IMPROVEMENT OF OUTCOMES AFTER CORONARY ARTERY BYPASS

A randomized trial comparing intraoperative high versus low mean arterial pressure

Background **The objective of this randomized clinical trial of elective coronary artery bypass grafting was to investigate whether intraoperative mean arterial pressure below autoregulatory limits of the coronary and cerebral circulations was a principal determinant of postoperative complications. The trial compared the impact of two strategies of hemodynamic management during cardiopulmonary bypass on outcome. Patients were randomized to a low mean arterial pressure of 50 to 60 mm Hg or a high mean arterial pressure of 80 to 100 mm Hg during cardiopulmonary bypass.** *Methods* **A total of 248 patients undergoing primary, nonemergency coronary bypass were randomized to either low (n = 124) or high (n = 124) mean arterial pressure during cardiopulmonary bypass. The impact of the mean arterial pressure strategies on the following outcomes was assessed: mortality, cardiac morbidity, neurologic morbidity, cognitive deterioration, and changes in quality of life. All patients were observed prospectively to 6 months after the operation.** *Results* **The overall incidence of combined cardiac and neurologic complications was significantly lower in the high pressure group at 4.8% than in the low pressure group at 12.9% (p = 0.026). For each of the individual outcomes, the trend favored the high pressure group. At 6 months after coronary bypass for the high and low pressure groups, respectively, total mortality rate was 1.6% versus 4.0%, stroke rate 2.4% versus 7.2%, and cardiac complication rate 2.4% versus 4.8%. Cognitive and functional status outcomes did not differ between the groups.** *Conclusion* **Higher mean arterial pressures during cardiopulmonary bypass can be achieved in a technically safe manner and effectively improve outcomes after coronary bypass. (J THORAC CARDIOVASC SURG 1995;110: 1302-14)**

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Coronary artery bypass grafting (CABG) prolongs life among patients with severe triple vessel or left main coronary artery disease.[1, 2] Refinements in surgical and anesthetic techniques over the past decade have significantly reduced the risk of postoperative cardiac morbidity.[3, 4] The incidence of neurologic complications, however, has not decreased significantly.[5, 6]

Efforts to understand the pathophysiology of neurologic and cognitive injury[7, 8] have focused on

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intraoperative issues unique to cardiac surgery, such as type of oxygenators,[9] size and types of arterial filters,[10] and anesthetic techniques during cardiopulmonary bypass (CPB). Hemodynamic patterns during CABG, especially mean arterial pressures (MAPs) and fixed flow rates, have received less attention.[11] Our hypothesis was that intraoperative MAP below the autoregulatory limits of the coronary and cerebral circulations may be a principal determinant of postoperative complications. Therefore, patients maintained at higher MAPs would have better outcomes.

The objective of this trial was to compare the impact of two strategies of hemodynamic management during CPB on outcome. Patients were randomized to an MAP of either 50 to 60 mm Hg (usual range) or 80 to 100 mm Hg (intervention group). The impact of the MAP strategies on outcomes of mortality, cardiac morbidity, neurologic morbidity, cognitive deterioration, and changes in quality of life were assessed.

Methods

Patient eligibility. Between October 1991 and February 1994, patients undergoing primary elective multivessel CABG for left main or multivessel coronary artery disease at The New York Hospital–Cornell Medical Center were eligible for enrollment. Exclusion criteria included inability to complete the neuropsychologic tests (blindness, deafness, language difficulties), participation in other studies, and inability to return for follow-up. A total of 423 eligible patients were identified. Two-hundred fifty-one patients agreed to participate. All patients gave informed written consent per institutional review board guidelines.

Baseline evaluation. Cardiac and neurologic status, comorbidity,[12] depression (assessed by the CES-D[13]), and physical examination were documented. Cognitive function[14] was assessed with an eleven-test neuropsychologic battery (WAIS-R Digit Span, Trail Making A and B, Boston Naming, Benton Visual Retention and Recognition Test, Controlled Oral Word Association, WAIS-R Digit Symbol, Mattis-Kovner Verbal Recall and Recognition, and Finger Tapping Test) evaluating memory (recall and recognition), linguistic, attention, and psychomotor functions. The Ammons Quick Test[15] was used as a proxy for verbal intelligence quotient. Quality of life was measured by the SF-36 Health Survey, which evaluates seven functional domains: physical, social, role, energy, mental, pain, and general health.[16]

Randomization procedure and treatment protocol. Randomization was based on a table of random numbers. On entrance into the operating room, patients were randomized to either low or high MAP during CPB. In the low MAP (control) group, MAP during CPB was maintained between 50 and 60 mm Hg, and in the high MAP (experimental) group, between 80 and 100 mm Hg. In both groups, CPB flow by body surface area and temperature were held constant, and vasoactive drugs were used to maintain MAP in the desired range. Three patients were dropped from the trial. One of these patients did not undergo CABG because of severe aortic calcification and two patients required valve replacement, as detected by transesophageal echocardiography at the time of the operation. Initially, CABG reoperation was not an exclusion and one patient undergoing reoperation was enrolled. Patients undergoing reoperation were subsequently excluded.

