

The hypoxic pulmonary vasoconstriction: From physiology to clinical application in thoracic surgery

ABSTRACT

More than 70 years after its original report, the hypoxic pulmonary vasoconstriction (HPV) response continues to spark scientific interest on its mechanisms and clinical implications, particularly for anesthesiologists involved in thoracic surgery. Selective airway intubation and one-lung ventilation (OLV) facilitates the surgical intervention on a collapsed lung while the HPV redirects blood flow from the “upper” non-ventilated hypoxic lung to the “dependent” ventilated lung. Therefore, by limiting intrapulmonary shunting and optimizing ventilation-to-perfusion (V/Q) ratio, the fall in arterial oxygen pressure (P_{aO_2}) is attenuated during OLV. The HPV involves a biphasic response mobilizing calcium within pulmonary vascular smooth muscles, which is activated within seconds after exposure to low alveolar oxygen pressure and that gradually disappears upon re-oxygenation. Many factors including acid-base balance, the degree of lung expansion, circulatory volemia as well as lung diseases and patient age affect HPV. Anesthetic agents, analgesics and cardiovascular medications may also interfere with HPV during the perioperative period. Since HPV represents the homeostatic mechanism for regional ventilation-to-perfusion matching and in turn, for optimal pulmonary oxygen uptake, a clear understanding of HPV is clinically relevant for all anesthesiologists.

Key words: Hypoxemia; inhalational anesthesia; intrapulmonary shunt; intravenous anesthesia; pulmonary flow; ventilation-perfusion mismatch

Introduction

Hypoxic pulmonary vasoconstriction (HPV) represents an intrinsic property of pulmonary vascular smooth muscle cells (VSCMs) and an important homeostatic mechanism that helps to ensure correct gas exchange in physiological and pathological conditions.


In 1946, von Euler and Liljestrand, first described the opposing hypoxic responses in the pulmonary and systemic circulations

as manifested by vasoconstriction and vasodilatation, respectively.^[1] Until delivery, the non-ventilated lungs of the baby exhibit a low alveolar O_2 pressure (P_{AO_2}) that triggers widespread HPV resulting in elevated pulmonary vascular resistance (PVR) and subsequent diversion of the oxygenated placental blood flow through the foramen ovale and the ductus arteriosus directly into the systemic arteries. Upon the first breath at birth, sensing the rising alveolar

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P_AO_2 by pulmonary VSCMs interrupts the HPV response in the newborn, allowing the deoxygenated blood flow to be distributed to the ventilated lung areas through a low resistive pulmonary circulation whereas the foramen ovale and the ductus arteriosus obliterate to prevent right-left shunting.

The HPV plays an important role in patients presenting with heterogeneous lung diseases such as pneumonia, atelectasis, chronic obstructive bronchopulmonary disease and acute respiratory distress syndrome. The severity of hypoxemia is attenuated by adapting the ventilation-to-perfusion (V/Q) ratio in various parts of the lungs.^[2] In contrast, when the whole lung is exposed to hypoxia (e.g., high altitude, sleep apnea, pulmonary fibrosis), HPV can be detrimental resulting in pulmonary hypertension and acute cor pulmonale owing to progressive increase in right ventricular afterload.

The HPV also plays an important role during one-lung ventilation (OLV) in thoracic surgery and during pneumological procedures to reduce intrapulmonary shunt and preserve blood oxygenation. During awake fiberoptic bronchoscopy, the HPV response has been described using technetium-99m labeled macroaggregated albumin lung perfusion scan.^[3] After inflating a balloon-tipped catheter within the left lower bronchus, as the P_AO_2 and alveolar carbon dioxide pressure (P_ACO_2) distal to the tip of the occluding balloon reach almost the same value as mixed venous PO_2 and PCO_2 within 80-300 sec, lobar blood flow decreases by 50% and the majority of blood is redistributed to well ventilated parts of the lungs.

Given the importance of oxygen supply in body homeostasis and survival, this review describes the HPV response and its modulating factors that interact in patients undergoing thoracic surgery.

Physiology of Hypoxic Pulmonary Vasoconstriction (HPV)

The hypoxic signal in different tissues

Phylogenetically, the mammalian homeostatic O_2 sensing system has developed a multicomponent defense mechanism involving a network of specialized cells such as VSMCs and endothelial cells (ECs), glomic cells in the carotid body, renal myofibroblasts, adrenomedullary chromaffin cells and neuroepithelial bodies in the airways.^[4] Detection of low O_2 tension by these cells initiates organ-specific responses orchestrated by the hypoxic inducible factor (HIF) involving the HPV, the release of catecholamines, vascular endothelial growth factors and erythropoietin. Accordingly, to adapt to the high-altitude hypoxic environment, mountaineers develop

various degree of hyperventilation, pulmonary hypertension, polycythemia, stimulation of the sympathetic system as well as increased density of muscular capillaries and intracellular mitochondria to optimize oxygen delivery and aerobic performance.^[5]

The HPV response chiefly operates within arteriolar and venular pulmonary vessels (diameter <900 microns), veins accounting for 20% of the total increase in PVR. By distorting the alveolar wall, contractile interstitial cells located within the alveolar septa further contribute to reduce capillary blood flow and increase PVR.^[6] In addition, the ECs modulate the HPV through the local release of vasodilators (nitric oxide [NO], prostacyclin [PGI_2]) and vasoconstrictors (endothelin [ET], epoxyeicosatrienoic acid [EET], thromboxane A2 [TXA_2], and platelet activating factor [PAF]).^[7,8]

From ex-vivo ventilated/perfused lungs in whom alveolar and blood O_2 tension were modified independently, Marshall *et al.* demonstrated that acute elevation in PVR was predominantly triggered by sensing low P_AO_2 and less by sensing deoxygenated blood in mixed venous blood ($P_{mv}O_2$).^[9,10] Accordingly, the stimulus of HPV (PO_2S) has been modeled using the following equation: $PO_2S = P_AO_2^{0.62} + P_{mv}O_2^{0.38}$

When pulmonary VSCMs or isolated lungs are exposed to decremental levels of local PO_2 , the HPV develops at a threshold of 85-90 mmHg, to reach a maximum around 65-70 mmHg and declining thereafter to stop around 5 mmHg [Figure 1].^[11]

The O_2 sensing area is thought to extend from precapillary arterioles to upstream pulmonary arteries with different vasoconstrictive responses according to the size of the vessels.^[12] The small arteries (diameter < 0.5 mm) are closely exposed to P_AO_2 (from outside) and to $P_{mv}O_2$ (from inside) whereas larger arteries (diameter of 0.5 to 2 mm) are not

