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Cardiac Performance Preserved Despite Thiopental Loading

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Background: **Some cerebral artery aneurysms require cardiopulmonary bypass and deep hypothermic circulatory arrest to be clipped safely. During bypass these neurosurgical patients often are given large doses of thiopental in the hope that additional cerebral protection will be provided. However, thiopental loading during bypass has been associated with subsequent cardiac dysfunction in patients with heart disease. This study was undertaken to determine how patients without concomitant heart disease would respond to thiopental loading.**

Methods: **Twenty-four neurosurgical patients with giant cerebral aneurysms and little or no cardiac disease were anesthetized with fentanyl, nitrous oxide, and isoflurane. Thiopental was titrated to achieve electroencephalographic burst-suppression before bypass, and the infusion was continued until after separation. Prebypass hemodynamic and echocardiographic measurements were obtained during a stable baseline and 15 min after thiopental loading began. They were repeated after bypass.**

Results: **Prebypass thiopental loading increased heart rate from 61 ± 11 to 72 ± 13 beats/min and decreased stroke volume from 43 ± 10 to 38 ± 8 ml · beat^{-1} · m^{-2}, but arterial and filling pressures, vascular resistance, cardiac index, and ejection fraction remained the same. Before bypass, thiopental plasma concentration measured 28 ± 8 μg/ml. Loading continued for 2–3 h until after bypass was terminated, and the overall infusion rate was 18 ± 5 mg · kg^{-1} · h^{-1}. All patients were easily separated from bypass without inotropic support. Following bypass, vascular resistance was decreased; heart rate, filling pressures, and cardiac index were increased; stroke volume had returned to its baseline; and ejection fraction was unchanged.**

Conclusions: **It was concluded that if preoperative ventricular function is good, thiopental loading to electroencephalographic burst-suppression causes negligible cardiac impairment and does not impede separation from cardiopulmonary bypass.** (Key words: Anesthesia, neurosurgical. Anesthetics, intravenous: thiopental. Cardiopulmonary bypass: deep hypothermic circulatory arrest. Heart: ejection fraction. Surgery, neurosurgical: cerebral aneurysm.)

MANY giant cerebral artery aneurysms, particularly those of the vertebrobasilar system, are deemed inoperable because conventional neurosurgical techniques are fraught with an unacceptably high mortality. At several institutions, however, these complex cerebral aneurysms are clipped under deep hypothermic circulatory arrest and results are encouraging.[1,2] Cardiopulmonary bypass is established and patients are centrally cooled to about 15° C before the circulation is arrested. Thiopental is infused during bypass, in the hope that it will provide additional cerebral protection, especially during the vulnerable, relatively normothermic periods when cannulae are inserted to initiate and removed to terminate cardiopulmonary bypass.

Intraoperative thiopental loading to protect the brain during cardiac surgery also has been advocated.[3–5] A large total dose of thiopental is needed to achieve prolonged electroencephalographic (EEG) suppression, and studies show that patients with cardiac disease who receive thiopental during cardiopulmonary bypass require inotropic support afterward more often than do untreated control subjects.[4–6]

When cardiopulmonary bypass and hypothermic circulatory arrest are to be utilized to facilitate neurosurgery, patients with significant cardiac disease are precluded. This investigation, therefore, was undertaken to determine whether cardiac performance would be impaired by thiopental in patients without concomitant heart disease.

Methods

Both institutional approval and subjects' informed consent were obtained before the study. Twenty-four patients underwent deep hypothermic circulatory ar-

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rest for clipping of a complex cerebral artery aneurysm. All had a thorough preoperative cardiac evaluation and were found to have little or no cardiac dysfunction.

After sedation with oral diazepam, patients were brought to the operating room. Anesthesia was induced with midazolam (0.05 mg/kg), fentanyl (50 μg/kg), thiopental (5 mg/kg), and isoflurane (0.5%) in nitrous oxide and oxygen. Following administration of vecuronium, the trachea was intubated and the lungs ventilated to an arterial carbon dioxide tension (Pa_{CO_2}) of approximately 30 mmHg. Lidocaine (100 mg) and esmolol (1 mg/kg) were given to inhibit the increase in arterial pressure associated with intubation.

Thiopental loading began when it was determined that circulatory arrest would be necessary to proceed safely. Boluses of 100 mg were given every minute until the EEG became isoelectric, and thereafter, a 2.5% infusion was titrated to a burst-suppression ratio of 1:5. EEG leads C3–P3 and C4–P4 were displayed continuously.

