NEUROPSYCHOLOGICAL DEFICITS AS A FUNCTION OF THE HEART-LUNG MACHINE USED IN OPEN-HEART SURGERY: TWO LUNGS COMPARED

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BY

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ABSTRACT

Psychiatric and neurological symptoms, as well as neuropsychological test decrements, frequently occur after open-heart operations, and are seen much more commonly than after other types of surgery. A working hypothesis is that microbubbles of air escape from the heart-lung machine and enter the patient's bloodstream. These microbubbles, it is hypothesized, proceed to blood vessels in the brain, there causing blockages and then mental disturbances. 'Lungs' have accordingly been designed to minimize release of microbubbles. In the present study, two differently designed 'lungs' were compared with regard to patients' postoperative performances on eight neuropsychological tests. One of these, the membrane, is a newer model of more sophisticated technical design than the other, the bubbler.

Forty-one coronary bypass patients were divided into two groups matched for age, sex, education, and scores on the WAIS-R Vocabulary and the Conceptual Levels Analogy Tests. Testing took place one week preoperatively and at one and six weeks postoperatively. Multiple Analyses of Variance were performed on raw scores and on residuals remaining when effects of covariates were removed. Covariates comprised the matching variables, State and Trait Anxiety, Beck Depression, time on the heart-lung machine and total length of intraoperative periods of low blood pressure.

Postoperatively, the bubbler group scored significantly higher on two measures of new learning derived from the Rey Auditory Verbal Learning Test. The measures of new learning were the only ones to indicate robust group differences. These findings confirm those of some earlier authors in pinpointing new learning as a sensitive index of postsurgical organic impairment. They also suggest that the bubbler, though of less sophisticated design than the membrane oxygenator, is the safer of the two devices when used with an appropriate filter.

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Psychiatric and neurological symptoms, as well as neuropsychological deficits, occur more frequently after open-heart operations than after any other type of surgery. The high incidence of these disorders has been linked to the process of extracorporeal circulation (ECC), a procedure unique and central to open-heart surgery. In ECC, blood flowing into the patient's heart is channeled out of the body, through the heart-lung machine, and back into the body on the other side of the heart. This process enables the surgeon to work, since he/she cannot operate on the heart while it is still beating and while blood flows through it. A working hypothesis proposed to explain postoperative cerebral disorders is that microbubbles of air, also called microemboli, escape from the oxygenator in the heart-lung machine, and enter the patient's bloodstream. These microbubbles, it is suggested, proceed to blood vessels in the brain, there causing blockages which lead to mental disturbances. The technical design of the heart-lung equipment is important, because it can influence the extent to which emboli are a risk; consequently, numerous researchers have tested the effects of newly improved parts of the heart-lung equipment on postoperative mental functioning (Aberg and Kihlgren, 1977a; Landis, Baxter, Patterson, and Tauber, 1974; Boccalon, 1982; Willner, Caramonte, Garvey, Wolpowitz, Weisz, Rabiner, and Wisoff, 1982; Reed, Rogmanoli, Taylor, and Clark, 1974; Solis, Kennedy, Beall, Noon, and DeBakey, 1975). In the present study, two differently designed oxygenators, referred to as the bubbler and the membrane, are compared with regard to patients' postoperative performances on eight neuropsychological tests.

In the case of one of the two devices, the bubbler, blood is siphoned out of the patient's body into the heart-lung machine and is there mixed with a combination of oxygen and carbon dioxide. In penetrating the blood, oxygen and carbon dioxide take the form of bubbles, which would be a major hazard if they entered the patient's body, and must therefore be removed before the blood is returned to the body. The removal is achieved by passing the blood through a textile screen which breaks up the bubbles.

In the membrane oxygenator, blood is passed through a comparable textile screen immediately after it has entered the heart-lung apparatus, because the initial procedure of cannulating and channeling the patient's circulation into the machine is one in which air emboli are a particular hazard. This process is equally hazardous in operations where the bubbler is used; the fact that this precaution is taken at this early stage of the cardiopulmonary bypass procedure is hypothesized to be an advantage in the use of the membrane oxygenator. Once the blood has been screened in this way, it is passed through the oxygenation chamber. This chamber is divided by a membrane of fan-folded microporous polypropylene, such that the blood passes along one side of the membrane and the oxygen and carbon dioxide pass along the other. The gases can enter the blood through the micropores in the membrane. The important difference between the two oxygenators is that in the membrane, blood and gas do not come into direct contact. Gas bubbles are not introduced into the blood and therefore do not need to be removed.

