CASE REPORT

Clinical Case Reports Open Access WILEY

Nicardipine-induced acute respiratory failure: Case report and literature review

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Abstract

Hypoxic pulmonary vasoconstriction (HPV) is a major physiological mechanism that prevents the development of hypoxemia secondary to a regional decrease in the ventilation–perfusion ratio (the intrapulmonary shunt effect). Calcium plays a critical role in the cellular response to hypoxia and the regulation of the pulmonary vascular tone. Therefore, calcium channel antagonists such as nicardipine have the potential to interfere with the pulmonary response to hypoxia, increasing intrapulmonary blood shunt and thus worsening underlying hypoxemia. This article reports the case of a 40-year-old man suffering from lobar pneumonia, who developed a rapidly progressing hypoxemia after starting nicardipine infusion for blood pressure control. After ruling out all major causes of hypoxemic respiratory failure, the involvement of the calcium channel antagonist was strongly suspected. Hypoxemia caused by HPV release is an underreported side effect of calcium channel blockers. There are few clinical reports that describe the occurrence of this adverse event, and to our knowledge, only one other publication describes a patient suffering from infectious pneumopathy. In this article, we discuss the cellular mechanisms behind the HPV, as well as the pharmacology of calcium channel antagonists and their involvement in the development of acute respiratory failure. The purpose of this report is to remind clinicians dealing with patients affected by acute hypoxemia that pharmacologic HPV inhibition should be considered as part of the differential diagnosis, thus avoiding unnecessary costly and time-consuming assessments.

KEYWORDS
case report, hypoxemia, hypoxic pulmonary vasoconstriction, nicardipine

1 | CLINICAL PRESENTATION

A 40-year-old man was admitted to our intensive care unit (ICU) with severe hypoxemic respiratory failure (HRF) associated with drowsiness and complicated by severe acute renal failure requiring renal replacement therapy. His neurological condition did not allow for a good medical questioning. As only medical background, we found active smoking of an average of 20 cigarettes per day for the past 20 years, as well as heroin and cannabis addictions.

The first assessment carried out in the emergency room showed a severe disorder of consciousness which was briefly reversed after administering 0.4 mg of naloxone, with an initial Glasgow Coma Scale (GCS) estimated at 8/15. Pupil examinations revealed a tight myosis.

The patient was hypopneic, with a respiratory rate close to 10 breaths per minute and severely hypoxemic with a SpO$_2$ (pulsed oxygen saturation) at 63% in ambient air. The temperature taken at the inguinal fold was only 34.2°C.

Considering his poor condition, the patient was quickly intubated and assisted by mechanical ventilation. Sedation was maintained by continuous infusion of dexmedetomidine and propofol.

The first blood gas analysis revealed the following: hypoxemia with PaO$_2$ (partial arterial pressure in oxygen) at 43 mmHg, severe mixed acidosis with a pH of 6.97, PaCO$_2$ (partial arterial pressure in carbon dioxide) at 68 mmHg, bicarbonate at 15 mmol/L, hyperlactatemia at 94 mmol/L, as well as severe hyperkalemia at 9 mmol/L.

The patient maintained a 124/63 mmHg blood pressure and a 101 bpm heart rate. The electrocardiogram only showed a minor abnormality: a narrow QRS complex associated with large repolarization waves.

The patient received 1 g of calcium gluconate as well as 200 mL of 1.4% sodium bicarbonate. After the placement of arterial, central venous, and bladder catheters, he was transferred to the ICU, where continuous venovenous hemodiafiltration (CVVHDF) was rapidly started. The patient was actively warmed with a forced air blanket. and received 1 L of a balanced crystalloid solution in 30 min followed by a continuous infusion of 2 L in 24 h.

As depicted in Figure 1, the chest X-ray taken shortly after endotracheal tube insertion showed a parenchymal condensation in the right lower lobe. Moreover, laboratory findings revealed a significant inflammatory syndrome. Therefore, an empiric antibiotic therapy with 1 g/6 h amoxicillin–clavulanate was initiated, after collecting samples for microbiology analysis (i.e., blood cultures and endotracheal tube aspirates). Finally, a few hours later, urinary toxicology came positive to cannabinoids, cocaine, opiates, and benzodiazepines.

