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Management of Anaphylactic and Anaphylactoid Reactions During Anesthesia

Béatrice Eon,* Laurent Papazian, and F. Gouin

Department of Anesthesia, Pr Gouin, Sainte-Marguerite Hospital, BP 29, 13274 Marseille, cedex 09, France

Introduction

In most cases, allergic reactions (A.R.) during anesthesia have a very sudden onset and are completely unexpected. Outcome can be catastrophic (death or permanent cerebral damage). Dramatic cardiovascular changes and acute bronchospasm are the principal life-threatening complications of anaphylactoid reactions. The relation of these events with anaphylaxis is not always obvious and can lead, in some cases, to delay in accurate treatment. Anesthetists and personnel at all levels in the operating room must be prepared for such events.

Anesthesia departments should have written plans for the treatment of A. R. checklists, and protocols such as those presented here are of the utmost importance for making resuscitation of A.R. a success.

Hemodynamic Disorders During Anaphylactic and Anaphylactoid Reactions

Sudden onset, the need for immediate treatment, and rapid evolution are reasons for the lack of objective hemodynamic data

*Author to whom all correspondence and reprint requests should be addressed.

during AR. There have only been a few observations reported in the literature (*1–8*). Hemodynamic variations are correlated to plasma histamine levels and to levels of endogenous catecholamines (*2,9*).

Arterial hypotension is an almost constant manifestation associated with tachycardia. Hypotension is caused by the direct effect of the peripheral vasodilation of histamine. There are two reasons for the tachycardia: stimulation of cardiac H_2 receptors by the histamine and reactive secretion of endogenous cathecholamines that is secondary to the release of histamine (*5*). This acceleration of cardiac frequency caused by sympathoadrenergic release can be considered relatively beneficial. However, an initial bradycardia can be observed (*10,11*). This could be caused by vagal hypertonia. The severity of AR in patients on β-adrenergic antagonists (*12–16*) should be stressed, since the chronotropic response is absent in such patients. In this case, the response to classic treatment is mediocre. An epinephrine-resistant bradycardia can be observed as if the β receptors were refracted to adrenergic substances. Blockade of β receptors strengthens anaphylaxis by reducing the intracellular level of cyclic AMP, which is secondary to the inhibition of adenylate cyclase. The mediator-liberation threshold is then lowered. Cardiovascular and pulmonary responses to β-agonist treatment are decreased. Such resistance to treatment can lead to irreversible cardiocirculatory failure (*16*).

The initial phase of AR is characterized by hyperkinetism associating an increase in cardiac output to reduced systemic vascular resistance. Under the direct effect of histamine and the indirect effect of catecholamine liberation, the speed and force of myocardial contraction are increased. Endogenic sympathetic reactions are, however, not strong enough to correct the major vasodilation induced by the vasoactive mediators. Arterial pressure and systemic vascular resistance continue to collapse. Vasodilation is progressively generalized, and venous return is consequently dramatically decreased. This reduction in venous return subsequently causes a secondary reduction in cardiac output. The sudden reduction in left ventricular filling is associated with a reduction in contractility (*3*). At an advanced stage, transcapillar plasma loss further increases the reduction in venous return, leading to a type of shock with predominant reduction of "effective blood volume." Cardiac output and

filling pressures are low and arterial resistance increases subsequently (*17*). These hemodynamic disorders are presented in Fig. 1.

In certain cases, the severity of AR can be linked to immediately life-threatening cardiovascular manifestations, suggesting cardiac anaphylaxis (*18*). Severe rhythm problems or even immediate cardiac arrest can be observed. The latter could be the result of an antigen–antibody conflict at the myocardial level and also of the direct action of histamine on the heart. In addition, histamine can modify the threshold for ventricular fibrillation. Following in vitro studies, it should be concluded that special attention must be devoted to patients with unstable cardiac rhythm associated with a risk of histamine liberation (*9*).

Treatment of Cardiovascular Manifestations

Treatment must be undertaken immediately after diagnosis has been made, regardless of clinical manifestations. AR occurs essentially on induction (*19*). The majority of general anesthetic agents can be involved in AR: hypnotics (*20*), curares (*9, 21–24*), and narcotics (*9,25*). In a delayed manner compared to induction, the latex in surgical gloves has recently been shown to induce AR (*26–28*). Finally, AR can be induced at any moment during the preoperative period by the solutions used for fluid therapy (*29–31*). AR is also possible in locoregional anesthesia (*32,33*).

The diagnosis of AR can be evident when mucocutaneous, cardiovascular, and bronchial manifestations are combined. This is not true in the presence of isolated hemodynamic signs. Cutaneous signs are nonexistent in case of collapse. No matter what the cause of AR, treatment is unequivocal (*34*) and responds to a fixed sequence as presented in Table 1.