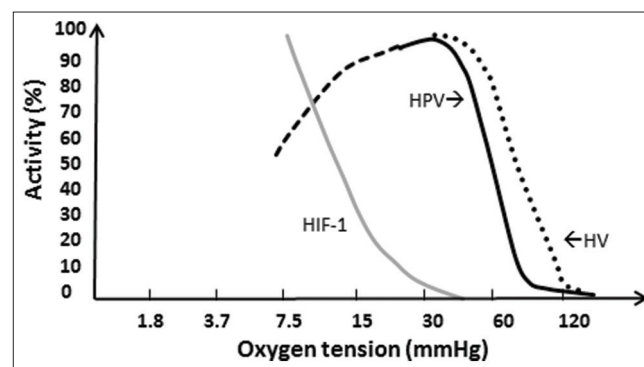


Figure 1: Thresholds for physiological responses to low oxygen tension. HIF, hypoxic inducible factor; HPV, hypoxic pulmonary vasoconstriction; HV, hypoxic ventilation

exposed to $P_A O_2$ but to $P_{mv} O_2$ (from inside) and to arterial O_2 pressure ($P_a O_2$ from outside, through vasa vasorum). Hence, variable diffusion O_2 gradients are generated through the wall of pulmonary arteries that determine the true stimulus for HPV ($PO_2 S$), being predominant in smaller than in larger arteries. Interestingly, when mild hypoxemia starts ($P_a O_2 < 80$ mmHg), bronchial arteries progressively dilate (like any systemic vessel) and the HPV response is attenuated by collateral intrapulmonary flow in pathological conditions such as cyanotic heart diseases, mitral stenosis and pulmonary thromboembolism.^[13]

The oxygen sensing and effector mechanisms of HPV

In eukaryotic cells, mitochondria are acting as powerhouses using O_2 to convert nutrients into chemical energy in the form of adenosine triphosphate (ATP). Since mitochondrial respiration continues even at very low O_2 level (~ 7 mmHg) to generate ATP, it is unlikely that variations in ATP concentrations may trigger the hypoxic response.^[14] Series of oxidation-reduction reactions involve the transfer of electrons from nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH₂) across the electron transport chain (ETC).

Through the process of oxidative phosphorylation, O_2 serves as the terminal electron acceptor of the ETC to form H_2O while leaking electrons at multiple sites along the ETC react with O_2 , forming reactive oxygen species (ROS) such as superoxide and hydrogen peroxide. In pulmonary VSMCs, the most plausible mechanism to detect hypoxia is the mitochondrial PO_2 -sensitive system that adjust the production of diffusible ROSs and/or alter the cytosolic redox state. Although controversies surround the issue on whether ROSs generated by the ETC decrease or increase in response hypoxia, there is strong evidence that HPV is triggered by mitochondrial signals that launch a coordinated response involving membranar and sarcolemmal potassium and calcium channel receptors [Figure 2].^[15] As proposed by Smith and Schumacker,^[15] upon exposure to hypoxia, mitochondrial ROSs promote an intracytoplasmic shift from oxidized to reduced cellular redox state (e.g., proteins, glutathione and NAD/NADH). These hypoxia-induced ROS and redox changes trigger calcium mobilization by: 1) inhibition of voltage-gated potassium channels (Kv) causing membrane depolarization which promotes the opening of voltage-gated calcium channel (VGCC), 2) activation of phospholipase C (PLC) to generate diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP₃) that stimulate calcium release respectively from membranar receptor-operating channels (ROC) and sarcolemmal IP₃ receptor, 3) activation of ryanodine receptors (RyR) by oxidation of cysteine residues, 4) by increasing the ratio of adenosine monophosphate (AMP)

to ATP, low O_2 tension stimulates AMP-kinase (AMPK) resulting in activation of the RyRs and further calcium release from the sarcoplasmic reticulum. Taken together, the elevation of intracellular calcium concentrations induces calcium binding to calmodulin, subsequent activation of myosine light chain (MLC) kinase, myosin phosphorylation and ultimately contractions of VSMCs. Moreover, after activation of Rho kinase and MLC phosphatase, myofibrillar proteins become more sensitized to the effects of calcium sensitization resulting in sustained contractions of pulmonary VSMCs.

When exposed to hypoxia, both pulmonary and systemic VSMCs share the same effector mechanisms of calcium-mediated changes in vascular tone while pulmonary VSMCs present the unique property to detect low levels of O_2 tension and transmit signals to mobilize calcium close to myofibrillar proteins. Mitochondria are located closer to plasmalemmal membrane in pulmonary VSMCs compared with systemic VSMCs.^[16] Therefore, a greater structural and functional coupling between mitochondria and Kv channels in pulmonary VSMCs could explain the specific O_2 sensitivity and HPV response.

Time course of HPV

Hypoxic exposure of pulmonary VSMCs results in a *biphasic* vasoconstrictive response. The early phase starts within 100 msec, peaking at 5-20 min as a result of transient elevations of intracellular calcium concentrations. The phase 2 develops more gradually peaking at 60-120 min as a result of myofibrillar calcium-sensitization coupled with enhanced endothelial release of vasoconstrictive compounds (ET-1 and EET) and decreased production of NO [Figure 3].^[11] When

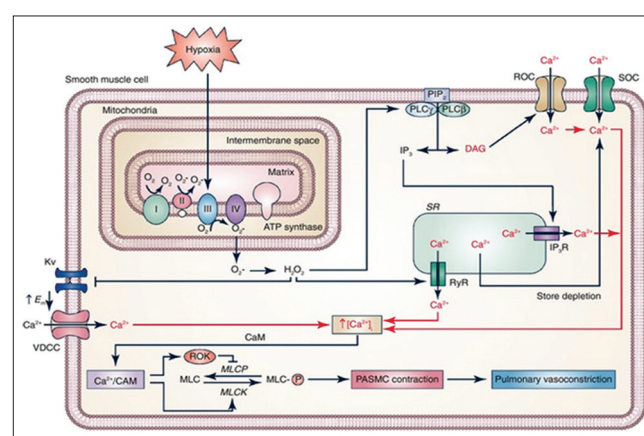


Figure 2: Oxygen sensing and cellular response (reproduced from Smith and Schumacker^[15]). CaM, calmodulin; CRAC, calcium release-activated Ca₂; DAG, diacylglycerol; IP₃, inositol 1,4,5-trisphosphate; K_v channels, voltage gated-potassium channel; MLC, myosin light chain; MLCK, myosin light chain kinase (MLCK); PIP₂, phosphatidylinositol bisphosphate; PLC, phospholipase; ROC, receptor-operated Ca²⁺ channels; ROS, reactive oxygen species; RyR, ryanodine receptors; SR, sarcoplasmic reticulum; VDCC, voltage-dependent Ca²⁺ channels