Intraoperative monitoring. All hemodynamic parameters including blood pressure, heart rate, temperature, and pulmonary artery pressures were downloaded every 10 seconds from a Marquette 7000 monitor (Marquette, Milwaukee, Wis.). All operative events, pharmacologic agents, and bypass parameters were recorded on-line by a research assistant using a locally developed program synchronized with Marquette downloading. Anesthesia was induced with thiopental (1 to 2 mg/kg) and fentanyl (25 μg/kg). Pancuronium provided muscle relaxation. Anesthesia was maintained with a fentanyl bolus (1 to 5 μg/kg, to a total of 50 to 70 μg/kg), midazolam, or isoflurane (pre-CPB and post-CPB periods only). After sternotomy and pericardial incision, heparin was administered to maintain an activated clotting time of more than 480 seconds. After cannulation of the aorta and right atrium, nonpulsatile CPB with a membrane oxygenator and a 40 μm blood filter (Pall Biomedical, East Hills, N.Y.) was instituted. A Bio-Medicus centrifugal pump (Medtronic Bio-Medicus, Eden Prairie, Minn.) or a roller pump (Cobe Cardiovascular Inc., Arvada, Colo.) was used as available. Flow rates were set at 1.6 and 2.4 L/min per square meter during cooling and warming, respectively. The alpha-stat protocol[17] for blood gas management was used, and body temperature was cooled to 28° to 30° C. Combinations of antegrade and retrograde cold blood cardioplegia were used with a potassium concentration of 28 mEq/L. If the MAP increased above the target level and was unresponsive to fentanyl or midazolam, sodium nitroprusside infusion was administered. If the MAP fell below the target level, phenylephrine was used. If necessary, norepinephrine or metaraminol was added. Intraoperative ischemia was managed by an identical algorithm in both groups (Appendix 1).

Follow-up. The study cardiologist and neurologist, blinded to the intraoperative management, performed standardized examinations at 1, 2, and 7 days after the operation and at 6 months. The neuropsychologic battery was administered on postoperative day 7 and at 6 months. At 6 months, an interval history including the patient's symptoms, medications, and hospitalizations was obtained, and the SF-36 and CES-D tests were readministered.

Definitions of trial outcomes. The outcomes assessed at 6 months were mortality, cardiac morbidity, neurologic morbidity, deterioration in cognitive status, and deterioration in quality of life. All deaths before 6 months were counted. Cardiac complications were myocardial infarction, pulmonary edema, adult respiratory distress syndrome, low flow state/cardiogenic shock, and cardiopulmonary arrest (Appendix 2). Final designation of cardiac

Table I. *Baseline comparability of the two MAP groups**

	Low MAP (n = 124)	*High MAP (n = 124)*
Demographic		
Age (yr, mean ± SD)	66.2 ± 10.1	65.4 ± 8.6
Male	78	82
Caucasian	91	95
Widowed	15	11
High school education or higher	93	87
Working	44	56
Cardiac and neurologic history		
Symptom duration (yr, mean ± SD)	5.4 ± 7.7	5.0 ± 7.3
Previous angioplasty	6	10
No angina	14	27
Canadian Cardiovascular Society class		
I	19	16
II	25	23
III	15	11
IV	27	23
Ejection fraction (%, mean ± SD)	48.8 ± 12.7	47.6 ± 12.3
Left main disease	16	10
Previous myocardial infarction	38	48
Congestive failure	9	6
Valvular disease (aortic or mitral)	5	3
Previous stroke	5	6
Comorbidity		
Comorbidity score		
0-1	56	59
2-3	32	28
≥4	12	13
Body surface area (m^2, mean ± SD)	1.9 ± 0.2	1.9 ± 0.2
Hypertension	44	56
Diabetes	23	18
Renal dysfunction	3	5
Cancer	11	12
COPD or asthma	6	13
Cigarette smoking		
Never	27	25
Former	59	61
Current	9	3
Medications		
Diuretics	20	18
Calcium channel blockers	60	66
Beta blockers	54	59
Nitrates	63	46
Aspirin	51	52
Antihypertensives	19	15

COPD, Chronic obstructive pulmonary disease; *SD,* standard deviation.
*Each entry is given in percent unless otherwise specified.

complications was determined by agreement of two cardiologists blinded to the protocol.

Definite stroke was the principal neurologic complication determined by the neurologist. Stroke included the new onset of a localized and persistent neurologic deficit (e.g., paresis, plegia, aphasia, hemianopsia, cortical blindness).

Deterioration on three or more cognitive tests was defined as a cognitive complication. For each test, the assessment was based on within-patient change in test performance from preoperative baseline. Changes from preoperative to postoperative function that would be considered clinically important were determined a priori by a panel of experts (Appendix 3). Deterioration in quality of life was defined as a decline of more than five points on the physical component summary score of the SF-36.[18]

Statistical analysis. Baseline characteristics and trial outcomes in the two groups were compared by means of an intention-to-treat analysis. Subsequently, a pragmatic analysis (based on achieved MAP) was performed in which the frequency of outcomes was examined by the actual MAP achieved, regardless of randomization group. Either the χ^2 or Fisher's exact test was used to compare the proportions in the two groups. Confidence intervals were also used to assess the overall difference between the two groups. Logistic regression was used to ensure that differences in baseline clinical characteristics or intraoperative management did not confound the results.

Results

Comparability of treatment groups. A total of 124 patients were randomized to each treatment arm. Baseline characteristics for the two groups are shown in Table I. The mean age was 65.8 ± 9.4 years, and 80% were male. Approximately 50% were college graduates and 50% were working before the operation. Half had a history of hypertension, 43% a previous myocardial infarction, and 8% previous angioplasty. The preoperative MAP, an average of the three most recent blood pressures recorded before entrance into the operating room, was 81 mm Hg in both groups. The angiographically determined mean ejection fraction was 48%, and 13% had left main disease. Although 20% of patients had no chest pain, 37% had Canadian Cardiovascular Society class III or IV angina.[19] Six percent of patients reported a previous stroke. The two MAP groups were similar with regard to demographic and clinical characteristics. However, patients in the high MAP group were more likely to be working ($p = 0.042$) and angina-free ($p = 0.008$) before the operation, whereas those in the low MAP group were more often taking prescription nitrates before the operation ($p = 0.007$).