The purpose of the present study is to contrast the postoperative performances of the bubbler and membrane groups on neuropsychological tests. In this way, this study comprises a consumers' quality test of the two oxygenators, in which neuropsychological tests were the indices of quality. The pragmatic question for the surgical team at the Health Sciences Centre, St. John's, Newfoundland, was whether the superiority of the membrane oxygenator, which is the newer device of more advanced design and greater price, could be substantiated through its correlation with superior neuropsychological outcomes.

In the next section the nature and incidence of postsurgical dysfunctions will be considered, and the reasoning behind sample selection and assignment to groups in the study will be given. The relevance of the several covariates to be included in the data analysis will be discussed, and earlier studies which have compared bubbler and membrane oxygenators will be reviewed. Lastly, there will be a brief discussion of the advantages of neuropsychological testing for investigations in this field, and the tests appropriate for use in this investigation will be described.

Nature and Incidence of Disorders Occurring after Open-Heart Surgery

Studies comparing postoperative dysfunctions in patients undergoing open-heart surgery with those in control patients having either closed-heart or general thoracic noncardiac surgery have invariably found that mortality and complications occur more often after open-heart surgery. Lee, Brady, Rowe and Miller (1971) compared 71 open-heart patients with 24 cardiac patients undergoing surgery that did not entail extracorporeal circulation (ECC). While only 54 of 71 (76%) open-heart patients survived, and 31% of the original sample displayed psychiatric and neurologic symptoms, all the control patients survived, and none showed postoperative complications. Though the two groups were compared on a large number of hemodynamic, historical, and metabolic variables, no significant differences between the groups were found on any of these variables. The authors concluded that the prime factor responsible for cerebral damage was simply the use of ECC. Paech, Klinner, Meyendorf, Reichart and Kreuzer (1982), reviewed the medical charts of a large sample of 1,360 patients and found higher mortality rates and higher incidences of psychiatric and neurologic symptomatology among patients whose operations had entailed ECC than among patients in the remainder of the sample. Several other studies support these findings (Layne and Yudofsky, 1971; Lee, Miller, Rowe, Hairston and Brady, 1969; Egerton and Kay, 1964; Hale, Koss, Kerstein, Camp and Barash, 1977). Evidence of other kinds, including greater electoencephalographic (EEG) changes, larger deficits on neuropsychological tests, and neuropathological findings have corroborated these clinical observations (Lehmann, Grahmann, Hauss, Rodewald, and Schmitz, 1968; Aberg and Kihlgren, 1974, 1977a, b, 1982; Aguilar, Gerbode and Hill, 1970).

It is well established, then, that psychiatric and neurologic complications occur more often in open-heart patients than in other groups. These disturbances have attracted researchers since the early years of open-heart surgery in the mid-1950s, partly because they are dramatic, and partly because of their great frequency. A wide spectrum of symptoms has been observed. Patients have tried to climb out of bed, to pull out nasal oxygen and intravenous lines, and to jump out of windows (Gilman, 1965; Surman, Hackett, Silverberg and Behrendt, 1974; Meyendorf, 1979). Disoriented, such patients have been combative, incontinent, and incapable of fulfilling simple commands. Speech may be incoherent; hallucinations often occur, which may be visual, tactile, or auditory. Delusions and hallucinations may be pleasant and nonthreatening: Patients have imagined they were at a circus, or an Olympic stadium. Alternately, they have often expressed fears about being poisoned, guns being pointed through windows, etc. (Gilman, 1965; Freyhan, Gianelli, O'Connell, and Mayo, 1971; Danilowicz and Gabriel, 1971; Sveinsson, 1975; Rabiner, Willner, and Fishman, 1975). Postsurgical signs of depression and anxiety are common, and may occur in all degrees of severity (Kimball, 1969, 1972; Freyhan et al., 1971; Morgan, 1971). Memory losses, though usually transient, also are frequent (Kimball, 1969; Tufo, Ostfeld and Shekelle, 1970; Bethune, 1980).