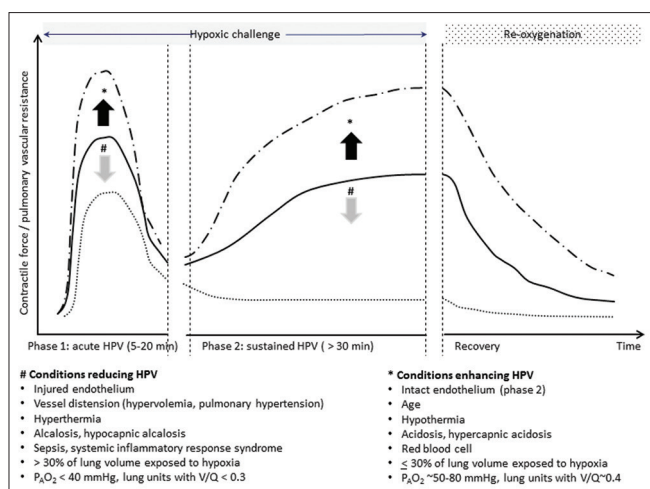


Figure 3: Time course and factors influencing hypoxic pulmonary vasoconstriction (HPV)

normoxia is restored after a short hypoxic phase (<20 min), the HPV declines and PVR normalizes as pulmonary blood flow increases in the re-oxygenated areas. In contrast, after a prolonged period of hypoxia, the HPV only disappears after several hours despite full re-oxygenation, resulting in greater ventilation-perfusion (V/Q) mismatch and consequently larger alveolar-to-arterial O_2 pressure gradient (A-a PO_2).

After starting the second stage of bilateral surgical procedures, the residual and prolonged HPV response on the dependent ventilated lung (non-ventilated lung during the first stage) causes V/Q mismatch and impaired O_2 uptake that requires higher inspiratory oxygen fraction (F O_2) to maintain satisfactory Pa O_2 .

Neurohumoral modulation of HPV

Exposures to intermittent or chronic hypoxia (e.g., pulmonary diseases, altitude) represent stressful challenges that, by stimulating the sympathetic nervous and renin-angiotensin-aldosterone systems (SNS and RAAS), result in elevation of systemic and pulmonary arterial pressures.

Airways and pulmonary vessels are innervated by autonomic and sensory nerve fibers, the highest density of noradrenergic and cholinergic neural endings being found around extrapulmonary and hilar arteries and decreasing towards the periphery (artery size >60-80 μ m).^[17] Vagal stimulation causes mild vasorelaxation mediated by the endothelial release of NO and vasoactive intestinal factor. Stimulation of the sympathetic nervous system produces the release of norepinephrine from sympathetic neural endings close to arterial wall and of epinephrine from the adrenal medulla in the blood stream. Stimulation of alpha-1-adrenergic-receptors (AAR-1) with norepinephrine causes vasoconstriction whereas stimulation of beta-1 and beta-2 adrenergic receptors (BAR-1 and

BAR-2) with epinephrine results in potent vasodilatation owing to activation of the cAMP-dependent protein kinase pathway and the release of NO from ECs. In contrast with normoxic conditions where the sympatho-vagal system plays a negligible role on the pulmonary vasomotor tone, in hypoxic conditions, pulmonary BAR-mediated vasodilatation predominates over AAR-1 vasoconstriction, partially blunting the potent acute HPV.^[18] Therefore, in patients with sleep apnea, BAR-mediated relaxation of pulmonary arteries offsets HPV, mitigates the elevation of PVR and alleviates the workload of the right ventricle. Lending support to these clinical findings, experimental data have demonstrated that the HPV response is attenuated with alpha-adrenergic blockers and enhanced with beta-adrenergic blockers.^[19]

Hypoxic challenge also stimulates the renin angiotensin aldosterone system (RAAS). Indeed, exposure to hypoxia has been shown to increase the activity of renal adrenergic receptors (AA-1 and BAR-1) in juxtaglomerular cells resulting in increased renin secretion and release of angiotensin II (Ang II) by the action of angiotensin converting enzymes (ACE) largely present in the endothelium of pulmonary capillaries and in other tissues (e.g., brain, heart). In VSCMs, Ang II exerts dual effects on angiotensin receptors type 1 and 2, vasoconstriction mediated by AT-1R and vasodilatation mediated by AT-2.^[20] The attenuation of HPV in patients chronically treated with ACE inhibitors supports the predominant constrictive effect of Ang II.^[21]

Altogether, there is strong evidence suggesting that hypoxia-induced stimulation of the SNS and RAAS results in systemic cardiovascular and renal changes (e.g., tachycardia, hypertension, oliguria), a blunted HPV response owing to the predominant pulmonary BAR-2 vasodilatory effects which partially offset the constricting effects on AAR-1 and AT-1 receptors.^[22] Interestingly, a preserved HPV response has been reported in patients after bilateral lung transplantation, despite the loss of the autonomic neural innervation.^[23]

Physiological variations in HPV responses

In healthy individuals breathing air at sea level, pulmonary vessels are almost fully dilated, atelectatic areas are absent and consequently HPV is inactive.^[24] Noteworthy, the pressure-flow relationship is not linear since pulmonary vessels offer greater distensibility and recruitability than systemic arteries to accommodate to higher blood flow and to minimize therefore the initial elevation in pulmonary arterial pressure (PAP).^[25] For instance, a reduction in CO (e.g., head-up position, blood loss) leads to a larger drop in pulmonary vascular driving pressure, even though the vasomotor tone remains *per se* unchanged.^[26] Conversely, as

pressure along the entire circuit increases, the pressure-flow curve becomes more linear since the fully distended vessels are by definition no longer distensible. Hence, when left atrial pressure increases with fluid loading or head-down position, the ability of HPV to redirect blood flow or reduce conductance is curtailed. This concept of HPV dependence on circulatory volume supports the clinical observations that restrictive fluid regimen compared with liberal strategy are associated with better oxygenation in patients with acute lung injury.^[27]

Lung volume also influences pulmonary vascular resistance (PVR) as described by the parabolic U-shaped PVR-Volume curve. The PVR reaches a nadir at the functional residual capacity (FRC) and it increases at higher inflating pressures as alveolar capillaries are “squeezed” by elevated alveolar pressures or, when breathing operates below the FRC as the extra-alveolar vessels become distorted and obstructed offering greater resistance to blood flow.