Table II shows the 11 preoperative neuropsychologic test scores for the two treatment groups. There

were no significant differences in baseline test scores for any test, including verbal intelligence quotient. The preoperative scores for the domains of the SF-36 are shown in Fig. 1. There were no significant differences in domain or summary scores between the treatment groups. The physical component summary score was 40.5 ± 9.9 in the low MAP and 42.2 ± 11.2 in the high MAP group.

The details of the management of the two groups during the operative period are shown in Table IIIa. The durations of CPB and of crossclamp and side-biter clamp application were comparable. Patients in the low MAP group received an average of 3.1 bypass grafts versus 2.9 in the high MAP group, and 80% of patients received an internal mammary graft. A centrifugal pump during CPB was used in more of the patients in the high MAP group (84.7% versus 72.6%, $p = 0.02$). Flows during CPB normalized for body surface area were identical in the two groups. The mean blood temperature achieved after systemic cooling was 28.4° C in the low MAP group and 28.5° C in the high MAP group.

The target blood pressures of 50 to 60 mm Hg for the low MAP and 80 to 100 mm Hg for the high MAP group corresponded to the MAP achieved at full flow. However, during CPB, there are episodes of low flow (typically lasting 30 to 60 seconds) necessitated by surgical technique (e.g., when the heart was retracted for examination of the distal vessels or to visualize anastomotic sites obscured by collateral bleeding). During CPB at full flow, an MAP of 59 ± 5 mm Hg was achieved in the low MAP group and an MAP of 82 ± 8 mm Hg in the high MAP group ($p = 0.0001$). During CPB, including all brief periods of low flow, the mean MAP was 52 ± 5 mm Hg for the low MAP group and 69 ± 7 mm Hg for the high MAP group.

Management during CPB required that patients in both groups receive similar drugs, but in different dosages (Table IIIb). The high MAP group received significantly higher mean doses of phenylephrine (the first-line vasopressor) than did the low MAP group ($p = 0.0001$). Few patients in either group received the second-line vasopressors—epinephrine, norepinephrine, or metaraminol. Thirty-six percent of the low MAP group and 4% of the high MAP group received sodium nitroprusside (the first-line vasodilator), with patients in the low MAP group receiving significantly higher mean doses. The low MAP group also received significantly higher mean doses of nitroglycerin and fentanyl (Bonferroni, $p < 0.0001$ for all).

Table II. *Preoperative neuropsychologic test scores*

	Low MAP		*High MAP*	
	Mean	*SD*	*Mean*	*SD*
Ammons IQ	105.7	14.8	105.4	13.2
Linguistic function				
Boston Naming Test	24.6	4.4	24.6	4.6
Controlled Oral Word Association	37.5	13.1	37.6	13.4
Memory				
Benton Recall correct	5.3	2.1	4.9	2.4
Benton Recognition	7.8	1.7	7.6	1.8
Mattis-Kovner Verbal Recall	10.6	3.5	10.5	3.4
Mattis-Kovner Recognition	2.7	0.8	2.7	0.7
Psychomotor function				
Trails A	43.7	22.3	45.2	24.7
Trails B	104.6	60.8	102.6	49.3
Digit Symbol	40.9	13.7	41.4	10.7
Digit Span	14.8	3.9	14.2	4.0
Finger Tapping Test (dominant)	46.6	10.3	46.2	10.1

SD, Standard deviation; *IQ*, intelligence quotient.

Overall, 93% of the low and 91% of the high MAP group received vasopressors, and 79% of the low and 48% of the high MAP group received vasodilators. There was no relationship between the doses of vasoactive drugs and major cardiac or neurologic outcomes.

Trial outcomes. At 6 months, the attrition rate was 4% (11/248 patients). In the low MAP group, three patients refused follow-up, one was lost to follow-up, and one moved. In the high MAP group, four patients refused follow-up and two patients moved.

The major outcomes are mortality, cardiac morbidity, permanent neurologic deficit, cognitive complications, and deterioration in quality of life. For the 248 patients, the total mortality rate at 6 months was 4% in the low MAP and 1.6% in the high MAP group ($p = 0.25$). In the low MAP group, three patients (2.4%) died of cardiac or neurologic complications during hospitalization, and by 6 months two additional deaths (multisystem failure, lung cancer) were reported. In the high MAP group, two patients (1.6%) died of cardiac complications after the operation, and there were no additional deaths by 6 months (Table IV).

The overall incidence of major cardiac and neurologic outcomes was 12.9% in the low MAP and 4.8% in the high MAP group ($p = 0.026$); the difference of 8.1% had a 95% confidence interval from 1.0% to 15.1%. Neither the differences in baseline characteristics (work status, freedom from angina, need for nitrates) nor the difference in type