Twenty-four hours after admission, the patient's body temperature was normalized and ionic disorders were corrected. His sedation was limited to dexmedetomidine infusion only, and his awakening went without any issues. The patient was calm with a Richmond Agitation-Sedation Scale (RASS) score of −1. Therefore, controlled ventilation was switched to spontaneous ventilation with inspiratory support at 8 cmH$_2$O and PEEP (positive end-expiratory
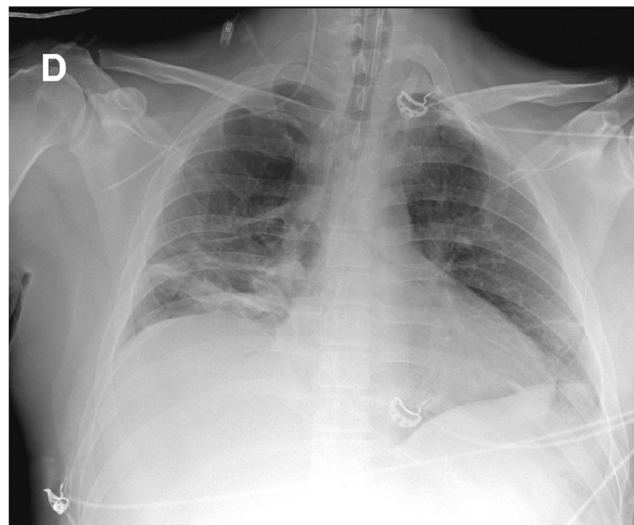

FIGURE 1 Chest radiography taken shortly after the endotracheal tube insertion in the emergency department. It shows a parenchymal condensation in the right lower lobe.

pressure) at 5 cmH$_2$O. However, the oxygen requirements remained high, with an SpO$_2$ of 92% despite an FiO$_2$ (inspiratory oxygen fraction) at 40%.

A few hours after the sedation decrease, the blood pressure and the heart rate gradually increased from 132/67 mmHg and 87 bpm to 204/106 mmHg and 107 bpm, respectively. However, the patient remained calm with a RASS of −1 and did not report any pain. The rate of dexmedetomidine infusion was then increased.

Nevertheless, 1 h later, blood pressure and heart rate remained high (178/103 mmHg and 93 bpm). A continuous infusion of nicardipine at a 3 mg/h rate was then started after an initial 1 mg bolus. The infusion rate was finally increased to 4 mg/h.

Two hours after the start of nicardipine infusion, the hemodynamic parameters normalized. Blood pressure and heart rate dropped to 133/78 mmHg and 78 bpm, respectively. However, the patient began to develop a rapidly progressive hypoxemia (Table 1). FiO$_2$ was increased to 80% to maintain an SpO$_2$ > 90%. At auscultation, the ventilation remained symmetrical. A chest X-ray was performed, showing no other lesion than the parenchymal condensation in the right base.

Therefore, the patient received a neuromuscular blocking agent and his sedation was increased. The ventilatory parameters were switched back to controlled volume up to 7 mL/kg of ideal body weight at a frequency of 16 breaths/min and PEEP was increased to 10 cmH$_2$O.

A fibrobronchoscopy was then performed, showing a nonselective tracheal tube as well as a small amount of mucous secretions without an obvious plug. A thoracic angio-scan excluded any pulmonary embolism and

TABLE 1

	−4 h	−2 h	0 h	+2 h	+4 h	+6 h	+8 h
SpO_2	97%	100%	100%	89%	99%	92%	100%
PaO_2	72 mmHg	–	86 mmHg	54 mmHg	102 mmHg	70 mmHg	–
V. Mode	PSV	PSV	PSV	VCV	VCV	VCV	VCV
PEEP	5 cmH$_2$O	5 cmH$_2$O	5 cmH$_2$O	10 cmH$_2$O	10 cmH$_2$O	10 cmH$_2$O	8 cmH$_2$O
FiO_2	40%	40%	40 %	80 %	100 %	40 %	45%
P/F	180	–	215	67	102	175	–
APS	160 mmHg	180 mmHg	160 mmHg	150 mmHg	120 mmHg	120 mmHg	140 mmHg
APD	100 mmHg	105 mmHg	100 mmHg	90 mmHg	80 mmHg	80 mmHg	90 mmHg
HR	83/min	103/min	93/min	95/min	78/min	57/min	56/min

Abbreviations: APD, Diastolic arterial pressure; APS, Systolic arterial pressure; FiO$_2$, inspiratory oxygen fraction; HR, Heart Rate; P/F, PaO$_2$/FiO$_2$ ratio; PaO$_2$, partial arterial pressure in oxygen; PEEP, positive expiratory pressure; PSV, Pressure support ventilation; SpO$_2$, pulsed oxygen saturation; V. Mode, mechanical ventilation mode; VCV, Volume control ventilation.