Besides the P_{A,O_2} and P_{mv,O_2} levels, the strength of HPV also depends on the basal vascular tone and the volume of the lung exposed to hypoxia. A more potent HPV response is elicited when PVR is low (near FRC) and it decreases when the lung is overdistended or collapsed. From animal studies, we know that if exposure to hypoxia exceeds 40% of the whole lung areas, the redistribution of blood flow to non-hypoxic pulmonary areas is decreased suggesting that the increased PAP tends to overcome the increased local arteriolar resistance generated by HPV.^[28] In isolated ventilated-perfused lungs, HPV is enhanced by hypercapnia and blunted by metabolic alkalosis and hyperventilation-induced hypocapnia.^[29]

Senescence

During exercise, elderly exhibit larger increases in PAP than in younger subjects, given lesser release of vasodilating mediators from the ECs, stiffening of the vascular wall and left ventricular diastolic dysfunction.^[30] Moreover, the greater fall in P_{mvO_2} due to a lesser increase in CO and higher O_2 extraction in active skeletal muscles, may further enhance HPV and contribute to PAP elevation during intense aerobic exercise.

At rest, middle-aged subjects exposed to moderate alveolar hypoxia ($P_{A,O_2} \sim 50$ mmHg) over 20 min exhibit a greater increase in PAP compared with younger individuals (+9 mmHg).^[31] Such age-related enhancement of HPV could be explained by a greater sensitivity of the O_2 sensing apparatus, greater propensity for calcium cell entry and/or greater activity of the calcium-calmoduline-dependent myosin light chain kinase within pulmonary VSMCs.^[31]

Effects of Patient Position, Anesthetic Technique and Mechanical Ventilation in Gas Exchange

From wakefulness to anesthetized state

The effectiveness of blood oxygenation is largely determined by the distribution of V/Q ratio through the lungs and the integrity of the alveolar-capillary layer. The multi-compartment lung model enables physiologists and clinicians to predict the changes in P_{A,O_2} based on V/Q ratio [Figure 4].^[32,33] As the strongest pulmonary vasoconstrictive effect occurs at a P_{A,O_2} around 65-70 mmHg and given the slope of the hemoglobin- O_2 dissociation curve, the effectiveness of HPV is greatest in lung units with moderately reduced V/Q ratio (~ 0.4) whereas in atelectatic areas ($V/Q < 0.1$), the very low P_{A,O_2} produces a weaker stimulus for HPV^[34] that is enhanced by low P_{mv,O_2} values and attenuated by low P_{aO_2} (dilatation of bronchial arteries with enhanced collateral flow).

In spontaneously breathing volunteers, Nyren *et al.* using single photon emission computed tomography showed that sevoflurane anesthesia at 1 minimal alveolar concentration [MAC] resulted in greater heterogeneity of V/Q ratios, a trend towards smaller median V/Q ratios and similar ventral-to-dorsal distribution of tidal volume compared with awake conditions.^[35]

Under mechanical positive pressure ventilation, the impairment in blood oxygenation is attributed to the generation of atelectatic areas and a wider dispersion of V/Q ratios, with preferential distribution of ventilation toward ventral lung regions whereas gravitational forces tend

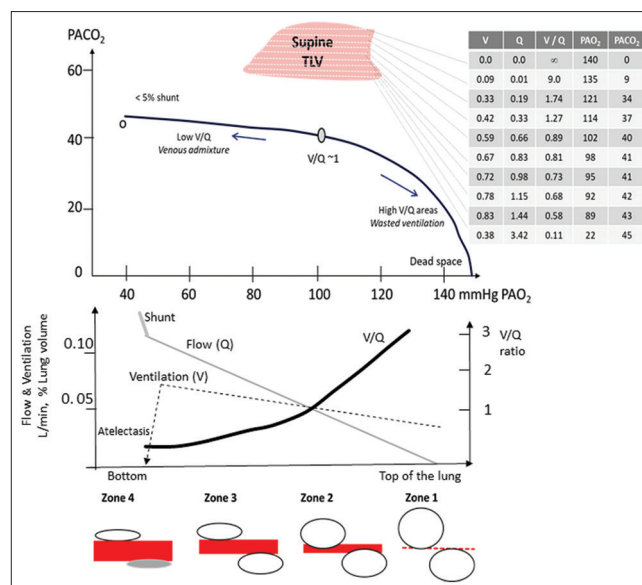


Figure 4: Distribution of blood flow (Q) and ventilation (V), V/Q ratio and alveolar partial pressure of oxygen (PAO_2) and carbon dioxide ($PACO_2$) through the lung in supine position

to direct blood flow in dorsal regions.^[36] Ventilation using oxygen-nitrogen mixture ($FI_{O_2} < 80\%$), PEEP and recruitment maneuvers have been shown to mitigate atelectasis formation, optimize V/Q ratios and improve respiratory compliance.^[37]

Body position

After anesthesia induction, the left and right lungs receive on average 45% and 55% of total CO. After turning the patient from supine to lateral position, blood flow as well as venous and capillary blood volumes are partially shifted from the non-dependent to the dependent lung [Figure 5].^[38] The dependent lung receives a larger proportion of CO (+5%) since the gravitational forces generate a vertical pressure gradient through the pulmonary circulation, PAP (and venous pressure) decreasing by 10 to 20 mmHg towards the top of the non-dependent lung. Alveolar areas with V/Q between 0.8 and 1.3 are located in the lower middle part of the dependent lung, the most dependent lung areas ($V/Q < 0.5$) contribute to venous admixture while “wasted” ventilation develops in the upper pulmonary zones ($V/Q > 3$, dead space).

In advanced stages of chronic obstructive pulmonary disease, the HPV response is less effective and the impact of patient’s position plays a greater role as gravitational forces augments the redirection of perfusion to the dependent lung and improves oxygenation.^[39]

This physiological concept supports the clinical practice of positioning critically-ill patients with unilateral hypoxemic pulmonary diseases with the “good lung down” in order to optimize V/Q matching.

In contrast to lung surgery that requires lateral positioning, cardiac robot-assisted surgery is performed in supine position and OLV facilitates the harvesting of the internal mammary artery. In a cohort study of 255 consecutive patients, Liu *et al.* reported only 9 cases of hypoxemic event ($PaO_2 < 70$ mmHg despite increases in PEEP level and FI_{O_2}), the mean PaO_2 level decreasing by approximately 30% on average, similar to the fall observed in thoracic surgery when patients are installed in lateral decubitus.^[40] These observations underline the importance of HPV during OLV in V/Q matching, patient position and gravity forces playing a minor role on pulmonary blood flow in healthy lungs.