With burst-suppression present, cardiopulmonary bypass was established without thoracotomy *via* femoral-femoral cannulation. A 21-French venous cannula was passed into the right atrium, and centrifugal bypass pumps were used with a membrane oxygenator to achieve a flow rate of 2.5 $L \cdot min^{-1} \cdot m^{-2}$. Hypothermia (16° C) was induced by decreasing the water bath heat-exchanger temperature to 5–10° C. A Mallinckrodt Mon-a-Therm fine wire thermocouple sensor (St. Louis, MO), placed in the parenchyma of the brain at the operative site, was used to measure central temperature. Although the EEG became isoelectric with cooling, thiopental administration continued unabated until circulatory arrest. After pump flow ceased, patients were exsanguinated into the bypass reservoir to relax the neurovasculature further. Mean arterial pressure decreased to almost zero, and the final neurosurgical dissection and clipping of the aneurysm took place under these conditions. Cardiopulmonary bypass was resumed, and patients were warmed to 37° C before separation was attempted. As bypass was resumed, thiopental administration began again at its previous rate and did not cease until the perfusion cannulae were removed.

Cardiovascular parameters were monitored by electrocardiogram, radial artery and pulmonary artery catheters, and transesophageal echocardiography. A Hewlett Packard (Ubiquitous, CA) 5.0 MHz phased-array ultrasonic-transducer probe was passed into the esophagus and positioned so that two-dimensional left-ventricular short-axis echocardiographic images could be obtained at the level of the papillary muscles. These images were displayed in real time by a Hewlett Packard 1000 echocardiographic unit and videotaped intermittently for future analysis.

Measurements were made at the following times: (1) just before the start of thiopental loading, (2) during the prebypass thiopental infusion when burst-suppression was evident on the EEG, and (3) after cardiopulmonary bypass cannulae were removed.

Each set of measurements was obtained simultaneously and included a hemodynamic profile, echocardiographic images, a thiopental plasma concentration, arterial blood gases, and hematocrit. Heparinized blood samples were collected and centrifuged, and the plasma was stored at −70° C until assayed for thiopental by high performance liquid chromatography using a C18 reverse-phase column with ultraviolet detection at 280 nm.[7] The sensitivity of our analysis was 0.25 μg/ml and the coefficient of variation was between 2.3% and 7.1%.

Echocardiographic recordings were examined and evaluated by a cardiologist who was blinded to the circumstances of the study. The quality of the echocardiographs from two patients was judged as poor, and these data were excluded from the final results, as were data from two other patients in whom the images did not remain at the same papillary muscle level. End-systolic and end-diastolic images were measured with a planimeter to ascertain left-ventricular internal cross-sectional areas. End-systole was identified by cavity size, and end-diastole, from the timing of the electrocardiogram. Only frames taken during expiration were chosen, and cross-sectional areas were determined from the average of five separate heart beats. Ejection fraction, expressed as a percentage was defined as follows: the value of the left-ventricular end-diastolic area minus the value of the left-ventricular end-systolic area, divided by the value of the left-ventricular end-diastolic area, and multiplied by 100. This area ejection fraction provides a quantitative assessment of left-ventricular performance,[8,9] but is confounded by being afterload- and preload-dependent.

Results are expressed as mean ± SD. Statistical comparisons were performed by repeated-measures analysis of variance, with $P < 0.05$ considered significant. Specific differences were isolated statistically using Fisher's progressive least squares differences method.

Results

Data were collected from 24 patients: 15 women and 9 men. Their mean age was 49 ± 14 yr and each had an ASA physical status of either 2 or 3. Ten had major neurologic deficits prior to surgery, and two had had a tracheostomy. No patient had other significant cardiovascular disease by history or physical examination, but six were hypertensive with electrocardiographic evidence of left ventricular hypertrophy.

Table 1 displays thiopental infusion rates and plasma concentrations, blood gas levels, hematocrit readings, hemodynamic parameters, and echocardiographic data.

Cardiopulmonary bypass was initiated 2 to 3 h after neurosurgical incision and long after anesthesia had become stable. Baseline measurements preceded bypass preparation, and these were followed by thiopental administration. The EEG became isoelectric after a loading dose of 340 ± 110 mg (3–4 min). Two patients experienced an initial decrease in arterial pressure of 22%, and in one patient, the hypotension was associated with a 25% decrease in cardiac output. By 15 min, when titration to a burst-suppression ratio of 1:5 was accomplished, two individuals demonstrated a decreased ejection fraction (one had decreased by 29% and the other, by 15%). At that time, the thiopental infusion rate was 18 ± 5 $mg \cdot kg^{-1} \cdot h^{-1}$ and the plasma concentration was 28 ± 8 μg/ml. Mean heart rate was increased 15% and stroke volume decreased 13%, but there were no significant changes in arterial or filling pressures, vascular resistance, cardiac output, or ejection fraction. Cardiopulmonary bypass was not always established immediately after the thiopental loading measurements were made, but hemodynamic parameters and echocardiographic data always remained stable thereafter, sometimes for more than an hour.