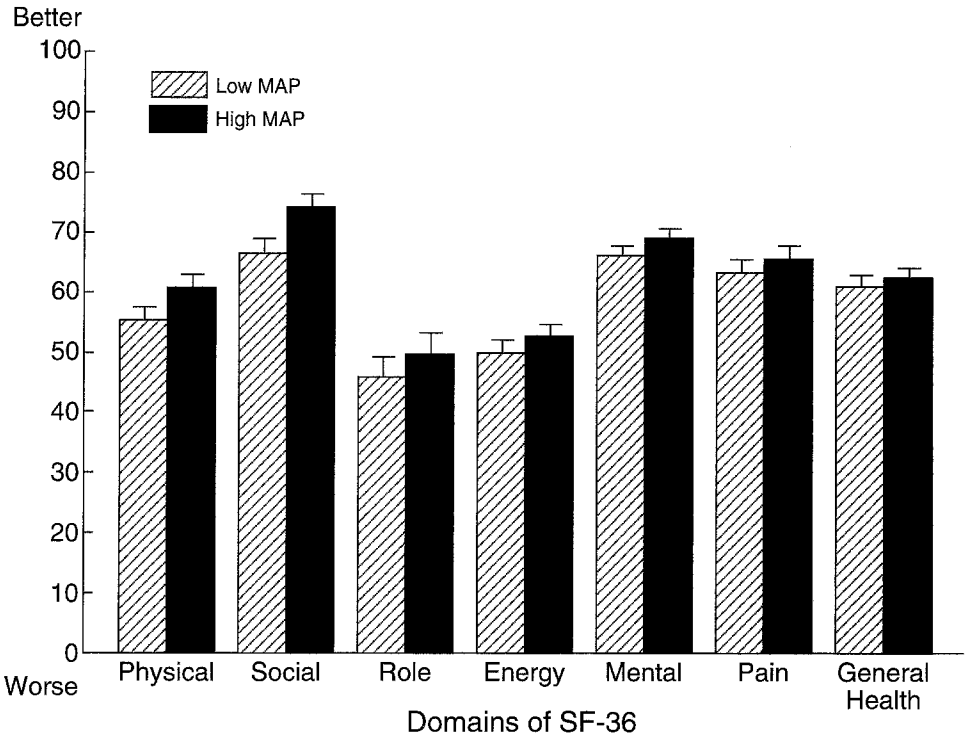

Fig. 1. Preoperative scores for the seven domains of the SF-36 in the high and low MAP groups.

of CPB pump used could explain these cardiac and neurologic outcomes. Stroke was more common in the low MAP group than in the high MAP group (7.2% versus 2.4%, $p = 0.076$). Cardiac complications were also more common in the low MAP group (4.8% versus 2.4%, $p = 0.3$). Thus all differences in mortality, cardiac morbidity, and neurologic morbidity favored the high MAP group.

Congestive heart failure (i.e., S_3 gallop, typical radiographic changes) occurred after the operation among 1.2.% of the low-MAP and 1.6% of the high MAP group without major cardiac events. Minor neurologic complications were defined as focal central nervous system deficits lasting less than 24 hours, including transient ischemic attacks, amaurosis fugax, or transient monocular blindness in patients without a new major focal deficit. In total, 3.2% of the low and 0.8% of the high MAP group sustained a minor neurologic complication. Differences in minor complications also favored the high MAP group.

Cognitive outcome was assessed by within-patient differences on the eleven-test battery. In total, 23 patients (9.3%) did not complete testing at 6 months: 11 were in the low MAP and 12 in the high MAP group (7 patients had died, 2 patients had a neurologic complication and could not complete testing, 3 patients refused, and 11 were lost to follow-up). Of those completing testing, 12% of the patients in the low and 11% of patients in the high MAP group demonstrated a clinically important decline on three or more tests (95% confidence interval for difference in deterioration in cognitive function between the two groups: −7.6% to 9.1%). Table V shows the mean within-patient change in scores from before to after operation for each neuropsychologic test for the two groups. There was no difference in change in score on any test except the Finger Tapper test ($p = 0.05$) between the two MAP groups. Thus the low and high MAP groups did not differ significantly with regard to preservation of cognitive function.

Fig. 2 shows the change in score for each of the seven domains of the SF-36. Change in functional status could not be assessed for 15 patients in each group (7 patients died, 11 patients were lost to follow-up, 2 patients had a neurologic event, and 10 patients did not complete the SF-36 before or after the operation). The majority of patients demonstrated significant improvement in all seven domains. The degree of improvement did not differ between the groups: 8.3% of patients in the low

Table IIIa. *Intraoperative management for the two treatment groups*

	Low MAP		*High MAP*	
	Mean	*SD*	*Mean*	*SD*
Premedications				
Lorazepam (mg)	2.4	1.0	2.5	1.0
Morphine (mg)	7.2	1.9	7.3	1.7
Induction medications				
Fentanyl (μg/kg)	40.1	20.0	40.1	14.0
Thiopental (mg/kg)	1.2	1.5	1.4	1.4
Heparin (units/kg)	315.4	92.0	306.6	92.6
Midazolam (mg)	5.8	3.3	6.3	4.4
Pancuronium (mg)	14.3	22.1	12.6	6.0
Pre-CPB cardiac output (L/min)	3.5	1.5	3.6	1.5
CPB time				
CPB duration (min)	89.4	31.5	84.9	28.3
Aortic crossclamp duration (min)	46.7	20.0	43.1	16.7
No. of grafts	3.1	0.8	2.9	0.8
Internal mammary graft (%)	77.4	3.8	80.7	3.5
Pump flows (L/min/m²)				
CPB on—warming	1.9	0.3	1.9	0.3
Warming—crossclamp off	2.0	0.3	1.9	0.3
Crossclamp off—CPB off	2.3	0.2	2.2	0.3
MAPs (mm Hg)				
CPB (full flow)	59.2	5.4	81.8	7.8
CPB (for all flows)	51.8	5.2	69.5	7.1
Aortic crossclamp on (full flow)	56.5	7.1	81.2	7.8
Aortic sidebiter clamp on (for all flows)	49.6	5.8	67.1	8.8
No. of low flow intervals	7.7	3.2	9.3	3.8
Hematocrit during CPB (%)	20.5	2.6	20.9	3.1
Returned to CPB (%)	1.6	1.1	2.5	1.4

SD, Standard deviation.

Table IIIb. *Medications during CPB*

	Low MAP			*High MAP*		
Medications during CPB	*Mean dose per treated patient*	*SD*	*No.*	*Mean dose per treated patient*	*SD*	*No.*
Fentanyl (μg/kg)	23.1	14.2	117	15.1	9.5	104
Nitroglycerin (μg)	1312.4	2801.3	78	558.5	509.4	59
Midazolam (mg)	6.7	3.7	106	5.4	4.7	97
Phenylephrine (mg)	2.4	2.1	111	5.2	4.8	112
Epinephrine (μg)	31.8	31.9	28	52.2	68.0	18
Norepinephrine (μg)	25.0	7.1	2	1525.0	1025.3	2
Metaraminol (mg)	4.0	0	1	5.1	2.3	6
Pancuronium (mg)	8.7	3.1	81	8.3	3.7	77

SD, Standard deviation.