From two-lung to one lung ventilation

At the start of thoracic surgery, switching mechanical ventilation from two lungs ventilation to OLV, always results in declining PaO_2 levels (-30 to 50%) consequent to the reduced surface area available for gas exchange and variable intrapulmonary shunting.^[41] Within the first 10 min after OLV, oxygen transfer from alveola to capillaries in the non-ventilated lung contribute to maintain blood oxygenation and the HPV is elicited when P_AO_2 progressively declines below a thresholds value of 85 mmHg. Then, the activated HPV in the “hypoxic” lung redirects blood flow to the dependent ventilated lung to minimize shunting (Q_s/Q_T) and venous admixture through the operated lung [Figure 5].^[42]

In the dependent lung, the distensibility and recruitability of pulmonary vessels attenuate the increase in PAP and right ventricular afterload while providing a larger capillary surface area for gas exchange to mitigate the fall in diffusion capacity. Along a vertical bottom-up distance, ventilation increases and perfusion of lung areas decreases that results in wider

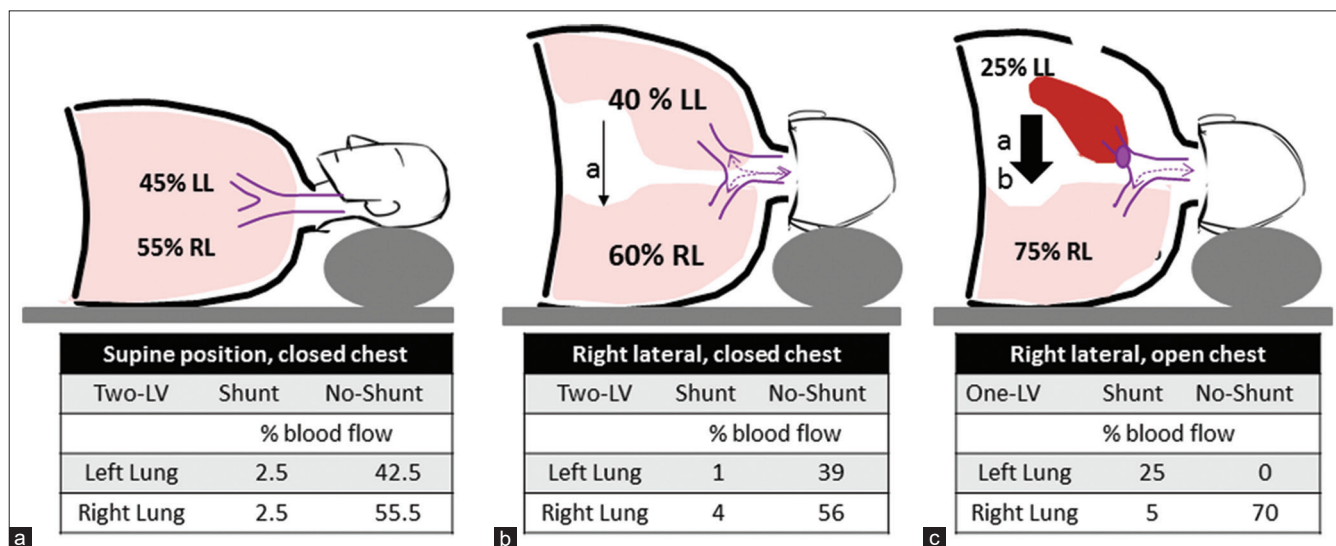


Figure 5: Perioperative changes in shunted and non-shunted pulmonary blood flow, in supine position (a), right lateral decubitus (b) and one-lung-ventilation (c). a, gravitational forces b, hypoxic vasoconstriction, loss of negative pleural pressure, elastic lung recoil, surgical manipulation

spread of V/Q ratios. Moreover, the weight of the mediastinal and abdominal organs on the dependent hemithorax results in higher pleural pressure ($P_{\text{pleural}} + 0.25 \text{ cmH}_2\text{O}$ per cm from upper to lower areas) that causes a further reduction in FRC in addition to the effects of anesthetic and neuromuscular agents on respiratory muscle tone.^[43] Therefore, both higher P_{insp} and PEEP levels are required to deliver the tidal volume and to maintain FRC, the driving pressure remaining unchanged ($\Delta P = P_{\text{insp}} - P_{\text{pleural}}$). Interestingly, Spadaro *et al.* reported that setting PEEP at 10 cmH_2O during OLV resulted in lower shunt fraction, decreased driving pressure and dynamic compliance along with improved oxygenation compared with PEEP at 5 cmH_2O .^[44] As the increased capillary blood flow tends to match the alveolar ventilation through the dependent lung with increasing V/Q ratios, the efficacy of gas exchange can be ensured during OLV.

Chest opening

Within 10-20 min after chest opening, the elastic lung recoil forces acting in the non-ventilated lung results in a progressive collapse of the lung. Several measures may accelerate lung deflation: 1) ventilation with 100% O_2 before lung exclusion to enhance resorption atelectasis, 2) transient ventilator disconnection (1-2 min) with balloon deflation to facilitate

alveolar gas clearance, 3) external lung compression by the surgeon. Besides HPV, mechanical vascular closure that parallels the collapse of bronchoalveolar tissues plays a secondary role in shifting pulmonary blood flow towards the dependent ventilated lung to minimize intrapulmonary shunt.^[45]

Impact of anesthetic drugs

In vitro studies^[46] using denervated pulmonary arteries and *in vivo* experiments using isolated perfused lungs strongly support a dose-response inhibition of HPV by volatile anesthetics in contrast to intravenous drugs such as propofol, ketamine, droperidol and barbiturates anesthetics which have no (or minimal) effect on the HPV response [Table 1].^[46,47]

In intact animal models, the HPV response is determined by the interaction between vasodilatory and cardio-depressive effects of anesthetic agents. The direct inhibition of HPV by volatile anesthetics is partially offset by their cardio-depressive effects, the decreased CO causing flow diversion and the low PmvO_2 directly enhancing the HPV response. In contrast, ketamine and propofol exert less negative inotropic effects, therefore HPV is maintained and slightly potentiated with propofol through inhibition of pulmonary vasodilatation mediated by K_{ATP} channels.^[48]

Table 1: Impact of perioperative drug and anesthetic management on cardiovascular control and hypoxic pulmonary vasoconstriction

