REVIEW ARTICLE

Drugs 2007; 67 (7): 1053-1076
0012-6667/07/0007-1053/$49.95/0

Controlled Hypotension

A Guide to Drug Choice

Christian-Serge Degoute

Service d'Anesthésie-réanimation, Centre Hospitalier-Universitaire Lyon-Sud, Pierre-Bénite, France

Contents

Abstract 1053
1. Definition and Objectives of Controlled Hypotension 1055
2. Physiological Basis of Controlled Hypotension 1055
3. Rationale for Controlled Hypotension in Blood Conservation During Surgery 1056
   3.1 Capacity to Improve the Quality of the Operative Field 1056
   3.2 Capacity to Reduce Haemorrhagic Loss and Transfusion 1056
   3.3 Limits and Complications 1057
   3.4 Other Techniques to Reduce Blood Loss 1057
   3.5 Summary 1059
4. Physical Measures and Pharmacological Agents for Controlled Hypotension 1059
   4.1 Physical Measures 1059
   4.2 Pharmacological Agents 1060
      4.2.1 Epidural and Spinal Anaesthesia 1060
      4.2.2 Inhalation Anaesthetics 1060
      4.2.3 Opioids 1062
      4.2.4 Vasodilators 1062
      4.2.5 Inhibitors of the Autonomic Nervous System 1066
      4.2.6 ACE Inhibitors 1067
5. Techniques of Controlled Hypotension According to Surgical Specialty 1068
   5.1 Ear, Nose and Throat Surgery 1068
   5.2 Paediatric Spinal Surgery 1069
   5.3 Other Surgeries 1070
6. Conclusion 1070

Abstract

For half a century, controlled hypotension has been used to reduce bleeding and the need for blood transfusions, and provide a satisfactory bloodless surgical field. It has been indicated in oromaxillofacial surgery (mandibular osteotomy, facial repair), endoscopic sinus or middle ear microsurgery, spinal surgery and other neurosurgery (aneurysm), major orthopaedic surgery (hip or knee replacement, spinal), prostatectomy, cardiovascular surgery and liver transplant surgery.

Controlled hypotension is defined as a reduction of the systolic blood pressure to 80–90mm Hg, a reduction of mean arterial pressure (MAP) to 50–65mm Hg or a 30% reduction of baseline MAP.

Pharmacological agents used for controlled hypotension include those agents that can be used successfully alone and those that are used adjunctively to limit dosage requirements and, therefore, the adverse effects of the other agents. Agents used successfully alone include inhalation anaesthetics, sodium nitroprusside, nitroglycerin, trimethaphan camsilate, alprostadil (prostaglandin E1), adenosine, remifentanil, and agents used in spinal anaesthesia. Agents that can be used alone or in combination include calcium channel antagonists (e.g. nicardipine), β-adrenoceptor antagonists (β-blockers) [e.g. propranolol, esmolol] and fenoldopam. Agents that are mainly used adjunctively include ACE inhibitors and clonidine.

New agents and techniques have been recently evaluated for their ability to induce effective hypotension without impairing the perfusion of vital organs. This development has been aided by new knowledge on the physiology of peripheral microcirculatory regulation. Apart from the adverse effects of major hypotension on the perfusion of vital organs, potent hypotensive agents have their own adverse effects depending on their concentration, which can be reduced by adjuvant treatment. Care with use limits the major risks of these agents in controlled hypotension; risks that are generally less important than those of transfusion or alternatives to transfusion.

New hypotensive drugs, such as fenoldopam, adenosine and alprostadil, are currently being evaluated; however, they have disadvantages and a high treatment cost that limits their development in this indication.

New techniques of controlled hypotension subscribe to the use of the natural hypotensive effect of the anaesthetic drug with regard to the definition of the ideal hypotensive agent. It must be easy to administer, have a short onset time, an effect that disappears quickly when administration is discontinued, a rapid elimination without toxic metabolites, negligible effects on vital organs, and a predictable and dose-dependent effect. Inhalation agents (isoflurane, sevoflurane) provide the benefit of being hypnotic and hypotensive agents at clinical concentrations, and are used alone or in combination with adjuvant agents to limit tachycardia and rebound hypertension, for example, inhibitors of the autonomic nervous system (clonidine, β-blockers) or ACE inhibitors. When they are used alone, inhalation anaesthetics require high concentrations for a significant reduction in bleeding that can lead to hepatic or renal injury.

The greatest efficacy and ease-of-use to toxicity ratio is for techniques of anaesthesia that associate analgesia and hypotension at clinical concentrations without the need for potent hypotensive agents. The first and oldest technique is epidural anaesthesia, but depending on the surgery, it is not always appropriate. The most recent satisfactory technique is a combination treatment of remifentanil with either propofol or an inhalation agent (isoflurane, desflurane or sevoflurane)

at clinical concentrations. In light of the current literature, and because of their safety and ease of use, these two techniques are preferred.

1. Definition and Objectives of Controlled Hypotension

Controlled hypotension is a technique that decreases arterial pressure until hypotension is reached to reduce blood loss and the need for transfusion during surgery, and to improve the quality of the surgical field. Controlled hypotension was first proposed by Cushing in 1917 and was developed 50 years ago.[1] The reduction of bleeding is essential in surgery of the middle ear, endoscopic sinus microsurgery, plastic and reconstructive microsurgery, ophthalmologic surgery and neurosurgery, which all have low haemorrhagic potential, to ensure a clear surgical field. Controlled hypotension is also used in various types of surgery with moderate or extreme haemorrhagic potential such as orthopaedic surgery, urologic surgery, cardiovascular surgery and hepatic transplantation in order to decrease the requirement for transfusion. However, hypotension should not adversely affect the blood supply to vital organs, and end-organ perfusion and tissue oxygenation must be maintained. Therefore, most studies define the objective of controlled hypotension as a fall in systolic blood pressure (SBP) to 80–90mm Hg, or mean arterial pressure (MAP) to 50–65mm Hg in patients without hypertension, or a fall of 30% of MAP in patients with hypertension.[2]

This review describes the physical and physiological considerations and constraints of controlled hypotension, the different agents that have been considered for controlled hypotension, developments in the techniques of controlled hypotension, including new pharmacological agents of the past 10 years, in a current context of increased anaesthetic and transfusional safety in different surgical procedures. A literature search of English language articles over the past 10 years was conducted (MEDLINE via PubMed). The original pharmacological articles were selected from levels I or II of the Sackett's classification. Only studies using the definition of controlled hypotension of a target MAP of 50–65mm Hg or SBP of 80–90mm Hg were considered for inclusion. The advantages and disadvantages of different techniques of controlled hypotension are analysed. The endpoints include blood loss issues, the quality of the surgical field, blood transfusion requirements, and the adverse effects and toxicities of the agents used. Finally, a discussion of the preferences of controlled hypotension techniques used at the author's institution is included.

2. Physiological Basis of Controlled Hypotension

An adequate level of hypotension for the reduction of bleeding is difficult to obtain for simple and more complex physiological and physical reasons. Given the definition that bleeding is a quantity of blood that appears in the operative field in a given time, it can be expressed in flow D (volume/unit of time) and is mathematically related to the pressure by the relationship D = P/R, where P is pressure and R represents vascular resistance. If the pressure P decreases, and the resistance R remains constant or increases (vasoconstriction), the flow D decreases. On the other hand, if the pressure P decreases, as well as the resistance R (vasodilatation), the flow D remains constant or varies little. Therefore, the result of hypotension in terms of bleeding depends on vascular resistance R. The difficulty in controlling the bleeding flow D by hypotension is because the target pressure aimed for is measured at the level of the large vessels, and this is different from the pressure at the level of tissue circulation in the operated zone where the bleeding occurs. The dif-

ference between these two pressures is a result of the complexity and intricacy of the mechanisms of regulation of SBP and the mechanisms of regulation of peripheral vascular resistance. Furthermore, the mechanisms of regulation of vasomotor tone are not homogeneous from one territory to another. P and R at the level of the surgical field are local pressure and local vascular resistance that depend: firstly, on the central blood pressure measured at the level of a large artery and on its regulation; secondly, on the regulation of the local arteriolar vasomotor tone by the sympathetic nervous system; and thirdly, on the microcirculatory autoregulation of the organ (when it exists) [figure 1].

In certain controlled hypotension techniques, the decrease in cardiac output is the determining factor in the reduction in blood loss; in other techniques, it is the fall in MAP that determines the levels of blood loss. The mechanisms responsible for the reduction of intraoperative bleeding depend on (i) the technique used (i.e. the effect of the agents used on the heart and the vascular network); (ii) the mechanisms of regulation that these agents antagonise; and (iii) the counter-regulatory mechanisms that they cause, which are intricate.[3,4] The mechanisms used to reduce intraoperative bleeding are reviewed for each agent in section 4.2.

3. Rationale for Controlled Hypotension in Blood Conservation During Surgery

3.1 Capacity to Improve the Quality of the Operative Field

Only a few studies advocate the advantages of controlled hypotension over other techniques in the improvement of the quality of the operative field, because of the difficulty in finding objective criteria and quantifiers apart from the visual approach to the question. The reduction in MAP from 90mm Hg to 50–65mm Hg or in SBP from 125mm Hg to 70–90mm Hg during endoscopic sinus surgery,[5] mandibular osteotomy[6] and tympanoplasty[2,7-10] provided a good operating field.

3.2 Capacity to Reduce Haemorrhagic Loss and Transfusion

The capacity of controlled hypotension to reduce blood loss was discussed during the previous half-century and the first controlled study was published by Eckenhoff and Rich[11] in 1966. This consisted of two series of 115 (controlled hypotension) and 116 (control) patients that demonstrated a significant 50% reduction in blood loss when MAP was decreased to 55–65mm Hg. Later studies continued to demonstrate the effectiveness of these levels of pressure by comparing new agents with a control series or with older agents. Controlled hypotension re-

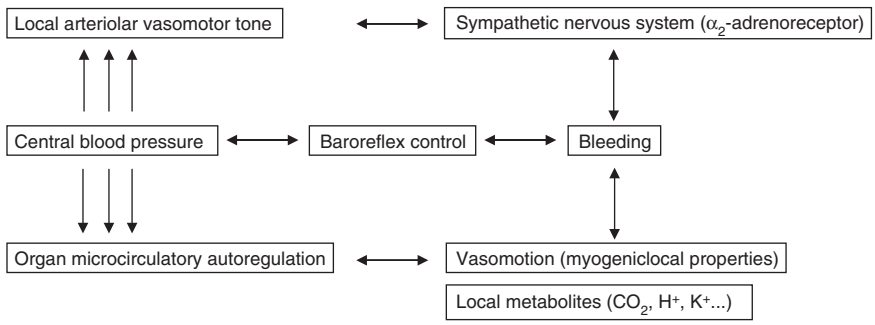

Fig. 1. Mechanisms of regulation of blood pressure and vasomotor tone responsible for the reduction of intraoperative bleeding. ↔ indicates reciprocal direction of action; ↑↑↑ and ↓↓↓ indicate predominant direction of action.

duced blood loss by half (from 304mL to 186mL) in mandibular osteotomy,[12] reduced blood loss by half (from 1297mL to 761mL) in paediatric spinal surgery,[13] and reduced blood loss from 1800mL to 1000mL in prosthetic surgery of the knee with a tourniquet.[14] It reduced blood loss from 667 to 480mL[15] and from 263 to 179mL[16] in surgery of the hip and reduced transfusion from 2.7 to 1.3 units of blood cells[17] and blood loss from 1000 to 600mL[18] in total hip replacement surgery. As a final example, controlled hypotension reduced blood loss from 1920 to 1260mL[19] and from 1335 to 788mL in radical prostatectomy.[20]

3.3 Limits and Complications

Any fall in blood pressure raises concerns about end-organ perfusion and tissue oxygenation. The risk of tissue hypoxia and the difficulty in evaluating this risk are very real, although there were no specific complications seen in a large series of patients subjected to severe controlled hypotension (MAP <50mm Hg) over a prolonged duration.[21] Controlled hypotension could result in tissue hypoxia by reducing or suppressing the microcirculatory autoregulation of the vital organs and by inhibiting the autonomic nervous system. The current goal of controlled hypotension is to maintain a pressure sufficiently low to allow a reduction in bleeding without suppressing the microcirculatory autoregulation of the vital organs (i.e. brain, heart or kidney).