MAP and 6.5% in the high MAP group reported a decline of more than five points in the physical component summary score. The 95% confidence interval for the difference in deterioration in functional status between the two groups was from −5.0% to 8.6%.

A pragmatic analysis was conducted to ascertain whether the extent of compliance with the target

Table IV. *Cardiac and neurologic outcomes in the two treatment groups (intention to treat)*

	Low MAP (n = 124)		*High MAP (n = 124)*		*Low − high MAP*		
	No.	*%*	*No.*	*%*	*No.*	*%*	*95% CI for % difference*
Fatal stroke	2	1.6	0	0.0			
Hemiparesis*	2	1.6	1	0.8			
Aphasia	3	2.4	1	0.8			
Cortical blindness	1	0.8	0	0.0			
Monocular blindness	1	0.8	0	0.0			
Other focal deficit	0	0.0	1	0.8			
Total permanent neurologic complications	9	7.2	3	2.4	6	4.8	−0.5, 11.0
Fatal cardiogenic shock	1	0.8	2	1.6			
Shock	1	0.8	0	0.0			
Myocardial infarction	4	3.2	1	0.8			
Total cardiac complications	6	4.8	3	2.4	3	2.4	−2.2, 7.1
Other death, total (not attributable to cardiac or neurologic causes)	2	1.6	0	0	2	1.6	−0.6, 3.8
Total mortality and major cardiac and neurologic morbidity	16†	12.9	6	4.8	10	8.1	1.0, 15.1

The last column shows the 95% confidence interval (CI) for the low MAP group percent minus high MAP group percent.
*Hemiparesis and aphasia; hemiparesis, apraxia, and hemianopsia; hemiparesis, aphasia, and hemisensory deficit.
†One patient had both a cardiac and a neurologic complication.

Table V. *Cognitive function 6 months after the operation: Mean within-patient change in score**

	Low MAP		*High MAP*	
	Mean	*SD*	*Mean*	*SD*
Linguistic function				
Boston Naming Test	0.4	2.0	0.8	2.3
Controlled Word Association	0.0	8.3	0.6	6.1
Memory				
Benton Visual Recall	0.5	1.9	0.8	1.9
Benton Recognition	0.1	2.2	0.1	2.0
Mattis-Kovner Recall	1.1	3.4	1.3	3.6
Mattis-Kovner Recognition	0.08	0.79	0.11	0.72
Psychomotor function				
Trails A	−2.7	15.4	−4.0	20.3
Trails B	−3.6	46.9	−13.9	39.3
Digit Symbol	2.5	5.9	3.7	6.7
Digit Span	0.0	3.1	0.4	2.9
Finger Tapping Test	−1.4	9.3	0.9	7.0

SD, Standard deviation.
*Score 6 months after the operation minus the preoperative score.

blood pressure range affected the results. As shown in Table VI, patients in whom higher pressures were achieved had lower complication rates ($p = 0.02$). Table VII shows that there were no technical complications related to the MAP strategy; there was no increase in bleeding, transfusion requirements, or length of stay in the intensive care unit for patients in the high versus low MAP group.

Discussion

Previous trials in adults undergoing cardiac operations for acquired disease have assessed the impact of different anesthetic agents (halothane, enflurane, isoflurane, and sufentanil),[20-22] pH management,[17] barbiturate infusions during CPB,[23, 24] filters,[25, 26] and oxygenators[9] on outcome after CABG and have not demonstrated significant differences in neurologic or cardiac complications.

Historically, MAP during CPB has been maintained in the range of 50 mm Hg,[11] and several studies have suggested that there was no adverse impact at this MAP.[27, 28] Several studies in noncardiac operations have pointed to the importance of maintaining pressure within the autoregulatory range of the patient.[29] This trial is the first to address the issue of blood pressure management during CPB in patients having CABG.

The physiology of autoregulation in the coronary and cerebral circulations is fundamental to the hypothesis that intraoperative blood pressure is related to the risk of complications. In the coronary and cerebral circulations, autoregulation preserves perfusion within a relatively narrow range.[30, 31] Systemic pressures outside the limits of autoregulation may produce changes in perfusion with subsequent tissue damage. Our hypothesis is that patients whose MAP is maintained at higher pressures closer to

