

α_2 -Adrenergic Agonists and Their Role in the Prevention of Perioperative Adverse Cardiac Events

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α_2 -adrenergic agonists have been shown to reduce the incidence of perioperative myocardial morbidity and mortality. The purpose of this review article is to summarize the current data pertaining to α_2 -adrenergic agonists and their role in the prevention of perioperative adverse cardiac events. The MEDLINE and Cochrane databases were searched for randomized trials from 1980 to 2006 that assessed perioperative α_2 -agonists and myocardial ischemia, myocardial infarction, and mortality. All recently published studies were reviewed and the data summarized.

The currently published randomized controlled tri-

als indicate that α_2 -agonists reduce the incidence of myocardial ischemic episodes in patients with known or suspected coronary artery disease undergoing non-cardiac surgery, and clonidine was shown to reduce mortality in noncardiac surgical patients. The authors of the studies concluded that while α_2 -agonists exert beneficial effects on hemodynamics and myocardial protection, large-scale, prospective, controlled trials are still needed.

Keywords: α_2 -Adrenergic agonists, clonidine, myocardial ischemia.

Cardiovascular disease affects more than 71 million Americans, and, according to the American Heart Association, 65 million people have hypertension and 13 million have coronary heart disease. Billions of healthcare dollars are spent annually to treat and prevent cardiovascular diseases. Millions more support the research and development of treatment modalities for a disease that claims more lives than cancer and HIV combined. Fortunately, through extensive research and clinical trials, medical therapies have been developed that significantly reduce perioperative morbidity and mortality in patients who have cardiovascular disease. α_2 -Adrenergic agonists have been tested in clinical trials to evaluate their effectiveness in reducing perioperative myocardial morbidity and mortality. This review aims to evaluate the literature on α_2 agonists and present in a clear and concise format the recommendations regarding their clinical use in preventing adverse perioperative cardiac events.

Myocardial oxygen supply is determined mainly by the arterial oxygen content of the blood, blood flow through the coronary arteries, and diastolic time. Multiple factors affect the oxygen content of blood, including hemoglobin level, oxygen saturation, temperature, pH, and levels of 2,3-diphosphoglyceric acid. Blood flow to the myocardium is also dependent on patent vasculature and coronary perfusion pressure. Coronary blood flow is autoregulated between 50 and 150 mm Hg to meet myocardial demands but fails in the presence of severe vessel stenosis, at which point perfusion becomes directly dependent on coronary perfusion pressure.

Ischemia occurs when the oxygen demands of the myocardium exceed the supply, aerobic metabolism ceases, and anaerobic metabolism ensues, and damage to the myocardium can occur if adequate blood flow and oxygenation are not restored. Since the myocardium maximally extracts oxygen, approximately 70% to 75% at rest, myocytes are especially vulnerable to ischemia and within minutes lose their ability to contract. This decrease in contractility further impairs blood supply to the myocardium, and, if it is not fully restored, infarction can result within approximately 20 minutes.¹ Of the physiological components that alter the supply-demand relationship, heart rate is by far the most important.² Slight increases in heart rate can dramatically increase oxygen consumption and cripple the supply at the same time.

Multiple strategies have been devised to detect perioperative ischemia. Electrocardiographic monitoring has proven to be the most useful and practical detection modality.³ Electrocardiographic monitoring is easy to interpret, automated with alarm systems, and relatively inexpensive. Studies support the use of multilead systems to detect ischemia, and Landesberg et al⁴ state that leads V3 to V5 provides maximal detection. Transesophageal echocardiography has been shown to be a sensitive detector of myocardial ischemia.⁵ Ischemia manifests as regional wall motion abnormalities, and, often, mechanical dysfunction precedes detectable electrocardiographic changes.³ However, transesophageal echocardiography requires extensive training and has not been proven to be a practical monitor because it cannot be used during critical times such as induction of anesthesia. Pulmonary artery

catheters and Holter monitors have also been used as ischemia-monitoring devices, but each has multiple drawbacks, and neither is supported in the literature as a first-line device. Finally, serum markers such as cardiac troponins offer higher sensitivity and specificity than do other cardiac isoenzymes and are proven to have some predictive value of postoperative morbidity and mortality.³

Ahlquist⁶ discovered in 1948 that adrenergic receptors (adrenoceptors) could be categorized into α or β based on their inhibitory or excitatory responses to circulating endogenous catecholamines. His study laid the groundwork for further discoveries that subdivided the α adrenoceptors into postsynaptic α_1 and presynaptic α_2 receptors. This division was later revised by Bylund and coworkers,⁷ who isolated 3 subtypes based on their affinity for specific α_2 agonists and antagonists.