Further, while numerous psychopathological symptoms have been observed, as many purely neurological signs have been described. Neurological symptoms have included coma, general and hemi-paresis, (paralysis of motion without loss of sensation), and mono-, hemi-, and quadriplegia (paralysis of one, two, or four limbs); generalized and focal seizures and convulsions; plantar responses (feet rigidly thrust forward), and snout and sucking reflexes. Dysphasia, aphasia, alexia, agraphia, anomia and acalculia have been observed. Transient loss of vision, diplopia (double vision), hemianopia, (defective vision or blindness in half the visual field), visual agnosias, (inability to understand what is visually perceived) and nystagmus (rolling of the eyeballs) have been reported. EEG abnormalities, such as diffuse slowing of basic frequencies, are also common both during and after surgery (Gilman, 1965; Tufo et al., 1970; Sachdev, Carter, Swank, and Blachly, 1967; Javid, Tufo, Najafi, Dye, Hunter and Julian, 1969; Branthwaite, 1972, 1973, 1975; Witozska, Tamura, Indeglia, Hopkins, and Simeone, 1973; Meyendorf, 1982; Juolasmaa, Outakoski, Hirvenoja, Tienari, Sotaniemi and Takkunen, 1981; Sotaniemi, 1980; Witozska and Tamura, 1980).

Not only have many kinds of postoperative disturbance been seen, but the incidence of these disorders has remained very high. In 1964, for example, Blachly and Starr cited 'postcardiotomy delirium' in 79 of 139 (57%) of their open-heart population, while Knox (1961) reported only one case of postoperative psychosis in 1500 non-cardiac, general surgery patients. Nearly 20 years later, Gotze, Flemming, Huse-Kleinstoll, Meffert, Reimer and Speidel (1982) found 51/100 of their open-heart population to be symptomatic in the early postoperative period, and Tienari, Outakoski, Hirvenoja, Juolasmaa, Takkunen, and Kampman (1982) reported that 36% (29/81) of their open-heart sample manifested either 'functional psychosis' or 'delirium.' Several investigators (Heller, Frank, Malm, Bowman, Harris, Charlton, and Kornfeld, 1970; Branthwaite, 1972; Reed et al., 1974; Witozska and Tamura, 1980; Barash, 1980; Aberg and Kihlgren, 1982; Bjork and Ivert, 1982) have reported decreases in incidence over time, thanks mainly to technical and surgical improvements. However, the majority of studies on open-heart samples have continued to report incidences of 25% or higher. A factor which may partially explain the consistently high figures is that technical and surgical advances have not been introduced at the same rate at all hospital centres. It is also possible that in recent years researchers have become more knowledgeable and thorough in the assessment of these disorders. In this way, they may be taking note of more of the subtle signs, so keeping incidence figures high, when the major and dramatic disturbances have actually declined in number (Meyendorf, 1982). Sotaniemi (1980) observed that assessment criteria used in earlier studies would have yielded an incidence of 9% in his sample, rather than the 37% he actually reported. However, the continuing high incidence of these disorders also reflects the fact that they are insufficiently understood, and in consequence inadequately controlled (Gotze, Huse-Kleinstoll, and Speidel, 1980; Dubin, Field, and Gastfriend, 1979).

<u>Methodological Considerations in the Evaluation of Postoperative Neuropsychological Deficits</u>

At least three major kinds of operation are called 'open-heart surgery': aortic valve replacement, mitral valve replacement, and coronary bypass grafting. Coronary bypass procedures are the most recently developed and now are certainly the most commonly performed (Bass, 1984; Stanton, Zyzanski, Jenkins, and Klein, 1982). Though air emboli are a hazard in both types of valve operation and in coronary bypass surgery, they are a greater danger in valve surgery. In valve surgery, the heart is actually opened, whereas in surgery for coronary artery disease, incisions into the heart wall do not penetrate it completely. In valve operations, air pockets may be trapped inside the heart's chambers when the heart is opened or closed. Tiny bits of matter may also become dislodged from calcified heart valves and enter the bloodstream, or minute particles of dust and lint from the operative field may be trapped inside the heart when it is opened. For these reasons, many investigators have emphasized that the coronary artery and valve populations should be studied separately (Branthwaite, 1972; Kornfeld, Heller, Frank, Edie, and Barsa, 1978; Flemming, Symposium Discussion, 1980; Huse-Kleinstoll, Flemming, Gotze, Meffert, Polonius, Reimer, and Speidel, 1982). In the present research, only coronary artery bypass grafting (CABG) patients were included.