Morbidity was not described in early studies that only focused on the cerebral, coronary, renal, splanchnic and hepatic microcirculatory disadvantages of controlled hypotension, and are detailed in section 5. The mortality ascribed to anaesthesia and to controlled hypotension was estimated at 0.055% in 1961,[1] a mortality rate that did not seem different from the rate of all types of anaesthesia (0.01–0.007%) at that time. Non-fatal complications, which were more frequent (3.3%), were described >50 years ago in 1953.[1] The morbidity resulting from major neurological complications (dizziness, cerebral, retinal and cerebellar thrombosis) had a very low variable incidence. Another potential complication was anuria.[1] None of the current data indicate that controlled hypotension with a MAP between 50 and 65mm Hg is a risk in young healthy patients. However, the majority of the candidates for controlled hypotension have organ dysfunctions that are not easily detectable by a clinical examination.

The most recent literature does not provide data on contraindications for the use of controlled hypotension. It is indicated for a rather broad range of surgeries and is also used when religious considerations make blood transfusions inappropriate. The contraindications cannot be rigorous because they depend on an appreciation of the tissue perfusion requirements of the patient and their evaluation. It is highly likely that patients presenting with a history of cerebral or renal vascular disease, vascular disease of the lower limbs, or hepatic, renal or coronary dysfunction, hypovolaemia or anaemia, could deteriorate when the effects of controlled hypotension wane. Patients with treated hypertension did not seem to present risks and for this reason, it was not considered an absolute contraindication for controlled hypotension in one study.[22] This holds true provided one takes into account drugs used to treat hypertension that could interfere with hypotensive drugs and anaesthetic agents, and the disturbances of the inherent mechanisms of regulation of pressure with hypertensive disease, which makes patients with hypertension more sensitive to vasodilators or to antiadrenergic agents.

3.4 Other Techniques to Reduce Blood Loss

Surgery with low haemorrhagic potential, but requiring a bloodless operative field for its achievement (sinus surgery, middle ear surgery, repairing microsurgery, ophthalmic surgery or neurosurgery)

profits from the new techniques of controlled hypotension after an analysis of the benefit/risk ratio.[2,5-9]

Surgery with mean or high haemorrhagic potential (orthopaedic, urological, cardiovascular, and solid organ transplant) is likely to profit from the other techniques of blood saving to reduce the quantity of allogenic transfusion, and the risk of infectious and non-infectious complications (see table I).

Alternatives to allogenic transfusion have been developed, including autologous transfusion,[24,25] normovolaemic haemodilution and intraoperative blood salvage (table II).

Autologous transfusion reduced the probability of homologous transfusion with the associated risks,[26] but its effects on post-transfusional immunosuppression remain controversial. Moreover, the risks of bacterial infection, volaemic overload and misidentification were the same as for homologous transfusion. The cost of autologous transfusion is important especially given that the unused units cannot be used elsewhere and must be destroyed.[27]

Preoperative acute normovolaemic haemodilution consists of taking blood immediately before surgery and then transfusing it thereafter; its effectiveness was reported in non-cardiac surgery[28] and the risk of secondary complications seemed difficult to evaluate.[29] A study of 78 patients undergoing hepatic surgery did not highlight any abnormality in liver, renal or coagulation tests with haemodilution to a target haematocrit of 24%. With blood transfusion indicated at a haemocrit of 20%, only four patients in the haemodilution group received at least one allogenic unit of blood compared with 14 patients in the control group.[30]

Table I. Complications of allogenic transfusions

Risk	Likelihood per unit of blood
Infection	
HIV	1/67 6000[23]
Other	
Benign	
Shiver without fever	1/100
Urticaria	1–3/100
Severe	
ABO incompatibility	1/25 000
Anaphylactic shock	1/20 000
Adult respiratory distress syndrome	1/100
Graft disease	<1/100
Purpura	<1/100
Volaemic overload	<1/100

Table II. Alternatives to blood transfusions in surgery and their associated complications

Type	Complication
Autologous transfusion	Infection, overloading, misidentifying
Acute normovolaemic haemodilution	Cardiac failure
Intraoperative blood salvage	Infection, disseminated intravascular coagulation, adult respiratory distress syndrome, gas embolism
Pharmacological agents	
desmopressin	Thrombotic potential
tranexamic acid	Thrombotic potential
aprotinin	Allergy, thrombosis

The intraoperative salvage of blood lost during an operation, with automated washing and transfusion of red blood corpuscles recovered in physiological salt solution, is useful in vascular and orthopaedic surgery.[31] However, its use in oncology surgery is controversial because of the risk of dissemination of cells with strong metastatic potential;[32] one study used recovered blood only after passage over a filter or irradiation.[32] There is also a risk of infection during aseptic but long and haemorrhagic interventions where micro-organisms and toxins are found in recovered blood.[33] Preoperative salvage in children with idiopathic scoliosis weighing <20kg encountered a problem with miniaturisation of the devices that filter red cells, and was deemed by the study authors unsuitable for spinal fusion surgery in the absence of autologous transfusion.[34] Although the risk of accidents with this technique is low, the problem of an increase in blood loss in the presence of heparin has been highlighted.[35] Disseminated intravascular coagulation and acute respiratory distress syndrome have also been

reported,[36] and there remains the risk of air embolism despite mechanisms for detection within the system.

Pharmacological agents intervening in the processes of haemostasis, coagulation or fibrinolysis are also alternatives to controlled hypotension.

Desmopressin has a beneficial effect on primary haemostasis. It has been used prophylactically in orthopaedic surgery with contradictory results for the reduction of intraoperative bleeding. The most recent studies with desmopressin have not found any reduction in bleeding or in transfusional needs.[37,38]

The haemostatic effect of aprotinin, an antifibrinolytic inhibitor of kallikrein, has been studied in cardiac, hepatic and orthopaedic surgery with reported results of a reduction in blood loss and transfusional needs. In prosthetic surgery of the hip, high-dose aprotinin reduced blood loss and perioperative red blood cell requirements by up to 50%, but the proportion of patients transfused with allogenic blood was not reduced.[39] Similarly, a modest transfusional profit (1 unit on average) was seen in prosthetic knee surgery.[40] This must be weighed against the frequent and extremely serious risk of allergic reaction with this allogenic protein; 20–50% of patients undergoing cardiac surgery (having received aprotinin in the last 6 months) have anti-aprotinin antibodies of type IgG.[41] The prevalence of allergic reactions in the event of a second exposure to aprotinin was close to 5%,[42] and in some cases resulted in anaphylactic shock causing death.[43] The thrombotic risk that exists in orthopaedic and, more seriously, hepatic surgery, did not appear to be increased by the use of aprotinin,[44] but it is doubtful that it is without harm in this regard and its systemic use in hepatic and orthopaedic surgery is not advised.

Despite their long history, the evaluation of synthetic antifibrinolytics for the reduction of bleeding is recent and incomplete. Tranexamic acid, in particular, has been shown to reduce bleeding in cardiac interventions,[45] liver transplant surgery[46] and orthopaedic surgery with a tourniquet,[47] but its impact on transfusional needs was inconstant. The thrombotic potential of antifibrolytics has been poorly evaluated and justifies prudence with their use.

3.5 Summary

Currently, allogenic transfusion has reached a level of safety such that risk of morbidity with transfusion of one blood product are considered <1/1000. The use of an agent or a technique for the reduction of bleeding supposes that the risks to which it exposes a patient are lower than those which it reduces. Consequently, any technique that induces a risk of morbidity of a few percent is questionable. The morbidity and mortality rates of controlled hypotension appear to be of the same level as those described for the alternative techniques, although no recent study has been carried out for controlled hypotension measuring morbidity and mortality rates compared with alternative techniques.

Thus, one can consider that the progress made in the fields of pharmacology, physiopathology and monitoring has improved the technique of controlled hypotension by increasing the benefit/risk ratio.

4. Physical Measures and Pharmacological Agents for Controlled Hypotension

4.1 Physical Measures

In placing the operated area higher than the heart, postural manoeuvres (e.g. a head-up tilt position in ear or maxillofacial surgery) have reduced blood pressure in this area and decreased venous pressure.[48] However, there is a risk of air embolism with this technique. The haemodynamic effects of

artificial ventilation have also been used: hyperventilation (by means of hypocapnia) involves a vasoconstriction and a fall in blood flow; and hypoventilation (by means of hypercapnia) induces vasodilatation and an increase in blood flow.[49]

4.2 Pharmacological Agents

The ideal agent to induce controlled hypotension does not exist. It must be easy to administer, have a short onset time, an effect that disappears quickly when administration ceases, a fast elimination without toxic metabolites, negligible effects on vital organs, and a predictable and dose-dependent effect.

Drugs used in controlled hypotension include the following (see also table III):

- primary agents successfully used alone, for example, inhalation anaesthetics, sodium nitroprusside, nitroglycerin, trimethaphan, alprostadil (prostaglandin E1), adenosine, remifentanil and agents for spinal anaesthesia;
- agents that can be used alone or as adjuncts to decrease the adverse effects of other agents, for example, calcium channel antagonists (e.g. nicardipine), β-adrenoceptor antagonists (β-blockers) [e.g. propranolol, esmolol] and fenoldopam;
- secondary agents used only adjunctively with primary agents, for example, ACE inhibitors and clonidine.

