Effects of Extracorporeal Circulation upon Behavior, Personality, and Brain Function:

Part II, Hemodynamic, Metabolic, and Psychometric Correlations

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IN the past decade a growing concern has become evident regarding an unusual incidence of postoperative cerebral dysfunction and behavioral disorder following reparative surgery for cardiac disease. Gross neurological damage, overt psychosis, "delirium," and various cerebral neuropathological lesions have been described in numerous reports in this span of time.[1, 3-7, 9, 11, 12, 15, 16, 18] Two years ago we reported the preliminary observations of a study designed to provide a controlled and correlated analysis of neurologic function, psychiatric status, psychometric and behavioral integrity in a prospective evaluation of a consecutive randomly selected patient population.[14] The present report offers the completed and expanded results of this investigation, and attempts to satisfy the objectives of three purposes: (1) To provide a simultaneous prospective evaluation of neurological damage, psychiatric abnormalities, and subtle behavioral and psychometric status in a randomly selected patient population, and to assess the influence of extracorporeal circulation upon these factors; (2) To examine and contrast the incidence of neurological deficit and postoperative psychosis as an index of cerebral damage in patients subjected to operations utilizing extracorporeal circulation and those who had cardiac operations without extracorporeal circulation; (3) To continue a systematic sequential analysis of the effect of extracorporeal circulation systems upon specific vital organ function in humans who undergo cardiac surgical operations, thus adding the central nervous system to those previously investigated. Correlated analysis of data regarding hemodynamic and metabolic function was included in order to qualify those effects attributed to extracorporeal circulation as opposed to other pathophysiologic elements. It was our hope that such a prospective controlled correlated analysis might offer clues as to the possible causes of central nervous system derangement and suggest solutions for prevention.

Presented at the Annual Meeting of the Southern Surgical Association, December 7–9, 1970, Boca Raton, Florida.

* The efforts in this work are dedicated in memorium to our colleague Dr. Junius Rowe, who died July 6, 1970.

Supported in part by U. S. Public Health Service Grant No. HE-12050 and The John and Mary R. Markle Foundation (Dr. Lee).

Materials and Methods

The basic protocol designed for this investigation is outlined in Table 1. Candidates for surgical treatment of heart disease were accepted for the study consecutively beginning October 1966 and ending February 1970. Since the volume and intricacy

TABLE 1. *CNS Function after Cardiac Surgery—Protocol Design*

I	All (consecutive) cardiac operative candidates (1968–70) were accepted for study except:
	a) Refusal to participate
	b) Physically unable to perform test
	c) I.Q. below 80
	d) Unable to read or write
II	a) Preop test battery (1–2 days before operation)
	b) 10 day postop. battery
	c) 3 month postop. battery
	d) Intra and para operative variables indexed (1–3 days)
III	Distribution of neurological deficits and psychiatric disturbances analyzed manually.
IV	Multiple variance matrix analysis by IBM 360 computer to assess effects of preoperative, intraoperative, and postoperative factors upon brain function and psychometric profile

of the test batteries precluded handling more than one patient at a time, random selection was achieved by simply choosing the first eligible patient upon the completion of the previous patient study. Candidates were rejected for the study only on the basis of their refusal to participate, physical inability to perform the tests, an I.Q. below 80, or inability to read. The preoperative test battery was administered one to two days prior to operation, repeated on the 10th postoperative day (or as near this day as possible), and about 3 months after operation. In addition, those variables which were suspected of being able to influence the outcome of the study during the operation and for the first 3 postoperative days were measured and indexed. The distributions of the neurologic deficits and psychiatric disturbances clinically encountered were statistically analyzed by the chi-square or "t" test method. The influence of preoperative, intraoperative, and postoperative hemodynamic, metabolic, historical and environmental factors upon brain function was analyzed in a multiple variance matrix analysis by an IBM 360 computer in a program designed by the staff of the Department of Biometry at the Medical University of South Carolina. The patient sample for this study represented a total population of 174. Thirty were rejected for low I.Q. (below 80). An additional 18 were rejected because of illiteracy. Finally, 40 were rejected because of failure to cooperate or logistic problems such as personnel sickness or equipment breakdown. Thus, 86 patients underwent complete studies for data analysis of the total protocol. Of these, 59 were females and 27 males, with age span of 16 to 58 years.

