 4.6‡
CO (L·min^{-1})					
Group-RPC	3.4 ± 0.5	3.5 ± 0.5	3.1 ± 0.5	2.9 ± 0.5*	2.9 ± 0.5*†
Group-C	3.7 ± 0.5	3.6 ± 0.6	2.5 ± 0.5*	2.4 ± 0.9*	2.2 ± 0.4*
PVR (dynes·sec^{-1}·cm^{-5})					
Group-RPC	339 ± 122	227 ± 108†‡	279 ± 90†	311 ± 106†	303 ± 107†
Group-C	359 ± 88	387 ± 87	448 ± 198	703 ± 435‡	725 ± 254‡
LAP (mmHg)					
Group-RPC	9.7 ± 2.8	9.7 ± 2.6	10.4 ± 2.8	9.8 ± 2.2	9.9 ± 2.3
Group-C	6.8 ± 3.3	7.0 ± 3.4	9.2 ± 5.8	8.4 ± 5.1	8.6 ± 3.5
PAP-LAP (mmHg)					
Group-RPC	14.2 ± 5.3	9.9 ± 4.8†	10.9 ± 4.3	10.9 ± 3.5†	10.6 ± 3.3§
Group-C	16.3 ± 3.2	17.0 ± 2.3	14.0 ± 6.0	17.2 ± 4.1	19.0 ± 4.8
CVP (mmHg)					
Group-RPC	8.5 ± 3.7	8.5 ± 3.6	8.0 ± 2.9	8.3 ± 2.6	9.0 ± 2.2
Group-C	7.0 ± 2.8	10.5 ± 2.1	11.0 ± 2.8	10.0 ± 2.8	11.0 ± 4.2
Hb (g·dL^{-1})					
Group-RPC	9.8 ± 1.8	9.9 ± 1.9	10.4 ± 1.6	10.3 ± 1.7	9.9 ± 1.6
Group-C	9.8 ± 0.9	10.0 ± 1.6	10.7 ± 1.1	10.9 ± 0.6	11.2 ± 2.1

Values are means ± standard deviations. HR = heart rate; MAP = mean arterial pressure; PAP = mean pulmonary pressure; CO = cardiac output; PVR = pulmonary vascular resistance; LAP = left atrium pressure; PAP-LAP = difference between PAP and LAP; CVP = central venous pressure; Hb = hemoglobin. *$P < 0.01$ *vs* baseline, †$P < 0.05$ *vs* Group-C, ‡$P < 0.05$ *vs* baseline, §$P < 0.01$ *vs* Group-C.

Group-C and Group-RPC. After 120 min reperfusion, the mean systemic arterial pressure and CO was lower in Group C than in Group RPC. Heart rate, LAP and central venous pressure did not change significantly over time in either group.

PaO_2 and PaO_2/F_IO_2 in Group-C decreased progressively after reperfusion and were lower than the baseline values after 120 min of reperfusion (Table III). However, no significant changes of PaO_2 and PaO_2/F_IO_2 were observed in Group-RPC throughout the procedure. After 120 min of reperfusion, PaO_2 and PaO_2/F_IO_2 in Group-C were lower than that in Group-RPC ($P < 0.05$). Concomitantly, $PaCO_2$ in Group-C increased after 90 min reperfusion and was higher than that in Group-RPC (Table III). In Group-RPC, $PaCO_2$ and pH values remained within the normal range after reperfusion.

TABLE III Arterial blood gases

	Baseline	*Preconditioned*	*30' reperfusion*	*90' reperfusion*	*120' reperfusion*
PaO_2 (mmHg)					
Group-RPC	249 ± 29	236 ± 51	201 ± 61	190 ± 73	192 ± 69*
Group-C	225 ± 84	204 ± 32	157 ± 83	127 ± 71	115 ± 54†
PaO_2/FIO_2					
Group-RPC	306 ± 64	294 ± 70	262 ± 60	237 ± 74*	241 ± 78*
Group-C	269 ± 98	255 ± 60	182 ± 94	147 ± 84	129 ± 64†
$PaCO_2$ (mmHg)					
Group-RPC	39.1 ± 4.2	41.8 ± 4.1	40.9 ± 2.8	40.5 ± 3.9*	42.1 ± 4.0
Group-C	37.5 ± 3.2	39.5 ± 4.0	41.8 ± 4.2	46.6 ± 5.7†	45.4 ± 7.3†
pH					
Group-RPC	7.42 ± .04	7.38 ± .03	7.38 ± .04	7.37 ± .04	7.36 ± .04
Group-C	7.40 ± .05	7.35 ± .08	7.32 ± .04	7.31 ± .06	7.31 ± .08
HCO_3 (mmoL·L^{-1})					
Group-RPC	25 ± 3	25 ± 3	24 ± 2	22 ± 4	23 ± 2
Group-C	23 ± 2	22 ± 4	21 ± 2	22 ± 2	21 ± 2

Values are means ± standard deviations. *$P < 0.05$ *vs* Group-C; †$P < 0.05$ *vs* baseline; PaO_2 = arterial oxygen partial pressure; FIO_2 = fractional inspired oxygen; $PaCO_2$ = carbon dioxide partial pressure; pH = blood pH value; HCO_3 = blood bicarbonate.

