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# Effect of prior statin therapy on capillary permeability in the lungs after cardiac or vascular surgery

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**ABSTRACT: Cholesterol-lowering statins can ameliorate severe forms of vascular hyperpermeability in experimental studies, and may thereby ameliorate acute lung injury and sepsis. It is unknown whether this also applies to humans. This study aimed to define whether or not prior statin therapy reduces mild post-operative increases in pulmonary capillary protein permeability associated with acute lung injury after cardiac or major vascular surgery.**

**A prospective observational study was performed in an intensive care unit of a university hospital on 64 patients, 37 after elective cardiac and 27 after major vascular surgery, of whom 68 and 44%, respectively, had received prior statin therapy. A mobile probe system was used to measure the pulmonary leak index (PLI), *i.e.* the transvascular transport rate of gallium-67-radiolabelled transferrin.**

**For all of the patients together, the mean PLI did not differ between the statin and control groups (22.9 *versus* 24.4 $\times 10^{-3}$ $min^{-1}$). The prevalence of an elevated PLI was 57% in the statin and 59% in the control group. Subgroup analysis did not reveal significant differences caused by statins in the PLI of these patients.**

**Prior statin therapy neither has an adverse effect on mildly increased pulmonary capillary permeability in patients after cardiac or major vascular surgery nor does it ameliorate this increased capillary permeability.**

**KEYWORDS: Acute lung injury, acute respiratory distress syndrome, endothelium, ischaemia/reperfusion, permeability, protein permeability**

Cardiac and major vascular surgery are major risk factors for post-operative acute lung injury (ALI)/acute respiratory distress syndrome (ARDS), which form a continuum from mild to severe lung damage [1–4]. The basic underlying abnormality is an increase in capillary permeability *via* pro-inflammatory factors, resulting in increased permeability oedema [4]. The incidence of ARDS after cardiac bypass surgery is 0.5–1.7%. It has a significant influence on patient outcome because of its high mortality rate (50.0–91.6%) [5]. The incidence of ARDS underestimates the number of patients with vascular leakage after cardiac bypass surgery since a third of patients exhibit an elevated pulmonary leak index (PLI) [6]. The PLI method successfully differentiates between hydrostatic and permeability oedema and may track clinical amelioration or deterioration of ALI/ARDS patients. It represents the change in extra- *versus* intravascular gallium-67-radiolabelled transferrin as a function of time, and, therefore, the transvascular transport rate of $^{67}$Ga-transferrin [7, 8].

Despite the medical importance of vascular leakage, few specific therapies are available today to counteract it, and current therapies often fail to do so. Interestingly, recent experimental *in vitro* and *in vivo* studies reported that 3-hydroxy-3-methylglutaryl coenzyme A inhibitors or statins used in the treatment of hypercholesterolaemia and atherosclerosis attenuate increased vascular leak, independent of cholesterol-lowering effects [9–19]. Statins have been shown to provide direct benefits to the endothelium in experimental *in vitro* studies, such as reduced RhoA activation [9], reduced permeability, improved anticoagulant properties, decreased cytokine-induced molecule expression and antiproliferative effects. Moreover, simvastatin pretreatment attenuates leukocyte accumulation and lung permeability in an *in vivo* model of ischaemic lung injury [15]. Similarly, statins reduce vascular permeability in

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models of cardiac and renal ischaemia-reperfusion [16, 18] and in adenosine-induced coronary microvascular hyperpermeability in hypercholesterolaemic pigs [20]. Thus, a large body of experimental evidence suggests that statins might ameliorate clinical forms of vascular leakage.

Since no clinical data have been reported regarding the effects of statins on pathological vascular leakage in humans, cardiac and major vascular surgery is associated with post-operatively increased permeability in the lungs [2, 6], and involves patients with coronary or peripheral vascular atherosclerosis taking statins, it was wondered whether prior statin therapy would ameliorate the increased permeability. Therefore, a prospective observational study was performed on 64 consecutive patients, 37 after cardiac and 27 after major vascular surgery, of whom 68 and 44%, respectively, were on prior statins. Post-operative pulmonary permeability was measured by means of the PLI using $^{67}$Ga-transferrin in the lungs [8].