The literature also indicates that a number of factors other than sample selection deserve consideration in studies on postoperative cerebral dysfunctions. For example, advanced age, intraoperative periods of low blood pressure (hypotension), time on the heart-lung machine (bypass time), and mood states such as anxiety and depression may all influence postoperative outcomes. While the research concerning such factors will be reviewed here, it should first be recognized that various factors probably interact to result in postoperative complications (Heller et al., 1970, 1979; Tufo et al., 1970; Paech et al., 1982; Dubin et al., 1979; Gotze and Dahme, 1980). Consider, for example, age and hypotension. In older patients, the circulatory system adjusts less well to a drop in blood pressure (Javid et al., 1969; Tufo et al., 1970; Branthwaite, 1972; Stockard, Bickford, and Schauble, 1973; Stockard, Bickford, Myers, Aung, Dilley, and Schauble, 1974; Aberg and Kihlgren, 1977a, b; Layne and Yudofsky, 1971). In addition, older patients, or those with longer preoperative histories of coronary artery disease, or with more severe cases of the disease, or some combination of these characteristics, might be more vulnerable to preoperative hypoxia, a disorder in which hardened and narrowed cardiac arteries compromise the blood's flow to the brain. Preoperative neurological damage caused by hypoxia could mean that patients' brains were more susceptible to further damage from abnormally low blood pressure levels (Javid et al., 1969). Such patients could also require more complex operations, which would lead to longer operations and bypass times, and which could, in turn, imply more postoperative physical complications and longer stays in Intensive Care. It is important, then, to keep these possible interrelations in mind when considering any given factor (Paech et al., 1982).

Age. Researchers who have found positive correlations between advanced age and postoperative symptoms have hypothesized that the cerebral blood vessels of older patients are more hardened in the first place. As a result, blood pressure in these vessels is already reduced, and consequently, older patients are less able to tolerate periods of low blood pressure during surgery (Javid et al., 1969; Tufo et al., 1970; Branthwaite, 1972; Stockard et al., 1973, 1974; Aberg and Kihlgren, 1977a, b; Layne and Yudofsky, 1971). Yet, for each study which has found age to be a risk variable, even in this secondary sense, another has found no effect (Kornfeld, Zimberg, and Malm, 1965; Kimball, 1969; Lee et al., 1971; Sveinsson, 1975; Sotaniemi, 1980; Kornfeld et al., 1978). In fact, the state of the regulatory mechanisms of the patient's circulation may be more important than age (Sotaniemi, 1980). In general, though findings concerning age have not been conclusive, enough evidence exists to warrant its inclusion in studies of postoperative disorders.

Hypotension. A number of researchers have found that periods of hypotension (low blood pressure) occurring during surgery have correlated, independently of age, with postoperative manifestations of neurological symptoms. During the operation, blood flow and blood pressure are maintained by means of the heart-lung apparatus, but may on occasion fall below an established safety mark. When this happens, the risk of inadequate cerebral blood flow increases. The resultant anoxia may cause serious damage. Several investigators have observed hypotensive episodes to be closely paralleled by EEG changes recorded during surgery, as well as by neurological signs diagnosed after surgery, and by neuropathological lesions found in autopsies (Stockard et al., 1973, 1974; Witozska et al., 1973; Brierley, 1963; Tufo et al., 1970; Gilman, 1965; Javid et al., 1969; Branthwaite, 1973). As is often the case with such risk factors, the effects of hypotension have usually been considered to interact with other variables (Quinlan, Kimball, and Osborne, 1974; Stockard et al., 1973, 1974; Tufo et al., 1970; Javid et al., 1969; Branthwaite, 1972; Aberg and Kihlgren, 1974). Unfortunately, the measurement of hypotension has not been a well standardized procedure. Investigators have had to choose among various aspects of the process to measure: the length of time blood pressure falls below the safety threshold, the extent to which it falls, or the rate at which it changes, among other technical indices (Tufo et al., 1970; Branthwaite, 1972; Sotaniemi et al., 1981; Stockard et al., 1973). Some measures may be unreliable (Branthwaite, 1972). Furthermore, some studies have not found correlations between hypotensive periods and postsurgical disturbances (Egerton and Kay, 1964; Sotaniemi, 1980; Sotaniemi et. al., 1981; Scheld, Davies-Osterkamp, Mohlen, Kahlbenn, Kramer, and Hehrlein, 1982). Sotaniemi (1980) has argued that it is not periods of low blood pressure, but the state of the individual patient's circulatory system and its ability to respond to these episodes which mediate dysfunctions. Nevertheless, enough evidence exists in the literature to justify the inclusion of hypotension as a covariate in the current investigation.