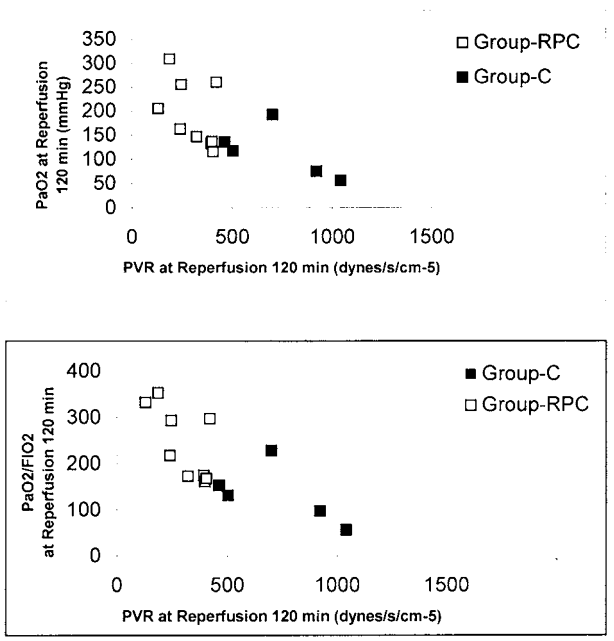

FIGURE 1 Correlation between pulmonary vascular resistance (PVR) and PaO_2 and PaO_2/FIO_2 after 120 min reperfusion. After 120 min reperfusion, PVR negatively correlated with PaO_2 (r = -0.6660, $P = 0.009$, top) and with PaO_2/FIO_2 (r = -0.7493, $P = 0.002$, bottom).

Figure 1 depicts the negative correlation between PVR and PaO_2 as well as PaO_2/FIO_2 after 120 min reperfusion ($P < 0.01$). As shown in Figure 2, changes of PVR 30 min after reperfusion were correlated with impaired PaO_2 and PaO_2/FIO_2 after 120 min of reperfusion.

Discussion

This experiment suggests that brief remote ischemic preconditioning prevents the increase in pulmonary artery pressures following consecutive multiple coronary arteries occlusion and reperfusion, a situation that mimics clinical OPCAB surgery. Our main findings are: (a) this experimental protocol with consecutive coronary occlusion-reperfusion increases PVR and jeopardizes lung gas exchange, which is evidenced by the reduced PaO_2 and PaO_2/FIO_2 after reperfusion in the control group; (b) RPC reduces PVR and improves lung gas exchange after repeated coronary artery occlusion and reperfusion, and reduces PVR.

Postoperative pulmonary dysfunction, a potentially lethal syndrome, has been reported to occur after OPCAB surgery,[2,4] vascular surgery[11] and after CPB.[12,13] It is associated with a significant decrease in PaO_2 and PaO_2/FIO_2. OPCAB surgery implies one or more coronary arteries to undergo occlusion and reperfusion. During reperfusion, specific myocardial enzymes (presumably leaked from damaged or necrotic tissue) and inflammatory cytokines[14] are being washed out and reach the lungs,[15] which might lead to lung injury. A series of acute experimental studies[5,16–18] has demonstrated that coronary artery occlusion and reperfusion resulted in pulmonary edema, evidenced by an increase in extra-vascular lung water. Increased pulmonary microvascular permeability is suggested as one of the possible mechanisms. Although the mediators of the rise in pulmonary per-

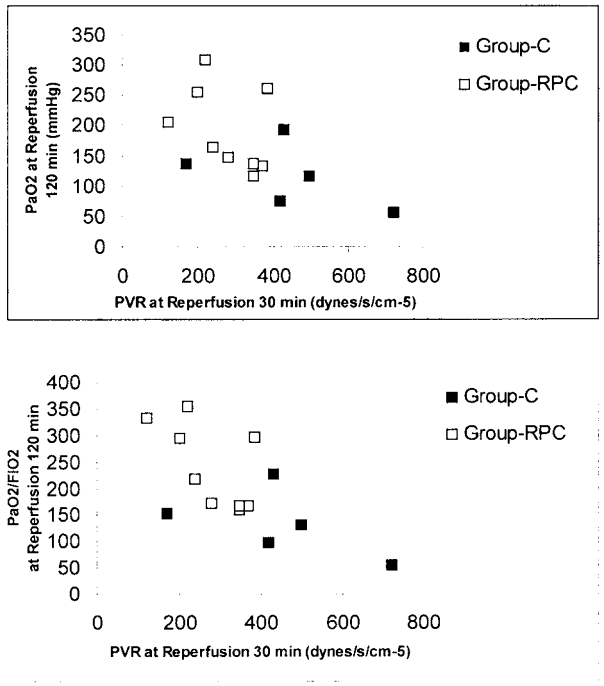

FIGURE 2 Pulmonary vascular resistance (PVR) after 30 min reperfusion predicted changes of PaO_2 and PaO_2/FIO_2 after 120 min reperfusion. PVR after 30 min reperfusion negatively correlated with PaO_2 (r = -0.5712, $P = 0.03$, top) and with PaO_2/FIO_2 (r = -0.6743, $P = 0.008$, bottom) after 120 min reperfusion.