FIGURE 2 A thoracic computed tomography angio-scan was performed as the patient's respiratory condition unexpectedly worsened. The major finding is a parenchymal condensation of the right lower lobe with a small pleural effusion. It also highlighted a centrilobular and para-septal emphysema of the upper lobes.
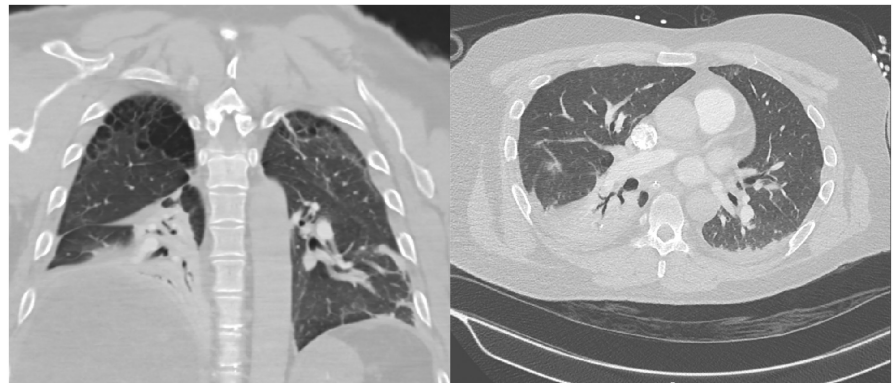
showed parenchymal condensation of the right lower lobe with a small pleural effusion. It also highlighted a centrilobular and paraseptal emphysema of the upper lobes (Figure 2).

At the end of our screening, the patient's respiratory parameters further deteriorated. His PaO$_2$ fell to 84 mmHg, despite FiO$_2$ reaching 100% and a PEEP set at 10 cmH$_2$O.

In the absence of any other obvious cause and witnessing the discrepancy between the clinical situation and the scan-imaging, the implication of calcium antagonist was suspected. Therefore, nicardipine infusion was stopped approximately 3.5 h after its beginning and 2 g of calcium gluconate was administered as a bolus.

Respiratory parameters quickly improved. Only half an hour after nicardipine discontinuation, FiO$_2$ could be reduced to 60% while maintaining a PaO$_2$ of 102 mmHg. Ten hours later, the sedation could be lightened again, allowing for a switch to spontaneous ventilation with inspiratory support at 8 cmH$_2$O and PEEP at 5 cmH$_2$O, FiO$_2$ could be reduced to 30%.

The patient was successfully extubated a few hours later. On the eighth day, he was discharged from the ICU. The antibiotic therapy with amoxicillin–clavulanate was continued for 8 days, although the blood and sputum samples did not reveal any bacterial pathogen.

2 | DISCUSSION

This clinical case describes the occurrence of rapidly progressive hypoxemia following the inhibition of hypoxic pulmonary vasoconstriction (HPV) caused by an antihypertensive treatment in a patient suffering from lobar pneumonia.

Hypoxemia is a common condition among patients hospitalized in ICUs. A large multicenter 1-day point prevalence study conducted in 2016 over 117 ICUs located in seven countries estimated the prevalence of patients with P/F (PaO$_2$/FiO$_2$ ratio) <300 mmHg at 54%, including 9% with severe hypoxemia (defined as P/F < 100 mmHg). Pneumonia was the leading cause,

encountered in more than a half of all hypoxemic patients.[1]

HRF, whether or not related to acute respiratory distress syndrome, is burdened with significant short-term mortality, ranging up to 46.5% at 60 days in the event of P/F < 100 mmHg.[2]

In the long term, patients who survived an episode of HRF have an increased risk of mortality at 2 years compared to a group of similar patients, but who did not develop hypoxemia.[3]

Furthermore, hypoxemia is a predictive marker of unfavorable outcome in patients with community-acquired pneumonia. Even in case of a moderate impairment, hypoxemic patients have an increased risk of ICU admission, inhospital death, as well as a greater length of hospital stay.[4,5]

As mentioned before, our patient developed a rapidly progressive hypoxemia, after the introduction of an antihypertensive treatment. In just 2 h, his P/F went from 215 mmHg to 67 mmHg (Table 1). We rapidly reviewed and eliminated common potential causes for acute isolated hypoxemia (Table 2).