4.2.1 Epidural and Spinal Anaesthesia

Epidural anaesthesia and spinal anaesthesia have been considered good techniques for controlled hypotension insofar as they reduce blood pressure and bleeding. Griffith and Gilles were the first to demonstrate this using an arachnoid block in 1940.[1]

Spinal anaesthesia results in a sympathetic block, which is responsible for a fall in peripheral vascular resistance and cardiac output via a reduction in venous return and, thus, systemic hypotension. The disadvantages of spinal anaesthesia lie in the absence of a relationship between drug dosage and drug effect, with the level of block and the degree of hypotension remaining unpredictable and difficult to control, and the duration of action very variable. Whichever local anaesthetic agent is used, the sympathetic blockade achieves a slow decrease in arterial pressure over 10 minutes. Hypotension can exceed the minimal target level, and so control of hypotension requires an adaptable continuous epinephrine (adrenaline) infusion. Low doses of epinephrine stabilise cardiac output and heart rate. Sometimes, small amounts of a local anaesthetic need to be infused to enhance hypotension. Moreover, the indications for this technique are limited to abdominal surgery and surgery of the lower limbs.[50]

Studies have shown that epidural anaesthesia without a tourniquet or spinal anaesthesia with a tourniquet have the same results on the reduction of blood loss in surgery of the knee (1800mL vs 1100mL)[14] and that bleeding was more abundant with spinal anaesthesia than with epidural anaesthesia in surgery of the hip (1000mL vs 600mL);[18] an increase in D-dimers and a fall in the thrombin time was described with spinal anaesthesia. However, no renal, neurological or cardiopulmonary complications have been noted.[16] Epidural anaesthesia can be a safely used technique even in patients with left ventricular dysfunction,[51] and resulted in less intraoperative blood loss than with propofol plus remifentanil total intravenous anaesthesia during primary total hip replacement surgery.[52]

On the basis of this evidence, hypotensive epidural anaesthesia appears to be the most effective technique for the reduction of bleeding in this type of surgery.

4.2.2 Inhalation Anaesthetics

In contrast to halothane and enflurane, isoflurane in moderate concentrations reduces blood pressure without increasing intracranial pressure. At higher concentrations, each agent induces a prevalent vasodilator effect that is responsible for an increase in

Table III. Drugs used in controlled hypotension during surgery

Drugs	Site of action	Predominant action	Major inconvenience
Anaesthetics			
Bupivacaine (spinal anaesthesia)	Medulla	Blockade of the	On/off
Ropivacaine (epidural anaesthesia)	Medulla	sympathetic nervous system	Need vasoconstrictor (ephedrine)
Inhalation anaesthetics:	Vessels: vasodilatation	Blockade of α-	Resistance
isoflurane, sevoflurane		adrenoceptors	Need high concentrations or adjuvants
Opioids: remifentanil	Heart: bradycardia	Blockade of the sympathetic nervous system	None
Vasodilators			
Sodium nitroprusside	Resistance/capacitance vessels: vasodilatation	Direct acting	Cyanide toxicity Heavy monitoring
Nitroglycerin	Capacitance vessels: vasodilatation	Direct acting	Resistance Adequate monitoring
Adenosine	Resistance vessels: vasodilatation	Direct acting	Cost Histamine release
Alprostadil	Resistance vessels: vasodilatation Heart: ↓ chronotrope effect	Direct acting	Cost
Calcium channel antagonists:	Resistance vessels: vasodilatation	Direct acting	None
nicardipine, diltiazem	Heart: ↓ inotropic effect		
Fenoldopam	Resistance vessels: vasodilatation	Dopamine DA_1-receptor agonist	None; cost?
Autonomic nervous system inhibitors			
Trimethaphan	Vessels: vasodilatation	Blockade of the ganglia of	Histamine release
	Heart: ↓ contractility	the autonomic nervous system	Resistance
Clonidine	CNS	Presynaptic α-adrenoceptor agonist	Unpredictable effect
Urapidil, phentolamine	Vessels: vasodilatation	Postsynaptic α-adrenoceptor antagonist	Unpredictable effect
Labetalol	Heart: ↓ contractility	α/β-adrenoceptor	Slow onset
	Vessels: vasodilatation	antagonist	
Esmolol	Heart: bradycardia, ↓ contractility	β-adrenoceptor antagonist	Resistance Cardiac failure
ACE inhibitors			
Captopril, enalapril	Vessels: vasodilatation	Angiotensin II inhibitors	Long duration of action

↓ indicates decrease.

cerebral blood flow and a deterioration in cerebral autoregulation. Corroborating this mechanism, lower concentrations (1 MAC [minimum alveolar anaesthetic concentration]) can increase intracranial pressure, with a loss of vascular compliance. It should be noted that reflex tachycardia and the risk of postoperative rebound hypertension are the result of a lack of inhibition of baroreflex control and of sympathetic stimulation by these anaesthetics. Increasing the concentration of inhalation anaesthetics decreases the evoked potentials used in the monitoring of neurosurgery and orthopaedic surgery of the medullar canal.[1] The use of inhalation anaesthetics alone is not recommended for controlled hypoten-

sion, and recent studies have used isoflurane in combination with alprostadil, nitroglycerin, adenosine, morphine, labetalol, esmolol or trimethaphan, in order to reduce the concentration of each agent and their respective adverse effects. Sevoflurane has only been used for this indication more recently[53,54] and has been compared with isoflurane;[55] these studies showed that sevoflurane like isoflurane has systemic and coronary vasodilator properties at average or high concentrations, without hepatic toxicity but with an increased risk of tubular renal function impairment. These drawbacks again suggest the addition of other hypotensive agents to reduce the concentration and toxicity of each agent.

On the basis of the evidence, the usefulness of inhalation anaesthetics is unquestionable because of their major role as hypnotics in current adult anaesthesia and increasingly in paediatric anaesthesia. At safe clinical concentrations only slight hypotension occurs, and adjuvant hypotensive agents are needed to induce a truly controlled hypotension without adverse effects.

4.2.3 Opioids

Usually used in anaesthesia for their analgesic effects, some opioids provoke a hypotension that is not always desirable. However, they have been skillfully used as additives to other hypotensive agents in the indication of controlled hypotension, without their beneficial effects being highlighted. Until the arrival of remifentanil, a new short-acting μ-opioid agonist, with a long elimination half-life and its corollary made the use of opioids (morphine, fentanyl, alfentanil or sufentanil) for controlled hypotension difficult. Two older studies reported the hypotensive effect of combination treatment with morphine and *d*-tubocurarine by means of the release of histamine and of sympathetic and parasympathetic blockade: the benefit was a reduction in blood loss in vertebral surgery.[56,57] Another retrospective study showed that a high dose of fentanyl enabled a reduction in blood loss in mandibular osteotomy.[58]

We have recently reported that remifentanil can reduce pressure to the desired level, reduce blood flow in the middle ear (as evaluated by laser-Doppler velocimetry) and maintain a bloodless operative field without any metabolic complications or impairment of autoregulation of the ear microcirculation. All this is attributable to the short elimination half-life and hypotensive effect of remifentanil, and when it is combined with propofol or sevoflurane, remifentanil substitutes well for sodium nitroprusside or esmolol in controlled hypotension for middle ear surgery; the likely mechanism of action is blockade of the sympathetic nerves.[2,9]

Remifentanil provided similar operating conditions and safety when combined with desflurane, isoflurane or sevoflurane.[10] It resulted in reduced blood loss and better visibility of the surgical field when combined with propofol than alfentanil plus isoflurane anaesthesia,[59] or sufentanil plus sevoflurane or fentanyl plus isoflurane anaesthesia[60] during functional endoscopic sinus surgery.

In light of the current literature, remifentanil combined with an inhalation anaesthetic or propofol provides the best controlled hypotension technique with regard to benefit/risk ratio, because as a standard anaesthetic technique, the addition of a potent hypotensive agent with its additional adverse effects, is not required to reduce bleeding and transfusion.

4.2.4 Vasodilators

Sodium Nitroprusside

Sodium nitroprusside has been the most used hypotensive agent since the 1950s and is always used as a reference agent. It has a direct peripheral vasodilator effect that initially relaxes the resistance vessels, causing venous dilation and a reduction in venous return, secondarily producing arterial dilatation. Its onset time is very fast (<30 seconds) and the

hypotensive effect does not exceed 2 minutes after administration stops. These qualities are matched by a number of well inventoried disadvantages including tachyphylaxis,[61] rebound hypertension,[62] myocardial ischaemia,[63] increased intracranial pressure,[64] increased intrapulmonary shunting, platelet dysfunction[65] and cyanide toxicity.[66] The peripheral vasodilatation causes baroreceptor-induced reflex tachycardia, and an increase in myocardial contractility. The sympathetic and renin-angiotensin systems are activated and this results in increased cardiac output, plasma catecholamine levels and renin activity, effects which last after the nitroprusside infusion has been discontinued and are responsible for the rebound hypertension seen with this agent.

One toxicity of sodium nitroprusside was highlighted very early in its use;[66] this is the accumulation in plasma of free cyanide and thiocyanates, which are breakdown products of sodium nitroprusside. The concentrations of these toxins are proportional to the total dose of sodium nitroprusside. Cyanide metabolism occurs in the liver and the thiocyanates produced are excreted by the kidneys. If conversion to thiocyanate is slow, cyanide concentrations can become high enough to induce hypoxia and metabolic acidosis. This is a risk in patients with hepatic impairment. Thiocyanate toxicity may occur with prolonged or high-dose administration or in patients with renal impairment. The symptoms of toxicity that appear for plasma thiocyanate concentrations of ~100 mg/L are muscular pain, mental confusion and nausea. Lack of efficacy and tachyphylaxis seen with sodium nitroprusside encouraged increasingly higher doses to be used, which were responsible for anoxic incidents; fortunately, these were not lethal because they are reversible. Because the complex issue of tachyphylaxis has not been elucidated, the administration of this agent must be carefully planned to prevent toxicity. The maximum recommended dose is 1.5 mg/kg as a bolus and 8 μg/kg/min as a continuous infusion not exceeding 2 μg/kg/min per day.[67]

As a result of the disadvantages described here, sodium nitroprusside has been combined with propranolol[68] or captopril as premedication;[69] these combinations reduced by >70% the amount of sodium nitroprusside required to obtain controlled hypotension and to avoid rebound hypertension. Studies of toxicity have shown sodium nitroprusside to be responsible for an activation of T lymphocytes and interleukin-6,[70] spontaneous aggregation of adrenergic origin platelets postoperatively,[71] a decrease in splanchnic perfusion and a certain degree of hepatic cytolysis.[72] A combination of sodium nitroprusside and diltiazem reduced operative bleeding while reducing the disadvantages related to the increase in respiratory frequency, thiocyanates and cardiac output seen in pilot studies where patients were only treated with sodium nitroprusside.[73] A combination of sodium nitroprusside and enalaprilat given as premedication reduced blood pressure to the desired level while significantly reducing the dose of sodium nitroprusside.[74]

Intravenous sodium nitroprusside as adjunctive therapy in isoflurane anaesthesia for endoscopic sinus surgery,[5] in propofol-alfentanil anaesthesia for tympanoplasty[2] and in sevoflurane anaesthesia in children,[9] reduced bleeding, reduced middle ear blood flow (as measured by laser-Doppler flowmetry) and its autoregulatory function, and improved the quality of the surgical field, but provoked lactic acidosis and increased hypercapnia. Sodium nitroprusside reduced blood loss during prostatectomy more than haemodilution or placebo in isoflurane plus fentanyl anaesthesia (1260mL vs 1820mL and 1920mL, respectively) and lowered the total cost by 40%.[19] Equivalent results were observed when sodium nitroprusside was used alone or in combination with haemodilution during desflurane plus fentanyl anaesthesia in dogs (788mL vs 861mL and 1335mL, respectively).[20] However, an increase in

the acute-phase response has since been described in dogs and attributed to sodium nitroprusside.[75]