Table 1. Thiopentol Infusion Rates and Plasma Concentrations, Blood Gases, and Hemodynamic and Echocardiographic Data

	Baseline	Thiopent	Off CPB
Thiopental infusion rate ($mg \cdot kg^{-1} \cdot h^{-1}$)	0	18 ± 5	0
Thiopental plasma concentration (μg/ml)	1.6 ± 1.2	28 ± 8*	13 ± 5*
Pa_{CO_2} (mmHg)	31 ± 5	32 ± 5	32 ± 6
pHa	7.46 ± 0.05	7.44 ± 0.06	7.41 ± 0.06
Heart rate (beats/min)	61 ± 11	72 ± 13*	81 ± 11*
Arterial press (mmHg)	84 ± 12	83 ± 13	80 ± 10
CVP (mmHg)	9 ± 3	9 ± 4	11 ± 3*
PAD press (mmHg)	11 ± 4	11 ± 4	14 ± 4*
Cardiac index ($L \cdot min \cdot m^{-2}$)	2.7 ± 0.7	2.7 ± 0.7	3.5 ± 0.6*
Stroke volume ($ml \cdot b^{-1} \cdot m^{-2}$)	43 ± 10	38 ± 8*	42 ± 8
Vascular resist (units)	28 ± 9	28 ± 9	20 ± 5*
Hematocrit (%)	33 ± 5	33 ± 5	23 ± 2*
End-systolic area (cm^2)	9 ± 3	9 ± 4	9 ± 3
End-diastolic area (cm^2)	19 ± 5	18 ± 5	19 ± 4
Ejection fraction (%)	53 ± 10	51 ± 11	55 ± 10

* Significantly different from baseline measurement, $P < 0.05$.

CVP = central venous pressure; PAD = pulmonary artery diastolic pressure; Baseline = during anesthesia and surgery, just before the start of the thiopental infusion; Thiopent = during the thiopental infusion, before the initiation of cardiopulmonary bypass; Off CPB = after separation from cardiopulmonary bypass.

With hypothermic cardiopulmonary bypass, the EEG changed from burst-suppression to become isoelectric, but the prevailing thiopental infusion rate was maintained until circulation was arrested. Cooling to 16° C took 29 ± 9 min. Twenty-two patients developed ventricular fibrillation during bypass and received potassium chloride (20-mEq boluses) to induce standstill. Circulatory arrest lasted 21 ± 12 min. After the extracorporeal circulation was reestablished, rewarming to 37° C took 62 ± 19 min. Between 26° and 33° C, sinus rhythm returned spontaneously in 16 patients; the others required ventricular defibrillation. Atrial fibrillation developed in one patient, who received digitalis, verapamil, and esmolol before the heart reverted to sinus rhythm. Cardiopulmonary bypass lasted 121 ± 25 min, and all patients were separated easily without the need for inotropic support.

The final set of measurements was obtained shortly after bypass cannulae were removed. A total dose of 3.2 ± 1.3 g thiopental (45 ± 11 mg/kg or 18 ± 5 $mg \cdot kg^{-1} \cdot h^{-1}$) had been given, and the plasma concentration was significantly less at that time than it had been during the infusion. After separation from bypass, patients were anemic, vasodilated, and a little more fluid-loaded than they had been in the control state. Heart rate and cardiac output both were increased by 30%, stroke volume had returned to its baseline value, and ejection fraction measured 55% (unchanged).

Shortly thereafter, surgery was concluded and patients were brought to the intensive care unit, where their lungs were ventilated overnight. Hemodynamic parameters remained satisfactory in all but one patient,

who required a vasopressor for an hour while volume repletion was carried out. No one demonstrated postoperative electrocardiographic changes or increases in cardiac enzymes. Sixteen patients were awake and underwent tracheal extubation the following morning; the others remained tracheally intubated for 2–4 days. Four patients had a poor neurosurgical outcome (three suffered intraoperative strokes and another died), and the rest did well.

Discussion

Barbiturates have been and continue to be administered as cerebral protective agents in special clinical situations, even though their effectiveness in that capacity is uncertain.[10] To achieve prolonged EEG suppression, a substantial dose of thiopental is necessary, and myocardial depression and even cardiovascular collapse have occurred in hypovolemic or otherwise compromised patients who have received large doses.[11] When thiopental is administered during cardiopulmonary bypass, many patients require subsequent inotropic support.[4–6] Nevertheless, thiopental has been used with relative safety for half a century, and it was our intention to try to determine whether it was the existence of heart disease or the thiopental administration that was responsible for the cardiovascular impairment seen in cardiac surgical patients after cardiopulmonary bypass.