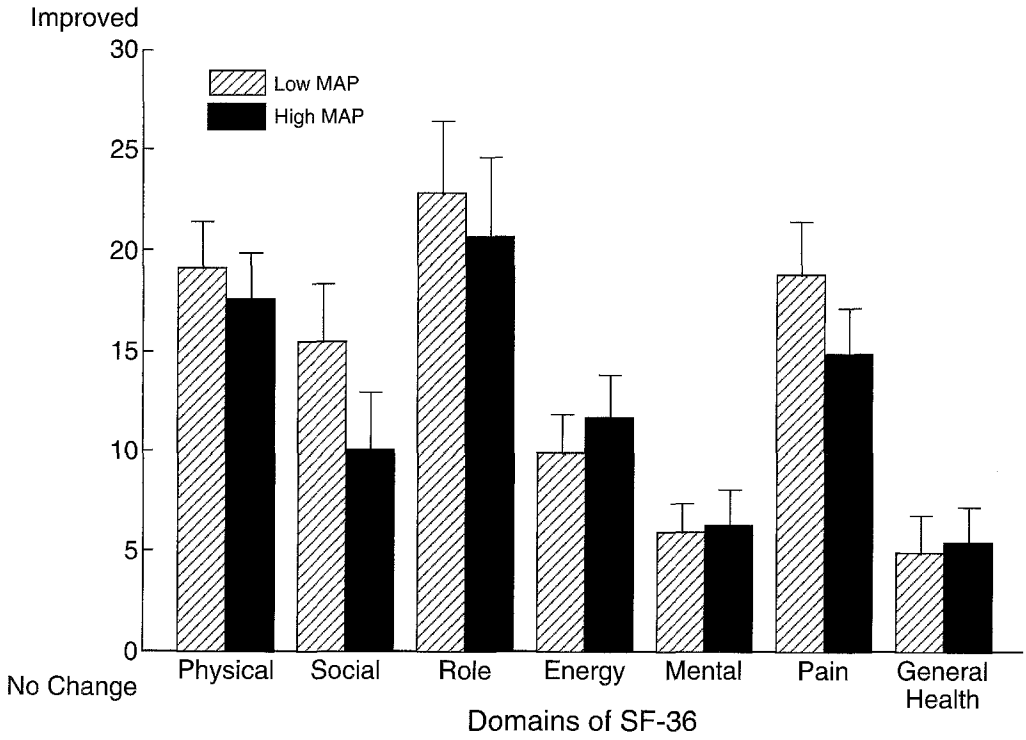

Fig. 2. Within patient change in SF-36 for the seven domains of the SF-36 for the high and low randomization groups.

Table VI. *Events up to 6 months after the operation stratified by actual MAP achieved during CPB (pragmatic analysis)*

	Actual MAP achieved (mm Hg)						
	<40	*40-49*	*50-59*	*60-69*	*70-79*	*>80*	*Total*
No. of patients	5	36	90	54	57	6	248
All cardiac complications	20%	3%	7%	0%	2%	0%	9%
All neurologic complications	0%	3%	10%	2%	2%	0%	12%
All other deaths, (not attributable to cardiac or neurologic causes)	0%	3%	1%	0%	0%	0%	2%
Combined mortality and major cardiac and neurologic morbidity	20%	8%	17%	2%	4%	0%	22%

Each entry is percent of patients in each MAP group who had a complication.

their autoregulatory range will have decreased postoperative morbidity and deterioration in quality of life after CABG.

There was prior evidence that MAP can be increased to achieve higher perfusion pressures in a manner that is technically safe while maintaining desirable patient outcomes.[32] This has been confirmed in the present trial. In this cohort, maintaining higher MAPs did not prolong total time on CPB, decrease distal coronary visualization, or increase duration of crossclamp or sidebiter clamp application. Further, there was no increase in bleeding, transfusion requirements, or length of stay for patients in the high MAP group.

Blood pressure targets were achieved during periods of full flow. Flow rates were maintained within the prescribed ranges, and all cointerventions were equivalent between the two MAP groups, except for expected differences in the use of vasoactive drugs.

The total mortality rate at 6 months was 2.8%, with most of the mortality occurring in the perioperative period. At 6 months after the operation, 3.5% had cardiac complications and 4.8% had neurologic complications. These rates compare favor-

Table VII. *Postoperative factors in the low and high MAP groups*

	Low MAP	*High MAP*
Length of intensive care unit stay (mean hours)	77 ± 250	60 ± 171
Length of hospital stay (mean days)	17 ± 25	13 ± 14
Packed red blood cells (mean units)	3.8 ± 5.4	4.0 ± 4.7
Length of intubation (mean hours)	24 ± 21	32 ± 118
Chest tube drainage at 24 hours (mean milliliters)	1011 ± 701	885 ± 500

ably to other outcome studies of elective CABG.[33] The rates of cognitive complications reported in other trials vary, primarily because the criteria used for defining the cognitive deterioration differ among these trials.[34, 35]

The individual occurrence of outcomes (mortality, cardiac, neurologic, cognitive, and functional) all favored the high MAP group. In some instances, very low complication rates contributed to the lack of statistical significance; the trial sample size was calculated in advance assuming higher rates of mortality and morbidity in the control group. When the results were analyzed by comparing the outcomes, the high MAP group had a significantly lower combined incidence of cardiac and neurologic morbidity and mortality.

A pragmatic analysis was performed to evaluate the relationship of achieved MAP to outcomes. This analysis confirmed that patients with lower achieved MAPs tended to have more cardiac and neurologic morbidity and mortality than those maintained at high MAPs.

In conclusion, this study demonstrates that higher MAPs can be achieved in a technically safe and reliable manner. This elevation of MAP during CPB effectively improves outcomes after elective CABG.

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Discussion

Dr. Randall B. Griepp *(New York, N.Y.).* The most important result of this clinical trial is that a high perfusion pressure during CABG reduces the prevalence of perioperative neurologic complications from about 7% to 2%. This conclusion differs from that of other studies in the past and, to my knowledge, is the first demonstration of a cerebral protective effect of high physiologic perfusion pressures during CPB. If these data are applicable to all patients undergoing CABG, many surgeons may wish to change their perfusion protocols. Therefore, a number of questions are appropriate.

First, was there no downside whatsoever to the high perfusion pressure, no problems with cannulation site bleeding, no increased incidence of clamp injury to the aorta?

Second, were there any factors other than perfusion pressure and development of aortic plaque as determined by transesophageal echocardiography that were predictive of stroke? In most contemporary studies age has been a powerful predictor of stroke. It would be of interest to know if this study is representative of and corresponds to findings in other studies as well.

Third, it appears that most of the neurologic complications occurred in the subgroups with severe aortic atherosclerosis as assessed by transesophageal echocardiography. If these subgroups are removed, is there any hint of a difference in neurologic outcome in the remaining majority of patients? If not, is it necessary to use high perfusion pressures in the majority of patients who do not have a high degree of aortic atherosclerosis?