## METHODS

The present prospective study was approved by the Ethical Committee of the VU University Medical Centre (Amsterdam, the Netherlands), and involved 37 consecutive patients after elective cardiac surgery and 27 after major vascular surgery, who took part in a fluid-loading trial [21]. The investigation conformed with the principles outlined in the Declaration of Helsinki [22]. Patients took the following statins orally until the day of surgery and study: simvastatin (>10 mg·day$^{-1}$/<50 mg·day$^{-1}$, n=17), atorvastatin (>10 mg·day$^{-1}$/<80 mg·day$^{-1}$, n=9), pravastatin (>10 mg·day$^{-1}$/<40 mg·day$^{-1}$, n=9), fluvastatin (40 mg·day$^{-1}$, n=1), or cerivastatin (0.3 mg·day$^{-1}$, n=1).

### *Inclusion*

#### Cardiac surgery

In the VU University Medical Centre, ~700 open-heart procedures are performed per year. Written informed consent was obtained pre-operatively from eligible cardiac surgery patients. The inclusion criterion was the presence of a pulmonary arterial (n=34) or central venous catheter (n=3), post-operatively. Exclusion criteria were an age of >79 yrs, life expectancy of <24 h and post-operative evidence of heart failure, manifested by a pulmonary capillary wedge pressure ($P_{pcw}$) of >15 mmHg or central venous pressure of >13 mmHg. On the day of surgery, anaesthesia was induced with sufentanil 3 μg·kg$^{-1}$ *i.v.*, pancuronium 0.1 mg·kg$^{-1}$ *i.v.* and midazolam 0.1 mg·kg$^{-1}$ *i.v.* and maintained *via* continuous infusion of 5 mg·mL$^{-1}$ propofol at 5 mL·h$^{-1}$. At induction, 50–100 mg dexamethasone were administered. Radial artery, central venous and pulmonary artery catheters were inserted for haemodynamic measurements and blood sampling. After tracheal intubation, the lungs underwent volume-controlled ventilation with a tidal volume ($V_T$) of 8–10 mL·kg$^{-1}$, resulting in an end-tidal carbon dioxide concentration of 4–5%, using an oxygen/air mixture with an inspiratory oxygen fraction ($F_{I,O_2}$) of 40% and a positive end-expiratory pressure (PEEP) of 5 cm$H_2O$ (inspiratory:expiratory 1:2). The patients underwent cardiopulmonary bypass (CPB), during which the lungs were not ventilated. The extracorporeal circulatory system was primed with 300 mL Ringer's lactate, 1,000 mL 4% gelatin, 100 mL 20% mannitol, 50 mL 8.4% sodium bicarbonate, 200 mL aprotinin and 5,000 IU heparin. After systemic heparinisation (300 IU·kg$^{-1}$), CPB (Stockert-Sorin S3; Sorin Biomedica, Mirandola, Modena, Italy) was started, provided that the activated clotting time was >480 s. The nonpulsatile flow rate was maintained at 2–3 L·min$^{-1}$·m$^{-2}$, depending on the acid–base balance, pre-operative cardiac output and lactate concentrations. Patients were cooled to a nasopharyngeal temperature of 32°C. Mean arterial pressure was maintained at 50–80 mmHg during CPB, and, if it declined to <50 mmHg, the blood flow rate was increased or vasoactive drugs given. After aortic cross-clamping, all patients received crystalloid cardioplegia for myocardial protection (in total ~2,000 mL, potassium 16 mM, 4°C). Patients were weaned from CPB using inotropic support, if necessary. After termination of CPB, heparin was neutralised using an equivalent dose of protamine sulphate 3 mg·kg$^{-1}$. Autologous blood and the residual volume from the extracorporeal circuit were infused as first-choice fluid administration. Guided by low systemic and filling pressures, sodium chloride 0.9%, gelatin or starches were infused additionally. If the haemoglobin concentration was <6 mM, packed red blood cell concentrates were infused. At the end of surgery, a 5F introducing sheath (Arrow, Reading, PA, USA) was inserted into the femoral artery, when feasible, for use in the study protocol (n=30).