	HR	MAP	SVR	PVR	CO	HPV	Raw
Intravenous Anesthetics							
Ketamine	+	+	+	+/0	+	0	-
Etomidate	0	0	0	0	0	0	0
Propofol	0/-	--	--	0	-	0	0
Midazolam	0	0/-	0/-	0	0/-	0	0
Analgesics							
Opiates	0	0	0	0	0	0	0 (+)
Dexmedetomidine	-	-	-	0	-	0	0
Nonsteroidal anti-inflammatory drugs	0	0	0	0	0	(-/0/+)	0
Volatile anesthetics							
Isoflurane	0/-	--	--	--	--	--	-
Sevoflurane	0/-	-	-	-	-	-	-
Desflurane	0/-	-	-	-	-	-	-
Inotropes, vasopressors, bronchodilators							
Dobutamine, Dopamine	+	+/0/-	0/-	0/-	+	-	0
Phenyléprine	0/-	+	+	+	0/-	0	0
Milrinone							0 (-)
Salbutamol	+	+/0/-	+	0/-	+	-	-
Anti-hypertensive drugs							
CCB	0/-	--	--	-	0/+	-	0
NTG, NPS	0/+	--	--	-	+	-	0
ACEI, ATA	0	-	-	0/-	+	0/-	0((+))
Beta-blockers	-	-	0/+	0/+	-	0	0/+

0, no change; +, increased; -, decreased; --, more decreased; CO, cardiac output; HPV, hypoxic pulmonary vasoconstriction; HR, heart rate; MAP, mean arterial pressure; PVR, pulmonary vascular resistance; Raw, airway resistance; SVR, systemic vascular resistance. ACEI, angiotensin-converting enzyme inhibitor; ATA, angiotensin II antagonist; CCB, calcium-channel blocker; NPS, nitroprussiate; NTG, nitroglycerine

During thoracic surgery, intravenous anesthetic drugs result in preserved or even enhanced HPV whereas inhalational anesthetics cause mild-to-moderate inhibition of HPV and peripheral vasodilation that mitigate cardiac depression by reducing left ventricular afterload. In a meta-analysis of 23 randomized controlled trials, volatile anesthetics were associated with higher intrapulmonary shunt (Q_s/Q_T 33% vs 27%, mean difference of - 5.4%), higher cardiac index (3.2 vs 2.9 L/min, mean difference of 0.19 L/min) and lower oxygenation index during OLV (PaO_2 with mean difference of -27 mmHg) compared with intravenous anesthesia.^[49] These data confirm that volatile anesthetics within the clinical dose range (from 0.5 to 1.5 MAC) slightly impair lung oxygen uptake by reducing the HPV response with a consequent increase in venous admixture. The impairment in lung oxygen uptake by inhalational anesthesia should be balanced against important benefits of volatile anesthetics: 1) direct bronchodilatation, particularly valuable in patients with asthma and COPD,^[50] 2) larger attenuation of the release of alveolar inflammatory mediators and oxidative stress coupled with reduced adhesion of platelets and leucocytes in endothelial pulmonary capillaries,^[51,52] 3) lesser incidence of postoperative pulmonary complications resulting from anesthetic preconditioning and protection of the alveolar-capillary membrane.

Effects of analgesics

Administration of iv opiates (e.g., morphine, fentanyl, sufentanil, buprenorphine) does not impair the capacity of the pulmonary circulation to respond to hypoxia. The lack of interference of opiates with the HPV response has been strongly established in animal and clinical studies.^[53,54]

Dexmedetomidine, an alpha-2 adrenergic agonist has been shown to preserve (or enhance) HPV response.^[55,56] Improvement in oxygenation and favorable clinical outcome in patients receiving dexmedetomidine could be attributed to lesser need for volatile anesthetics, blunting the neuroendocrine stress response, higher dynamic lung compliance, lower oxidative stress and anti-inflammatory effects.^[57-59]

With non-selective *cyclooxygenase (COX) inhibitors* that are used in the postoperative setting, the HPV response is minimally altered as the balance between vasoconstrictive (TXA_2) and vasodilatory mediators (PGI_2) remains stable.^[60] The production of PGI_2 is predominantly related to COX-1 activity in acute hypoxia and to COX-2 in chronic hypoxia. Therefore, celecoxib, a COX-2 inhibitor, was reported to attenuate the HPV in subjects exposed to a hypoxic environment, as the vasodilatory effects of PGI_2 are unopposed by the lower

concentrations of TXA_2 . In contrast, in patients with chronic hypoxemic pulmonary diseases, the HPV response can be re-inforced owing to reduced PGI_2 activity when COX-2 inhibitors are given.^[61,62]

Effects of cardiovascular drugs

Inotropes such as dobutamine, dopamine and epinephrine increase ventricular contractility and reduced ventricular afterload by activating cardiac BAR-1 and vascular BAR-2, respectively. The consequent increase in O_2 transport and O_2 availability may result in improved kidney, splanchnic or cerebral function in patients with heart failure. However, the BAR-2 mediated dilatation of pulmonary vessels attenuates the HPV response causing intrapulmonary shunt as manifested by greater $PA-aO_2$ gradient and impaired blood oxygenation.^[63]

Phenylephrine, an agonist acting on AAR-1, exerts both pulmonary and systemic vasoconstrictor effects. *Ephedrine*, an alkaloid derived from ephedra herb, stimulates the release of NE from sympathetic nerve endings and also acts directly on AARs and BARs. During OLV, administration of phenylephrine or ephedrine was shown effective to normalize blood pressure while blood oxygenation was maintained (or improved) and Q_s/Q_T unchanged.^[64] Likewise, Doering *et al.* reported that, in some patients with ARDS, a continuous infusion of phenylephrine resulted in higher PaO_2 (mean gain of 15 mmHg) suggesting the ability of AAR-1 agonists to enhance HPV along with minor increase in PAP and unchanged CO.^[65]

With inhaled BAR-2 agonists such as *salbutamol* or *terbutaline*, the occurrence of O_2 desaturation in bronchospastic patients has been attributed to greater heterogeneity in V/Q ratios owing to BAR-2 mediated vasorelaxation and blunting of the HPV response.^[66]

Most *anti-hypertensive drugs* such as NO donors (nitroglycerin, nitroprussiate), phosphodiesterase inhibitors, AAR-1 blockers, calcium-channel blockers, ACE inhibitors and angiotensin receptor antagonists (ATA), all attenuate HPV by acting on EC-derived modulators as well as signal transduction pathways in pulmonary VSCMs that limit calcium mobilization and gene-transcription. The vasodilatory effects of these drugs are particularly helpful to unload the right ventricle in patients with pulmonary hypertension. Interestingly, treatment with ACE inhibitors or ATA has been shown to attenuate the acute pulmonary hypertensive response in volunteers breathing a hypoxic mixture.^[21,67] After long-term therapy with ACEI in patients with heart failure, improvement in oxygenation has been observed that suggests a limited role

in drug-induced V/Q mismatch and the prominent effects of better O₂ delivery to respiratory muscles.^[68]