The adrenoceptor is a transmembrane receptor and is a classic example of a G protein-coupled receptor (Figure). The convoluted amino acid structure of the receptor is imbedded within the lipid bilayer of the cell membrane, and the polar sections are exposed to the extracellular space so the receptor can bind endogenous hormones or exogenous molecules such as drugs.⁸ α_2 Adrenoceptors are distributed presynaptically and postsynaptically. In the central nervous system, the presynaptic receptors inhibit the release of norepinephrine when stimulated. Postsynaptic α_2 adrenoceptors are distributed in the liver, pancreas, platelets, kidney, adipose tissue, and the eye, where they exert unique physiological functions.⁸ There have been 3 subtypes of α_2 adrenoceptors isolated based on their affinity for certain ligands: α_{2a} , α_{2b} , and α_{2c} .^{8,9} The α_{2a} -receptor subtype is thought to be responsible for sedative, analgesic, and sympatholytic responses (primarily hypotension and bradycardia). Sympatholysis typically results when the α_{2a} receptors concentrated in the medulla are stimulated; sedation when the receptors in the upper brainstem, namely the locus ceruleus, are stimulated; and analgesia is mediated via spinal cord receptors (Table).^{8,9} In addition, it has been postulated that the same α_{2a} receptor may also be responsible for cognitive performance and, when activated, may enhance memory rather than diminish it.⁹ Activation of the α_{2b} -receptor subtype, located on smooth muscle cells in the periphery, results in hypertension when heavily stimulated and has been speculated to be responsible for essential hypertension.⁹

The only 2 widely used and US Food and Drug Administration-approved α_2 -adrenoceptor agonists are clonidine and dexmedetomidine. However, another α_2 -receptor agonist not available in the United States and currently in phase 3 clinical development in Europe is mivazerol.¹⁰ Clonidine, dexmedetomidine, and mivazerol are different from other α_2 agonists in that they are selective for the α_2 receptor, unlike epinephrine and norepinephrine. Furthermore, these drugs exert many benefi-

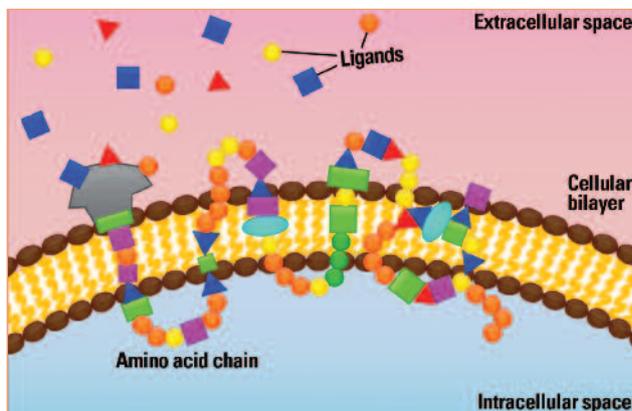


Figure. Structure of α_2 Adrenoceptors

Ligands are endogenous hormones or exogenous molecules (drugs).

(Illustration by Ryan Wilson.)

cial effects such as reducing central sympathetic nervous system activity, which results in hemodynamic stability, sedation, anxiolysis, and analgesia.

