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Small, Oral Dose of Clonidine Reduces the Incidence of Intraoperative Myocardial Ischemia in Patients Having Vascular Surgery

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Background: **Most new perioperative myocardial ischemic episodes occur in the absence of hypertension or tachycardia. The ability of α_2-adrenoceptor agonists to inhibit central sympathetic outflow may benefit patients with coronary artery disease by increasing the myocardial oxygen supply-and-demand ratio.**

Methods: **A randomized double-blind study design was used in 297 patients scheduled to have elective vascular surgical procedures to evaluate the effects of 2 $\mu g/kg^{-1}$ oral clonidine (n = 145) or placebo (n = 152) on the incidence of perioperative myocardial ischemic episodes, myocardial infarction, and cardiac death. Continuous real-time S-T segment trend analysis (lead II and V_5) was performed during anesthesia and surgery and correlated with arterial blood pressure and heart rate before and during ischemic events. Dose requirements for vasoactive and antiischemic drugs to control blood pressure and heart rate as well as episodes of myocardial ischemia (*i.e.*, catecholamines, β-adrenoceptor antagonists, nitrates, and systemic vasodilators) and fluid volume load were recorded.**

Results: **Administration of clonidine reduced the incidence of perioperative myocardial ischemic episodes from 39% (59 of 152) to 24% (35 of 145) ($P < 0.01$). Hemodynamic patterns, percentage of ischemic time, and the number of ischemic episodes per patient did not differ. Nonfatal myocardial infarction developed after operation in four patients receiving placebo compared with none receiving clonidine (day 2 to 21; $P = 0.07$). The incidence of fatal cardiac events (1 *vs.* 2) was not different. Dose requirements for vasoactive and antiischemic drugs did not differ between the groups, but the amount of presurgical fluid volume was slightly greater in patients receiving clonidine (951 ± 388 *vs.* 867 ± 381 ml; $P < 0.03$).**

Conclusion: **A small oral dose of clonidine, given prophylactically, can reduce the incidence of perioperative myocardial ischemic episodes without affecting hemodynamic stability in patients with suspected or documented coronary artery disease. (Key words: Heart: myocardial ischemia. Premedication: clonidine. Surgery: vascular surgery. α_2-agonists: clonidine)**

IN patients having surgery, considerable rates of morbidity and mortality and escalating costs are associated with coronary artery disease, specifically in persons undergoing major noncoronary vascular surgery.[1-6] Most perioperative ischemic episodes occur in the absence of any hemodynamic abnormalities,[7-9] which suggests that a reduced myocardial oxygen supply (inadequate flow) may be more causally related to ischemia than is increased myocardial oxygen demand.[10,11]

The ability of α_2-adrenoceptor agonists to inhibit central sympathetic outflow[12] and reduce the release of norepinephrine from peripheral presynaptic terminals[13] may benefit patients with coronary artery disease who are having surgery by dilating poststenotic coronary vessels[10,14] and by reducing the incidence and severity of hemodynamic abnormalities such as hypertension and tachycardia.[15,16] Small-scale studies have shown the benefits of alpha$_2$-adrenoceptor agonists such as clonidine.[17,18] However, conflicting results have been reported concerning these agonists' antiischemic abilities‖ and the need for greater use of inotropic agents and increased pacing requirements because of hemodynamic instability when large doses of α_2-adrenoceptor agonists (*i.e.*, 4 μg/kg clonidine) were used.[16,18]‖

Therefore, we tested the hypothesis that a small oral dose of clonidine (2 μg/kg) used as an adjunct in pa-

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tients undergoing noncoronary vascular surgery can reduce the incidence of new intraoperative myocardial ischemic events without affecting hemodynamic stability.