Non-selective *beta-blockers* such as propranolol have been shown to augment O₂ content in hypoxemic critically ill patients by blocking the pulmonary vasodilatation depending on BAR-2 and by reducing ventricular contractility depending on BAR-1.^[69] The diminished CO and in turn the reduced P_{mv}O₂ could enhance the HPV response in low V/Q lung areas.^[70]

Almitrine besylate, a diphenylmethylpiperazine derivative was initially used in COPD patients to improve gas exchange by a chemoreflex-mediated increase in minute ventilation and by optimizing V/Q matching along with enhanced HPV.^[71] In patients with acute respiratory failure, iv administration of almitrine has produced short-term improvement in blood oxygenation, particularly when it was combined with selective vasorelaxant drugs (e.g., inhaled NO and PGI₂) however, it has been abandoned given the occurrence of lactic acidosis, worsening pulmonary hypertension and liver dysfunction.^[72] In thoracic surgery, almitrine has been shown effective to attenuate the fall in PaO₂ during OLV under iv anesthesia but not under sevoflurane anesthesia.^[73-75]

Thoracic epidural anesthesia (TEA)

In unstressed individuals in supine position, the sympatho-adrenergic system is barely activated. Therefore, blocking the sympathetic efferent nerves with thoracic epidural anesthesia produces a mild reduction in blood pressure owing to vasodilatory effects in the visceral and cutaneous compartments.^[76]

During stressful perioperative events (e.g., hemorrhage, pain), activation of the sympatho-adrenal pathways results in systemic vasoconstriction (AAR-1), cardiac hyperactivity (BAR-1) as well as vasodilatation in the pulmonary circulation. Importantly, blunting of cardiac and vascular sympathetic drive induced by TEA with even low dose of local anesthetics (LA) results in vagal predominance along with attenuation of the baroreflex response, rendering patients less tolerant to cope appropriately with acute hypovolemia due to sudden blood losses.^[77]

Blood oxygenation has been reported to be unaffected, slightly impaired or enhanced by TEA, depending on the dose of LA, the general anesthetic regimen and the prevailing hemodynamic conditions.^[78-81] A dose-response has been observed between the concentrations of ropivacaine (0.75%, 0.5% and 0.25%) and the development of intra-pulmonary shunting with hypoxemia.^[82] At the highest concentrations of ropivacaine (0.75-0.5%), the potent sympathetic blockade

produces prominent cardiac depression and inhibition of AA1-mediated vasoconstriction in large pulmonary arteries. Attenuation of the HPV is mitigated by the TEA-induced reduction in CO, the consequent lower P_{mv}O₂ as well as by the lower anesthetic requirement if volatile anesthetics are used. At the lowest concentrations of LA which are routinely used in thoracic anesthesia, cardiac depression is less pronounced and the HPV response is barely affected, particularly under total iv anesthesia.

Choice of General Anesthetics

Worldwide, the majority of thoracic procedures are performed under inhalational anesthesia.^[83] Thoracic anesthesiologists justify this choice by valuable reasons: 1) safe and easy control of the depth of anesthesia, 2) relaxation of bronchial muscle tone, 3) potentiation of the effects of neuromuscular blockers on the motor end-plate, 4) organ protection against ischemia-reperfusion and septic-induced injuries.^[83]

In cardiac surgery, anesthetic preconditioning with volatile agents (e.g., isoflurane, desflurane or sevoflurane) is associated with lesser myocardial injury and shorter ICU stay.^[84,85] In thoracic surgery, a meta-analysis of 23 RCTs has demonstrated a 50% reduction in PPCs in patients receiving volatile anesthetics compared with those receiving total intravenous anesthesia.^[49] In agreement with these findings, an analysis of a multicentric cohort of patients undergoing non-cardiac surgery (N = 124'497), including 4'880 thoracic interventions, has demonstrated a dose-dependent protective effect of volatile anesthetics against PPCs, along with reduced 30-day mortality rate and lower hospital costs.^[86] However these anesthetic-organ preconditioning effects are opposed by a higher rate in cancer recurrence and a reduction in long-term survival in patients exposed to volatile agents compared with intravenous anesthesia.^[87,88] Experimental data lend support to the inhibitory effects of volatile anesthetics on cell-based immunity (e.g., natural killer cell activity) along with upregulation of the transcription of HIF, insulin growth factor and vascular endothelial growth factor which may facilitate intraoperative "seeding" of tumor cells, remodeling of lymphatic vessels and angiogenesis-induced tumor growth that may promote later cancer recurrence and metastasis.^[89] In contrast, propofol inhibits the host immunity to a lower extent, as the natural killer cell activity is better preserved. Moreover, propofol has demonstrated anti-tumor effects in non-small cell lung carcinoma resulting from disrupted regulation of HIF.^[90] Co-administration of low doses of ketamine may represent a valuable way to reduce the dose of volatile anesthetics, to attenuate surgery-induced immunosuppression through its

analgesic and anti-inflammatory effects, reducing leucocyte reactivity, ROS generation and cytokines overproduction while preserving interleukin-2 activity, a key regulator of both cellular and humoral immune response.^[91]

So far, clinical studies comparing intravenous and inhalational anesthesia have reported mixed results regarding long-term clinical outcome. A systematic review including 7'800 patients undergoing lung, oesophageal or breast cancer resection found that iv anesthesia was associated with improved recurrence-free survival compared with inhalation anesthesia (Hazard Ratio of 0.78, 95% confidence interval 0.65 to 0.94).^[92] Given the heterogeneity of patient populations, the various surgical procedures and the retrospective nature of the studies (one RCT, 5 cohorts), large randomized trials should be designed to confirm or refute the immunomodulatory effects of anesthetic agents.