- **Clonidine.** Clonidine is the prototypical α_2 -receptor agonist and is classified as an imidazoline because of the chemical structure and affinity it has for the imidazoline receptor.¹¹ Also, clonidine has a receptor selectivity ratio of α_2 to α_1 of 200:1 and an α_2 to imidazoline selectivity ratio of 16:1.^{8,11} Because of the lipid solubility of clonidine, it has the ability to rapidly cross the blood-brain barrier, redistribute quickly, and reach a peak plasma level in 60 to 90 minutes and has a half-life of 8 hours.^{8,11} The liver metabolizes 50% of the clonidine, and the remainder is excreted unchanged by the kidneys or gastrointestinal tract.⁸ Currently, clonidine is available for oral, transdermal, intramuscular, and epidural use within the United States and intravenously outside of the United States. Recommended dosages for adults are as follows: orally, 100 to 600 μg every 8 hours; transdermally, 0.1 mg every 7 days; and epidurally, a 30- $\mu\text{g}/\text{h}$ infusion.¹²

The principal use of clonidine is for the treatment of hypertension. The therapeutic effect is achieved via activation of α_2 -adrenergic receptors located in the medulla and peripheral sympathetic neurons. Activation inhibits the release of norepinephrine from the presynaptic neuron, thereby blocking sympathetic outflow from the autonomic nervous system. A second mechanism of action is the central hypotensive effect resulting from clonidine binding to the imidazoline receptors located within the ventrolateral medulla, which were discovered in 1987 by Ernsberger and coworkers,¹³ as mentioned in Khan et al.⁸ Therefore, at low doses, the dominant action of clonidine is sympatholysis; however, at higher doses, clonidine exerts more of a hypertensive response, which is mediated via the α_{2b} -adrenoceptor subtype located on smooth muscle cells.⁹ In addition, a bradycardic response is also seen when α_2 agonists are administered, which is thought to be due to unopposed vagal tone.⁸ Further-

Tissue/location	Receptor	Response from stimulation
Sympathetic nerve endings	Presynaptic α_2	Inhibit norepinephrine release
Brain		
Dorsal medullary motor complex	α_2	Hypertension, bradycardia
Locus ceruleus	α_2	Hypnosis, sedation
Spinal cord		
Intermediolateral cell column	α_{2a} and α_{2c}	Analgesia
Substantia gelatinosa	α_{2a} and α_{2c}	Analgesia
Dorsal horn	α_{2a}	Analgesia
Primary sensory neurons	α_{2a} and α_{2c}	Analgesia
Vagus nerve	α_2	Bradycardia

Table. Distribution of α_2 Adrenoceptors

more, clonidine exerts additional centrally mediated effects such as analgesia, sedation, and anxiolysis and has proven to be a useful anesthesia adjunct.

- *Dexmedetomidine.* Dexmedetomidine was approved by the US Food and Drug Administration in 1999 for the purpose of sedation in the intensive care setting. It is also an α_2 -adrenergic receptor agonist with an even higher selectivity ratio of α_2 to α_1 of 1,620:1 and an α_2 to imidazoline selectivity of 30:1, as compared with clonidine.¹¹ Dexmedetomidine has a relatively large volume of distribution at approximately 200 L and exhibits a nonlinear pharmacokinetic profile.⁸ It is metabolized by the liver via the cytochrome P-450 system and eliminated by the kidneys. Large intravenous bolus doses can result in hypertension and bradycardia, but because it exhibits a biphasic pharmacokinetic profile it will then cause hypotension from vasodilation as the serum concentration declines. Therefore, administering an intravenous bolus of dexmedetomidine slowly followed by a continuous infusion is recommended.⁸ Dosing guidelines are as follows: 10- to 300- $\mu\text{g}/\text{kg}$ intravenous bolus followed by a continuous infusion of 0.2 to 0.7 $\mu\text{g}/\text{kg}$ per hour.¹²

- *Mivazerol.* Mivazerol, a new selective α_2 -adrenergic agonist, has been under investigation in Europe as to its role in the prevention of perioperative cardiac events. It is approximately 50% protein-bound, establishes a plasma concentration within 30 minutes of administration, and has a distribution half-life of 4 hours.⁸ Mivazerol has a mixed metabolic pathway with approximately 20% to 25% being metabolized by the liver and a little less than 50% excretion of unchanged drug by the kidneys.⁸ The European Mivazerol Trial established safe dosing guidelines as a bolus dose of 4 $\mu\text{g}/\text{kg}$ followed by an infusion of 1.5 $\mu\text{g}/\text{kg}$ per hour.