General Measures

The following measures are required for any level of severity:

- Stopping the anesthesia and the administration of any other agents could limit the amplitude of AR. It is mandatory to stop all surgical stimulus.
- Establish a large venous route in order to ensure rapid fluid expan-

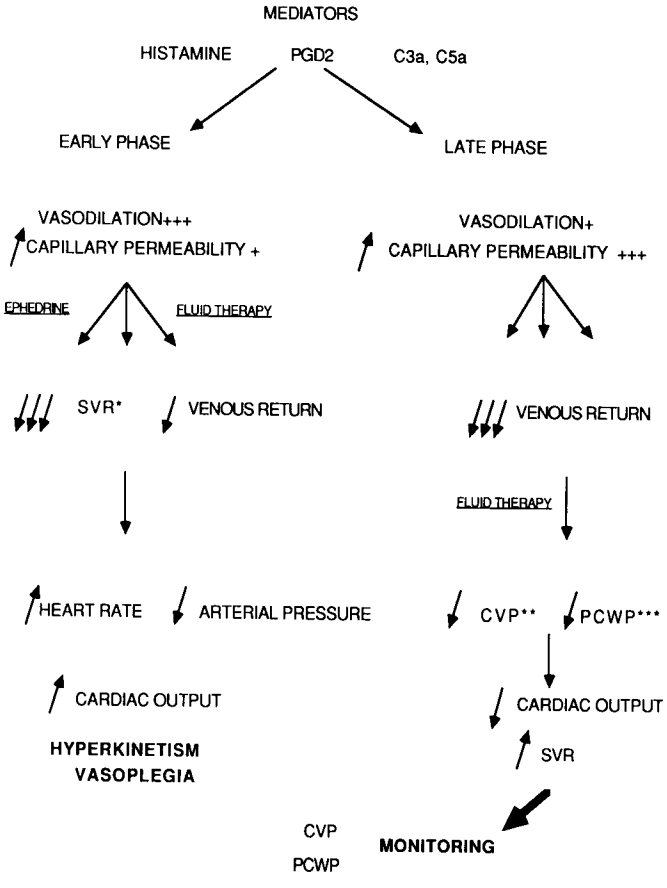

Fig. 1. Pathophysiology of cardiovascular changes.* Systemic vascular resistance, **Central venous pressure; ***Pulmonary capillary wedge pressure.

Table 1
Initial Management of AR

- Stop anesthesia except if bronchospasm
- Stop any drug administration that could be responsible
- Elevation of lower limbs
- Call for help
- 100% oxygen: Endotracheal tube if none, in case of severe airway obstruction.
- Epinephrine IV, IM, SC, intratracheal (depends on severity and possible administration route)
- Venous access: femoral introducer
- Fluid therapy: 1–2 L crystalloids
- Monitoring

sion. In such cases of extreme emergency, femoral vein catheterization with a plastic introducer can be performed in a few seconds.

- Administer oxygen at FiO_2 1 in order to correct the hypoxia resulting from shock rapidly. In a nonintubated patient with respiratory signs, intubation can be immediately required. This enables the physician to deal with the problem linked to the edema in the upper airways.
- Hypotension can be partially corrected by elevation of the lower limbs in order to increase venous return. However, excessive elevation will increase the pressure exerted by the abdominal viscera on the diaphragm. Thus, the increase in intrathoracic pressure reduces the pressure gradient between the right auricle and the inferior vena cava, limiting the beneficial effects of the increase in venous return. In addition, this posture can increase pulmonary resistance with an increase in insufflation pressures, which is not desirable in case of associated bronchospasm (*35,36*).
- Transfer of the patient to the ICU is mandatory for at least 48 h because of the possibility of recurrence of anaphylactic reaction (*34,37*).

Installation of a complete monitoring system is necessary in order to check the efficacy of treatment (*38*) (Table 2):

- Monitoring of the electrocardiogram: Choosing a Cb5 lead allows for simultaneous detection of arrythmias and of possible anterolateral myocardial ischemia. The negative electrode is positioned on the back of the right shoulder, and the positive electrode in position V5 (*39*).
- Arterial pressure is continuously monitored by automatic sphygmomanometer. Since this device can fail in case of a major fall in arterial pressure, radial-artery catheterization should be used often. In addition, arterial catheterization permits sampling of blood gases.
- SaO_2 monitoring by pulse oximeter can be useful for the qualitative observation of the pulse wave indicating the existence and rythm of systoles. SaO_2 value can, however, be underestimated, or the signal can be lost in cases of severe shock (*40,41*).
- When a capnograph is available in the operating room, a major reduction in $FECO_2$ could indicate low cardiac output. No $FECO_2$ is observed in cases of circulatory arrest, and observation of the capnogram can help in assessing the efficacy of cardiac massage (*42,43*).