#### Vascular surgery

Written consent was obtained pre-operatively in eligible patients for major vascular surgery. The inclusion criterion was the presence of a pulmonary arterial (n=12) or central venous catheter (n=15). Exclusion criteria and anaesthesia were as for cardiac surgery. Radial artery, central venous or pulmonary artery catheters were inserted for haemodynamic measurements and blood sampling. Three patients underwent surgical reconstruction of a thoracic (abdominal) aortic aneurysm with help of a left-left extracorporeal circulation system (Stockert-Sorin S3), primed with Ringer's lactate, 4% gelatin, mannitol, sodium bicarbonate and aprotinin. Heparin was given during extracorporeal support and neutralised with the help of protamine after discontinuation of the shunt (as above). At the end of surgery, a 4F introducing sheath (Arrow) was inserted into the femoral artery, only when puncture through newly inserted vascular prostheses could be avoided, for use in the study protocol (n=20). The aortic clamping time was recorded.

### *Study protocol*

On arrival of the patient in the intensive care unit (ICU), the patient was connected to the ventilator (Evita 3; Dräger, Lübeck, Germany) and volume-controlled ventilation was started with similar settings to those used during surgery. Demographics were recorded, including the Acute Physiology, Age, and Chronic Health Evaluation (APACHE) II score, and measurements of $^{67}$Ga-transferrin PLI, extravascular lung water (EVLW; normal value <7 mL·kg$^{-1}$) and haemodynamics were performed, and an anteroposterior chest radiograph was obtained with patients in the supine position. As statins show vasodilatory effects and hydrostatic pressure is the driving force for fluid extravasation, and thus for EVLW, haemodynamic variables and cardiac function were carefully analysed in the subgroups after surgery. Haemodynamic variables were measured after calibration and zeroing to atmospheric pressure at mid-chest level (Monitor Tramscope®; Marquette

Electronics, Milwaukee, WI, USA). Mean pulmonary arterial pressure, CVP and, after balloon inflation, $P_{pcw}$ were measured at end expiration, with patients in the supine position, if adequate tracings for the latter could be obtained (n=22 for cardiac surgery and n=11 for vascular surgery patients). Arterial blood samples were obtained for determinations of oxygen ($P_{a,O_2}$) and carbon dioxide tension and oxygen saturation (Rapidlab 865; Bayer Diagnostics, Tarrytown, NY, USA) at 37°C, haemoglobin, albumin and total protein levels (Roche/Hitachi 747; Roche Diagnostics Corporation, Indianapolis, IN, USA). Mixed (n=33) or central (n=31) venous blood was taken simultaneously for measurement of gas tensions and saturations. Venous admixture was calculated according to standard formulae, assuming that central can substitute for mixed venous blood (n=22 for cardiac and n=11 for vascular surgery patients). The plasma colloid osmotic pressure was measured using a membrane osmometer (molecular cut-off 20 kDa, normal ~24 mmHg; Osmomat 050; Gonotex, Berlin, Germany). The $F_{I,O_2}$, $V_T$, plateau inspiratory pressure and PEEP were read from the ventilator. The duration of mechanical ventilation was defined as the interval from admission to extubation. Doses of vasoactive drugs were recorded. Patients were cared for by intensive care physicians not involved in the study and followed until extubation and discharge/death in the ICU.