Materials and Methods

The Committee on Human Ethics of the Medical Faculty of the Heinrich-Heine-Universität, Düsseldorf, Germany, approved the protocol, and 297 consecutive patients gave informed written consent and were enrolled. Ninety-one women and 206 men ages 28 to 82 yr (mean age, 64 ± 9 yr; mean body weight, 74.7 ± 13.1 kg) were scheduled for one of the following elective procedures (table 1) between June 1993 and December 1994: (1) 106 abdominal aortic reconstructions (*i.e.*, abdominal aortic aneurysmectomy using the graft-inclusion technique, aortobifemoral or biiliac bypass, aortic or transaortic renal endarterectomy), (2) 86 supraaortic reconstructions (*i.e.*, carotid, subclavian, or vertebral endarterectomy, and aortobrachiocephalic trunk bypass), and (3) 105 infraaortic arterial revascularizations (*i.e.*, iliac and femoral artery reconstruction, or femorofemoral or femorocrural saphenic vein bypass). Based on the following reasons, 47 patients (34 having received clonidine and 13 receiving placebo) were excluded from postoperative data analysis: transfer of patients to other hospitals (n = 14) or other departments (n = 10) within the first 4 days after operation; redo cases (n = 8), especially for acute ischemia (*e.g.*, regrafting, thrombectomy); other types of surgery in the same patients (n = 8) within 1 week (*e.g.*, contralateral carotid endarterectomy, abdominal aortic aneurysm, and peripheral vascular procedures in the leg); missing data (n = 7; *e.g.*, postoperative electrocardiography [ECG], serum creatine kinase plus MB isoenzyme fraction concentrations). Thus preoperative and intraoperative data sets of 297 patients undergoing elective vascular surgery and 250 complete data sets (concerning preoperative, intraoperative, *and* postoperative [in-hospital] myocardial morbidity and mortality) were suitable for analyses.

Primary exclusion criteria for this study included chronic myocardial ischemia, preoperative digitalis or chronic clonidine medication, atrial fibrillation, left or right bundle-branch block, and second-degree or greater atrioventricular-nodal block in the preoperative ECG.

Table 1. Patient Characteristics

	Clonidine (n = 145)	Placebo (n = 152)	Significance* *P* Value
Age (yr)	64 ± 9	65 ± 9	0.87†
Age >60 yr (%)	67	70	0.72
Gender (% female)	30	31	0.87
Preoperative medication (%)			
β-blocking agents	18	18	0.92
ACE-inhibitors	27	25	0.79
Calcium channel blockers	37	41	0.37
Nitrates	19	23	0.34
Other antihypertensives	6	5	0.84
Cardiac history (%)			
History of MI	28	28	0.92
Previous ACBG/PTCA	11	6	0.11
No angina pectoris (AP 0)	32	29	0.58
Asymptomatic angina (AP A)	21	22	0.71
Typical angina pectoris‡			
AP I	20	25	0.29
AP II	18	17	0.72
AP III	7	5	0.55
AP IV	1	2	0.68
Type of surgery (%)			
Supraaortic reconstruction	29	29	0.92
Aortic reconstruction	37	34	0.62
Infraaortic reconstruction	34	37	0.78

ACBG = aortocoronary bypass grafting; PTCA = percutaneous transluminar coronary angioplasty; MI = myocardial infarction; AP = angina pectoris; ACE = angiotensin-converting enzyme.

* Logistic regression.

† Mann Whitney U test.

‡ Grading according to reference 19.

Patient Characteristics

Table 1 lists preoperative patient demographics, long-term medications, and cardiac history. All patients were classified using the grading score of angina pectoris given by the Canadian Cardiovascular Society.[19] The classification was modified by grouping patients without angina pectoris into two groups: AP 0 for those without signs and symptoms of coronary artery disease, and AP A for patients without symptoms (*i.e.*, silent ischemia or unknown previous myocardial infarction) but signs present in the preoperative ECG.

Randomization and Anesthetic Management

Using a random-number table, the patients were assigned either to receive clonidine or placebo. A standard 12-lead ECG (50 mm/s, 10 mm = 1 mV) was recorded the day before surgery and was used as a

reference for patient grouping and enrollment. The anesthesiologist visited each patient before operation. Patients fasted overnight. Approximately 90 min before scheduled induction of anesthesia, 1 mg flunitrazepam and the respective antianginal or antihypertensive medications in combination with clonidine or an identical-looking placebo were administered orally.