The preoperative and postoperative test batteries are outlined in Table 2. The numerous factors and items included under category IV in this table, historical, environmental, hemodynamic, and metabolic

TABLE 2A. *CNS Function after Cardiac Surgery—The Preoperative and Postoperative Test Batteries*

I	Neurological
	a) Neurological examination
	b) EEG
	c) Wechsler Adult Intelligence Scale
	d) The Trails Test
	e) The tapping test
	f) Graham-Kendall Memory for Designs Test
	g) Minnesota Percepto-Diagnostic Test
II	Psychiatric status
	All patients were interviewed by a clinical psychologist, a trained psychologic technician, and a psychiatrist when indicated.

TABLE 2B. *CNS Function after Cardiac Surgery—The Preoperative and Postoperative Test Batteries*

III	Psychometric profile, behavior, cerebration
	a) Intelligence scale (Wechsler)
	b) Minnesota Multiphasic Personality Inventory
	c) Cardiac adjustment scale
IV	Assessment of historical, environmental, hemodynamic and metabolic factors.
	480 variables were analyzed in 124 measured factors and correlated with changes in CNS function.
	Included were: type disease, symptom duration, sex, age, body build, type of operation, position, incision, arterial and venous pressure, urine volume, drug therapy, ICU time, pump time, catecholamine (blood levels and extrinsic therapy) pulmonary function, blood clotting factors.

TABLE 3. *CNS Function after Cardiac Surgery—Preoperative & Postoperative tests to 3 months for: Psychometric profile, I.Q., CNS damage, cardiorespiratory function.*

	Test Group Operated with E.C.C. 71 Patients	Control Group Operated without E.C.C. 24 Patients
Neurologic Deficit	23%	0.0%
Psychiatric Complications	14%	0.0%
All Neurologic & Psychiatric Problems	31%	0.0%
Mortality:		
Group $\bar{c}$ N.P. Comp.	45%	0.0%
Group $\bar{s}$ N.P. Comp.	14%	
		$p < 0.05$

factors, are too lengthy to include a complete list in the text. However, those factors which were significant either as to positive correlation or noncorrelation are listed further in the results.

The extracorporeal circulation system utilized in this investigation consisted of pump oxygenator perfusion with a Bentley bubble type oxygenator, disposable polyvinyl lines, using 50% hemodilution with Ringer's lactate for prime. In some cases low molecular weight dextran was also incorporated in the pump prime. This factor was analyzed and correlated as an independent function.

Results

The results have been analyzed in two fundamental categories, prospective and retrospective analyses.

In the prospective analysis the patients were divided into two groups consisting of a control group (24 patients) subjected to various cardiac reparative operative procedures without the use of extracorporeal circulation. The second group consisted of those patients who underwent cardiac operations utilizing extracorporeal circulation (71 patients). The purpose of this analysis was to determine the incidence, distribution, and significance of central nervous system damage, as influenced by the factor of extracorporeal circulation. The results are tabulated in Tables 3 and 4, indicating an incidence of neurologic deficits of 23% and an incidence of 14% psychiatric complications with an overall incidence of CNS disturbance of 31% in the perfused group of 71 patients. No patients in the control group (without perfusion) experienced any clinical neurologic deficit, psychiatric complications, or death. The mortality in the group which sustained neurologic or psychiatric complications was three-fold higher than in those patients in the perfused group who did not experience neurologic or psychiatric complications. The differences in these two groups are highly significant by statistical evaluation (95% confidence limits). In a further effort to assess the influence of the various hemodynamic, historical, metabolic, and environmental factors, mathematical expressions were developed for multiple variant correlation by the biometry staff and all data were analyzed in a temporal sequence over the 3-month period to index significance of influence upon these two groups. In a prospective analysis (by correlation coefficient) there were no significant differences, indicating that the prime factor determining the distribution of central nervous system complications was that of extracorporeal circulation, rather than changes in the measured parameters. The equation for the correlation coefficient and the linear mathematical model utilized in this analysis are represented as follows:

TABLE 4. *Postoperative Neurologic and Behavioral Complications Patient Numbers*

Psychotic	Neurological Deficit	Both	Total
6	12	4	22
Psychotic Behavior	5 Onset by 2nd Day		
	5 Onset 3–6th Day		
Neurologic Deficit	13 Immediate		
	3 Detected 2–7 Days		