Review of the Literature

A review of the literature revealed 7 randomized controlled trials, 2 meta-analyses, and a conclusive quantitative systematic review. Of the 7 randomized controlled trials, 5 studied the use of perioperative clonidine and 2

studied the use of mivazerol. To date, there have been no studies specifically aimed at testing cardiac events and outcomes with the other α_2 agonist, dexmedetomidine. Therefore, this review focuses only on clonidine and mivazerol.

The first 2 randomized controlled trials, reported by Ghignone et al¹⁴ in 1987 and Pluskwa et al¹⁵ in 1991, focused mainly on the control of hemodynamics elicited by the administration of oral clonidine preoperatively. In the study by Ghignone et al,¹⁴ 30 patients (ASA physical status II-III) with a known history of hypertension and scheduled for elective surgery under general anesthesia were randomly assigned to 2 groups. The study group that received a 5- $\mu\text{g}/\text{kg}$ oral dose of clonidine experienced rapid preoperative control of blood pressure and lack of reflexive tachycardia with laryngoscopy and endotracheal intubation. Furthermore, clonidine significantly reduced intraoperative hemodynamic lability and resulted in slower heart rates during recovery, and the anesthetic requirements for isoflurane were reduced by 40%.¹¹ The study by Pluskwa et al¹⁵ evaluated the effects of a 300- μg oral dose of clonidine on systemic arterial pressure, heart rate, and plasma norepinephrine levels. It was a double-blinded, placebo-controlled study in 29 patients undergoing carotid artery surgery. Pluskwa et al¹⁵ reported that clonidine decreased sympathetic tone during surgery, which led to decreases in heart rate and blood pressure. Although these 2 studies did not directly evaluate the effectiveness of clonidine on myocardial ischemia, morbidity, or mortality, they demonstrated the beneficial sympatholytic effects that can be achieved through the use of a perioperative α_2 agonist.

The third randomized, double-blind, placebo-controlled clinical trial was reported by Ellis et al¹⁶ in 1994. A sample of 61 patients with known or suspected coronary artery disease was studied. The hypothesis was that the addition of clonidine to a general anesthetic would provide adequate postoperative sympatholysis to patients at risk for a cardiac event.¹⁶ The patients in the study group received transdermal clonidine, 200 $\mu\text{g}/\text{d}$, starting

the night before surgery, and the patch was to be left in place for 72 hours. In addition, they were to receive oral clonidine, 300 µg, 60 to 90 minutes before surgery. The findings suggested that clonidine reduced myocardial ischemia in the intraoperative period but not in the postoperative period.¹⁶ Also, the incidence of tachycardia was reduced for the first, second, third, and fifth postoperative hours.¹⁶ The authors strongly suggested that a follow-up study using a larger dose of clonidine should be conducted.¹⁶

Stuhmeier et al,¹⁷ in 1996, reported the fourth randomized controlled trial that was reviewed. This study included 297 patients scheduled for elective vascular surgery who were to receive 2 µg/kg of oral clonidine 90 minutes before surgery. The study group demonstrated a statistically significant reduction in the incidence of perioperative myocardial ischemic episodes from 38.8% (59/152) to 24.1% (35/145).¹⁷ Four patients in the control group had nonfatal myocardial infarctions. Other measures such as hemodynamic patterns, ischemic time, and number of ischemic episodes per patient did not differ between groups.¹⁷ It was concluded that a dose of clonidine given before surgery to patients with coronary artery disease reduced the incidence of myocardial ischemic episodes.¹⁷

The final study evaluating the use of clonidine was reported by Wallace et al¹⁸ in 2004. This was a double-blind, randomized controlled trial in which 190 patients scheduled for noncardiac surgery were enrolled. The study group included 125 subjects, and 65 subjects were in the control group. The goal of the study was to demonstrate that prophylactic clonidine reduces the incidence of perioperative myocardial ischemia and death.¹⁸ The patients in the study group were given 200 µg of oral clonidine and a transdermal patch that delivered 200 µg/d that was placed the night before surgery. In addition, on the morning of surgery, the patients received another 200-µg oral tablet. The transdermal patch remained in place for 4 days and then was removed. The researchers reported a statistically significant reduction in the incidence of perioperative myocardial ischemia on the day of surgery and postoperative days 0 to 3 with clonidine, a 14% incidence vs a 31% incidence in the control group.¹⁸ The authors also concluded through long-term follow-up with the study participants that clonidine reduced postoperative mortality for up to 2 years (placebo, 29% vs clonidine, 15%), another statistically significant finding from the study.¹⁸