When patients arrived in the anesthesia holding area, ECG leads were attached and a seven-lead ECG (I, II, III, avR, avL, avF, V_5) was recorded with a standardization of 1 mV = 10 mm and compared with the ECG recorded on the day before surgery. The recording system (Sirecust D 220; Siemens AG, Erlangen, Germany) complied with the recommendations of the American Heart Association (diagnostic quality, 0.05 to 100 Hz). The S-T segment trends of lead II and V_5 were monitored continuously 60 ms after the J-point of the QRS-complex (Sirecust 1280; Siemens AG) from the beginning of the preanesthetic preparation until the patient left the operating room. Serial traces of ECG lead II and V_5 calibrated to 10 mm/mV^{-1} were recorded at 25 mm/s^{-1} for 15 s when the S-T segment trend analysis suggested ischemia; that is, when the S-T segment tended to deviate from baseline. Ischemia was diagnosed by the treating anesthesiologist using the ECG traces. The criteria used to validate ischemia were new reversible horizontal or downsloping S-T segment depression of at least 0.1 mV at the J point + 60 ms unless that point fell within the T wave, in which case it was shortened to a minimum of J + 40 ms. If T-wave changes occurred with S-T depression, we also required that the J point fell below baseline. In addition, S-T segment elevation of at least 0.2 mV was required at the J point. Episodes lasting for at least 1 min were analyzed.

Furthermore, arterial blood pressure and central venous pressure were recorded continuously with the Sirecust monitoring system. In addition, pulmonary artery pressure was monitored in 34 of the 297 patients. In a small number of patients (n = 32) undergoing infraaortic vascular surgery, blood pressure was measured using an oscillometric system joined to the monitoring system and recorded at 3-min intervals.

Anesthesia was induced with 2 to 4 mg/kg thiopental and 0.1 to 0.4 mg fentanyl administered intravenously, and muscle relaxation was achieved with vecuronium (0.1 mg/kg initially for tracheal intubation). Anesthesia was maintained with isoflurane and nitrous oxide in oxygen (50%) and supplemented with small to moderate doses of fentanyl (less than 6 μg/kg for the entire operation), depending on surgical requirements. Eucapnia was produced as assessed by capnography and blood gas analyses.

Anesthetic, surgical techniques, and postoperative treatment did not change during the 18-month study. If, despite adequate anesthesia, vasodilators were needed, either nitroglycerin or nifedepine was used, depending on clinical circumstances and patients' preoperative medications.

To maintain mean arterial blood pressure within narrow limits during aortic or carotid artery cross-clamping, sodium nitroprusside was infused when mean arterial blood pressure increased to more than 110 mmHg. If mean arterial blood pressure decreased to less than 70 mmHg, volume was replaced (primarily during induction of anesthesia) or catecholamines (dopamine or dobutamine) were administered.

Two staff anesthesiologists (K.D.S. and B.M.) and five staff surgeons participated in this study as part of their regular duty. Assignment of anesthesiologists to patients in this study was by chance alone.

For data analyses, all intraoperative ECG traces and the trend were reviewed after operation by one investigator unaware of patients' allocation to specific groups. In addition, to compare hemodynamic patterns in cases of ischemia, heart rate, mean blood pressure, and rate pressure product (RPP = heart rate · systolic blood pressure) for each time period (−10, −5, and −2 min before and 2, 5, and 10 min after onset of myocardial ischemia) for each ischemic episode were derived and analyzed. In the postoperative period, serial 12-lead ECG traces and serum creatine kinase and MB isoenzyme fraction analyses were performed immediately after surgery and 12 and 24 hours later. A final 12-lead ECG was recorded in every patient immediately before discharge from the general ward. Myocardial infarction was considered present with typical ECG findings (new persistent Q-waves lasting at least 0.04 s) in the absence of bundle-branch blocks or major QRS axis changes or when the creatine kinase and MB isoenzyme fraction exceeded 10% of creatine kinase concentrations or 40 U/l. Cardiac death was diagnosed if the patient died from dysrhythmias or congestive heart failure.

In case of new myocardial ischemic episodes, treatment was instituted immediately after recording ECG traces according to the probable cause. The following treatments were used. (1) Hypotension (systolic blood pressure <90 mmHg) in combination with blood loss: fluid replacement and decrease of volatile anesthetic concentration; if bradycardia was associated with arte-

rial hypotension, atropine was given. (2) Hypertension (systolic blood pressure >180 mmHg): increase of anesthetic depth by increasing inspired volatile anesthetic concentration or administration of fentanyl followed by nitroglycerin or nifedepine. (3) Tachycardia (>110 beats/min^{-1}): after excluding hypovolemia, increase of anesthetic dose as noted previously followed by 80 μg pindolol administered intravenously. (4) Ischemia without hemodynamic disturbances: administration of nitroglycerin.