### Pulmonary leak index

In order to evaluate whether prior statin treatment ameliorated pulmonary capillary leakage, a mobile probe system was used at the bedside to measure the PLI of $^{67}$Ga-transferrin as a measure of capillary permeability in 64 patients, as previously within 3 h after surgery and transfer to the ICU [8]. In brief, autologous red blood cells were labelled with technetium-99m (11 MBq; physical half-life 6 h; Mallinckrodt Diagnostica, Petten, the Netherlands). Transferrin was labelled *in vivo*, following *i.v.* injection of $^{67}$Ga-citrate (4.5 MBq; physical half-life 78 h; Mallinckrodt Diagnostica, Petten, the Netherlands). Patients were in the supine position and two scintillation detection probes (Eurorad C.T.T., Strasbourg, France) were positioned over the right and left lung apices. Starting at the time of injection of $^{67}$Ga, radioactivity was detected every minute for 30 min. The count rates were corrected for background radioactivity, physical half-life and spillover and expressed in counts per minute (cpm) per lung field. Until 30 min after $^{67}$Ga injection, blood samples (2 mL aliquots) were taken. Each blood sample was weighed and radioactivity was determined using a single-well well counter, corrected for background radioactivity, physical half-life and spillover (LKB Wallac 1480 WIZARD; Perkin Elmer, Life Science, Zaventem, Belgium). Results were expressed in cpm per gram. For each blood sample, a time-matched cpm over each lung was obtained. A radioactivity ratio was calculated, ($^{67}$Ga$_{lung}$/$^{99m}$Tc$_{lung}$)/($^{67}$Ga$_{blood}$/$^{99m}$Tc$_{blood}$), and plotted against time. The PLI was calculated, using linear regression analysis, from the slope of the increase in radioactivity ratio divided by the intercept. The PLI represents the transport rate of $^{67}$Ga from the intravascular into the extravascular space of the lungs and is, therefore, a measure of pulmonary vascular permeability [7]. The values for both lung fields were averaged. The upper limit of normal for the PLI is $14.7 \times 10^{-3} \cdot min^{-1}$, with a median of $9.4 \times 10^{-3} \cdot min^{-1}$ [7] and measurement error of ~10% [8]. The PLI is typically elevated >3- or 4-fold in ARDS (lower limit $23.0 \times 10^{-3} \cdot min^{-1}$, with a median of $31.8 \times 10^{-3} \cdot min^{-1}$) [7].

### Transpulmonary thermal-dye dilution

This measurement involves a central venous injection of 15 mL ice-cold indocyanine green (ICG), 1 $mg \cdot mL^{-1}$ 5% dextrose in water. The thermal-dye dilution curve was obtained at the femoral artery (COLD Z-021; Pulsion Medical Systems, Munich, Germany), with the help of a 3F catheter (PV 2024; Pulsion Medical Systems), introduced *via* the introducing sheath. This allowed calculation of transpulmonary thermodilution cardiac output and both the thermal volume and the ICG distribution volume, the intrathoracic blood volume. The difference between the volumes is the extravascular thermal volume in the lungs, an estimate of EVLW. EVLW is typically 2–3-fold elevated in the case of overt (radiographic) pulmonary oedema. The pulmonary blood volume is derived from cardiac output and the down-slope time of the ICG dilution. The global end-diastolic volume (GEDV) is derived from intrathoracic thermal volume minus pulmonary thermal volume, the latter derived from the down-slope time of thermal dilution. The global ejection fraction, as a measure of cardiac function, can be calculated from stroke volume multiplied by four and divided by GEDV. Measurements were performed in duplicate, irrespective of the ventilatory cycle, and averaged. GEDV was indexed to body surface area calculated from weight and height, whereas EVLW was indexed to body weight. The cardiac index can be calculated from cardiac output divided by body surface area.

### Radiography and lung injury score

The lung injury score (LIS) was calculated from the number of quadrants on the chest radiograph with opacities, PEEP, $P_{a,O_2}/F_{I,O_2}$ and dynamic total respiratory compliance. Compliance was calculated from $V_T$/plateau pressure PEEP. The chest radiograph was scored by a consultant radiologist, blinded to the study, who evaluated the number of quadrants with alveolar opacities ranging 0–4. The LIS ranges 0 (no injury)–4, with values of >2.5 indicative of ARDS, and of 0–2.5 indicative of ALI.

### Statistical analysis

Cardiac and vascular surgery patients were divided into those taking and not taking statin up to the day of surgery. Continuous data are expressed as median (range), and as mean±confidence interval in figures. Fisher's exact test was used for categorical and the Mann–Whitney U-test for continuous variables. A p-value of <0.05 was considered significant. All tests were two-sided.

## RESULTS

### General features

Table 1 summarises the patient characteristics. The patient groups receiving and not receiving statin, whether subjected to cardiac or vascular surgery, were comparable prior to surgery with respect to age, sex and underlying illness. Table 2 shows the haemodynamic and respiratory variables in the subgroups. No significant differences between outcome groups were observed. In cardiac surgery patients, however, statin therapy appeared to be associated with greater venous admixture after surgery and somewhat prolonged mechanical ventilation (NS).