Despite the significant ability of sodium nitroprusside to provide well controlled hypotension, its adverse effects due in part to tachyphylaxis require monitoring of arterial pressure and of metabolic disorders by arterial catheterisation. While it has been used as a reference agent, we have shown it could be replaced by effective techniques based on standard anaesthesia that improve the benefit/risk ratio of controlled hypotension.[2,9]

Nitroglycerin

Nitroglycerin has a non-specific, direct vasodilator effect on the venous capacitance vessels and incidentally on the arteries; it has a short half-life and no clinically toxic metabolites. It increases venous blood volume and reduces venous return, so cardiac output is proportionally reduced. The adrenergic response is partially blocked by anaesthetic agents that limit the arterial vasoconstriction resulting from this phenomenon.[76] Compared with sodium nitroprusside, nitroglycerin is not as effective at inducing hypotension, and does so more slowly, but does not produce toxic metabolites, rebound hypertension or myocardial ischaemia[77] However, nitroglycerin is associated with tachycardia, an increase in cerebral blood volume[78] and an increase in intrapulmonary shunting, comparable with sodium nitroprusside. As the fall in blood pressure depends on the total blood volume, an excessive fall in blood pressure could occur among patients with low blood volume and could compromise their coronary blood flow. Amounts of nitroglycerin >5 mg/kg may produce methaemoglobinaemia. The reduction of platelet aggregation[79,80] is less than with sodium nitroprusside and does not alter haemostasis.[81] Studies have shown that used alone,[6,17,82] or in combination with a β-blocker,[83] nitroglycerin enabled a significant decrease in blood pressure and in blood loss, and reduced blood transfusion requirements without complications being observed. While it has reduced the risk of hepatic toxicity with sevoflurane by enabling a lower dose of sevoflurane to be used, nitroglycerin was less effective than isoflurane in reducing bleeding during mandibular surgery.[6]

In summary, nitroglycerin has not demonstrated a better capacity to reduce bleeding than other vasodilators such as sodium nitroprusside and, while it has a better benefit/risk ratio than sodium nitroprusside, it still requires adequate monitoring. By comparison, a standard hypotensive anaesthesia technique with remifentanil does not require such a protocol.

Adenosine

A natural substance derived from purines, adenosine is formed from the metabolism adenosine triphosphate after intravenous administration; further metabolism results in the formation of uric acid. Adenosine causes systemic and coronary arterial vasodilatation that is dose-dependent. Its administration results in an increase in plasma renin activity[84] and catecholamine levels,[85] in addition to an increase in cerebral blood flow and impairment of the autoregulatory function of the cerebral microvascular circulation.[86,87] The plasma half-life of adenosine is only 10–20 seconds and this makes it useful when administered via a central venous catheter. Because it is rapidly degraded, losing its effectiveness, higher concentrations are needed. However, this phenomenon can be counteracted by the addition of dipyridamole, which inhibits the degradation of adenosine. Although adenosine does not produce tachyphylaxis, rebound hypertension or tachycardia, it slows down intra-cardiac conduction and accentuates a tendency for myocardial ischaemia in those with a predisposition.[77,88] Studies have highlighted a deleterious vasoconstrictive effect on the pre-glomerular related vessels, which results in a decreased glomerular filtration rate and renal blood flow;[89] this can be prevented by premedication with a selective adenosine A_1-receptor antago-

nist.[90] Bronchial spasm has also been described[91] and postulated mechanisms include: a direct effect of adenosine on bronchial smooth muscle, the release of histamine by mast cells, cholinergic stimulation, stimulation of adenosine receptors and alterations in intracellular cyclic adenosine monophosphate levels. Adenosine is an expensive product that requires the concomitant use of dipyridamole to limit the dose required and its adverse effects. It has been used in combination with a nerve block and isoflurane, which reduced the dose required and, in this study, it significantly reduced the blood loss during mandibular surgery.[92]

Compared with other vasodilators, adenosine does not have one of the best benefit/risk ratios and it has a high treatment cost. More importantly, it could be expected that its benefit/risk ratio is lower than hypotensive spinal or hypotensive remifentanil anaesthesia.

Alprostadil

Alprostadil is a natural substance that causes a decrease in arterial pressure by lowering vascular resistance. Alprostadil has a myriad of effects: it inhibits platelet aggregation, interferes with immune responses, possesses anti-inflammatory effects and stimulates blood coagulation factor X. However, it has an intrinsic negative chronotropic effect that limits the reflex tachycardia noted with other vasodilators. It is very rapidly metabolised, which enables it to be administered as a continuous infusion; 70% of the drug is eliminated by the lungs at the time of the first passage, while the metabolites are eliminated by the kidneys. Alprostadil produces an increase in glomerular filtration by dilating the renal small arteries, and an increase in sodium excretion and diuresis.[93] The lack of adverse effects on cerebral blood flow and the autoregulation of the cerebral vasculature seen with alprostadil has led to its use in neurosurgery[94,95] and cardiac surgery.[96]

The adverse effects seen with alprostadil consist of respiratory depression leading to apnoea, bronchial constriction, bradycardia, abdominal pain, diarrhoea and hyperthermia. One clinical study showed that prolonged administration of alprostadil (>120 minutes) in combination with haemodilution during surgery of the hip could result in hepatic failure.[97] When combined with isoflurane and haemodilution, alprostadil produced a significant increase in the activity of the renin-angiotensin-aldosterone system.[98] Clinical studies have shown that when used as a hypotensive agent during anaesthesia with isoflurane, alprostadil did not modify the medullar blood flow in spinal surgery compared with trimethaphan;[99,100] improved cardiac output as evaluated by echocardiography by maintaining venous tone during surgery of the knee compared with trimethaphan;[101] and did not modify oxygen uptake and carbon dioxide elimination in the surgery of the breast or in the surgery of the tympanum as nitroglycerin did.[102] In combination with isoflurane or sevoflurane, alprostadil reduced blood loss during surgery of the hip, but caused phlebitis in the site of puncture.[103]

The benefit/risk ratio for alprostadil in controlled hypotension is not so favourable, and adverse effects must be taken into account and compared with those of other techniques previously described.

Calcium Channel Antagonists

The calcium channel antagonists verapamil, diltiazem, nicardipine and nifedipine, although of a different nature, all inhibit the cellular entry of calcium through calcium channels. Nifedipine has not been used for controlled hypotension and verapamil was used only once in 1981 in a study without a control group.[104] Although the physiological effects of each agent are different, classically they all produce vasodilatation, a reduction in the force of contraction of the myocardium, and a deceleration of conduction. Diltiazem has negative chronotrope and dromotrope effects, whereas nicardipine has a peripheral vasodilator effect via relaxation of smooth muscle fibre and, in particular, sympathetic

nerve inhibition.[105] Although the force of myocardial contraction is decreased by both agents, the sympathetic nerve responses thwart the reduction in inotropism and cause an increase in the cardiac output.

Diltiazem, a benzothiazepine, has been used successfully as an adjunct[106] to reduce blood loss and to reduce the dose of sodium nitroprusside by half during spinal surgery. Nicardipine, a dihydropyridine, had a vasodilator effect on systemic, coronary and cerebral vessels with tiny beneficial effects on myocardial contraction and pulmonary circulation in dogs.[107] A combination of diltiazem plus nicardipine did not modify the low-frequency sympathetic-induced variations of heart rate during controlled hypotension more than nicardipine used alone.[108] Nicardipine, unlike nitroglycerin and alprostadil, caused a decrease in cerebral microvascular autoregulation during anaesthesia with propofol plus fentanyl.[109] It has been used mainly in orthopaedic surgery, where it reduced blood losses as a result of a sometimes prolonged hypotension; thus, it avoided rebound hypertension, despite an increase in plasma renin activity and catecholamine levels.[110,111] In spinal surgery, nicardipine reduced blood loss to the same extent as isoflurane, while it increased vertebral muscle blood flow as measured by laser-Doppler velocimetry.[112] The utility and effectiveness of nicardipine have also been reported in paediatric surgery in association with isoflurane and sufentanil.[113-115]

Fenoldopam

The direct vasodilator fenoldopam is a selective peripheral dopamine DA_1-receptor agonist that acts on the renal, coronary, cerebral, muscular skeletal and splanchnic circulations. Fenoldopam produces arterial vasodilatation and lowers blood pressure. Compared with sodium nitroprusside, it increased renal blood flow[116] and produced diuresis, without a rebound hypertension.[117] It has been used in severe hypertension, in children, and in recovery from cardiac surgery without impairing coronary revascularisation or causing coronary spasm,[118] but it increased the intraocular pressure.[119] It has been shown to maintain renal blood flow and glomerular filtration during hypotension in dogs,[120] and to produce a reduction in cerebral blood flow despite the restoration of pressure by phenylephrine.[121] In a retrospective study in children,[122] fenoldopam was effective and well tolerated in controlled hypotension, but its capacity to reduce blood loss during spinal surgery was not evaluated in this study. Further evaluation of the efficacy and adverse effects of fenoldopam in this indication is needed.

4.2.5 Inhibitors of the Autonomic Nervous System

Trimethaphan Camsilate

Trimethaphan camsilate blocks the synaptic transmission of sympathetic nerve ganglia, thus inducing arterial and venous vasodilatation, and a reduction in the myocardial contractility and cardiac output,[123] without hormonal sympathetic nerve response or modification in plasma renin activity, and without rebound hypertension after administration is discontinued. However, the parasympathetic block that can persist causes tachycardia, mydriasis and urinary retention. The mydriasis is the result of blockade of the ciliary ganglia and can impose a risk for cerebral ischaemia. Compared to other agents already discussed, trimethaphan camsilate does not produce vasodilatation of the cerebral vessels, has minimal effects on intracranial pressure and respects to a certain extent autoregulation of the cerebral blood flow.[94] However, medullar blood flow was affected by trimethaphan more than with alprostadil during spinal surgery,[99] and a study in rats showed that even with a very low MAP (30mm Hg) the cerebral blood flow is maintained at correct values with sodium nitroprusside and less so with trimethaphan.[124] Trimethaphan is metabolised by plasma cholinesterases, has a very short half-life and is excreted via the kidneys. It can cause tachyphylaxis, which can involve histamine release and

bronchial spasm. Trimethaphan inhibits plasma cholinesterase, thereby prolonging the effect of curares.[125] These disadvantages have resulted in a decline in its use, in particular in neurosurgery where it had its advantages.

Clonidine

Clonidine, a central α2-adrenoceptor agonist, reduces sympathetic nerve impulses and consequently induces bradycardia and hypotension, indicating a use as an adjunct to other agents in controlled hypotension (isoflurane, labetalol, urapidil). Clonidine allows a reduction of the concentrations of these other agents as it reduces their adverse effects (tachycardia, toxicity, rebound hypertension), while reinforcing their hypotensive effect.[126-129] However, it has only been successfully used as an oral premedication because it has a sustained and unpredictable effect. When combined with alprostadil, it reduced the amount of alprostadil needed to obtain the level of controlled hypotension desired and a significant reduction in blood loss.[130]

Urapidil and Phentolamine

Urapidil and phentolamine produce vasodilatation via the peripheral α2-adrenoceptors. In addition, urapidil interacts with serotonin receptors in the CNS, which explains the absence of a sympathetic nervous system response.[131,132] These agents have few effects on cerebral circulation, but they do not produce levels of blood pressure low enough for controlled hypotension and have not been further studied in this indication.