Without any alternative explanation, adverse drug reaction on nicardipine was suspected, thus the continuous infusion of the calcium antagonist was suspended and 2000 mg of calcium gluconate was administered. A rapid improvement in gaz exchange was noticed shortly after nicardipine discontinuation (Figure 3).

Afterward, the probability of nicardipine implication in acute hypoxemia experienced by our patient was assessed using the Naranjo scale (i.e., the adverse drug reaction probability scale Table 3).[6] Considering the chronology of events, the absence of plausible alternative explanations and the previous clinical reports, the reaction described in our clinical case reached a score of 6 out of 13, which is considered a probable drug reaction.

TABLE 2 A summary of differential diagnosis regarding our patient's sudden onset of hypoxemia.

Differential diagnosis	Elements excluding this diagnosis
Selective displacement of the endotracheal tube	Stable plateau pressure
	Symmetric auscultation
	Chest x-ray
Pneumothorax	Stable plateau pressure
	Symmetric auscultation
	Chest x-ray
Mucous plug	Fibroscopy
Pulmonary embolism	Thorax angiography
Pulmonary edema	Hemodynamic stability
	Chest x-ray

2.1 | Hypoxic pulmonary vasoconstriction

It is not surprising to see that HRF is predictive of poor outcome in intensive care settings as it reflects the severity of lungs parenchyma injury and the extent of ventilation and perfusion ratio (V/Q) mismatch. An increase in non-ventilated areas is responsible for a vascular shunt from the right to the systemic circulation, responsible for a drop in the V/Q ratio.[7,8] HPV is a physiological mechanism that limits the imbalance of the V/Q ratio by promoting perfusion of ventilated areas of the lungs.

The main stimulus causing pulmonary vasoconstriction is the decrease in PO_2 (partial pressure of oxygen) within the alveolar septa, itself determined by alveolar PO_2 as well as pulmonary arterial PO_2. In a normal situation, alveolar PO_2 largely prevails over the arterial component. However, in non-ventilated areas, tissue PO_2 approaches the value of mixed venous blood within the pulmonary arteries.[9]

The main effector site of pulmonary vasoconstriction is the network of resistive arterioles located just upstream of the alveolar capillary bed. Subjected to hypoxia, pulmonary arteriole smooth muscular cells (PAMCs) contract and redirect the mixed venous blood flow to better ventilated areas of the lungs. The response of PAMCs to hypoxia is almost immediate, and does not require any mediator, as evidenced by studies on denervated lungs and even on deepithelialized preparations.[10–12]

The hypoxic threshold responsible for the increase in pulmonary vascular tone depends greatly on the species and the experimental protocol used for the study. Nevertheless, depending on the pattern of the pulmonary vascular response, we can distinguish a pulmonary reaction on a moderate or a severe hypoxia.

In the event of moderate hypoxia (i.e., with a tissue PO_2 approximately between 30 mmHg and 50 mmHg), the curve of pulmonary vascular resistance as a function of time has a biphasic appearance. During the first minutes, there is a rapid increase in vascular tone, reaching a plateau after 15–45 min. It is then followed by a more progressive increase in vascular resistance, reaching a maximum only 2 h after hypoxia exposure.

For lower tissue PO_2 values (<30 mmHg), an initial peak is preceded by a paradoxical drop in pulmonary vascular resistance. The PAMC tone reaches its maximum value after 30–180 min.[13]

2.2 | Cellular response to hypoxia

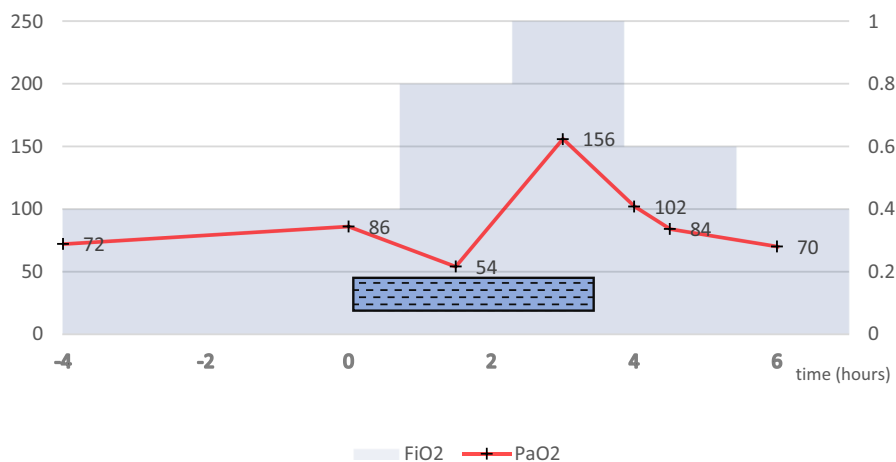The coupling between hypoxic stimulation and PAMC contraction is dependent on the intracellular $[Ca^{2+}]$