**TABLE 1** Patient characteristics

| | Cardiac surgery | | Vascular surgery | |
|---|---|---|---|---|
| | Statin | No statin | Statin | No statin |
| **Patients n** | 25 | 12 | 12 | 15 |
| **Age yrs** | 64 (52–75) | 57 (38–74) | 64 (53–75) | 65 (51–75) |
| **Males/females** | 20/5 (80/20) | 10/2 (83/17) | 11/1 (92/8) | 12/3 (80/20) |
| **Statin** | | | | |
| Simvastatin | 11 (44) | | 6 (50) | |
| Miscellaneous | 14 (56) | | 6 (50) | |
| **Underlying illness** | | | | |
| Prior myocardial infarction | 12 (48) | 3 (25) | 4 (33) | 1 (7) |
| Diabetes mellitus | 3 (12) | 4 (33) | 3 (25) | 1 (7) |
| **Type of surgery** | | | | |
| CABG | 23 (92)# | 9 (75) | | |
| OPCABG | 5 (20) | 2 (17) | | |
| AVR | 5 (20) | 3 (25) | | |
| TAAA | | | 1 (8) | 2 (13) |
| AAA | | | 9 (75) | 9 (60) |
| Mesenteric VD | | | 2 (17) | 2 (13) |
| False aneurysm | | | 0 | 2 (13) |
| **CPB duration min** | 114 (77–198) | 121 (40–190) | 117 (n=1) | 110 (80–113) (n=3) |
| **Aortic clamping time min** | 76 (43–140) | 73 (26–155) | 96 (45–175) | 95 (50–135) |
| **Vasoactive therapy $\mu g \cdot kg^{-1} \cdot min^{-1}$** | | | | |
| Dopamine | 2 (0.5–10) (n=17) | 2 (1–4) (n=8) | 2 (1–17) (n=9) | 2 (0.2–10) (n=11) |
| Nitroglycerine | 1 (0.5–5) (n=22) | 1 (0.4–2) (n=9) | 1.5 (0.5–3) (n=8) | 1 (0.1–5) (n=10) |

Data are presented as median (range) or n (%) as appropriate, unless otherwise stated. CABG: coronary artery bypass grafting; OPCABG: off-pump CABG; AVR: aortic valve replacement; TAAA: thoracoabdominal aortic aneurysm; AAA: abdominal aortic aneurysm; VD: vascular disease; CPB: cardiopulmonary bypass. #: patients may also undergo AVR.

### *Pulmonary leak index*

The mean PLI after cardiac and vascular surgery was 20.5 (6.0–73) $\times 10^{-3}$ $min^{-1}$ and 27.7 (6.0–101) $\times 10^{-3}$ $min^{-1}$ respectively (fig. 1; NS), which is considerably higher than the median of $9.4 \times 10^{-3} \cdot min^{-1}$ previously reported in a control group [7]. For all of the patients together, the prevalence of an elevated PLI was 57% in the group on statin and 59% in the group not on statin (fig. 2; NS). A power analysis based on a two-sided Fisher's exact test revealed that 5,687 patients are necessary per arm in order to detect a difference in percentage of patients with supranormal PLI by statin therapy ($\alpha$=0.05, $\beta$=0.80). Given mean values for PLI of $22.9 \times 10^{-3}$ $min^{-1}$ in the group on statin and 24.4 in the group not on statin (fig. 2; NS), it can be calculated that $\geqslant$2,128 patients per treatment arm are necessary in order to detect a difference (two-sided $\alpha$=0.05, $\beta$=0.80) in PLI between groups. Finally, the PLI inversely correlated only with compliance ($r_S$= -0.30, p=0.017), without a contribution by statin therapy, on multivariate analysis.

## DISCUSSION

The present data indicate that prior statin therapy neither affects nor ameliorates mildly increased pulmonary capillary permeability after cardiac or major vascular surgery in the group of patients studied.