Management of Intraoperative Hypoxemia

Application of minimal monitoring standards including pulse oximetry since the 1990s has contributed to a 20-fold decrease in anesthesia-related mortality, much of this decline being attributed to earlier diagnosis and correction of hypoxemia.^[93] Intraoperative hypoxemia is classically defined by $SpO_2 < 90\%$ corresponding to $PaO_2 < 58-62$ mmHg (7.7-8.3 kPa) and severe hypoxemia by $SpO_2 < 85\%$ corresponding to $PaO_2 < 50-54$ mmHg (6.7-7.2 kPa). Due to the sigmoid shape of O_2 -Hb dissociation curve, changes in SpO_2 poorly reflect the early impairment in blood oxygenation, particularly when high FIO_2 are used. Based on electronic anesthesia records, hypoxic events were reported in 6.8% and severe hypoxemia in 3.5% of 95'407 non-thoracic cases. During thoracic surgery with OLV, the incidence of sustained oxygen desaturation ($SpO_2 < 90\%$) ranges between 2 to 10% but the limits of tolerability and impact on postoperative outcome remain debatable.^[41,94] Interestingly, hypoxic preconditioning

characterized by three cycles of 5-min “no-ventilation” with 3 min ventilation of the dependent lung has been shown to increase intraoperative PaO_2/FIO_2 ratio (+10%), to enhance recovery of lung function and reduce the hospital length of stay after VATS.^[95]

The mechanism of intraoperative hypoxemia is chiefly related to intrapulmonary shunting and venous admixture under general anesthesia and mechanical ventilation. Anesthesia-related atelectasis, misplacement of the double-lumen tube or bronchial blocker, acute bronchospasm and accumulation of secretions or blood in the airways all may result in heterogenous distribution of tidal volume and increase in lung areas with very low V/Q ratio. If the total intrapulmonary shunt (anatomical and physiologic) is less than 15 to 20% of the CO, hypoxemia can easily be corrected by increasing FIO_2 , whereas lesser gains in PaO_2 are achieved in the presence of shunt exceeding 20% as the slope of the PaO_2 - FIO_2 curve decreases and flattens when the shunt approximates 50% [Figure 6].^[96,97]

The stepwise approach of intraoperative management of hypoxemia entails the following sequence^[94,98]: 1) increase the FIO_2 level, avoid hypervolemia and restore normal blood pressure (vasopressor, head up/down position), 2) ensure proper lung isolation technique by adjusting the position of the double-lumen tube or bronchial blocker, 3) exclude any obstruction in the ventilator tubings and airways, clear any secretions or blood clot, alleviate any bronchospasm with a beta-1 adrenergic agonist, 4) re-expand collapsed alveola in the dependent lung by a recruitment maneuver and titrate the level of PEEP to improve respiratory compliance, 4) enhance the collapse of operated lung by disconnecting the ventilator from the airway, deflating the tube's balloon and asking the surgeon to “squeeze” parts of the lung to facilitate gas elimination, 5) alternatively, cautious re-expansion of the operated lung by continuous

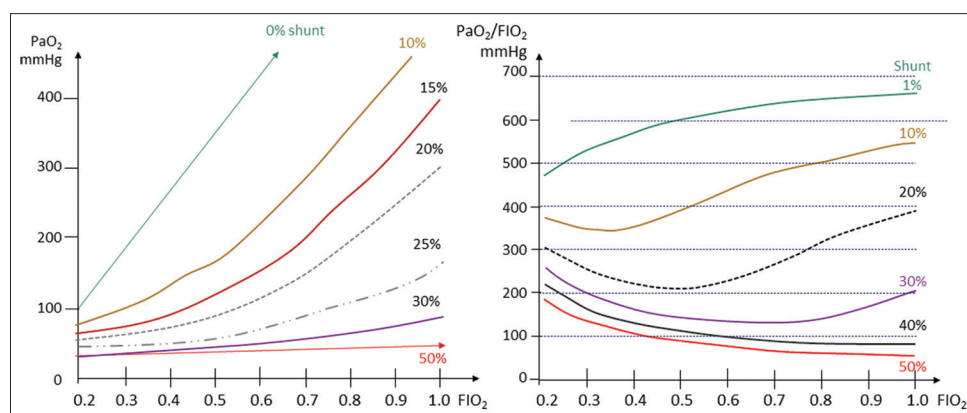


Figure 6: Iso-shunt diagram describing the relationship between PaO_2 or PaO_2/FIO_2 ratio and FIO_2 in the presence of variable pulmonary shunt fraction (adapted from Feiner et al.^[61] and Benatret al.^[62])

positive airway pressure, intermittent low positive pressure or apneic oxygenation (e.g., high jet ventilation) that lead to increase the surface area available for blood gas exchange.^[99] Finally, switching from inhalational to iv anesthesia is the last option to manage refractory hypoxemia by favoring the HPV response. In case of pneumonectomy, clamping of the pulmonary artery by the surgeon eliminates the shunt through the operated lung resulting in better oxygenation.

Conclusions

The HPV is a physiological reflex response effective in pulmonary diseases and during OLV that minimizes intrapulmonary shunt, optimizes V/Q ratios and limits alterations in blood oxygenation.

The initiation of OLV is always associated with a fall in PaO₂ but the incidence of severe hypoxemia is low and can be avoided/treated by proper placement of the double-lumen tube/bronchial blocker and adjustment of ventilatory settings while ensuring hemodynamic control.^[94]

The strongest pulmonary vasoconstrictive effect occurs when 20-40% of the lung volume is exposed to P_AO₂ around 65-70 mmHg and it results in diversion of blood flow to the remaining ventilated areas. After the start of OLV and chest opening, pulmonary blood flow is preferentially directed to the dependent ventilated lung according to gravitational forces and the effectiveness of the HPV response through the non-dependent “hypoxic” lung.

With TEA and intravenous anesthetic agents (e.g., ketamine and propofol), the HPV is well preserved and reduces the intrapulmonary shunt by 20-40% during OLV in lateral position [Figure 7]. Volatile anesthetics dose-dependently attenuate the HPV response although within the clinical dose range (0.5 to 1.5 MAC), the impairment in lung oxygen uptake is relatively mild owing to small increases in venous admixture.

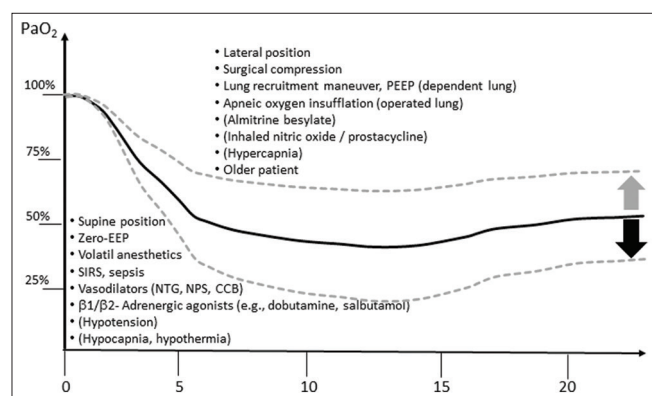


Figure 7: Time course of arterial PO₂ after initiation of one-lung ventilation and modulating factors

Moreover, modern agents such as sevoflurane and desflurane offer valuable benefits in terms of bronchial relaxation, organ protection and anti-inflammatory effects that contribute to lower the risk of postoperative pulmonary complications.

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Conflicts of interest

There are no conflicts of interest.

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