In a search of the literature, 2 randomized, placebo-controlled trials involving mivazerol were found. The first study was published in 1997 by The Multicenter Study of Perioperative Ischemia European Research Group.¹⁹ This research group consisted of 40 investigators from more than 25 medical centers in Europe. The premise of the study was to assess the efficacy and safety

of mivazerol during perioperative stress by measuring hemodynamic stability and myocardial ischemia.¹⁹ However, by the authors' own admission, the study was sufficiently powered to detect differences only in hemodynamics, not myocardial ischemia. The study enrolled 300 patients with known coronary artery disease undergoing vascular surgery in 23 European medical centers. The study participants were divided into 3 groups. The first group received high-dose mivazerol (1.5 µg/kg); the second received low-dose mivazerol (0.75 µg/kg); and the third was the placebo group. The study results demonstrated that the incidence of tachycardia, hypertension, and myocardial ischemia were reduced in the high-dose and low-dose mivazerol groups compared with the control group. In addition, there were no significant episodes of hypotension or adverse events, leading to the conclusion that the administration of mivazerol to high-risk patients seems to be safe.¹⁶ The authors stated that while the study demonstrates clinically safe reductions in certain hemodynamic variables, a larger trial is needed to evaluate adverse cardiac outcomes.¹⁹

The second study, the European Mivazerol Trial, was published in 1999.²⁰ It was also a double-blind, randomized controlled trial and involved 61 European centers. The study enrolled a total of 2,854 patients and was conducted during a 2.5-year period. The study focused on patients with coronary artery disease during noncardiac surgery. The study group received a bolus dose of mivazerol (4.0 µg/kg) administered during 10 minutes followed by an infusion of 1.5 µg/kg per hour that was started 20 minutes before the induction of anesthesia and continued for up to 72 hours.²⁰ The results demonstrated moderate reductions in the number of cardiac deaths during the perioperative period for patients undergoing vascular surgery.²⁰ The study did not demonstrate any statistically significant reductions in myocardial infarction or death rates among other noncardiac surgical patients.²⁰ Therefore, the authors concluded that further investigation is warranted into whether α_2 agonists are truly beneficial for patients with known coronary heart disease undergoing vascular surgery.²⁰

A meta-analysis reported in 2002 by Nishina et al²¹ suggested that the use of an α_2 agonist, clonidine, reduced episodes of perioperative ischemia in patients at high risk for or with known coronary artery disease. However, a second meta-analysis reported in 2003 by Wijeyesundera et al²² found that the previous meta-analysis had significant limitations. The authors justified a second meta-analysis on the grounds that the first was underpowered, searched only English-language literature, focused on perioperative ischemia, and did not include the other α_2 agonists, mivazerol and dexmedetomidine.²² Wijeyesundera et al²² found that patients undergoing vascular surgery received the greatest benefit from the use of perioperative α_2 -adrenergic agonists, with

reduced mortality and infarction rates. However, α_2 agonists reduced only myocardial ischemia in cardiac surgical patients, with no demonstrated reductions in mortality or infarction rates.²² It was concluded that despite the benefits demonstrated in vascular surgery patients and the support in the literature for the use of α_2 agonists, additional large, randomized trials are needed to further explore the benefits of these agents.

The final piece of significant literature reviewed was a quantitative systematic review reported by Stevens et al²³ in 2003. This review focused on multiple pharmacologic modalities used to decrease the number of cardiac complications in patients undergoing noncardiac surgery.²³ The goal of the review was to identify all randomized controlled trials assessing the cardioprotective benefits of β -blockers, α_2 agonists, calcium channel blockers, and nitrates.²³ The authors also wanted to estimate the efficacy and risks of these agents and provide a framework for their comparison.²³ The systematic review evaluated 11 randomized trials using β -blockers, 6 using clonidine or mivazerol, 3 using diltiazem or verapamil, and 1 trial using nitroglycerin. The review concluded that β -blockers and α_2 agonists offer patients undergoing major noncardiac surgery protection against cardiac events perioperatively.²³ The review also elucidated that α_2 agonists reduced myocardial ischemia during surgery and significantly decreased the risk of cardiac death.²³ The recommendations of this review were similar to those of the previous studies reviewed; the authors believe that further studies are needed that directly compare β -blockers with α_2 agonists or a combination of the two.²³ Furthermore, the authors concluded that the pathophysiology of myocardial ischemia and infarction is complex and that the drugs studied in the review evaluated only catecholamine influences on myocardial oxygen supply and demand and did not address other pathways that lead to myocardial compromise.²³