FIGURE 3 Evolution of the patient's PaO$_2$ (expressed in mmHg) as well as FiO$_2$, before and after nicardipine infusion. Zero on the horizontal axis corresponds to the start of the drug infusion. The dashed box represents the duration of nicardipine intake (i.e. 3.5 h). 2 h into the nicardipine infusion, the patient's PaO$_2$ dropped as low as 54 mmHg despite FiO$_2$ increasing up to 80 %. Only four hours later, after stopping the drug administration, FiO$_2$ could be lowered back to 60 %.

TABLE 3 The probability of nicardipine implication in acute hypoxemia experienced by our patient was assessed using the Adverse Drug Reaction probability scale. (Naranjo & al, *Clin pharmacol & therapeutics,* 1981).

ADR probability scale [6]	Yes	No	Unknown
Are there previous conclusive reports on this reaction?	1	0	0
Did the adverse event appear after the suspected drug was administered?	2	-1	0
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	1	0	0
Did the adverse reaction reappear when the drug was readministered ?	2	-1	0
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	2	0
Did the reaction reappear when a placebo was given?	-1	1	0
Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	1	0	0
was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	1	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	1	0	0
Was the adverse event confirmed by any objective evidence ?	1	0	0

(calcium concentration) increase. As a reminder, the increase in intracellular [Ca^{2+}] activates myosin light-chain kinase which is an enzyme responsible for the phosphorylation of myosin's light chain, thus allowing for its interaction with actin. The resulting actin–myosin coupling macroscopically translates into a contraction of the smooth muscle cell.[14]

The intracellular [Ca^{2+}] increase required by HPV depends as much on the mobilization of extracellular calcium as on the intracellular stock retained by the sarcoplasmic reticulum. These two mechanisms are intimately interdependent and complementary.

The entry of extracellular calcium into the cytosol is mainly ensured by the voltage-dependent calcium

channels (VDCCs). The depolarization required to open these channels is induced by an initial inhibition of potassium currents that ensure the membrane resting potential.

A series of voltage-dependent potassium channels sensitive to hypoxemia have been identified. Although the exact physiological mechanisms leading to channel closure are still poorly understood, they likely involve changes in the cellular oxidation state, via the production of reactive oxygen species (ROS).[15,16]

Extracellular calcium is essential for HPV. Not only as the main source of calcium influx into the cytosol, but also as a modulator of the cellular response to hypoxia via calcium sensing receptor (CaSR), which is a membrane receptor that responds to the variation in extracellular $[Ca^{2+}]$.

The CaSR is a G-protein-coupled receptor, ubiquitously expressed within the endothelial and smooth muscle cell membranes. Its activation enhances diacylglycerol (DAG) and inositol-3-phosphate (IP3) production. Those bind to intracellular receptors which allows the calcium influx from the extracellular medium, as well as the mobilization of the intracellular stock.

The cellular sensitivity to extracellular $[Ca^{2+}]$ is further enhanced when exposed to hypoxia. The mitochondrial ROS increase modulates the response of CaSR, resulting in an increase in the intracellular $[Ca^{2+}]$ and consequently in an increase in the smooth muscle cell tone.

The cellular pathway resulting from CaSR activation is far from negligible for HPV. In animal preparations, CaSR knockdown subjects see their PAMC response to hypoxia greatly diminished. In addition, this receptor appears to be strongly involved in the development and progression of hypertensive pulmonary artery diseases.[17,18]

Another family of ionic channels plays a significant role in HPV. These channels are nonspecific cation channels, of which the transient receptor potential channel 6 variant (TRPC6) is widely expressed in the PAMC membrane. This is a large family of nonspecific channels permeable to potassium, sodium, calcium, and magnesium. TRPC6 plays an essential role in the immediate phase of the vascular response to hypoxia. The acute phase of HPV (<20 min) seems nearly abolished in mice knocked down for TRPC6, without this having a significant impact on the late phase (60–160 min).