Fourth, what would you propose as a mechanism of protection against neurologic injury by high perfusion pressures in the presence of severe aortic plaque? It is logical that the brain with intracranial stenotic cerebrovascular disease might fare better with a higher perfusion pressure. However, aortic plaque is thought to predispose to cerebral injury caused by atheroembolism, and how a high perfusion pressure would prevent or ameliorate such events is not obvious. Do you have an explanation?

A further clinical point. Although perioperative neurologic events were much more frequent in the high pressure group, there was no long-term difference in functional or cognitive status. How important then were the perioperative events?

Finally, what is your current clinical practice? Do you and your colleagues routinely use a perfusion pressure of 80 to 100 mm Hg in all patients undergoing CABG? If not, in which groups do you not do so?

My questions are not meant as criticism of this fine article but merely to emphasize the importance of work in this area. It may be too late for some members of our Association to benefit from it, but by the time I need my CABG, I would like to know that the problem of perioperative neurologic dysfunction has been eliminated.

Dr. Gold. Thank you, Dr. Griepp, for your insightful questions. The first question dealt with the complications associated with the high mean arterial perfusion pressure. There actually were none. As a matter of fact, there were slightly shorter crossclamp times and less perioperative bleeding. The only difficulty we had was convincing the seven-member surgical faculty that high pressure CPB was indeed safe. There were no complications.

Factors other than the pressure during the perfusion and the echocardiographic grade of the aorta for predicting stroke included some standard predictors such as age older than 75 years and preexisting neurologic abnormality.

Indeed, in our study the groups at very low risk, meaning patients with minimal or no atherosclerosis on transesophageal echocardiography, did not have any of the strokes that were detected after the operation. However, with our increasing use of echocardiography, we have noted that the extent of disease in the transverse arch and in the ascending arch with and without epicardial and epiaortic echocardiography and the extent of disease in the descending aorta sometimes is very difficult to measure. Sometimes one will just catch the corner of a plaque that may be a significantly larger structure when fully evaluated. We therefore think that the technique is beneficial to all categories of patients undergoing coronary surgery.

Regarding the mechanisms of injury, we and others have gathered a wealth of data with the use of transcranial Doppler echocardiography. The embolic components of atherosclerosis of the aorta are significant. However, we believe that atherosclerosis of the aorta, and indeed the presence of coronary disease, are markers for fixed intercerebral vascular stenoses that are better managed with higher perfusion pressures. If you allow the perfusion pressure to remain within the normal autoregulatory range, you overcome some of these stenoses and therefore get better end-organ perfusion, not only of the brain but of the heart, the gut, and other organs.

With regard to clinical status, this has been a bit of a hard sell. Even within our own institution, in patients with absolutely no visible atherosclerosis of the aorta on transesophageal echocardiography, we keep the pressure between 65 and 75 mm Hg. We do study all of these patients during the operation (if not before). In patients with moderate or advanced disease of the ascending aorta, we would keep the mean perfusion pressure above 80 mm Hg. If I were the patient, I would want the perfusion pressure to be high.

Dr. Thomas A. Pfeffer *(Los Angeles, Calif.).* I have two questions. The first concerns the technique of performing the proximal anastomoses. Was a partial aortic occluding clamp used for all proximal anastomoses or were some performed with a single total occlusion clamp with all distal and proximal anastomoses performed during the same period of aortic crossclamping? Did the detection of aortic atherosclerotic disease affect this technique? Were any patients considered candidates for an aortic endarterectomy procedure, as advocated by Dr. Kouchoukos?

Second, although maintaining a desired perfusion pressure is generally easy during CPB, that frequently is not the case in the period immediately after discontinuation of CPB. The patients are usually vasodilated and hemodiluted and we are dependent on our colleagues in anesthesiology for assistance in maintaining adequate perfusion pressure. Were there any differences in these two groups of patients, concerning their blood pressure and hemodynamics, in the period immediately after discontinuation of CPB? Could you comment on the requirement for vasopressors during this period?

Dr. Gold. All of these patients underwent creation of a proximal anastomosis with the application of a partial occlusion clamp. Although we are now studying a single-clamp versus a two-clamp protocol using the same type of neurologic and cognitive monitoring that has been proposed in other institutions, for purposes of this study a partial occlusion clamp was always used.

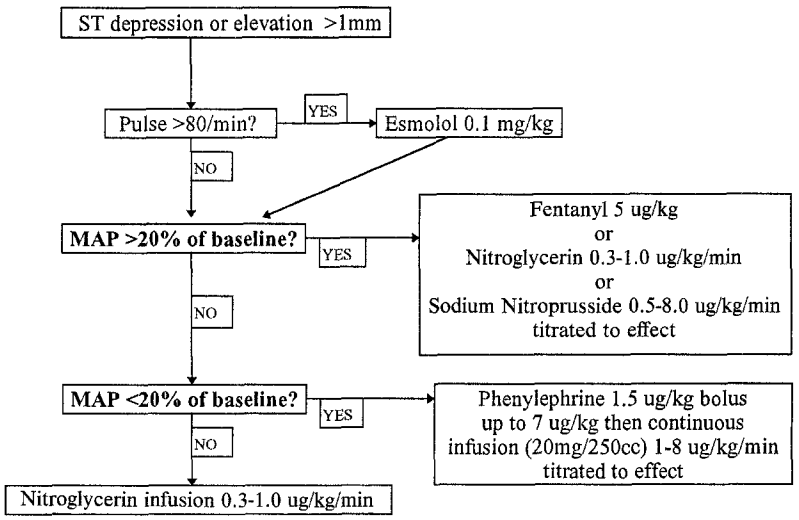
None of the patients had severe enough disease in the ascending aorta to warrant an aortic endarterectomy. Perhaps in the patients who did have a stroke, we should have considered endarterectomy. Maybe we should reconsider this type of procedure in the future in patients with advanced disease.