Discussion

α_2 -Adrenergic agonists are useful anesthesia adjuncts that can provide patients with known or suspected coronary artery disease some myocardial protection in the perioperative period. It has been estimated that 60 million Americans have cardiovascular disease.²⁴ Heart disease is this country's leading cause of death. Of the 600,000 patients undergoing cardiac surgery, 17% will have a cardiovascular event this year in the United States, as will 5% of patients undergoing noncardiac surgery.²⁴ Patients undergoing surgery are sicker than ever, and their cardiovascular complications cost the healthcare system more than \$20 billion dollars annually.²⁴ It has been demonstrated that a reduction in perioperative cardiac morbidity and mortality can be achieved through pharmacologic interventions at a relatively low cost. For example, β -blockers are now an accepted medical therapy with noted

benefit in preventing perioperative cardiac morbidity. The β -blockers are highly effective at controlling heart rate; however, once the stress response has been activated, rate control may not be possible, subjecting the myocardium to an oxygen debt.¹¹ Furthermore, not all people can tolerate β -blockers, including patients with severe asthma, conduction disturbances, or metabolic derangements such as diabetes mellitus.²⁴ Therefore, an alternative medical therapy is needed, and α_2 agonists as reviewed, demonstrate a reduction in the incidence of myocardial ischemia when used perioperatively, especially in vascular patients, and have been shown to reduce 30-day and 2-year surgical mortality.²⁴

The first 3 randomized controlled trials reviewed for this article, evaluating the clinical usefulness of clonidine, used small samples, and their focus was to measure the effect of sympatholysis on hemodynamics, serum catecholamine levels, and anesthetic requirements. While these studies support the beneficial effects of clonidine on hemodynamics, they did not focus on cardiac outcomes. The studies by Stuhmeier et al¹⁷ and Wallace et al¹⁸ focused on the reduction of cardiovascular morbidity and mortality; however, the study groups were small and the studies had multiple limitations that precluded application of the results to the general population; both groups of authors acknowledged that further studies were needed to fully explore the impact of α_2 agonists on cardiovascular outcomes. The 2 reviewed studies of mivazerol had large samples but did not have the same conclusive results as the studies of clonidine. The study by the Multicenter Study of Perioperative Ischemia European Research Group¹⁹ showed that mivazerol decreased the incidence and treatment for tachycardia, hypertension, and myocardial ischemia but did not demonstrate significant reductions in myocardial infarction or death. Both groups of authors concluded that further large-scale trials are needed because there is some compelling evidence that α_2 agonists can have a role in myocardial protection in the perioperative period.

Conclusion

Clonidine has been in use since the 1970s to effectively treat hypertension. Since then, additional uses of clonidine have been explored and newer α_2 agonists have been developed. It is evident that α_2 agonists provide safe and effective central and peripheral sympatholysis that exerts a beneficial control of hemodynamics. In addition, it has been demonstrated that clonidine can be a useful adjunct to anesthesia, reducing the use of opioid and volatile agent while providing effective anxiolysis. Multiple attempts at exploring the clinical effectiveness in preventing adverse perioperative cardiovascular complications with the use of α_2 agonists have been undertaken. While some studies show promising results, no conclusive study with significant power has been conducted to thor-

oughly elucidate the benefits of α_2 agonists or that fully explores their role in the prevention of cardiac morbidity and mortality. To date, no other pharmacological agent on the market has a more diverse therapeutic profile than α_2 agonists. In today's climate of rising healthcare costs with more patients seeking surgical services, the need for medical therapies to prevent crippling cardiac events has never been greater.

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