Endothelial barrier function is maintained principally by cytoskeletal elements that determine cell shape, facilitate cell adhesion to the subendothelial matrix and participate in formation of junctional complexes. The major cause of vascular leakage under inflammatory conditions is altered interaction of cortical actin filaments with junctional proteins, resulting in reduced structural integrity of endothelial monolayers. This is accompanied by formation of small gaps between cells [23]. Various authors have identified at least four independent signalling pathways that contribute to barrier dysfunction: $Ca^{2+}$-dependent activation of myosin light chain kinase, a RhoA/Rho kinase signalling pathway acting in a $Ca^{2+}$-independent manner, a protein tyrosine kinase pathway that disrupts intercellular junctions, and a new pathway that involves the atypical protein kinase C isoform, PKC$\zeta$ [9, 23]. Rho kinase is a regulatory protein associated with the actin filaments of the endothelial actin cytoskeleton. Activation of RhoA and Rho kinase leads to phosphorylation of the myosin light chain, resulting in cell contraction and gap formation [24]. Direct inhibition of RhoA/Rho kinase signalling reduces vascular hyperpermeability induced by a variety of vasoactive agents, including thrombin [9, 25], hydrogen peroxide [26], bacterial toxins, leukocytes and oxidised low-density lipoprotein [27]. RhoA activation requires translocation of RhoA to the membrane, to which it binds *via* a farnesyl group. Activation of RhoA can be inhibited with statins, which inhibit the cholesterol synthesis pathway that provides the farnesyl group to RhoA [19].

**TABLE 2** Post-operative haemodynamics and pulmonary capillary permeability and gas exchange

| | Cardiac surgery | | Vascular surgery | |
|---|---|---|---|---|
| | Statin | No statin | Statin | No statin |
| **Subjects n** | 25 | 12 | 12 | 15 |
| **Haemodynamics** | | | | |
| Cardiac frequency beats·min$^{-1}$ | 71 (55–101) | 78 (60–88) | 71 (63–87) | 70 (46–98) |
| $P_{pcw}$ mmHg | 7 (1–13) (n=17) | 7 (3–10) (n=5) | 7 (6–10) (n=5) | 6 (4–7) (n=6) |
| $\bar{P}_{pa}$ mmHg | 15 (8–28) | 15 (10–21) | 19 (13–24) | 16 (12–17) |
| MAP mmHg | 73 (52–104) | 77 (63–96) | 72 (63–107) | 82 (55–113) |
| CI L·min$^{-1}$·m$^{-2}$ | 3.1 (2.1–4.8) | 2.9 (2.2–3.9) | 3.0 (1.6–4.7) | 3.1 (2.2–4.5) |
| GEDVI mL·m$^{-2}$ | 839 (537–1108) (n=20) | 833 (584–1180) (n=10) | 903 (547–1149) (n=7) | 957 (629–1563) (n=13) |
| GEF % | 23 (11–29) | 19 (11–27) | 20 (14–32) | 20 (7–41) |
| **Respiratory variables** | | | | |
| PLI $10^{-3}$·min$^{-1}$ | 15 (6–73) | 16 (7–53) | 23 (6–73) | 19 (10–101) |
| Supranormal[#] PLI | 13 (52) | 6 (50) | 8 (67) | 10 (67) |
| EVLW mL·kg$^{-1}$ | 6.1 (2.1–13.2) (n=20) | 6.8 (2.9–20.0) (n=10) | 7.2 (5.2–13.8) (n=7) | 5.9 (2.5–46.8) (n=13) |
| $P_{a,O_2}$ mmHg | 116 (84–181) | 126 (88–185) | 123 (76–178) | 130 (70–220) |
| $F_{I,O_2}$ % | 41 (37–62) | 40 (39–50) | 48 (39–60) | 41 (39–58) |
| $P_{a,O_2}/F_{I,O_2}$ mmHg | 270 (140–454) | 298 (176–472) | 264 (127–445) | 289 (121–537) |
| $Q_S/Q_t$ % | 17 (9–62) | 14 (9–20) | 22 (9–40) | 20 (4–45) |
| PEEP $cmH_2O$ | 7 (4–16) | 7 (5–12) | 7 (5–10) | 6 (5–10) |
| Plateau pressure $cmH_2O$ | 17 (13–33) | 18 (14–24) | 20 (12–23) | 19 (14–24) |
| Tidal volume mL | 571 (400–1110) | 514 (395–690) | 645 (430–710) | 600 (450–730) |
| Total dynamic compliance mL·$cmH_2O^{-1}$ | 51 (37–91) | 49 (39–67) | 53 (31–94) | 49 (28–91) |
| Radiographic quadrants with opacities | 0 (0–3) | 0 (0–2) | 2 (0–3) | 1 (0–3) |
| Lung injury score[¶] | 0.8 (0.3–2.8) | 0.9 (0.3–1.8) | 1.5 (0.3–2.0) | 1.0 (0.3–2.0) |
| Duration of mechanical ventilation h | 13 (6–494) | 9 (5–316) | 18 (7–1992) | 14 (1–457) |