Labetalol

Labetalol is a competitive antagonist at β_1- and β_2-adrenoceptors and α_1-adrenocoptors at a ratio of 7 : 1. It decreases myocardial contractility and heart rate via its β-adrenoceptor effects, and causes vasodilatation via its antagonistic effects on α-adrenoceptors. The time to onset is slow (5–10 minutes), with a peak effect from 1–3 hours. It has an unpredictable effect and its effectiveness depends on the anaesthetic technique involved. Synergy was optimal with isoflurane.[133,134] Labetalol does not modify intracranial pressure but has all the adverse effects of a β-adrenoceptor antagonist, i.e. risk of intra-cardiac conduction block, bronchial spasm, heart failure and prolonged hypotension. Its use in this indication has been limited.

Esmolol

Esmolol is a short-acting antagonist of cardiac β_1-adrenoceptors. The time to onset of action is ~3 minutes and its duration of action is 10 minutes. Esmolol is hydrolysed by erythrocyte esterases and its elimination is independent of hepatic and renal function. It can be used alone or in combination with other agents. It produces a reduction of cardiac output by reducing heart rate,[2] and a reduction in plasma renin activity and catecholamine levels resulting in a decrease in arterial pressure,[135] and an increase in peripheral vascular resistance leading to a reduction in myocardial contractility.[136] There is a risk of heart failure and so esmolol should be used carefully.[137] In mandibular surgery,[137] it reduced blood loss and improved the quality of the operative field to a greater extent than sodium nitroprusside. Compared with sodium nitroprusside and remifentanil, it decreased the blood flow to the middle ear and improved the quality of the surgical field in tympanic surgery, but without metabolic complications and while reducing microcirculatory autoregulation without impairing it.[2]

Compared with other techniques of controlled hypotension such as inhalation or remifentanil anaesthesia, the benefit/risk ratio of esmolol is not as favourable.

4.2.6 ACE Inhibitors

Only the ACE inhibitors captopril and enalapril have been used as adjuncts for controlled hypotension. Their pharmacokinetic characteristics (long duration of action, long time delay to onset of action and elimination) confer an unpredictable effect. The

hypotensive effects of these ACE inhibitors results from the inhibition of the direct vasoconstrictive actions of angiotensin II. Used as oral premedication, the role reserved for captopril and enalapril is to remove the sympathetic nervous system response which occurs at the time of administration of vasodilators and to reduce the amount of sodium nitroprusside required.[73,74,138] The danger of the use of captopril is the risk of renal insufficiency in the event of pre-existing stenosis of the renal artery, because of vasodilatation of the efferent small artery and the subsequent fall in glomerular filtration pressure. Captopril in combination with fentanyl and propofol, compared with sodium nitroprusside, enhanced the reduction of blood loss and improved the quality of the surgical field in endoscopic sinus surgery.[139]

5. Techniques of Controlled Hypotension According to Surgical Specialty

5.1 Ear, Nose and Throat Surgery

Surgeons need a bloodless operative field in middle ear surgery because of the microscopic features of the area where only a few drops of blood can prevent one from seeing. Controlled hypotension is indicated here because of the high level of difficulty and the shear impossibility of controlling bleeding by using clamps on afferent vessels (vertebral-basilar artery and external carotid artery). This is even more the case in endoscopic sinus surgery.

Table IV. Drugs used in controlled hypotension for ear, nose and throat surgery

Drug	Dosage	Anaesthesia	Advantage	Disadvantage
Sodium nitroprusside	IV 0.25 μg/kg/min	Isoflurane for endoscopic sinus surgery[5] Propofol + alfentanil for tympanoplasty[2]	↓ Bleeding[5] ↓ Middle ear blood flow[2] ↑ Quality of the surgical field[2]	↓ Autoregulatory function[2] Lactic acidosis and hypercapnia[2]
Esmolol	IV 100–330 μg/kg/min	Fentanyl + isoflurane[5,7] Alfentanil + propofol[2]	↓ Middle ear blood flow[2] ↑ Quality of the surgical field[2]	Cardiac failure[5] ↓ Autoregulatory function[2]
Clonidine	PO 300μg	Fentanyl 79–57 μg/kg, and isoflurane 1.1–0.63 volume %.[126]	↓ Bleeding[126]	
Propranolol + sodium nitroprusside	IV 7.25 mg/kg/min IV 2.1 μg/kg/min	Morphine + propofol[139] Morphine + thiopental + halothane[140]	↓ Tachycardia	Tachycardia
Captopril	PO 12.5mg	Fentanyl + propofol[138] for endoscopic sinus surgery	↓ Bleeding	No improvement compared with IV sodium nitroprusside 1–2.5 μg/kg/min
Nitroglycerin or alprostadil	IV 5 μg/kg/min IV 0.3 μg/kg/min	Inhalation anaesthesia for tympanoplasty[102]	↑ Quality of the surgical field	No alteration of oxygen uptake or carbon dioxide elimination
Remifentanil	IV 0.20–0.5 μg/kg/min	Propofol (2 μg/mL)[2] desflurane, isoflurane or sevoflurane[10]	↓ Middle ear blood flow[2] ↑ Quality of the surgical field[2]	↓ Autoregulatory function[2]
Alfentanil		Isoflurane in endoscopic sinus surgery[59]	↓ Bleeding	More blood loss than remifentanil/propofol[59]
Sufentanil		Sevoflurane[59]	↓ Bleeding	More blood loss than remifentanil/propofol[59]
Fentanyl		Isoflurane[60]	↓ Bleeding	More blood loss than remifentanil/propofol[60]

IV = intravenous; **PO** = oral; ↑ indicates increase; ↓ indicates decrease.

Table V. Drugs used in controlled hypotension for paediatric surgery

Drug	Dosage (μg/kg/min)	Anaesthesia	Advantage	Disadvantage
Nicardipine	IV 0.5–7	Isoflurane+sufentanil in spinal surgery[113,114,141]	↓ Blood loss[106,107] more than IV sodium nitroprusside 0.2–1 μg/kg/min[113] ↑ Lumbar blood flow[141]	27-minute prolonged hypotension[113,114]
Fenoldopam	IV 0.5–1.4	Isoflurane+remifentanil in spinal surgery[115]	↓ Blood loss	↓ Oxygen tension[122]
Remifentanil	IV 0.20–0.5	2% volume sevoflurane in middle ear surgery[9]	↓ Middle ear blood flow[9] ↑ Quality of the surgical field[9]	↓ Autoregulatory function[9]
Sodium nitroprusside	IV 0.25	2% volume sevoflurane+alfentanil in middle ear surgery[9]	↓ Middle ear blood flow[9] ↑ Quality of the surgical field[9]	↓ Autoregulatory function[9] Lactic acidosis and hypercapnia[9]
Clonidine	IV 5 μg/kg	Isoflurane+fentanyl for oromaxillofacial surgery[142]	↑ Quality of the surgical field ↓ Isoflurane, ↓ fentanyl, ↓ labetalol	

IV = intravenous; ↑ indicates increase; ↓ indicates decrease.

Randomized controlled trials have demonstrated the efficacy of some techniques of controlled hypotension in reducing bleeding and improving the quality of the surgical field. Pharmacological measures have been associated with physical ones such as the head-up tilt 15–20° position. Chronologically, sodium nitroprusside, propranolol, esmolol, labetalol, nitroglycerin, alprostadil, clonidine, urapidil, captopril and remifentanil have been used successfully (table IV).

5.2 Paediatric Spinal Surgery

Halothane, isoflurane and sevoflurane provided controlled hypotension during paediatric spinal sur-

Table VI. Drugs used in controlled hypotension for orthopaedic surgery

Technique	Dosage	Anaesthesia	Advantage	Disadvantage
Epidural: 1% ropivacaine	5mL epidurally	25–35mL ropivacaine 1% in T1–2 dermatome for knee[14] or hip[18] arthroplasty	↓ Bleeding 600mL,[18] 1100mL[14] Less bleeding than propofol/remifentanil[52]	
Spinal: 5% bupivacaine	2mL intrathecally	Bupivacaine T10 dermatome		Bleeding 1000mL,[18] 1800mL[14]
Alprostadil + normovolaemic haemodilution		Isoflurane in hip arthroplasty[17]	1.3U transfusion	
Nitroglycerin	IV 1–2 μg/kg/min	Isoflurane in hip arthroplasty[97]	2.3U transfusion	
Isoflurane		Isoflurane in hip arthroplasty[17,97]	2.7U transfusion	Less haemodynamic stability than desflurane[143]
Desflurane		Desflurane for spinal surgery[143]	Haemodynamic stability	
Sevoflurane		Sevoflurane[144]		Renal dysfunction
Trimethaphan	IV 26.7 μg/kg/min	Sevoflurane[145]	No hepatic dysfunction	↓ Epidural blood flow[99]
Prostaglandin E1	IV 0.142 μg/kg/min IV 0.5–2 μg/kg/min	Sevoflurane[145]	No hepatic dysfunction[143] ↑ Cardiac output[94]	
Nitroglycerin	IV 4.7 μg/kg/min	Sevoflurane[145]	No hepatic dysfunction	

IV = intravenous; **T** = thoracic; ↑ indicates increase; ↓ indicates decrease.

Table VII. Drugs used in controlled hypotension for oromaxillofacial surgery[a]

Drug	Dosage	Anaesthesia	Advantage
Isoflurane	0.5–1%	Isoflurane for mandibular osteotomy[6]	Good surgical conditions
Nitroglycerin	IV 0.5–1.5 μg/kg	Isoflurane for mandibular osteotomy[6]	Good surgical conditions
Fentanyl	IV 30 μg/kg	Nerve block[58]	↓ Blood loss
Nicardipine	IV 1–7 μg/kg/min	Nerve block[115]	↓ Blood loss
Adenosine	IV 5–50 μg/kg/min	Nerve block[92]	↓ Blood loss

a No specific disadvantages noted in these references.

IV = intravenous; ↓ indicates decrease.

gery and produced good results when used alone or with nicardipine, sodium nitroprusside or fenoldopam. Remifentanil associated with sevoflurane (2%) in children enabled controlled hypotension during middle ear surgery, reduced middle ear blood flow (as measured by laser-Doppler flowmetry) with a moderate impact on microcirculatory auto-regulation and provided satisfactory surgical conditions without any complication (table V).

5.3 Other Surgeries

Studies on the specific use of drugs in controlled hypotension techniques for orthopaedic surgery (table VI), oromaxillofacial surgery (table VII), urological surgery (table VIII) and neurosurgery (table IX) have also been tabulated for ease of reference.