<u>Bypass time</u>. The process of extracorporeal circulation entails numerous potential physiological risks (Gotze, Huse-Kleinstoll, and Speidel, 1980). Many researchers have tested the hypothesis that the length of time the patient is sustained on the heart-lung machine (called 'perfusion time,' 'bypass time,' or 'pump time') could, by itself, be correlated with the occurrence of postoperative disorders. One fact which has confounded the evidence has been that mean perfusion times have tended to decrease over the years. While studies from the mid-sixties (Kornfeld et al., 1965) mention times as long as four hours, in recent years upper limits come nearer to two and a half hours (Heller, Kornfeld, Frank, and Hoar, 1979; Bethune, 1980; Aberg and

Kihlgren, 1982). As a rule, perfusion times of longer than two hours have been linked with higher incidences of mortality and cerebral disorders (Sotaniemi, 1980; Sotaniemi, Juolasmaa, and Hokkanen, 1981; Witozska et al., 1973; Boccalon, 1982; Lee et al., 1971; Vasquez and Chitwood, 1975). Bypass time may interact with any of the major risk variables associated with postsurgical complications, and Sotaniemi has suggested that evidence correlating perfusion time with postoperative dysfunctions points to the "cumulatively damaging character of cardiopulmonary bypass conditions" (1980, p.133; see also Branthwaite, 1972; Stockard et al., 1973, 1974; Paech et al., 1982). Overall, no consistent pattern of evidence either supports or disproves the harmfulness of longer perfusion times (Aguilar et al., 1970; Willner, Rabiner, Wisoff, Hartstein, Struve, and Klein, 1976; Kornfeld et al., 1978; Scheld et al., 1982). In the present study, the potential effects of bypass time on performance tasks were monitored by treating this variable as a covariate in the data analysis.

<u>Anxiety and depression</u>. Many writers have reported on the considerable anxiety and depression commonly felt by patients before and after open-heart surgery, and have reported that these mood states often contribute to the development of postoperative disturbances (Gotze and Dahme, 1980; Tienari et al., 1982; Heller et al., 1970; Blachly and Starr, 1964; Morgan, 1971; Kimball, 1969, 1972, 1973). Kimball (1969, 1972, 1973) and Morgan (1971) found that

patients who were notably depressed or anxious before the operation manifested greater incidences of psychiatric morbidity and mortality after the surgery. Several research teams have made attempts to classify postoperative disturbances into syndromes or symptom clusters, and in each case, one of these syndromes has constituted emotional, situational, and transient reactions, as contrasted with more severe psychiatric or neurological symptoms (Quinlan et al., 1974; Freyhan et al., 1971; Dahme and Gotze, 1980; Davies-Osterkamp, Mohlen, Lindemann, and Scheld, 1980; Scheld et al., 1982; Gotze and Dahme, 1980). Furthermore, there is evidence that emotional state in the perioperative period may influence performances on psychometric and neuropsychological tests (Jakubik, 1972; Frank, Heller, and Kornfeld, 1972). In the present study, state and trait anxiety and depression were measured by means of standardized scales and treated as covariates.