Data are presented as median (range) or n (%) as appropriate, unless otherwise stated. $P_{pcw}$: pulmonary capillary wedge pressure; $\bar{P}_{pa}$: mean pulmonary arterial pressure; MAP: mean arterial pressure; CI: cardiac index; GEDVI: global end-diastolic volume index; GEF: global ejection fraction; PLI: pulmonary leak index; EVLW: extravascular lung water; $P_{a,O_2}$: arterial oxygen tension; $F_{I,O_2}$: inspiratory oxygen fraction; $Q_S/Q_t$: venous admixture; PEEP: positive end-expiratory pressure. [#]: $>14.7 \times 10^{-3}$·min$^{-1}$; [¶]: Murray lung injury score, based on plain chest radiograph findings, oxygenation, minute ventilation, lung compliance and PEEP.

Interestingly, in contrast to previous reports that experimental hyperpermeability can be ameliorated by indirect inhibition of RhoA/Rho kinase signalling with statins [7, 8], the present findings show that statins do not ameliorate mildly increased permeability. This apparently contradictory result could be explained by at least three differences between the present study and the experimental studies. First, the present patients showed a mild increase in permeability compared to the hyperpermeability in experimental models. Secondly, low doses of statins were used compared to the experimental studies. Thirdly, withdrawal of statin therapy on the day of surgery might result in suboptimal circulating statin levels, whereas the experimental studies continued statin therapy. Statin therapy in the experimental setting requires only minutes to achieve inhibition of RhoA [28], although it is not known exactly how long the statin effects last. VECCHIONE and BRANDES [29] showed that endothelium-dependent relaxation of mouse aortic rings did not change during the first 4 days after statin withdrawal. After 4 days, it was impaired. LAUFS *et al*. [30] reported that withdrawal of statins in mice resulted in a transient increase in Rho activity and a suppression of endothelial nitric oxide production not earlier than after 2 days. The data suggests that statin effects could last long enough to influence the post-operative permeability in the present study.

The present patients exhibited mild vascular leakage, as evidenced by a PLI slightly greater than the upper limit found in control patients, compared to the 3- or 4-fold increase observed in ARDS patients. The risk of developing ARDS in elective cardiac and vascular surgery may be less than after sepsis, multiple trauma and transfusion, near drowning and pancreatitis. ARDS may closely resemble the models in which positive effects of statins were observed, and remains to be investigated. Treating patients at risk of more severe forms of vascular leakage, such as during ARDS, with high doses of statins can thus be considered. The recent finding that statin treatment in the experimental setting requires, in contrast to its cholesterol-lowering effects, only minutes to achieve inhibition of RhoA [28] offers unique opportunities for treatment in the acute situation of the ICU setting. High doses of statins may be considered in the treatment of ARDS because of observations in experimental *in vivo* and *vitro* studies. For example, VAN NIEUW AMERONGEN *et al*. [9] treated rabbits with 15 mg·kg$^{-1}$ simvastatin for 1 month. This reduced vascular leakage in both the thoracic and abdominal part of the aorta. JACOBSON *et al*.