6. Conclusion

Controlled hypotension still has an important role in reducing operative bleeding and in blood conservation. It is indicated in the reduction of operative bleeding for surgery requiring a bloodless operative field, with low or moderate haemorrhagic potential, such as microsurgery (middle ear), ophthalmologic surgery and neurosurgery in light of the benefit/risk ratio. The benefit does not appear to be much higher than the risk if one considers the noxious effects of certain pharmacological agents, the considerable treatment costs of some agents and the risks of monitoring techniques such as arterial catheterisation required for other agents. The hypotensive effect of the new inhalation agents (isoflurane, desflurane and sevoflurane), or of total intravenous anaesthesia with propofol, added to the easily controlled new opioid, remifentanil, avoid the use of the specific potent hypotensive agents and, thus, improves the benefit/risk ratio. This 'hypotensive' anaesthesia, used at standard clinical concentrations, could be carried out without arterial catheterisation.

The use of controlled hypotension has decreased or disappeared in surgery with high haemorrhagic potential, such as cardiac surgery or liver transplant surgery, as the absence of studies in this area in the recent medical literature shows. The need to maintain a pressure of perfusion close to basal values, the contribution of antifibrinolytics and methods of

Table VIII. Drugs used in controlled hypotension for urological surgery

Technique	Dosage (μg/kg/min)	Anaesthesia	Advantage	Disadvantage
Sodium nitroprusside	1 (estimated)	Isoflurane + fentanyl for prostatectomy[19]	↓ Bleeding (1260mL) more than haemodilution (1820mL) or placebo (1920mL) ↓ Cost by 40%	
Sodium nitroprusside	1 (estimated)	Desflurane + fentanyl for prostatectomy[20]	↓ Bleeding (788mL) more than haemodilution (861mL) or placebo (1335mL)	↑ Acute-phase response[75]

↑ indicates increase; ↓ indicates decrease.

Table IX. Drugs used in controlled hypotension for neurosurgery

Drug	Dosage	Anaesthesia	Advantage	Disadvantage
Sodium nitroprusside + enalapril	IV 0.6 μg/kg/min PO 0.1 mg/kg	Balanced anaesthesia[74] for intracranial aneurysm repair + enalapril vs control	Satisfactory operative field	More sodium nitroprusside required
Sodium nitroprusside control	IV 1.4 μg/kg/min			
Esmolol	IV 300 μg/kg/min	Isoflurane[135]	Satisfactory operative field	

IV = intravenous; **PO** = oral.

programmed autologous transfusion could explain the disaffection for controlled hypotension in these indications.

Surgery with moderate haemorrhagic potential, such as vascular surgery, prosthetic orthopaedic surgery of the hip, knee or spine, mandibular osteotomy or prostatectomy, profits from the combination of haemodilution with autologous transfusion and with controlled hypotension, which preserves its use in these indications.

Over the last 10 years, new techniques based on agents that have only been used recently in controlled hypotension have emerged: the anaesthetic agents fentanyl, remifentanil and sevoflurane, the autonomic nervous system inhibitor clonidine as an oral premedication, the ACE inhibitors captopril and enalapril as oral premedications, and the 'natural' substances adenosine and fenoldopam.

Sodium nitroprusside has been most widely used agent for controlled hypotension in clinical trials, in combination with isoflurane or propofol, despite the high risks of toxicity, mainly because it was used as a reference in comparison with new agents. Isoflurane and other inhalation agents, have the advantage of being hypnotic and hypotensive agents at clinical concentrations, and are used alone or in association with adjuvant agents (such as inhibitors of the autonomic nervous system [clonidine, β-adrenoceptor agonists] or ACE inhibitors) to limit tachycardia and rebound hypertension. Other vasodilators, such as nicardipine, have been increasingly used for children; and fenoldopam, adenosine and alprostadil are currently being evaluated, but have cerebral, pulmonary or cardiac disadvantages in addition to a high treatment cost that limit their development in controlled hypotension.

The best efficacy combined with ease of use and lack of toxicity belongs to techniques of hypotensive anaesthesia that associate analgesia and hypotension at clinical concentrations. The first and oldest option is epidural anaesthesia, but this is not always practical with all surgeries. The most recent satisfactory technique is the combination of remifentanil with either propofol or an inhalation agent (isoflurane, desflurane or sevoflurane) at clinical concentrations. In light of recent literature and because of their safety and ease of use, both techniques are preferred.

Acknowledgements

The author would like to thank Mathias Degoute (University of PARIS IV-Sorbonne) for his contribution to the manuscript. No sources of funding were used to assist in the preparation of this review. The author has no conflicts of interest that are directly relevant to the content of this review.

References

1. Leigh JM. The history of controlled hypotension. Br J Anaesth 1975; 47 (7): 745-9
2. Degoute CS, Ray MJ, Manchon M, et al. Remifentanil and controlled hypotension; comparison with sodium nitroprusside or esmolol during tympanoplasty. Can J Anesth 2001 Jan; 48 (1): 20-7
3. Thompson GE, Miller RD, Stevens WC, et al. Hypotensive anesthesia for total hip arthroplasty: a study of blood loss and organ function (brain, heart, liver, and kidney). Anesthesiology 1978; 48: 91-6
4. Miller JM, Ren TY, Nuttal AL. Studies of inner ear blood flow in animals and human beings. Otolaryngol Head Neck Surg 1995; 112: 101-13
5. Boezaart AP, van der Merwe J, Coetzee A. Comparison of sodium sodium nitroprusside- and esmolol-induced controlled

hypotension for functional endoscopic sinus surgery. Can J Anaesth 1995; 42: 373-6
6. Schindler I, Andel H, Leber J, et al. Moderate induced hypotension provides satisfactory operating conditions in maxillofacial surgery. Acta Anaesthesiol Scand 1994; 38: 384-7
7. Pilli G, Guzeldemir ME, Bayhan N. Esmolol for hypotensive anesthesia in middle ear surgery. Acta Anaesthesiol Belg 1996; 47: 85-91
8. Marchal JM, Gomez-Luque A, Martos-Crespo F, et al. Clonidine decreases intraoperative bleeding in middle ear microsurgery. Acta Anaesthesiol Scand 2001; 45: 627-33
9. Degoute CS, Ray MJ, Gueugniaud PY, et al. Remifentanil induces consistent and sustained controlled hypotension in children during middle ear surgery. Can J Anesth 2003; 50 (3): 270-6
10. Dal D, Celiker V, Ozer E, et al. Induced hypotension for tympanoplasty: a comparison of desflurane, isoflurane and sevoflurane. Eur J Anaesthesiol 2004; 21 (11): 902-6
11. Eckenhoff JE, Rich JC. Clinical experiences with deliberate hypotension. Anesth Analg 1966; 45: 21-8
12. Enlund M, Andersson J, Hartvig P, et al. Cerebral normoxia in the rhesus monkey during isoflurane- or propofol-induced hypotension and hypocapnia, despite disparate blood-flow patterns: a positron emission tomography study. Acta Anaesthesiol Scand 1997; 41: 1002-10
13. Hersey SL, O'Dell NE, Lowe S, et al. Nicardipine versus sodium nitroprusside for controlled hypotension during spinal surgery in adolescents. Anesth Analg 1997; 84: 1239-44
14. Juelsgaard P, Larsen UT, Sorensen JV, et al. Hypotensive epidural anesthesia in total knee replacement without tourniquet: reduced blood loss and transfusion. Reg Anesth Pain Med 2001; 26: 105-10
15. Yukioka H, Asada K, Fujimori M, et al. Prostaglandin E1 as a hypotensive drug during general anesthesia for total hip replacement. J Clin Anesth 1993; 5: 310-4
16. Sharrock NE, Mineo R, Urquhart B, et al. The effect of two levels of hypotension on intraoperative blood loss during total hip arthroplasty performed under lumbar epidural anesthesia. Anesth Analg 1993; 76: 580-4
17. Karakaya D, Ustun E, Tur A, et al. Acute normovolemic hemodilution and nitroglycerin-induced hypotension: comparative effects on tissue oxygenation and allogeneic blood transfusion requirement in total hip arthroplasty. J Clin Anesth 1999; 11: 368-74
18. Niemi TT, Pitkanen M, Syrjala M, et al. Comparison of hypotensive epidural anaesthesia and spinal anaesthesia on blood loss and coagulation during and after total hip arthroplasty. Acta Anaesthesiol Scand 2000; 44: 457-64
19. Boldt J, Weber A, Mailer K, et al. Acute normovolaemic haemodilution vs controlled hypotension for reducing the use of allogeneic blood in patients undergoing radical prostatectomy. Br J Anaesth 1999; 82: 170-4
20. Suttner SW, Piper SN, Lang K, et al. Cerebral effects and blood sparing efficiency of sodium sodium nitroprusside-induced hypotension alone and in combination with acute normovolaemic haemodilution. Br J Anaesth 2001; 87: 699-705
21. Kerr AR. Anaesthesia with profound hypotension for middle ear surgery. Br J Anaesth 1977; 49: 447-52
22. Sharrock NE, Mineo R, Urquhart B. Haemodynamic effects and outcome analysis of hypotensive anaesthesia in controlled hypertensive patients undergoing total hip arthroplasty. Br J Anaesth 1991; 67: 17-25
23. Schreiber GB, Busch MP, Kleinman SH, et al. The risk of transfusion-transmitted viral infections. The Retrovirus Epidemiology Donor Study. N Engl J Med 1996; 334: 1685-90
24. Kasper SM, Baumann M, Radbruch L, et al. A pilot study of continuous ambulatory electrocardiography in patients donating blood for autologous use in elective coronary artery bypass grafting. Transfusion 1997; 37: 829-35
25. Hardy JF, Bélisle S, Décary F. Cardiac surgical patients must not be denied the benefits of autologous blood predonation. Can J Anaesth 1994; 41: 1021-6
26. Report of the Expert Working Group. Guidelines for red blood cell and plasma transfusion for adults and children. CMAJ 1997; 156 Suppl.: S1-23
27. Etchason J, Petz L, Keeler E, et al. The cost effectiveness of preoperative autologous donations. N Engl J Med 1995; 332: 719-24
28. Feldman JM, Roth JV, Bjoraker DG. Maximum blood savings by acute normovolemic hemodilution. Anesth Analg 1995; 80: 108-13
29. Bryson GL, Laupacis A, Wells GA. Does acute normovolemic hemodilution reduce perioperative allogenic transfusion? A meta-analysis. The International Study of Perioperative Transfusion. Anesth Analg 1998; 86: 9-15
30. Matot I, Scheinin O, Jurim O, et al. Effectiveness of acute normovolemic hemodilution to minimize allogenic blood transfusion in major liver resections. Anesthesiology 2002; 97: 794-800
31. Williamson KR, Taswell HF. Intraoperative blood salvage: a review. Transfusion 1991; 31: 662-75
32. Perseghin P, Vigano M, Rocco G, et al. Effectiveness of leukocyte filters in reducing tumor cell contamination after intraoperative blood salvage in lung cancer patients. Vox Sang 1997; 72: 221-4
33. Ezzedine H, Baele P, Robert A. Bacteriologic quality of intraoperative autotransfusion. Surgery 1991; 109: 259-64
34. Siller TA, Dickson JH, Erwin WD. Efficacy and cost considerations of intraoperative autologous transfusion in spinal fusion for idiopathic scoliosis with predeposited blood. Spine 1996; 21: 848-52
35. Kang YG, Aggarwal S, Virji M, et al. Clinical evaluation of autotransfusion during liver transplantation. Anesth Analg 1991; 72: 94-100
36. Bull BS, Bull MH. The salvage blood syndrome: a sequel to mechanochemical activation of platelets and leucocytes? Blood Cells 1990; 16: 5-23
37. Guay J, Reineberg C, Poitras B, et al. A trial of desmopressin to reduce blood loss in patients undergoing spinal fusion for idiopathic scoliosis. Anesth Analg 1992; 75: 405-12
38. Theroux MC, Corddry DH, Tietz AE, et al. A study of desmopressin and blood loss during spinal fusion for neuromuscular scoliosis: a randomized, double-blinded study. Anesthesiology 1997; 87: 260-7