To provide a more comprehensive evaluation of the systolic performance of the heart, we chose to supplement standard hemodynamic monitoring with transesophageal echocardiographic analysis. More definitive methods exist, but they are impractical in the usual operating room setting. Urbanowicz *et al.*[8] and Clements *et al.*[9] recently compared technetium-99–gated pool scintigraphy with single-plane left-ventricular short-axis echocardiographic imaging to determine ejection fraction in surgical patients and found a good correlation. Ejection fraction is afterload- and preload-dependent, however, and during the persistent hemodilution and volume-loading that followed cardiopulmonary bypass, these variables were not constant. Both decreased afterload and increased preload tend to maintain ejection fraction in the face of declining ventricular function,[12] and this fact is a major limitation of the study.

The sensitivity of the echocardiographic measurements is another aspect of this study that bears scrutiny; for although stroke volume, measured by thermodilution, decreased with thiopental loading, this change was not reflected in our end-diastolic and end-systolic area data. Thermodilution is the gold standard with respect to volume measurement. Transesophageal echocardiographic planimetry is limited to a single two-dimensional plane, and quantification assumes a uniform ventricular cavity amenable to mathematical modeling. The areas we examined may not have been representative of the entire ventricle, and dyskinetic regions may have been missed. Ejection fraction is a ratio between two area measurements, and, as such, lacks precision; however, it is the best available clinical estimate of systolic ventricular performance and is a useful predictor of outcome.[12]

This paper presents information concerning two separate but related issues. The prebypass data demonstrate that thiopental loading is well tolerated by healthy anesthetized patients. A small decrease in stroke volume was matched by an equal increase in heart rate; cardiac output and the other measured cardiovascular variables did not change. Similarly, Todd *et al.* found minor hemodynamic disturbances as thiopental was administered to otherwise healthy young neurosurgical patients;[13] however, thiopental is rarely administered in large doses for prolonged periods, and the literature contains only this one study for comparison.[13] Todd *et al.* infused thiopental at 75 $mg \cdot kg^{-1} \cdot h^{-1}$ and detected an isoelectric EEG and thiopental concentrations of 51–75 $\mu g/ml$.[13] Our prebypass infusion rate was titrated to achieve burst-suppression, so we delivered only one fourth as much thiopental as did Todd *et al.* and measured a plasma concentration of 28 $\mu g/ml$. At that plasma concentration, ventricular performance was not impaired.

Thiopental has been administered to patients by numerous investigators, but study protocols and measured parameters have varied. An induction bolus has been reported to induce mild transient hypotension and minor systolic function impairment whether evaluated by systolic time intervals,[14–16] dP/dt,[17] or transesophageal echocardiography.[18,19] Our data may seem to contradict these findings, but the experimental designs were not comparable. When loading takes place in conjunction with cardiopulmonary bypass, burst-suppression is the usual endpoint and occurs between 19 and 35 $\mu g/$

ml.[13,20–22],‖ Total dose and duration of bypass vary from study to study, and some patients receive a continuous infusion whereas others get a single bolus at the outset. Burst-suppression was achieved in our patients at a midrange plasma concentration and infusion rate.[3–6,20,22] Nevertheless, several grams of thiopental was administered, and all patients were separated from bypass without inotropic support or the demonstration of significant myocardial depression. Here, our data are contrary to that reported in the literature[4–6] and raise the question of why our patients behaved differently than those in previous studies.

Several explanations for these discrepancies seem evident. First, none of our patients demonstrated preoperative cardiac disease. This fact is important because anesthetics have been shown to induce an additive and, thus, a more significant reduction in contractile force when heart muscle strips are already failing.[23,24] Second, the profound hypothermia employed in this study reduced myocardial oxygen consumption to less than 10% of the normal rate.[25] Third, the patients in this study did not undergo cardiac surgery, which impairs function initially after bypass.[26] Fourth, the ischemic time our patients experienced during circulatory arrest was short in comparison with the usual period of aortic cross-clamping. Fifth, the prolonged period of coronary reperfusion, as myocardium rewarms prior to bypass termination, "rests the heart" and improves performance immediately thereafter.[27] We believe all of these factors contributed to the better ventricular performance we observed in this study.

In summary, this work demonstrates that if ventricular function is not impaired preoperatively, a very large dose of thiopental can be administered during surgery without the fear of inducing significant myocardial depression or of impeding the separation from cardiopulmonary bypass.

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