In answer to your last question, immediately after CPB and in the perioperative period in the intensive care unit, there were some minor differences between the two groups of patients. Patients treated with more vasopressor in the intraoperative period required less vasopressor after the operation, required less fluid, had less weight gain, had a shorter period ventilatory support, and actually were released from the intensive care unit slightly (but not statistically) faster. Certainly, there was no downside from using high perfusion pressure.

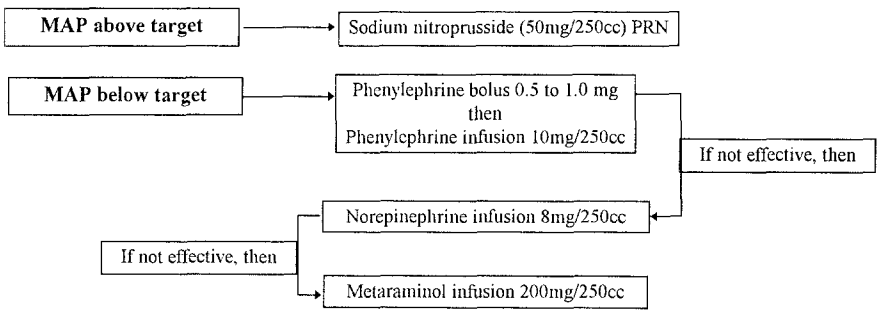
Dr. Watts R. Webb *(New Orleans, La.).* Did you measure cerebral blood flow during these studies? The conventional studies have usually shown that autoregulation of blood flow to the brain ranges from 50 up to 150 mm Hg, and, with hypothermia, down to 28° C or less; autoregulation may continue down to as low as 20 mm Hg. I would like to know both the temperatures that you used and the blood flows that you measured during this period of time.

Dr. Gold. We did not measure cerebral blood flow. The only flows that we measured were total systemic blood flow during CPB. We used 28° C (moderate hypothermia) for the major part of the aortic crossclamp interval.

Although your comments about autoregulation of the brain are correct, perhaps in patients with advanced atherosclerosis of the cerebrovascular system some alteration in those numbers needs to be made. If you evaluate integrated electroencephalographic cerebral function and other measurements of cerebral ischemia, you will see that as pressures fall in patients with fixed stenoses, regional cerebral perfusion suffers.



Appendix Fig. 1. Management of intraoperative ischemia.



Appendix Fig. 2. Management of intraoperative MAP. *PRN*, As required.

Appendix 1

Management of intraoperative ischemia. Before or after CPB, ischemia (ST elevation or depression >1 mm) was managed by a nitroglycerin infusion (0.13 to 1 μg/kg per minute) if there were no hemodynamic changes. If ischemia occurred with an increase in MAP of more than 20%, fentanyl (5 μg/kg), nitroglycerin (0.3 to 1 μg per minute), or sodium nitroprusside was used. For pulse rates greater than 80 beats/min, esmolol (0.1 mg/kg) was used. If the MAP was less than 20% of baseline, phenylephrine (1.5 μg/kg) was given to minimize ischemic electrocardiographic changes (Appendix Fig. 1).

Management of blood pressure on CPB. The method for blood pressure management during CPB was as follows for both randomization groups (Appendix Fig. 2): for MAP above target, sodium nitroprusside (50 mg/200 ml) infusions were used as necessary. For MAP below target, a phenylephrine bolus (0.5 to 1.0 mg) was given; phenylephrine infusions (10 mg/250 ml) were given if boluses were insufficient. If the patient was unresponsive to phenylephrine, norepinephrine infusion (8 mg/250 ml) was used as a second-line vasopressor. Metaraminol (200 mg/250 ml) was used as a third-line vasopressor if the first- and second-line vasopressors failed.

Appendix 2. Definitions of cardiac complications

Postoperative myocardial infarction: New persistent Q waves of more than 0.03 msec and greater than 1 mV in depth required in two contiguous leads on a standard twelve-lead electrocardiogram, in the absence of a new conduction abnormality or a marked change in the QRS axis.[36]

Pulmonary edema: (1) Rales occupying two thirds of the lung fields and a typical x-ray picture for pulmonary edema or (2) pulmonary capillary wedge pressure persistently greater than 25 mm Hg. These findings were associated with refractory hypoxemia (arterial oxygen tension/inspired oxygen fraction <200).[37]

Adult respiratory distress syndrome: Diffuse interstitial pattern on the roentgenogram, a pulmonary capillary wedge pressure less than 18 mm Hg, and refractory hypoxemia.

Cardiogenic shock: A syndrome of end-organ hypoperfusion (i.e., urine output < 10 ml/hr for >2 hours)

with a systolic blood pressure less than 90 mm Hg or a mean blood pressure less than 65 mm Hg and a pulmonary capillary wedge pressure greater than 18 mm Hg in combination with a decline in the cardiac index to less than 2.2 L/min per square meter. The elevated central venous pressure or right atrial pressure in the absence of tamponade constituted evidence of right heart failure, if the cardiac output was less than 2.2 L/min per square meter. This includes the finding of systemic hypotension unresponsive to fluid administration, with an elevated pulmonary artery or wedge pressure in the setting of a cardiac index less than 1.5 L/min per square meter and evidence of end-organ hypoperfusion.

Appendix 3. *The clinically important differences for the neuropsychologic test battery*

Boston Naming	Decrease > 4
Controlled Oral Word Association	Decrease > 12
Benton Visual Retention Test	Decrease > 2
Benton Recognition Test	Decrease > 2
Mattis Kovner Verbal Recall	Decrease > 3
Mattis Kovner Recognition	Decrease > 0.7
Trail Making A	Increase > 22
Trail Making B	Increase > 84
WAIS-R Digit Span	Decrease > 3
Finger Tapping Test	Decrease > 6
WAIS-R Digit Symbol	Decrease > 11