The TRPC6 is part of a subgroup of channels coupled to a receptor. Its opening is mediated by intracellular messengers, in particular DAG, causing an influx of calcium and, to a lesser degree, sodium. This results in an increase in intracellular $[Ca^{2+}]$, as well as in the membrane depolarization which, combined with the inhibition of potassium currents, allows for further VDCC recruitment.[19,20]

2.3 | Nicardipine pharmacology

Nicardipine is a dihydropyridine (DHP) class calcium channel blocker, with high specificity for L-type calcium channels (LTCCs). LTCCs are a super-family of VDCCs composed of a transmembrane domain sensitive to membrane potential variations (α1 subunit) and modulating subunits.

The α1 subunit is a heterotetramer composed of four pores, each one containing six transmembrane segments (S1–S6). There are no less than 10 variants of this ion channel, defining its electrochemical and pharmacological properties. The Cav 1.2 isoform is the primary target of DHP. It is found within vascular smooth muscle cells and cardiomyocytes.[21]

DHPs act preferentially on vascular smooth muscle cells, with minor effect on cardiomyocytes. This tropism is partly explained by the electrophysiological properties of the tissues.

In fact, the affinity of DHP for the ion channel is dependent on its activation state. After opening, the canal goes through an inactive state (i.e., unavailable for subsequent opening), before returning to its resting conformation. DHPs preferentially bind to the receptor while in an inactive state and reversibly block it in this conformation. The high resting membrane potential as well as the prolonged cycle of depolarization found in vascular tissue promote this inactive state which increases its affinity for DHP. In addition, vascular and cardiac calcium channels are Cav 1.2 isoforms derived from a single gene but produced by alternative splicing, which also explains the difference in affinity related to DHP.[22–24]

Nicardipine is commonly used in an acute medical settings in situations which require rapid control of arterial blood pressure such as:[25,26]

1. severe arterial hypertension, with or without organ damage;
2. per- and post-operative hemodynamic control;
3. hemodynamic control in neurovascular patients.

This molecule is highly lipophilic and is largely bound to plasma proteins. It is available as an injectable solution and is commonly used for rapid control of high arterial blood pressure. Although the intestinal absorption is excellent, this molecule undergoes an extensive first pass metabolism in the liver, which severely limits its oral administration.[27]

This DHP is well tolerated, the main side effects being linked to its vasodilator properties (e.g., arterial hypotension, tachycardia, and headaches). Its hypotensive effect correlates well with the plasma concentration of the drug.

In addition to its safe therapeutic profile, nicardipine benefits from a relatively fast onset of action. In a group

of patients with moderate chronic arterial hypertension, the drop in arterial pressure is observed only 20 min after the continuous infusion of nicardipine at a rate of 4 mg/h. However, the maximum effect is only reached after 12 h of administration.[28]

As mentioned before, the elimination is largely hepatic. Nicardipine is metabolized by cytochromes P450 (isoforms 2C8, 2D6, and 3A4). When suspending continuous administration, plasma concentration drops rapidly following a tricompartmental model. A rapid redistribution (half-life of 1–2 min) is followed by a slower distribution phase (half-life of the order of 1 h). Elimination is much slower (half-life of 14.4 h).[25]

2.4 | Nicardipine-induced inhibition of HPV

Hypoxemia secondary to HPV release is an underrated but well-documented side effect of calcium channel blockers, as evidenced by various clinical reports,[29–33] one of which concerning a patient suffering from an acute infectious pneumonia.[33]

In all of these cases, hypoxemia occurred rapidly after the start of calcium channel antagonist infusion: a few hours after the beginning of nicardipine and clevidipine infusion,[29,30] but it took less than 30 min following nimodipine administration.[31,32] Each time, the hypoxemia was transitory and resolved soon after the drug discontinuation.

Inhibition of VDCCs by calcium channel blockers attenuates, at least in part, HPV. Work on isolated rat muscle cells conducted by Robertson et al. showed that calcium antagonists decrease the amplitude of the initial response, although, without disturbing the late contraction phase.[34] Other studies showed similar results, suggesting the involvement of other cellular pathways responsible for an increase in intracellular $[Ca^{2+}]$, in particular via the mobilization of the intracellular stock of the sarcoplasmic reticulum, but also by the activation of nonspecific cation channels.[34–36]

In our report, the diagnosis of lobar infectious pneumonia was retained considering the right lower lobe condensation and a significant inflammatory syndrome shown by blood sample analysis.