Table 2
Monitoring During Anaphylaxis

Electrocardiogram: Cb5
Blood Pressure: Automated pressure cuff
Invasive (radial artery)
PaO_2: Pulse oxymetry
Blood gases
PaCO: Blood gases
End tidal CO_2: capnometry
Heart filling pressures:
Central venous pressure
Pulmonary capillary wedge pressure
Hourly diuresis
Temperature

Drug Treatment for Cardiovascular Manifestations

The two most important therapeutic interventions are sympathomimetic drugs and fluid therapy (*44*).

Sympathomimetic Drugs

Epinephrine should be administered immediately. Its alpha effects correct the arterial and venous vasodilation, restore systemic arterial pressure, and reduce capillar permeability. Its beta-1 effects reinforce cardiac inotropism and improve cardiac output. By its direct beta-2 effects on the bronchial smooth muscle, epinephrine has an immediate bronchodilator effect (*45*). In addition, by stimulating the synthesis of cyclic AMP, it can slow down the degranulation of the mast cells (*46*).

Epinephrine must be administered without delay. Rate and routes of administration depend on the severity of the signs. Subcutaneous and intramuscular administration can only be performed for minor manifestations resulting from the poor resorption of the drug in cases of shock. In other cases, iv routes should be used: epinephrine is diluted and administered by bolus using a titration technique (*47*). This technique consists in diluting 1 mg of epinephrine in 10 mL of saline solution and injecting 0.1–0.2 mg with reinjection every 5–20 min or less, depending on the effects obtained (*37*). In

the absence of complete resolution, continuous administration of epinephrine can be carried out by electric syringe.

In intubated patients without a venous catheter, an alternative is intratracheal administration, since the epinephrine is rapidly absorbed by the tracheobronchial mucosa. In addition, epinephrine is the drug of choice in cases of cardiocirculatory arrest (*48*).

It should be noted that greater than usual doses are required for AR occurring during epidural anesthesia, where a sympathetic block exists (*34*). The indication for norepinephrine would appear to be limited to refractory hypotension. Alphamimetics are responsible for an increase in mediator liberation, which should limit their use (*31*). Ephedrine and metaraminol have been used to treat a fall in blood pressure. Their effects are indirect by liberation of norepinephrine endogen reserves, which explains their limited efficacy (*46*).

In cases of AR in patients previously treated with β-adrenergic antagonists, we have stressed the inefficacy of classic treatment. In this case, a strong dose of dopamine is recommended (10–30 μg/kg/min) (14,15,49) alone or in combination with isoproterenol (0.1–0.5 μg/kg/min) (*49*). Glucagon can also be efficient (1–5 mg bolus) (*16*). The properties and doses of the principal drugs used are presented in Tables 3 and 4.

Fluid Therapy

Great volumes of fluid are often required: 1000–2000 mL can rapidly be necessary, depending on arterial pressure, at a rate of 5–10 mL/kg in the first 5 min. The quantities used in cases of AR in β-blocked patients can go up to 5–7 L before hemodynamic stability is obtained (*14,15*).

In the first few minutes, fluid resuscitation can be guided by clinical improvement. When rapid resolution of shock is not obtained, guidelines for fluid resuscitation are of primary importance to avoid pulmonary edema. The first guideline should be monitoring of central venous pressure (CVP). The end point for CVP is between 10–14 cm H_2O. Depending on the patient's cardiac condition, a Swan-Ganz catheter can be used in order to obtain pulmonary capillary wedge pressure (PCWP). An optimum PCWP of 12 mmHg is the objective of fluid resuscitation (*50*). At the same time, the Swan-Ganz catheter makes it possible to monitor cardiac output and calculate sys-

Table 3
Effects of Sympathomimetic Amines
on Adrenergic Receptors in Cardiovascular System

	Alpha 1	Beta 1	Beta 2-vessels
Epinephrine			
0.04–0.2 μg/kg/min	++	+++	
0.2–0.4 μg/kg/min	+++++	++++	0
Dopamine			
>10 μg/kg/min	++++	++	+
Norepinephrine			
0.5–1μg/kg/min	++++	+++	0
>1 μg/kg/min	+++++	+++	0
Isoproterenol	0	++++	++++
Ephedrine	+++	++	+