meability have not been clearly identified, increasing evidence suggests that IL-6, IL-8[14] and prostaglandins[19] are among the potential contributors. Infusing indomethacin[19] reduced extra-vascular lung water after coronary artery occlusion in dogs. In a sheep model, Stamler *et al.*[20] and Friedman *et al.*[21] showed that myocardial ischemia and reperfusion was associated with an increase in PVR, which was accompanied by an increase in plasma thromboxane. Inhibition of thromboxane synthesis eliminated the lung injury seen in this model.[21] Extra-vascular lung water was not measured in our model. Given the increase of PAP and PVR in Group-C, combined with a continuous decrease of PaO_2 and PaO_2/FIO_2 as well as an increase in $PaCO_2$, pulmonary edema may be one of the major contributors to the deterioration of pulmonary function in our model.

Recently, Fehrenbach *et al.*[19] reported that the extent of lung epithelial injury increased with PVR using an isolated heart-lung ischemia-reperfusion model, suggesting PVR is a reliable indirect indicator of lung injury. The fact that PVR increased after coronary artery occlusion-reperfusion in Group-C, and that PaO_2 and PaO_2/FIO_2 after 120 min reperfusion were negatively correlated with this early rise in PVR further supports this finding (Figure 2). This suggests that changes in PVR could serve as a sensitive predictor for pulmonary function deterioration after coronary occlusion/reperfusion in this model. Acute postoperative pulmonary hypertension and elevated PVR may cause morbidity and mortality in patients undergoing cardiac surgery involving CPB.[22] Recently, Li *et al.*[10] reported that two cycles of three minutes of aortic cross clamping and two minutes of reperfusion (cardiac ischemic preconditioning) before cardioplegic arrest improves lung function in patients undergoing valve replacement operations. In their observations, two cycles of brief cardiac ischemic preconditioning were associated with a reduced PVR index and mean pulmonary artery pressure, which was accompanied by improved cardiac index as well as enhanced PaO_2 after reperfusion. Also, histological findings confirmed a reduced alveolar injury in the cardiac ischemic preconditioned group.[10] However, the method of global ischemic cardiac preconditioning is not applicable when OPCAB surgery is performed, since no aortic cross-clamping is possible during beating heart surgery. Furthermore, this method carries the risk of neurological damage by embolism of atheromatous material in the aorta during the cross-clamping. Therefore preconditioning by a short occlusion of a peripheral region or organ as performed in our experiments might clinically be far more relevant.

We report that sheep, submitted to a clinically relevant model mimicking OPCAB surgery, show an increase in PVR and jeopardized lung gas exchange. RPC induced by short ischemia of a non-vital organ completely prevented the increase of PVR and preserved lung gas exchange following coronary artery occlusion and reperfusion in our model. The underlying mechanism of the observations described in this experiment and in that of Li *et al.*[10] needs to be further elucidated. It is not clear whether the same underlying mechanism is responsible for both observations. It is tempting, although speculative, to attribute a role to the K_{ATP} channel, since: 1) activation of this channel causes pulmonary vascular vasodilatation;[23,24] and 2) the end effector of myocardial protection by ischemic preconditioning is at least in part the K_{ATP} channel.[25,26] Further studies are warranted to unravel the underlying mechanism.

One may argue that the improvement in pulmonary function seen in Group-RPC might be attributable to the improvement in cardiac function as

evidenced by increased CO and systemic arterial pressure in our experiment. We cannot completely exclude this possibility but think that this is not likely the major mechanism for the improvement in pulmonary function after repeated coronary occlusion and reperfusion in our model. Significant differences in CO and systemic arterial pressure between the groups were not observed until after 120 min reperfusion, while PaO_2/FIO_2 was already significantly lower and $PaCO_2$ significantly higher in Group-C than in Group-RPC after 90 min of reperfusion (Tables II and III). Furthermore, there was no correlation between CO or systemic arterial pressure and pulmonary function described by PaO_2/FIO_2 and PaO_2.

A weakness of our study is the fact that no control group was included without RPC and without coronary occlusions. Addition of this group might have clearly demonstrated the effect of the consecutive episodes of myocardial ischemia and reperfusion in itself. We had chosen to start with a model that mimics clinical OPCAB surgery, and then to try to reduce the pulmonary functional deterioration in this model by RPC.

In conclusion, the present study shows that in this sheep model, brief periods of ischemia followed by reperfusion in a remote peripheral non-vital organ can prevent pulmonary dysfunction following myocardial ischemia and reperfusion. This study may have clinical implications in OPCAB surgery. It might be of particular importance to those patients who have preexisting high PVR and pulmonary hypertension.

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