As mentioned before, infectious pneumonia causes hypoxemia by generating pulmonary V/Q mismatch. The latter is due to a combination of intrapulmonary shunt and persistent mixed venous blood perfusion to regions with low V/Q ratio. To a lesser degree, but impressive nonetheless, PaO_2 in blood leaving damaged lungs areas could be even lower than mixed venous blood due to an increased metabolic activity of inflammatory cells in those regions.[7,35,37,38]

As shown by in vivo animals and human studies, pulmonary vascular response to hypoxia is severely impaired in case of acute infectious pneumonia. As a result, HPV is not able to prevent venous admixture from regions with a low V/Q ratio. Considering these data, it seems unlikely that our patient's respiratory distress was only caused by an HPV release as this latter should already be severely impaired by infectious activity.[39,40]

Nonetheless, there is evidence suggesting a certain degree of HPV preservation in acute pneumonia. An animal study showed a notable increase in pulmonary vasoconstriction in pneumonia-affected lungs that was greatly reversible during 100% FiO_2 breathing. Later, a human study by Gea et al. showed a significant increase in pulmonary blood flow distribution in patients with pneumonia after breathing 100% FiO_2.[7,8]

Therefore, it is possible that HPV is still present to some extent in diseased lungs. Consequently, nicardipine could be responsible for an increase in venous blood admixture leading to a significant drop in PaO_2.

Furthermore, the diagnosis of infectious lobar pneumonia (despite being the most probable one) could be challenged. As a reminder, our patient presented severe cognitive impairment, profound hypoxmia and hypothermia associated with acute kidney failure, mixed acidosis, and hyperlactatemia. He clearly met the criteria for systemic inflammatory response syndrome, although none of these signs is specific to an infectious process. In fact, his poor clinical condition could be entirely explained by narcotics intoxication with bronchial inhalation, prolonged immobilization, and hypovolemia. In this scenario, there is no infectious process interfering with HPV; therefore, the acute onset of hypoxemia could be caused by the HPV inhibition secondary to calcium antagonist infusion.[41]

In our case, the diagnosis of severe sepsis caused by lobar bacterial pneumonia was retained as a delayed treatment of an unrecognized sepsis could have had adverse consequences.[42] Our patient had a strongly positive sequential organ failure assessment (SOFA) score at his initial assessment, predicting a 33% mortality risk. Interestingly, q-SOFA (Table 4) score failed to identify our patient as being at risk of poor outcome.[43]

2.5 | Other molecules responsible for HPV inhibition

Other molecules with vasodilatory properties have the potential to interfere with HPV. Those are essentially molecules that interfere with the cyclic guanosine monophosphate (cGMP) cellular pathway, that is, nitric oxide (NO) donors (nitroglycerine [NTG], isosorbide

TABLE 4 According to the last consensus definition on sepsis and septic-shock (SEPSIS-3), among patients with suspected infection, SOFA (Sequential Organ Failure Assessment) score could be used to help identify those at risk for poor outcome. Also, a simplified version, termed quick SOFA (qSOFA), could be used as alternative with the same predictive validity as the full SOFA in emergency department setting[43].

SIRS		
Temperature	34,2°C	1
Heart rate	101 bpm	1
Respiratory rate	8	0
White blood cell count	15 570/μL	1
q-SOFA		
Glasgow Coma Scale	Y2V2M4	1
Mean arterial pressure	83 mmHg	0
Respiratory rate	8/min	0
SOFA		
PaO_2/FiO_2	205 mmHg no mechanical ventilation	2
Platelets count	173 000/μL	0
Glasgow Coma Scale	Y2V2M4	3
Bilirubin level	0.62 mg/dl	0
Mean arterial pressure/ vasoactive agents	83 mmHg no vasoactive agents	0
Serum creatinine/urinary output	7.20 mg/dL urinary output <200 mL/day	4

Note: According to the last consensus definition on sepsis and septic-shock (SEPSIS-3), among patients with suspected infection, SOFA score could be used to help identify those at risk of poor outcome. Also, a simplified version, termed q-SOFA, could be used as alternative with the same predictive validity as the full SOFA in emergency department setting.[43]
Abbreviations: SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment; q-SOFA, quick SOFA.

dinitrate [IDN] and sodium nitroprusside [SNP]) or phosphodiesterase inhibitors (sildenafil).