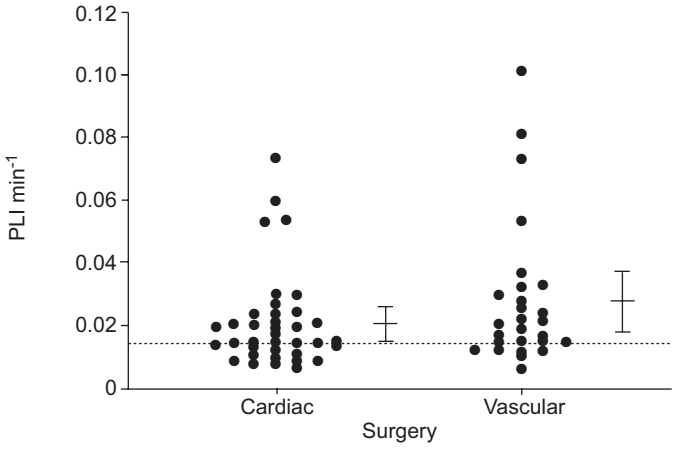


**FIGURE 1.** Pulmonary leak index (PLI) in 37 patients who underwent cardiac surgery and 27 patients who underwent major vascular surgery. The PLI was supranormal (·····: values above this line are considered elevated) in 19 (51%) and 18 (67%) patients, respectively. Individual data are shown; horizontal bars represent mean and vertical bars the 95% confidence interval. No significant differences were observed.

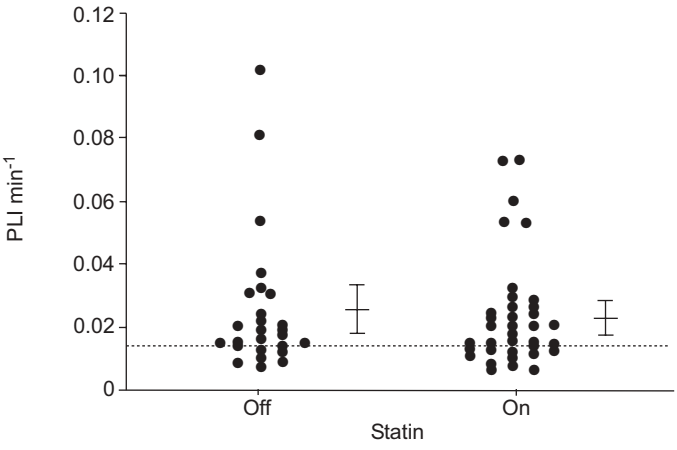


**FIGURE 2.** Pulmonary leak index (PLI) in 37 patients receiving statins and 27 patients not receiving statins. The PLI was supranormal (·····: values above this line are considered elevated) in 21 (57%) and 16 (59%) patients, respectively. Individual data are shown; horizontal bars represent mean and vertical bars the 95% confidence interval. No significant differences were observed.

[14] treated mice with 20 $mg \cdot kg^{-1}$ simvastatin and found attenuation of vascular leak in lung tissue.

The major limitation of the present study is the lack of double-blind randomisation of treatment and a placebo control arm. Obviously, the execution of such randomisation and start of therapy are hampered by the recognised reasons for prescribing statins in many of these patients, and thus by the difficulty of withholding therapy in patients exhibiting pertinent indications for statin therapy. Despite lack of randomisation, the present patient groups receiving and not receiving statin, whether subjected to cardiac or major vascular surgery, were comparable prior to surgery with respect to age, sex and underlying illness, and, after surgery, with respect to cardiac function and haemodynamics. Another limitation is that the number of patients may have been too small to detect group differences. The power analysis, however, suggests that very large numbers of patients would be needed to detect any difference in PLI. Conversely, potential adverse effects associated with pulmonary vasodilatation, increased venous admixture, a lower $P_{a,O_2}/F_{I,O_2}$ ratio and prolonged ventilation would require attention in such a trial, even though there were no significant differences in these variables between statin groups. Statins may ameliorate ischaemia-reperfusion of the lungs by upregulating endothelial nitric oxide synthase, and this may explain the increased venous admixture in cardiac surgery patients using statins. It is probably associated with diminished matching of ventilation to perfusion. That this seemed less apparent in patients after major vascular surgery may be associated with the tendency to greater vascular injury (and higher PLI) and less vasodilator reserve. Statin groups did not differ in PLI, cardiac function and EVLW after surgery, but this does not exclude differences in cardiac function pre-operatively, which were not measured.

In conclusion, the present cohort study suggests that regular doses of statins, widely used in the treatment of cardiac and vascular surgery patients, neither protect against pulmonary vascular hyperpermeability/leakage evoked by surgery-associated ischaemia-reperfusion nor affect it. This paves the way for a placebo-controlled study using high doses of statins in more severe forms of vascular leakage, such as in acute respiratory distress syndrome.

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