39. Janssens M, Joris J, David JL, et al. High-dose aprotinin reduces blood loss in patients undergoing total hip replacement. Anesthesiology 1994; 80: 23-9
40. Thorpe CM, Murphy W, Logan M. Use of aprotinine in knee replacement surgery. Br J Anaesth 1994; 73: 408-10
41. Peters DC, Noble S. Aprotinin: an update of its pharmacology and therapeutic use in open heart surgery and coronary artery bypass surgery. Drugs 1999; 57 (2): 233-60
42. Dietrich W, Späth P, Ebell A, et al. Prevalence of anaphylactic reactions to aprotinin: analysis of two hundred forty-eight reexposures to aprotinine in heart operations. J Thorac Cardiovasc Surg 1997; 113: 194-201
43. Diefenbach C, Abel M, Limpers B, et al. Fatal anaphylactic shock after aprotinin reexposure in cardiac surgery. Anesth Analg 1995; 80: 830-1
44. Capdevila X, Calvet Y, Biboulet P, et al. Aprotinin decreases blood loss and homologous transfusions in patients undergoing major orthopaedic surgery. Anesthesiology 1998; 88: 50-7
45. Brown RS, Thwaites BK, Mongan PD. Tranexamic acid is effective in decreasing postoperative bleeding and transfusions in primary coronary artery bypass operations: a double-blind, randomized, placebo-controlled trial. Anesth Analg 1997; 85: 963-70
46. Kaspar M, Ramsay MAE, Nguyen AT, et al. Continuous small-dose tranexamic acid reduces fibrinolysis but not transfusion requirements during orthotopic liver transplantation. Anesth Analg 1997; 85: 281-5
47. Hiippala ST, Strid LJ, Wennerstrand MI, et al. Tranexamic acid radically decreases blood loss and transfusions associated with total knee arthroplasty. Anesth Analg 1997; 84: 839-44
48. Enderby GEH. Controlled circulation with hypotensive drugs and posture to reduce bleeding during surgery: preliminary results with pentamethonium iodide. Lancet 1950; I: 1145-7
49. Kallinen J, Didier A, Miller JM, et al. The effects of CO2 and O2 gas mixtures on laser Doppler measured cochlear and skin blood flow in guinea pigs. Hear Res 1991; 55: 255-62
50. Carpenter RL, Caplan RA, Brown DL, et al. Incidence and risk factors for side effects of spinal anesthesia. Anesthesiology 1992; 76: 906-16
51. Sharrock NE, Bading B, Mineo R, et al. Deliberate hypotensive anesthesia for patients with normal and low cardiac output. Anesth Analg 1994; 79 (5): 899-904
52. Eroglu A, Uzunlar H, Erciyes N. Comparison of epidural anesthesia and hypotensive total intravenous anesthesia on intraoperative blood loss during total hip replacement. J Clin Anesth 2005; 17 (6): 420-5
53. Tobias JD. Sevoflurane for controlled hypotension during spinal surgery: preliminary experience in five adolescents. Paediatr Anaesth 1998; 8: 167-70
54. Sato J, Saito S, Takahashi T, et al. Sevoflurane and nitrous oxide anaesthesia suppresses heart rate variabilities during deliberate hypotension. Eur J Anaesthesiol 2001; 18: 805-10
55. Tomiyasu S, Hara T, Hasuo H, et al. Comparative analysis of systemic and coronary hemodynamics during sevoflurane-and isoflurane-induced hypotension in dogs. J Cardiovasc Pharmacol 1999; 33: 741-7
56. Stoelting RK. The hemodynamic effects of pancuronium and d-tubocurarine in anesthetized patients. Anesthesiology 1972; 36: 612-5
57. Anderson M. Posterior spinal fusion with Harrington rod instrumentation using 'balanced anesthesia'. South Med J 1978; 71: 660-1
58. Purdham RS. Reduced blood loss with hemodynamic stability during controlled hypotensive anesthesia for LeFort I maxillary osteotomy using high-dose fentanyl: a retrospective study. CRNA 1996; 7: 33-46
59. Eberhart LH, Folz BJ, Wulf H, et al. Intravenous anesthesia provides optimal surgical conditions during microscopic and endoscopic sinus surgery. Laryngoscope 2003; 113 (8): 1369-73
60. Manola M, De Luca E, Moscillo L, et al. Using remifentanil and sufentanil in functional endoscopic sinus surgery to improve surgical conditions. ORL J Otorhinolaryngol Relat Spec 2005; 67 (2): 83-6
61. Amaranath L, Kellermeyer WF Jr. Tachyphylaxis to sodium sodium nitroprusside. Anesthesiology 1976; 44: 345-8
62. Khambatta HF, Stone JG, Khan E. Hypertension during anesthesia on discontinuation of sodium sodium nitroprusside-induced hypotension. Anesthesiology 1979; 51: 127-30
63. Rowe GG, Henderson RH. Systemic and coronary hemodynamic effects of sodium sodium nitroprusside. Am Heart J 1974; 87: 83-7
64. Michenfelder JD, Milde JH. The interaction of sodium sodium nitroprusside hypotension and isoflurane in determining cerebral vasculature effects. Anesthesiology 1988; 69: 870-5
65. Hines R, Barash P. Infusion of sodium sodium nitroprusside induces platelet dysfunction in vitro. Anesthesiology 1989; 70: 611-5
66. Tinker JH, Michenfelder JD. Sodium sodium nitroprusside: pharmacology, toxicology and therapeutics. Anesthesiology 1976; 45: 340-54
67. Michenfelder JD, Theye RA. Canine systemic and cerebral effects of hypotension induced by hemorrhage, trimetaphan, halothane or sodium nitroprusside. Anesthesiology 1977; 46: 188-95
68. Khambatta HJ, Stone JG, Khan E. Propranolol alters renine release during sodium nitroprusside-induced hypotension and prevents hypertension on discontinuation of sodium nitroprusside. Anesth Analg 1981; 60: 569-73
69. Woodside J Jr, Garner L, Bedford RF, et al. Captopril reduces the dose requirement for sodium sodium nitroprusside-induced hypotension. Anesthesiology 1984; 60: 413-7
70. Heesen M, Dietrich GV, Boldt J, et al. Beta 2-adrenoceptor density of human lymphocytes after sodium nitroprusside-induced hypotension. Anesth Analg 1995; 81: 1250-4
71. Dietrich GV, Heesen M, Boldt J, et al. Platelet function and adrenoceptors during and after induced hypotension using sodium nitroprusside. Anesthesiology 1996; 85: 1334-40
72. Suttner SW, Boldt J, Schmidt CC, et al. The effects of sodium sodium nitroprusside-induced hypotension on splanchnic perfusion and hepatocellular integrity. Anesth Analg 1999; 89: 1371-7

73. Bernard JM, Moren J, Demeure D, et al. Diltiazem reduces the dose requirement for sodium nitroprusside-induced hypotension. Anesth Analg 1993; 77: 318-23
74. Tohmo H, Karanko M, Scheinin M, et al. Enalapril premedication attenuates the blood pressure response to tracheal intubation and stabilizes postoperative blood pressure after controlled hypotension with sodium sodium nitroprusside in neurovascular patients. J Neurosurg Anesthesiol 1993; 5: 13-21
75. Piper SN, Suttner SW, Schmidt CC, et al. Acute phase response to sodium nitroprusside-induced controlled hypotension in patients undergoing radical prostatectomy. Anaesthesia 2000; 55: 131-6
76. Vatner SF, Higgins CB, Milland RW, et al. Direct and reflex effects of nitroglycerin on coronary and left ventricular dynamics in conscious dogs. J Clin Invest 1972; 51: 2872-82
77. Habazettl H, Vollmar B, Christ M, et al. Heterogeneous microvascular coronary vasodilatation by adenosine and nitroglycerin in dogs. J Appl Physiol 1994; 76: 1951-60
78. Rogers MC, Hamburger C, Owen K, et al. Intracranial pressure during nitroglycerin-induced hypotension. Anesthesiology 1979; 51: 227-9
79. Werns SW, Rote WE, Davis JH, et al. Nitroglycerin inhibits experimental thrombosis and reocclusion after thrombolysis. Am Heart J 1994; 127: 727-37
80. Aoki H, Inoue M, Mizobe T, et al. Platelet function is inhibited by nitric oxide liberation during nitroglycerin-induced hypotension anaesthesia. Br J Anaesth 1997; 79: 476-81
81. Graybar G, Lobar D, Jones J. Comparison of sodium nitroprusside and nitroglycerin in perioperative blood loss with open heart surgery. Crit Care Med 1974; 2: 240-2
82. Kadam PP, Saksena SG, Jagtap SR, et al. Hypotensive anaesthesia for spine surgery: nitroglycerin vs. halothane. J Postgrad Med 1993; 39: 26-8
83. Bembridge JL, Moss E, Grummitt RM, et al. Comparison of propofol with enflurane during hypotensive anaesthesia for middle ear surgery. Br J Anaesth 1993; 71: 895-7
84. Sollevi A, Lagerkranser M, Irestedt L, et al. Controlled hypotension with adenosine in cerebral aneurysm surgery. Anesthesiology 1984; 61: 400-5
85. Kien ND, White DA, Reitan JA, et al. Cardiovascular function during controlled hypotension induced by adenosine triphosphate or sodium sodium nitroprusside in the anesthetized dog. Anesth Analg 1987; 66: 103-10
86. Van Aken H, Puchstein C, Anger C, et al. Changes in intracranial pressure and compliance during adenosine triphosphate-induced hypotension in dogs. Anesth Analg 1984; 63: 381-5
87. Lagerkranser M, Bergstrand G, Gordon E, et al. Cerebral blood flow and metabolism during adenosine-induced hypotension in patients undergoing cerebral aneurysm surgery. Acta Anaesthesiol Scand 1989; 33: 15-20
88. Belardinelli L, Mattos EC, Berne RM. Evidence for adenosine mediation of atrioventricular block in the ischemic canine myocardium. J Clin Invest 1981; 68: 195-205
89. Zall S, Eden E, Winso I, et al. Controlled hypotension with adenosine or sodium sodium nitroprusside during cerebral aneurysm surgery: effects on renal hemodynamics, excretory function, and renine release. Anesth Analg 1990; 71: 631-6
90. Barrett RJ, Wright KF. A selective adenosine A1 receptor antagonist attenuates renal dysfunction during controlled hypotension with adenosine in rats. Anesth Analg 1994; 79: 460-5
91. Aggarwal A, Farber NE, Warltier DC. Intraoperative bronchospasm caused by adenosine. Anesthesiology 1993; 79: 1132-5
92. Noma T, Ichinohe T, Kaneko Y. Inhibition of physiologic stress responses by regional nerve block during orthognathic surgery under hypotensive anesthesia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998; 86: 511-5
93. Yamaguchi H, Harukuni I, Dohi S, et al. Lumbar epidural anesthesia prevents prostaglandine E1-induced diuretic effect in enflurane anesthetized patients. Can J Anaesth 1993; 40: 619-24
94. Abe K, Demizu A, Kamada K, et al. Local cerebral blood flow with prostaglandine E1 or trimetaphan during cerebral aneurysm clip ligation. Can J Anaesth 1991; 38: 831-6
95. Abe K, Iwanaga H, Yoshiya I. Carbon dioxide reactivity and local cerebral blood flow during prostaglandine E1- or nitroglycerin-induced hypotension. Can J Anaesth 1992; 39: 799-804
96. Kadoi Y, Saito S, Kunimoto F, et al. Cerebral oxygenation during prostaglandin E1 induced hypotension. Can J Anaesth 1998; 45: 860-4
97. Fukusaki M, Maekawa T, Yamaguchi K, et al. Combined effects of prolonged prostaglandin E1-induced hypotension and haemodilution on human hepatic function. Eur J Anaesthesiol 1997; 14: 157-63
98. Fukusaki M, Maekawa T, Kobayashi I, et al. Catecholamine and renin-angiotensin response during controlled hypotension induced by prostaglandin E1 combined with hemodilution during isoflurane anesthesia. J Clin Anesth 1997; 9: 321-7
99. Abe K, Kakiuchi M, Shimada Y. Epidural blood flow during prostaglandin E1 or trimetaphan induced hypotension. Prostaglandins Leukot Essent Fatty Acids 1993; 49: 873-6
100. Abe K, Nishimura M, Kakiuchi M. Spinal cord blood flow during prostaglandin E1 induced hypotension. Prostaglandins Leukot Essent Fatty Acids 1994; 51: 173-6
101. Tsubo T, Hashimoto Y, Dobashi N, et al. Haemodynamic changes during induced hypotension: comparison of trimetaphan with prostaglandin E1 assessed using transoesophageal echocardiography. Can J Anaesth 1995; 42: 126-9
102. Shiraishi Y, Mochizuki T, Ikeda K. Oxygen uptake and carbon dioxide elimination during controlled hypotension induced by prostaglandin E1 or nitroglycerin. Br J Anaesth 1994; 72: 439-42
103. Yukioka H, Asada K, Fujimori M, et al. Prostaglandin E1 as a hypotensive drug during general anesthesia for total hip replacement. J Clin Anesth 1993; 5: 310-4
104. Zimpfer M, Fitzal S, Tonczar L. Verapamil as a hypotensive agent during neuroleptanalgesia. Br J Anaesth 1981; 53: 885-9
105. Leenen FH, Ruzicka M, Huang BS. Central sympathoinhibitory effects of calcium channel blockers. Curr Hypertens Rep 2001; 3: 314-21
106. Bernard JM, Moren J, Demeure D, et al. Diltiazem reduces the dose requirement for sodium nitroprusside-induced hypotension. Anesth Analg 1993; 77: 318-23