Correlation Coefficient

$$SS_X = \Sigma X^2 - \frac{(\Sigma X)^2}{N}$$

$$SS_Y = \Sigma Y^2 - \frac{(\Sigma Y)^2}{N}$$

$$r = \sqrt{\left(\Sigma XY - \frac{(\Sigma X)(\Sigma Y)}{N}\right) \Big/ (SS_X)(SS_Y)}$$

The Linear Model

$$Y_{ijk} = \mu + \alpha_i + \delta_{ij} + \tau_k + (\alpha\tau)_{ik} + \epsilon_{ijk}$$

where

Y_{ijk} = denotes the observation for the kth time, jth individual and ith pump time
μ ≡ the overall mean
α_i ≡ the effect of the ith pump level
δ_{ij} ≡ the effect of the jth individual on the ith pump level
τ_k ≡ the effect of the kth time
$(\alpha\tau)_{ik}$ ≡ the interaction effect of the ith pump level and the kth time
ϵ_{ijk} ≡ the effect denoting the random deviation associated with the kth time of the jth individual on the ith pump level

In order to assess the influence of the various hemodynamic, environmental, historical and metabolic factors in the production of central nervous system damage *within* the group of patients subjected to extracorporeal circulation, a retrospective statistical analysis was also carried out. In this analysis, the patients were divided into three groups as follows: Group I consisted of patients having extracorporeal circulation and sustaining clinical central nervous system damage; Group II was those patients having extracorporeal circulation, but without central nervous system damage; Group III was the control group of patients who did not undergo extracorporeal circulation.

There were a considerable number of factors analyses which failed to show significant correlation with central nervous system damage in either the prospective or retrospective statistical analyses. Some of these factors have been previously suggested as playing major roles as possible etiologic elements especially in the production of behavioral disturbances.[3, 4, 6, 7, 9, 18] Others, by logic, would be suspect as factors of importance in the production of neurologic defects. The lists of those factors which did not reveal significant correlation with central nervous system damage in either prospective or retrospective analysis are displayed in Table 5. Further mention of some of these will be made in the discussion of this report.

Factors Displaying Positive Correlation with CNS Damage

Duration of Symptoms of Heart Disease

Although neither prospective nor retrospective analysis revealed a positive correlation between duration of symptoms and central nervous system damage, a stepwise discriminant analysis with a chi-square test for distribution validation revealed that patients having symptoms for 5 years or longer had a significantly higher chance of sustaining central nervous system damage when subjected to extracorporeal circulation (Table 6). Seventy-three per cent of the patient group having symptoms over 60 months were in the group of patients who sustained CNS damage ($p < 0.01$). The significance of this distribution was not influenced by age, as the analysis for age displayed no significant correlation.

Objective Tests for Brain Damage

Within the patient group subjected to extracorporeal circulation specific objective tests for brain damage confirmed the clinical diagnosis and the difference between the two groups of patients both at 10 days and at 3 months postoperative. Figures 1 and 2 demonstrate significant differences in

TABLE 5. *CNS Function after Cardiac Surgery—Factors which failed to show significant Correlation with CNS damage in Prospective or Retrospective analysis include*:

Age (mean age 35 years all groups)	Cardiac power index
Sex	Duration of steroid therapy
Type of heart disease (congenital, acquired)	Blood pH (acidosis or alkalosis)
Serotonin levels, 1st & 2nd postop. days	Mannitol therapy
Norepinephrine, 1st postop. day	Total blood transfusion
Dextran in pump prime	Urine volume
Preop. pulmonary function	Aortic cross-clamp time
A.H.A. functional class	Blood volume
Cardiac index	Body surface area
Percepto-diagnostic	Digitalis dosage
Cardiac adjustment scale	Trials test
	MMPI
	Occupation
	Marital status

Height
Weight
Position/incision
I.Q. except "performance" scores
Central venous pressure
(extent or duration of elevation 1st & 2nd postop. days)

I.Q. performance and object assembly, tapping test with right and left hand, and recent memory impairment. The means of the differences at 3 months were not as striking as might be expected, but this is partially explained by the fact that almost half of the patient group which sustained central nervous system damage were dead by the time of the 3 months postoperative tests. A summary of both the prospective and retrospective analyses of all objective tests for brain damage is displayed in Table 7. It is of interest that in the prospective analysis 5% of the control group displayed abnormalities at 10 days and 3% at 3 months. No clinical evidence of such abnormality was detected, however. In the retrospective analysis, the objective tests for brain damage clearly separated the patients having brain damage at 10 days, but statistical separation of these patients at 3 months was not possible. This is related both to the fact that resolution and improvement of behavioral disturbances and neurologic impairment occurred by the 3-month interval, and also to the fact that many patients in the group displaying clinical brain damage died before the 3-month battery was administered.