Statistics

Data were collected, stored, and analyzed on an Intel 80486-based microcomputer using the Statistical Package for Social Science (SPSS/PC; SPSS-Software, Munich, Germany). Quantitative data were presented as means (±SD) with 95% confidence intervals. Comparisons of quantitative data (age, sex) were made using the Mann-Whitney U test. Logistic regression (group assignment) or chi-squared analysis with continuity correction was applied for categorical and frequency data. Fisher's exact test (*e.g.*, for myocardial infarction) was used when appropriate. Hemodynamic variables between groups were compared using a two-way analysis of variance for repeated measures and at each time using one-way analysis of variance (Kruskal-Wallis test). Differences were considered significant when $P < 0.05$.

Results

Patient Population

When our study was complete, 152 patients received placebo and 145 received clonidine. Patients in both groups were comparable in regard to their preoperative cardiac assessment, medication, and cardiac history, as summarized in table 1. Before operation, about 70% of our patients in both groups had ECG or clinical signs and symptoms of coronary artery disease.

Incidence of New Myocardial Ischemia and Patient Outcomes

The incidence of new perioperative myocardial ischemic episodes differed significantly between clonidine- and placebo-treated patients ($P < 0.01$; table 2): Among the 145 patients given clonidine, 35 patients (24%) showed evidence of new reversible myocardial ischemia (table 2). Of 152 patients who received placebo, 59 patients (39%) had signs of new reversible myocardial ischemia. There were no differences in the number of patients in whom nonfatal myocardial (0 *vs.* 4) infarctions developed, or in patients dying from major cardiac events (1 *vs.* 2) after operation (table 2).

Table 2. Incidence, Characteristics, and Complications of Perioperative Myocardial Ischemia in 297 Vascular Surgical Patients

	Clonidine (n = 145)	Placebo (n = 152)	*P* Value
No. of patients with ischemic episodes	35 (24%)	59 (39%)	0.01
No. of patients with 1 ischemic episode	21	39	0.75
No. of patients with 2 ischemic episodes	12	12	0.16
No. of patients with 3 ischemic episodes	2	4	0.52
No. of patients with >4 ischemic episodes	0	4	0.15
Ischemic episodes	51	96	
Ischemic episodes per patient [confidence interval]	1.5 ± 0.6 [1.2–1.6]	1.6 ± 0.9 [1.4–1.8]	0.88
Episodes with ST-elevations	5 (10%)	7 (7%)	0.24
No. of patients with ST-elevation	3 (9%)	6 (10%)	0.75
No. of patients with ST-depression	32	53	
No. of ST-depressions −0.1 to −0.14 mV	16	29	0.75
No. of ST-depressions −0.15 to −0.19 mV	12	22	0.48
No. of ST-depressions <−0.2 mV	18	38	0.65
Total ischemic time/total recording time per ischemic patient [confidence interval]	9.0 ± 12 [5.0–13.0]	13 ± 13 [9.7–16.3]	0.14
Postoperative nonfatal myocardial infarctions*	0	4 (3%)	0.07
Postoperative cardiac deaths*	1 (1%)	2 (1%)	0.65

* Referring to those patients in whom complete data sets were suitable for analysis (111 patients in the clonidine group, 139 patients in the placebo group).

Characteristics of Myocardial Ischemia

Hemodynamic patterns from 10 min before to 10 min after onset of ischemia did not differ between groups (fig. 1). Furthermore, the percentage of episodes with