Table 4
Doses for Sympathomimetic Drugs

Epinephrine
Minor manifestations (urticaria, pruritus)
0.3–0.5 mg (1/1000 solution) subcutaneous or intramuscular
0.25 mg x 4 subcutaneous as relay of successful iv therapy
Severe reaction (cardiovascular manifestations)
0.1–1 mg every 3 min intravenously
Titration technique with a 1/10000 solution
1–4 mg intratracheal
0.1–0.5 μg/kg/min (constant infusion rate)
Dopamine
10–30 μg/kg/min
Norepinephrine
3 μg/min initially then titration technique until PA > 60 mmHg
0.1–0.5 μg/kg/min
Isoproterenol
0.1–0.5 μg/kg/min

temic vascular resistance. Their values will guide therapeutic choice between α-mimetic or both α- and β-mimetic drugs.

From a qualitative point of view and taking into account AR risks linked to gelatine, dextrans, and hydroxyethylamidon, the choice of fluids is limited to crystalloids. Albumin, which carries only

a very small risk of AR, can be an alternative, but not in the initial phase. The advantage of hypertonic crystalloid solutions has yet to be evaluated in this context.

Adjuvant Drug

Histamine Antagonists. They play a very limited role because by the time AR is manifest, the histamine receptors are already saturated with histamine. They can only offer protection if they reach the receptors before the histamine. In addition, it is possible for a new afflux of histamine to displace them from the receptors. They can be systematically prescribed (*34*) or only when mucocutaneous signs persist after hemodynamic disturbances have been corrected.

The role of H_2 blockers is now controversial in that certain H_2 receptors have a negative retrocontrol influence on the liberation of histamine (*51,52*). The principal drugs used are H_1-blocker Diphenhydramine (1 mg/kg) and H_2-blocker Ranitidine (1 mg/kg).

Steroids. Having no effect on hemodynamic disorders, they could limit the liberation of potentially proinflammatory mediators. Given their delayed action, they are of minor interest. They are systematically given in cases of bronchospasm. They decrease edematous manifestations and reinforce the actions of sympathomimetics. The drugs and doses are presented in Table 5. Complete management of AR is presented in Tables 1 and 6.

BRONCHOSPASM

Bronchospasm under anesthesia can rapidly be life-threatening. This dangerous manifestation of an anaphylactic or anaphylactoid reaction can be associated with cardiovascular and mucocutaneous manifestations, or it can be isolated. It occurs less frequently than cardiovascular signs (*53*). The mediators liberated during AR have a tropism for the respiratory tract, which is marked by bronchoconstriction, pulmonary vasoconstriction, and an increase in bronchial secretion. The mediators involved are hist-amine by its action on H_1 receptors and "irritant" receptors (*51*), F_2 α and D_2 prostaglandines (*54,55*), and C_4, D_4, and E_4 leucotrienes (*56, 57*). The physiopathology of bronchospasm is presented in Fig. 2. From a

Table 5
Doses of Steroids

Hydrocortisone	
Hydrocortisone®	4–6 mg/kg every 4–6 h
Methylprednisolone	
Solumedrol®	1–2 mg/kg every 6 h
Hemisuccinate	
of Hydrocortisone (HSHC)	100 mg every 2–4 h or 1–2 g/24 h
Dexamethasone (DMS)	
Soludecadron®	0.75 mg DMS = 25 mg HSHC 3 mg every 2–4 h

Table 6
Secondary Management in Case of Persistent Shock

- Intensive care unit
- Monitoring-CVP-PCWP-(SwanGanz catheter)-Arterial catheterization
- Aim of fluid therapy: CVP = 14 cmH_20
  PCWP = 12 mmHg
  SVR > 400 $dyn/s/cm^5$
- Drug choice: Epinephrine
  Dopamine
  Norepinephrine
  Glucagon (if β-blocker treatment)
- Antihistamines ?
- Corticosteroids

clinical point of view, bronchospasm under anesthesia is characterized by insufflation difficulty owing to the increase in bronchial resistance and to the reduction in thoracopulmonary compliance. This can be felt in the manual insufflation bag or results in an increase in ventilator insufflation pressure. A wheezing can be heard (*58*).

Management of Bronchospasm

This clinical manifestation justifies the maintenance or even the deepening of general anesthesia with discontinuation of harmful stimulations (*58,59*).