NO donors are commonly used vasoactive drugs producing NO. NTG and IDN undergo enzymatic bioactivation while SNP interacts with oxyhemoglobin to form NO as well as cyanide and methemoglobin.[44,45]

NO is a highly lipophilic molecule that easily crosses the cellular membrane and activates the soluble guanylate cyclase which converts guanosine triphosphate in cGMP. The latter is a cellular messenger that mediates vasodilatation via several mechanisms. First, via activation of PKG (cGMP-mediated protein kinase) which reduce myofilament calcium sensitivity. Second, via cellular membrane hyperpolarization, and lastly via inhibition of IP3-dependent calcium influx.[46]

The system downregulation is ensured via cGMP degradation by a phosphodiesterase. Sildenafil is a specific inhibitor of PDE5, a phosphodiesterase isoform responsible for cGMP metabolism in PAMCs.[47]

Among those molecules, sodium nitroprusside and nitroglycerine are frequently cited as responsible for HPV inhibition. Their impact on regional perfusion of the lung was largely investigated by animal[48–50] and human studies.[51–53] However, their effect on the ventilation-perfusion mismatch seems to be limited at clinical relevant doses.

Among commonly used antihypertensive agents, urapidil seems to best preserve HPV.[32] This molecule exerts its antihypertensive properties by blocking alpha-1 adrenergic receptors, thus decreasing systemic arterial resistance. To a lesser degree, it has a partial agonist effect on $5-HT_{1A}$ (serotonin 1A receptors).[54–56]

As mentioned above, although alpha-1 receptors are expressed on PAMCs, the coupling between the hypoxic stimulation and PAMC contraction is independent of adrenergic stimulation. Therefore, urapidil decreases systemic and pulmonary vascular tone, without interfering with pulmonary response to hypoxia.[54–56]

2.6 | Use of calcium gluconate as a nicardipine antagonist

Presuming that an increase in serum calcium concentration will antagonize the pulmonary vasodilatation induced by nicardipine, 2000 mg of calcium gluconate was administered.

Calcium salts are one of the few therapeutic options available in case of calcium antagonist poisoning. Despite poor evidence supporting its use (mainly based on animal studies and human case series), several studies reported that calcium administration is associated with significant hemodynamic improvement.[57,58]

However, the dose used is highly variable (ranging from 1 g of calcium gluconate to 7 g of calcium chloride) and the effect remains inconsistent. Furthermore, in the case described above, the dose of nicardipine was within therapeutic range and its use was not accompanied by hemodynamic impairment. And finally, there are no data supporting the use of calcium salts to reverse hypoxemia induced by DHP administration.

Moreover, an animal study realized by Drop et al. showed that pulmonary vasomotor tonus remains stable for a very wide range of plasmatic $[Ca^{2+}]$.[59] Indeed, increasing $[Ca^{2+}]$ as high as 1.9 mM did not seem to have any impact on pulmonary arterial pressure, and it took a major decrease in $[Ca^{2+}]$, well below clinically encountered levels to see any significant drop in vascular resistance caused by HPV.[59]

Nevertheless, calcium gluconate injection might be of some interest even in that case. A brief increase in extracellular $[Ca^{2+}]$ will increase its transmembrane gradient, thus facilitating its passage through the few

calcium channels still available. Moreover, as discussed earlier, extracellular $[Ca^{2+}]$ is also a CaSR agonist, whose sensitivity is increased in the case of tissular hypoxia. Activation of this receptor leads to an intracellular $[Ca^{2+}]$ increase via pathways independent from VDCCs.

3 | CONCLUSION

The pharmacologic inhibition of HPV is a well-known, but still uncommon cause of HRF in ICUs. Calcium channel antagonists, including nicardipine, are often incriminated. But this adverse effect could potentially occur with any molecule having vasodilating properties.

It should be emphasized that the management of a hypertensive critical patient starts by identifying the underlying cause of increased arterial blood pressure, such as increased vascular tone, fluid overload, but also pain, stress, and withdrawal.[60] In this way, it is often possible to avoid unnecessary vasodilator treatment with potentially detrimental respiratory effects. Nevertheless, if vasodilators must be used on a patient with pulmonary disease, urapidil seems to best preserve HPV.

Pharmacologic inhibition of HPV should be considered as part of the differential diagnosis when confronted with an unexpected occurrence of rapidly progressive hypoxemia. Practitioners should be aware of this adverse effect, as it is an easily reversible cause of hypoxemic respiratory failure, thus avoiding unnecessary costly and time-consuming assessments.

AUTHOR CONTRIBUTIONS
Timour Gizzatullin: Writing – original draft; writing – review and editing. **Frédéric Vallot:** Supervision; validation. **Olivier Simonet:** Validation. **Didier Ndjekembo Shango:** Conceptualization; investigation; validation.

CONFLICT OF INTEREST STATEMENT
All authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT
None

CONSENT STATEMENT
Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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