Central Nervous System Damage and Duration of Pump Oxygenator Perfusion

In an attempt to evaluate the influence of all measured variables in the production of central nervous system damage in the group undergoing extracorporeal circulation, multiple variant correlations were

TABLE 6. *CNS Function after Cardiac Surgery—Duration of Symptoms (Heart Disease)*

Prospective correlation (control group vs. perfusion group)	No correlation
Retrospective correlation (CNS damage vs. no CNS damage)	No correlation
Stepwise discriminant analysis (chi-square test) for distribution in CNS damage group vs. non-CNS damage group, with symptoms for 5 years or longer	Positive correlation

Symptoms over 60 months

CNS damage group = 73%
No CNS damage group = 39%
$(0.008 < p < 0.014)$

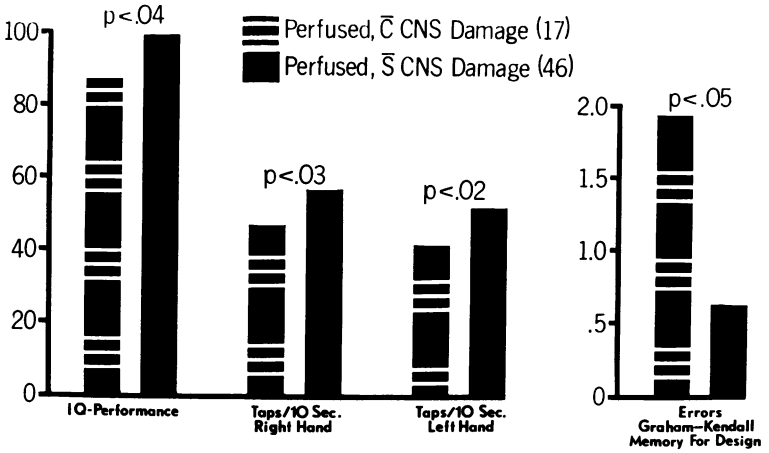

FIG. 1. CNS function after cardiac surgery—10 days post-op. tests.

made for all measured factors, dividing the patients into those displaying CNS damage and those without CNS damage. One of the most striking correlations is displayed in Figure 3. It would appear that the risks of developing brain damage increase progressively with duration of pump oxygenator perfusion, climbing steeply between 15 minutes and one hour, with a slower increase between 1 and 2 hours, and reaching a plateau of incidence at around 2 hours of perfusion, with little increase for the next hour.

Hypotension and Blood Transfusion

Influence of duration of operative hypotension and the volume of blood transfused at operation upon the probability of developing central nervous system damage associated with extracorporeal circulation is displayed in Figure 4. The highly significant correlation between duration of operative hypotension (mean arterial blood pressure below 50 mm. Hg) and the development of central nervous system damage associated with extracorporeal circulation is lost by the first postoperative day. Confidence limits of 99% decreased to 89% following 24 hours. It is noteworthy that the means for operative hypotension in the perfused group without central nervous system damage and the nonperfused controls are almost identical. The signal lack of correlation between perfusion time and operative hypotension, however, in covariance analysis suggests that these two factors op-

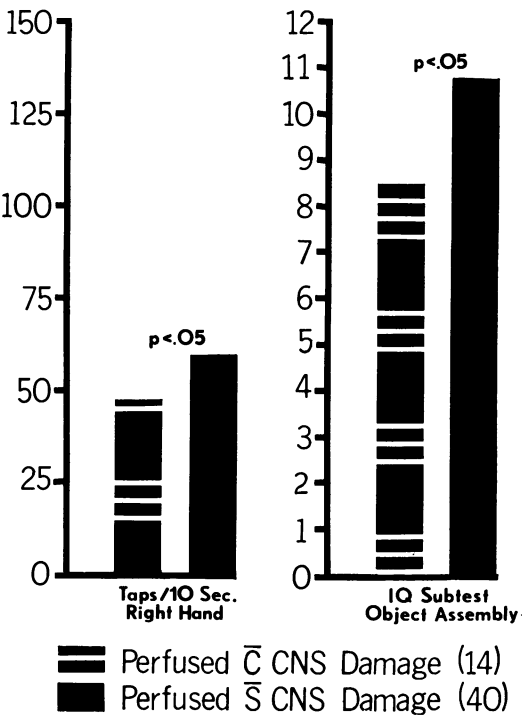

FIG. 2. CNS function after cardiac surgery—3 months post-op. tests.