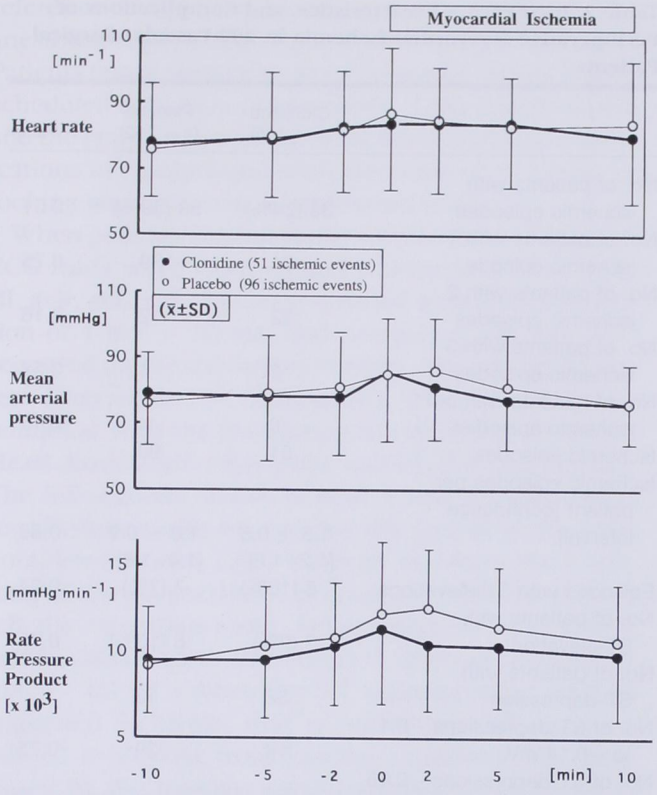

Fig. 1. Plot of heart rate, mean arterial pressure, and rate pressure product (mean ± SD) during the nonischemic time 10, 5, and 2 min before, and 2, 5, and 10 min after onset (0 min) of ischemia in patients receiving clonidine and in those receiving placebo, respectively. There was neither a difference between the groups nor between time points.

S-T elevation, mean duration, and total ischemic time in relation to total recording time did not differ between groups (table 2). Myocardial ischemia was associated with hemodynamic changes in both groups in approximately 25% of cases. The hemodynamic changes were tachycardia (heart rate >110/min; about 16%), hypertension (systolic blood pressure >180 mmHg; about 5%), or hypotension (systolic blood pressure <90 mmHg; about 5%).

In addition, during surgical stimulation, significantly fewer patients had myocardial ischemic episodes after receiving clonidine (30 of 145) compared with those receiving placebo (48 of 152, $P < 0.01$; table 3). The prevalence of myocardial ischemia during arrival, induction, and emergence from anesthesia did not differ (table 3).

Perioperative Management

With the exception of a slightly greater preoperative fluid volume load in the clonidine group (951 ± 388 *vs.* 867 ± 381 ml; $P < 0.03$) the requirements for vasoactive drugs to maintain the predetermined blood pressure did not differ between groups. The incidence of atropine to treat bradycardia associated with hypotension and the need for medical intervention in the case of ischemia was not statistically different (table 4).

Type of Surgery

The incidence of new reversible myocardial ischemia in relation to the three types of vascular surgical interventions were similar. They were 41% for supraaortic, 35% for aortic, and 41% for infraaortic procedures in patients receiving placebo, and 24%, 20%, and 29% in those receiving clonidine, respectively.

Discussion

The risk of new reversible myocardial ischemic episodes as shown by S-T segment deviation can be reduced by approximately one third when using a single oral dose of clonidine (2 μg/kg). Hemodynamic stability remained unaffected throughout anesthesia and surgery as judged from the need for vasoactive drugs. Although the preoperative crystalloid volume necessary to maintain predetermined levels of blood pressure was slightly greater in the clonidine group (approximately 1.4 ml/kg; $P < 0.03$), this did not appear to be clinically relevant.

The incidence of new reversible pre- and intraoperative myocardial ischemic episodes (39%) in the placebo group appears high, but it is in accord with previously reported data for patients having vascular surgery.[2,5,6,9] Two possible mechanisms that may have led to a reduction of new reversible myocardial ischemia in patients receiving clonidine include decrease of myocardial ox-

Table 3. Episodes of New Perioperative Myocardial Ischemia

Perioperative Period during Which Ischemic Episodes Were Observed	Clonidine (n = 145)	Placebo (n = 152)	*P* Value
No. of ischemic episodes	51	96	
Arrival	4 (3%)	11 (7%)	0.08
Anesthetic induction	2 (1%)	7 (5%)	0.1
Surgical stimulation	30 (21%)	48 (32%)	0.01
No. of episodes*	36	68	
Tracheal extubation	9 (6%)	10 (7%)	0.88

* During surgical stimulation.