Ketamine as an anesthetic agent is a good indication for some authors because of its bronchodilator effects (*58,59*). Inhalation

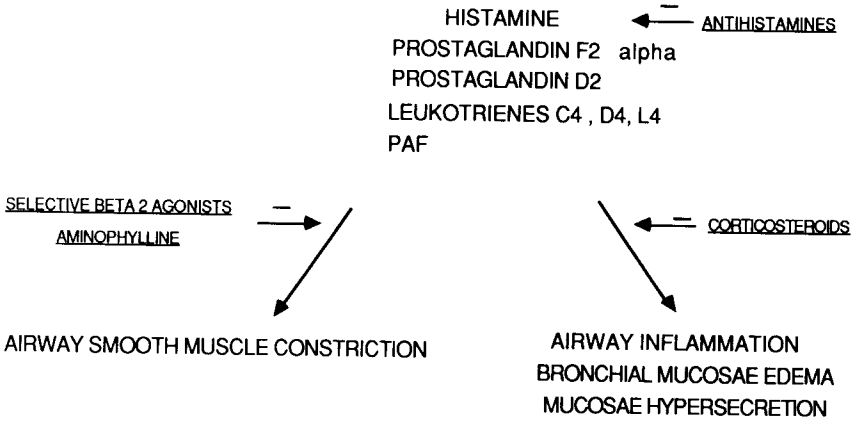

Fig. 2. Pathophysiology of bronchospasm: Sites of action of therapeutics.

anesthetics are also an alternative: halothane, ethrane, or isoflurane can be used (*60,61*). A combination of halothane and epinephrine or halothane and theophylline can have arrythmogenic effects (*62*).

In the nonintubated patient, intubation can be necessary to remove respiratory problems linked to laryngeal or supralaryngeal edema. During intubation, xylocaine with epinephrine local spray can help prevent tracheobronchial and glottic edema. When intubation is impossible, tracheotomy or a needle catheter cricothyreotomy is indicated (*63*).

In an intubated patient with clinical signs of bronchospasm, the anesthesist should go through the following checklist (*64*):

- Verification of the ventilator and anesthesia circuit.
- Verification of endotracheal tube permeability, its position, and the absence of bending. If there are any doubts, extubation, then reintubation.
- Eliminate uni- or bilateral pneumothorax.
- Check for inhalation of gastric liquid.
- Chest X-ray should be performed as soon as possible.
- Oxygen therapy ($FiO_2 = 1$) and monitoring of blood gases and/or SaO_2 are imperative.

The capnograph should not be neglected. Its curve may indicate bronchospasm by a peak aspect, and the value of $FECO_2$ is an element that should be monitored in the evolution of AR (*65*).

Drug Therapy

Epinephrine administered for associated cardiovascular signs can alone provide relief from bronchospasm. This drug is used in acute forms of asthma.

In the absence of hemodynamic problems, the treatment of choice would first appear to be β-2 mimetics. Some authors have reported that the administration of inhaled β-2 mimetics is of interest, because high concentrations reach the airways, and therefore, increase therapeutic effects and minimize side effects. It is possible to connect an aerosol to the inspiratory circuit and administer the drug. There is another possibility with the installation of a nebulizer (*66*).

If aerosol treatment fails, the iv route should be chosen, with terbutaline (0.5 mg/1 mL) or salbutamol (0.5 mg and 5 mg/5 mL). salbutamol is administered at 0.1–1 μg/kg/min.

A recent study by Tobias and Hirshman has reported the effectiveness of salbutamol associated with halothane for the treatment of histamine-induced bronchospasm in dogs (*67*). In less severe forms of bronchospasm, the subcutaneous route is possible (terbutaline 0.5 mg/1 mL, salbutamol 0.5 mg/1 mL). The use of β-2 mimetics requires electrocardiographic monitoring (*68*).

Aminophylline is frequently used for bronchospasm, especially in asthmatic patients. However, it has not been proven to be superior to β-2 mimetics (*69*). It is nevertheless recommended at a loading dose of 4–6 mg/kg administered in 20 min followed by a maintenance dose of 0.6–0.9 mg/kg/h. Afterwards, doses should be adapted to plasma levels (therapeutic levels: 10–20 μg/mL).

Direct iv injections are prohibited, and the patient should be monitored for possible arrhythmias. The interactions with halothane, cimetidine, and benzodiazepines should be known. If aminophilline is used, it is preferable to use isoflurane or ethrane for general anesthesia (*64,66*).

Successful treatment of A.R. during anesthesia requires rapid recognition and immediate management. Epinephrine, fluid therapy, maintenance of airway, and careful monitoring are the keys to success. Drug therapy (ways of administration, doses) should be titrated to severity of symptoms and desired effects.

As life-threatening events, A.R. should be prevented. This prevention raises several issues (stated in other articles in this vol-

ume) not yet fully answered. Even with clear knowledge of risk factors, A.R. will remain unpredictable in some patients. Anesthetists and personnel in the operating room should be prepared to face such rare but dramatic events adequately.

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