TABLE 7. *Effects of Perfusion on CNS Function—all Objective Tests for Brain Damage*

	Prospective Analysis			
	10 Days Postop.		3 Months Postop.	
	No. of Test	% Abnormal	No. of Test	% Abnormal
Group A (control non-perfused)	74	5%	79	3%
Group B (all perfused)	306	12% ($0.08 < p < 0.15$)	289	8% ($0.08 < p < 0.15$)

	Retrospective Analysis			
	10 Days Postop.		3 Months Postop.	
	No. of Test	% Abnormal	No. of Test	% Abnormal
Group I perfused (with clinical CNS damage)	83	18% ($p < 0.04$)	75	11% ($p < 0.31$)
Group II perfused (with no clinical CNS damage)	223	9% ($p < 0.31$)	214	7% ($p < 0.31$)
Group III control (no perfusion)	74	5%	79	3%

erate independently to contribute to production of central nervous system damage.

Influence of Valve Prostheses

Figure 5 displays the effect of implantation of a valvular prosthesis. A highly significant increase in central nervous system damage is noted in the patient group having replacement of one or more valves as compared to those undergoing extracorporeal circulation without insertion of a prosthesis. The possibility that the perfusion time for valve replacement resulted in this association is refuted by the comparison of mean pump times for the valve replacement group and the group without valve replacement (almost identical). Positive correlation for the effect of the Intensive Care Unit duration of stay upon CNS damage in these groups of patients is partially explained by the observation from Table 4 noting that the onset of signs of CNS dysfunction occurred by 48 hours after operation in the majority of the cases. The 13 immediate neurologic deficits tended to prolong Intensive Care Unit stay for this group of patients as an effect rather than as a causative factor. The prospective analysis of Intensive Care Unit duration of stay comparing the perfused group with the nonperfused group revealed no significant differences.

Rehabilitation

Finally, in Figure 6 an attempt to estimate the potential for rehabilitation using the cardiac adjustment scale is graphically portrayed. All surviving patients tend to improve slightly both at 10 days and 3 months postoperative. The degree of improvement, although valid over the 3 months period for each group independently, does not suggest any difference in the potential for rehabilitation between the three groups of patients. The results displayed must be qualified by the observation that many of the patients in the group which sustained CNS damage had died and therefore were not in the final analysis.

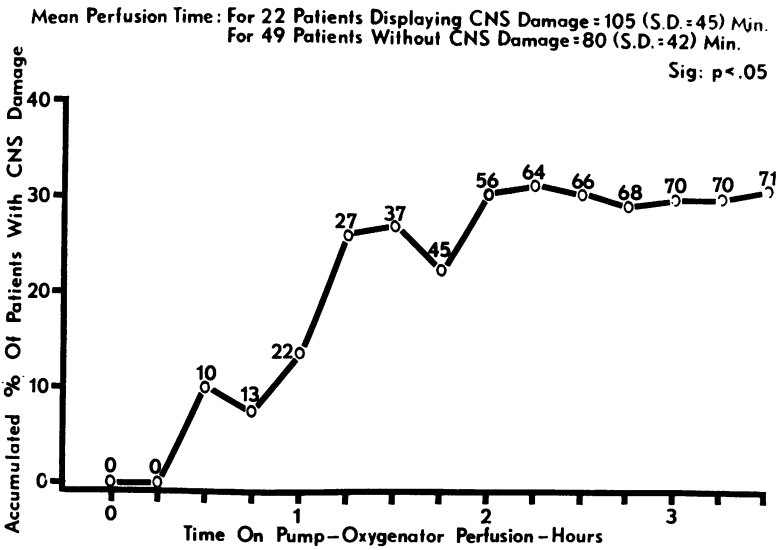

FIG. 3. CNS damage and duration of perfusion.