107. Takeda S, Ozawa Y, Tomaru T. Haemodynamic effects of hypotension induced by KRN2391 and nicardipine in isoflurane anaesthetized dogs. Can J Anaesth 1997; 44: 1002-7
108. Kimura T, Ito M, Komatsu T, et al. Heart rate and blood pressure power spectral analysis during calcium channel blocker induced hypotension. Can J Anaesth 1999; 46: 1110-6
109. Endoh H, Honda T, Ohashi S, et al. The influence of nicardipine-, and prostaglandine E1-induced hypotension on cerebral pressure autoregulation in adult patients during propofol-fentanyl anesthesia. Anesth Analg 2002; 94: 169-73
110. Bernard JM, Pinaud M, François T, et al. Deliberate hypotension with nicardipine or sodium nitroprusside during total hip arthroplasty. Anesth Analg 1991; 73: 341-5
111. Bernard JM, Passuti N, Pinaud M. Long term hypotensive technique with nicardipine and sodium nitroprusside during isoflurane anesthesia for spinal surgery. Anesth Analg 1992; 75: 179-85
112. Lee TC, Buerkle H, Wang CJ, et al. Effect of isoflurane versus nicardipine on blood flow of lumbar paraspinal muscles during controlled hypotension for spinal surgery. Spine 2001; 26: 105-9
113. Hersey SL, O'Dell NE, Lowe S, et al. Nicardipine versus sodium nitroprusside for controlled hypotension during spinal surgery in adolescents. Anesth Analg 1997; 84: 1239-44
114. Tobias JD, Hersey S, Mencio GA, et al. Nicardipine for controlled hypotension during spinal surgery. J Pediatr Orthop 1996; 16: 370-3
115. Tobias JD. Nicardipine for controlled hypotension during orthognathic surgery. Plast Reconstr Surg 1997; 99: 1539-43
116. Aronson S, Goldberg LI, Roth S, et al. Preservation of renal blood flow during hypotension induced with fenoldopam in dogs. Can J Anaesth 1990; 37: 380-4
117. Brogden RN, Markham A. Fenoldopam: a review of its pharmacodynamic and pharmacokinetic properties and intravenous clinical potential in the management of hypertensive urgencies and emergencies. Drugs 1997; 54: 634-50
118. Halpenny M, Lakshmi S, O'Donnell A, et al. The effects of fenoldopam on coronary conduit blood flow after artery bypass graft surgery. J Cardiothorac Vasc Anesth 2001; 15: 72-6
119. Brath PC, MacGregor DA, Ford JG, et al. Dopamine and intraocular pressure in critically ill patients. Anesthesiology 2000; 93: 1398-400
120. Halpenny M, Markos F, Snow HM, et al. Effects of prophylactic fenoldopam infusion on renal blood flow and renal tubular function during acute hypovolemia in anesthetized dogs. Crit Care Med 2001; 29: 911-3
121. Prielipp RC, Wall MH, Groban L, et al. Reduced regional and global cerebral blood flow during fenoldopam-induced hypotension in volunteers. Anesth Analg 2001; 93: 45-52
122. Tobias JD. Fenoldopam for controlled hypotension during spinal fusion in children and adolescents. Paediatr Anaesth 2000; 10: 261-6
123. Knight PR, Lane GA, Hensinger RN, et al. Catecholamine and renine-angiotensin response during hypotensive anesthesia induced by sodium sodium nitroprusside or trimethaphan camsylate. Anesthesiology 1983; 59: 248-53
124. Tsutsui T, Maekawa T, Goodchild C, et al. Cerebral blood flow distribution during induced hypotension with haemorrhage, trimetaphan or sodium nitroprusside in rats. Br J Anaesth 1995; 74: 686-90
125. McCubbin JW, Page IH. Nature of the hypotensive action of a thiophanium derivative (Ro 2-2222) in dogs. J Pharmacol Exp Ther 1952; 105: 437-42
126. Marchal JM, Gomez-Luque A, Martos-Crespo F, et al. Clonidine decreases intraoperative bleeding in middle ear microsurgery. Acta Anaesthesiol Scand 2001; 45: 627-33
127. Lee J, Lovell AT, Parry MG, et al. I.V. clonidine: does it work as a hypotensive agent with inhalation anaesthesia? Br J Anaesth 1999; 82: 639-40
128. Woodcock TE, Millard RK, Dixon J, et al. Clonidine premedication for isoflurane-induced hypotension: sympathoadrenal responses and a computer-controlled assessment of the vapour requirement. Br J Anaesth 1988; 60: 388-94
129. Toivonen J, Kaukinen S. Clonidine premedication: a useful adjunction producing deliberate hypotension. Acta Anaesth Scand 1990; 34: 653-6
130. Murakami K, Mammoto T, Kita T, et al. Oral clonidine reduces the requirement of prostaglandin E1 for induced hypotension. Can J Anaesth 1999; 46: 1043-7
131. Kolassa N, Beller KD, Sanders KH. Involvement of brain 5-HT1A receptors in the hypotensive response to urapidil. Am J Cardiol 1989; 64: 7-10D
132. Kolassa N, Beller KD, Sanders KH. Evidence for the interaction of urapidil with 5-HT1A receptors in the brain leading to a decrease in blood pressure. Am J Cardiol 1989; 63 (6): 36-9C
133. Toivonen J, Kuikka P, Kaukinen S. Effects of deliberate hypotension induced by labetalol with isoflurane on neuropsychological function. Acta Anaesthesiol Scand 1993 Jan; 37: 7-11
134. Matson AM, Shaw M, Loughnan BA, et al. Pituitary-adrenal, hormonal changes during induced hypotension with labetalol or isoflurane for middle-ear surgery. Acta Anaesthesiol Scand 1998; 42: 17-22
135. Ornstein E, Young WL, Ostapkovich N, et al. Are all effects of esmolol equally rapid in onset? Anesth Analg 1995; 81: 297-300
136. Shah N, Del Valle O, Edmondson R, et al. Esmolol infusion during sodium nitroprusside-induced hypotension: impact on hemodynamics, ventricular performance, and venous admixture. J Cardiothorac Vasc Anesth 1992; 6: 196-200
137. Blau WS, Kafer ER, Anderson JA. Esmolol is more effective than sodium nitroprusside in reducing blood loss during orthognathic surgery. Anesth Analg 1992; 75: 172-8
138. Fahmi NR. Impact of oral captopril or propranolol on sodium nitroprusside: induced hypotension [abstract]. Anesthesiology 1984; 61: A41
139. Jacobi KE, Bohm BE, Rickauer AJ, et al. Moderate controlled hypotension with sodium sodium nitroprusside does not improve surgical conditions or decrease blood loss in endoscopic sinus surgery. J Clin Anesth 2000; 12: 202-7
140. Abdulatif M. Sodium sodium nitroprusside induced hypotension: haemodynamic response and dose requirements during propofol or halothane anaesthesia. Anaesth Intensive Care 1994; 22: 155-60
141. Tobias JD. Controlled hypotension in children: a critical review of available agents. Paediatr Drugs 2002; 4: 439-53

142. Hackmann T, Friesen M, Allen S, et al. Clonidine facilitates controlled hypotension in adolescent children. Anesth Analg 2003; 96 (4): 976-81
143. Beaussier M, Paugam C, Deriaz H, et al. Haemodynamic stability during moderate hypotensive anaesthesia for spinal surgery: a comparison between desflurane and isoflurane. Acta Anaesthesiol Scand 2000; 44: 1154-9
144. Hara T, Fukusaki M, Nakamura T, et al. Renal function in patients during and after hypotensive anesthesia with sevoflurane. J Clin Anesth 1998; 10: 539-45
145. Fukusaki M, Miyako M, Hara T, et al. Effects of controlled hypotension with sevoflurane anaesthesia on hepatic function of surgical patients. Eur J Anaesthesiol 1999; 16: 111-6

Correspondence: Dr *Christian-Serge Degoute*, Service d'Anesthésie-Réanimation, Centre Hospitalier-Universitaire Lyon-Sud, 69495-Pierre-Bénite, France.
E-mail: christian.degoute@wanadoo.fr