Table 4. Incidence, Dosage of Drugs, and Preoperative Volume Load Used to Preserve Hemodynamic Stability and Treat Myocardial Ischemia

Drug	Dose	Clonidine (n = 145) [no. (%)]	Placebo (n = 152) [no. (%)]	*P* Value
Epinephrine		20 (14)	26 (17)	0.34
Dopamine	$\leq 3.4\ \mu g \cdot kg^{-1} \cdot min^{-1}$	3 (2)	3 (2)	0.89
	$< 7.5\ \mu g \cdot kg^{-1} \cdot min^{-1}$	42 (29)	49 (32)	0.49
	$\geq 7.5\ \mu g \cdot kg^{-1} \cdot min^{-1}$	6 (4)	14 (9)	0.08
Sodium-nitroprusside	$\leq 2.5\ \mu g \cdot kg^{-1} \cdot min^{-1}$	36 (17)	32 (21)	0.32
	$< 2.5\ \mu g \cdot kg^{-1} \cdot min^{-1}$	6 (4)	7 (5)	0.92
	$\geq 2.5\ \mu g \cdot kg^{-1} \cdot min^{-1}$	3 (2)	1 (1)	0.27
Urapidil		23 (16)	25 (17)	0.88
Nitroglycerin	$\leq 0.7\ \mu g \cdot kg^{-1} \cdot min^{-1}$	26 (18)	25 (17)	0.83
	$< 1.5\ \mu g \cdot kg^{-1} \cdot min^{-1}$	28 (19)	33 (22)	0.47
	$\geq 1.5\ \mu g \cdot kg^{-1} \cdot min^{-1}$	4 (3)	4 (3)	0.92
Pindolol		16 (11)	29 (19)	0.06
Atropine		23 (16)	30 (20)	0.3
Preoperative volume load (ml; Mean ± SD)		951 (388)	867 (381)	0.03

ygen demand and increase in supply. Because the incidence of ischemia associated with hypertension or tachycardia did not differ among groups and subgroups (patients having supraaortic, aortic, and infraaortic surgical procedures), our data support conclusions from previous studies that factors other than hemodynamic abnormalities are more causally related to ischemia than is increased oxygen demand.[6-9]

Although the incidence of new reversible perioperative myocardial ischemia was similar to that of previous studies,[2,5,6,9] the incidence of infarction and fatal cardiac outcome was less compared with those previously reported.[20-22] This might be attributed to the use of an on-line S-T segment trend analyzer and immediate provision of therapy.

Although the number of patients in both groups was reasonably large, and the preoperative patient characteristics concerning cardiac history and modified grading of angina pectoris[19] (including a 12-lead baseline ECG) did not differ, we cannot exclude group differences in the acute preoperative ambulatory pattern of ischemia, because Holter monitoring was not performed, which might have helped to characterize both groups more meticulously. However, by randomizing a large number of patients, it appears unlikely that significant differences in the acute preoperative prevalence for and severity of (silent) myocardial ischemia would influence the results.

Because most patients already received (long-term) antianginal and antihypertensive medication, interpretation of the results might be ambiguous. However, because there were no differences between both groups, chronic medication should not have affected our results. Furthermore, given the dynamic nature of the intraoperative period, vascular surgical maneuvers such as aortic cross-clamping and declamping require vasoactive drugs, which might have induced desired reactions (antiischemic) and contributed to higher heart rates (catecholamines) and, possibly, myocardial ischemia. However, because the frequency of therapeutic interventions and dosages used did not differ between groups, the drug regime routinely used probably did not affect the results.

Finally, although the sensitivity to detect myocardial ischemia using leads II and V_5 ranges from 80% during anesthesia[23] to 96% during exercise,[24] as compared with a standard 12-lead ECG, we might have underestimated the incidence of new intraoperative myocardial ischemia. Furthermore, it is debatable if other (possibly more sensitive and more expensive) techniques such as transesophageal echocardiography or 12-lead real-time ECG monitoring have greater clinical value in identifying acute myocardial ischemia[25] that might benefit certain subsets of patients (*i.e.*, patients with thoracic aortic aneurysms in whom thoracic electrodes could not be attached during left-sided thoracotomy). Nevertheless, this limitation would have affected findings in both groups and thus should not have influenced the results. Accordingly, the lower incidence of new reversible intraoperative myocardial ischemic

episodes appears attributable to the added clonidine premedication.

A single small oral dose of clonidine is a simple and effective method to reduce the prevalence of new reversible intraoperative myocardial ischemia without affecting hemodynamic stability in patients with suspected or documented coronary artery disease who are having vascular surgery. Further studies are necessary to determine if larger doses of α_2-agonists help to reduce the incidence of ischemic events or if side effects (*i.e.*, hemodynamic instability) would mitigate this prophylactic effect.

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