Discussion

The unusual incidence of central nervous system damage as manifested by neurologic deficit and acute psychotic episodes occurring postoperatively in patients subjected to extracorporeal circulation for cardiac operation as documented in this report, has been previously reported by several authors.[3, 5-7, 9, 16, 18] However, a rigid statistical comprehensive correlation of historical, environmental, metabolic, and hemodynamic factors with the incidence of distribution of central nervous system dysfunction in a controlled population has been lacking. The difficulties inherent in such a study are manifested by the high rejection rate in the sample population on the basis of low I.Q. and illiteracy. Further problems result from the high incidence of personality disturbances found in all patients having organic heart disease. Only about half of the patients in the control group were normal by MMPI or initial preoperative evaluation. Approximately 70% of all patients displayed *some* abnormality preoperatively, suggesting subtle brain damage by one or more of the objective tests for brain damage. We have reviewed our own views and those of others previously regarding these difficulties[1, 3-7, 11, 12, 14, 16, 18] and despite differences in terminology and definition of "delirium," there would seem to be little debate regarding the validity of the observation that evidence of brain damage and abnormal behavior is present in an unusually high incidence in those patients who undergo "open-heart surgery." The basic and urgent question which remains is obvious. What is the cause or causes of this phenomenon? How may it be prevented or treated?

Early in this study, the participating psychiatrist believed that careful evaluation by

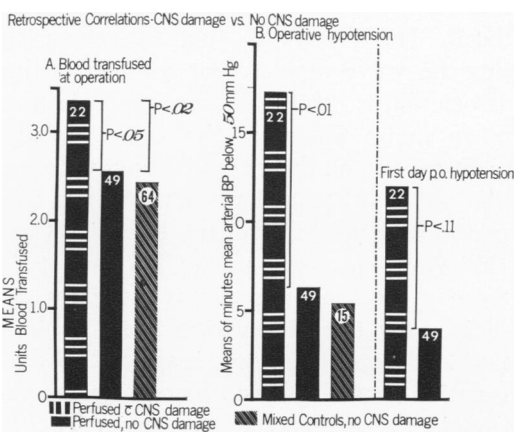

FIG. 4. CNS function after cardiac surgery.

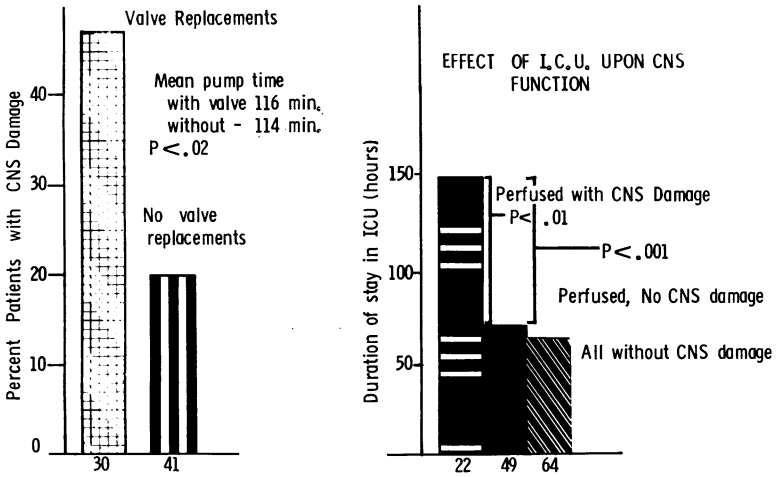

FIG. 5. Effect of valve replacement on CNS function.

interview and the MMPI might enable prediction of potential for postoperative psychosis, for example, and with supportive psychotherapy the problem might be prevented. Perhaps many potential cases of stress-induced psychosis were thus avoided, but in general the distribution of cases refuted the belief that the acute psychotic reactions encountered in this study could be predicted, or prevented.

Many contributing factors have been implicated as playing contributing roles in the etiology of this phenomenon. The role of the Intensive Care Unit as a stressful environment evoking acute psychotic behavior may certainly be debated as a contributing factor,[4, 6, 7, 11] especially in the few delayed psychotic episodes which occur between the third and seventh day postoperative. This could hardly be a primary factor, however, in the production of neurologic deficits and is an improbable cause of those psychotic episodes which occur within the first 48 hours. Half of the acute psychotic episodes in this study were manifest within the first 48 hours after operation.

Age has been suggested by Heller[7] as a factor of primary importance in the development of central nervous system damage. This study, however, fails to confirm their observation. The mean age of the patients in all groups in this study was almost identical, and is considerably younger than that of the group in which age appeared to be a controlling factor as reported by Heller.[7] The fact remains that in a patient population with mean age of 35 years, there was no correlation between patient age and central nervous system damage. The observation of Tufo *et al.*[18] in a recent report clearly and concisely demonstrated the association between operative hypotension and central nervous system dysfunction. The data obtained from our study, how-

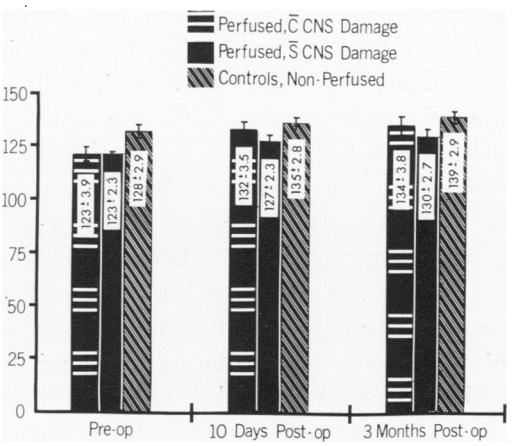

FIG. 6. Cardiac adjustment scale.

ever, although confirming this important association suggest that operative hypotension plays a contributing and aggravating role, independent of the primary factor (or factors) inherent in the extracorporeal circulation situation. In the prospective statistical analysis the trends of operative hypotension were statistically similar in both perfused and nonperfused groups. Only when examining operative hypotension *within* the group of patients experiencing extracorporeal circulation (comparing CNS damaged and non-damaged groups) does this factor operate to produce central nervous system damage. Similarly, although catecholamine levels and serotonin levels correlate well with low cardiac output and operative hypotension, the prospective correlations do not implicate them as primary factors in producing central nervous system damage. From the data obtained in this investigation and the previous observations supplied by earlier reports,[2, 10, 14, 17] we have arrived at a working hypothesis regarding the general mechanisms operating to produce central nervous system damage in extracorporeal circulation. This hypothesis concludes that the basic pathophysiologic event consists of a perfusion defect at the microcirculatory level, not necessarily associated with arterial hypoxemia, hypotension, or low cardiac output, although any combination of these may precipitate or aggravate overt and lasting cellular damage. The striking difference in CNS damage between those patients having valve replacement and those who undergo perfusion without valve replacement suggests the mechanism of the microvascular perfusion defect may be related to particulate aggregation in circulating blood induced by the surface effect of the extracorporeal system. The most logical mechanisms for the generation of such microemboli or particulate debris would be those of platelet aggregation,[2, 17] cellular aggregation (erythrocyte or leucocyte),[10, 15, 17] protein denaturation and aggregation,[13] or lipid embolization resulting from altered suspension stability of blood lipids (alone or in combinations).[8, 13] The alternative hypothesis of possible air embolism also remains a possible cause of defective microvascular perfusion.

Summary

A controlled prospective evaluation of cerebral dysfunction in patients undergoing cardiac operations utilizing extracorporeal circulation has confirmed an unusual incidence of neurologic deficits and acute psychotic behavior postoperatively. Approximately one third of such patients manifest evidence of central nervous system dysfunction when careful clinical and objective analysis is carried out. The mechanism and cause of this phenomenon remain uncertain. Definite contributing factors which precipitate or aggravate the CNS complications, however, include operative hypotension, implantation of valve prostheses, the duration of perfusion time, and the presence of long-standing organic heart disease. Many factors previously considered as possible contributing elements are refuted by the data obtained in this investigation. The etiologic hypothesis which remains most likely is that of a microvascular perfusion defect generated by factors inherent in the extracorporeal circulation system, most of which might be deleted or ameliorated by substitution of effective transmembrane gas exchange for the gas-blood interface of current clinical oxygenator systems, and perhaps by the use of suitable filtering devices.

Acknowledgment

The authors gratefully acknowledge the participation and help of O. M. Hamrick, Jr., Ph.D., for his interpretations of the psychological tests following Dr. Rowe's demise; C. B. Loadholt,

Ph.D., of the Department of Biometry, for his major contribution to the statistical analysis; and James Richardson, Ph.D., Department of Pharmacology, for analysis of blood and urine catecholamine levels.

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