In total, eight factors were assessed for use in the present research as covariates in the data analysis. These were age, education, vocabulary, State and Trait Anxiety, Beck Depression, time on the heart-lung machine, and total length of intraoperative periods of low blood pressure. The goal in treating variables as covariates is to statistically monitor and remove the extent of their influence on the major outcome measures. The outcome data, having been transformed by this process, represent a more accurate and ecologically valid reflection of subjects' abilities. Also, while the most robust findings in a study may become apparent whether any covariates are accounted for or not, refinement of the data through removal of the covariates may serve to improve statistical power such that weaker effects are found.

Comparison of Bubbler and Membrane Oxygenators

Two studies have compared the effects of membrane and bubbler oxygenators on postoperative neuropsychological performances (Landis et al., 1974; Boccalon, 1982). The earlier of these reports (Landis et al.) had a two-by-two design in which subjects were assigned to the bubbler or membrane oxygenator groups, which were further subdivided into 'filtered' and 'unfiltered' groups. In the 'filtered' groups, a mesh screen filter was placed at the end of the cannula through which blood is returned from the heart-lung machine to the patient's body, the filter's purpose being to trap microemboli generated through oxygenation. The neuropsychological outcome measure used in this study was the Bender-Gestalt Visual Motor Test (Bender, 1938). The 28 subjects included a mixture of patients suffering from valve, coronary artery, and congenital heart diseases. During the operations of some, but not all patients, air microemboli generated in the different oxygenator-filter combinations were counted by means of ultrasound techniques. The 'filtered' groups had significantly better postoperative Bender-Gestalt scores than the 'un-filtered' groups, and clear trends in both Bender-Gestalt scores and ultrasonic counts favored the membrane oxygenator. Both findings support the hypothesis that air microemboli are responsible for postsurgical cognitive dysfunctions. However, these findings are less precise than they might have been because of the heterogeneity of the cardiac diagnostic groups. Further, the theoretical validity of the Bender-Gestalt test is controversial (Lyle and Quast, 1976; Butler, Coursey, and Gatz, 1976; Dana, Field, and Bolton, 1983). The authors maintained that because each individual's preoperative score was treated as that subject's baseline, subjects acted as their own controls, and therefore that neither group matching or covariate analysis were required. However, large preoperative group differences in mean age or intelligence, for instance, might have skewed outcomes; these figures were not reported. Further, the oxygenators which were tested in the study by Landis et al. are technically outdated by current standards. These considerations limit the generalizability of the findings.

The study by Boccalon (1982), though more recent, also has methodological weaknesses. Again, the sample contained a mixture of diagnostic groups. Patients were not blindly assigned to the bubbler or membrane groups, but were selected for each type of oxygenator by their surgeons. Since the surgeons may have preferred one or the other oxygenator for some classes of disease or for given degrees of illness severity, group assignment was not necessarily random; no information was given concerning how the surgeons made these decisions. The groups were not matched on any variables which might have affected postoperative performance on the neuropsychological measures; and although all the tests were designated as memory tests, they were inadequately identified. In addition, the criteria for impairment on these tests may have been too lax, deterioration being rated whenever a patient's postoperative score failed to improve by at least 10%. This criterion may take practice effects too much for granted, and may not make sufficient allowance for normal postoperative fatigue and lack of motivation. Lastly, nine patients of unspecified group assignment who had bypass times longer than 115 minutes and who manifested disturbances were excluded from examination. These, however, are dubious reasons for excluding subjects; if anything, their test performances would have been of special interest. Although Boccalon's report favored the membrane oxygenator, the various factors mentioned weaken the result.

The Advantages of Using Neuropsychological Assessment Measures

Frequently, researchers in the field of post-open-heart disorders have neglected to use standardized assessment measures which could be readily applied by other investigators. Data from interview methods, for example, have been hard to interpret because of terminological variations and differing diagnostic criteria between studies. Since postoperative disturbances have lacked clear, set definitions, they have been re-observed and re-defined with each new team of researchers (Dubin et al., 1979; Gotze, Huse-Kleinstoll, and Speidel, 1980). Interviews, also, rely heavily on self-reports (Blacher, 1972; Rabiner et al., 1975). Furthermore, the interview process may emotionally prepare and protect patients against mental disturbances (Kornfeld, Heller, Frank, and Moskowitz, 1974). Several researchers have, however, used neuropsychological assessment measures either as alternatives or as supplements to psychiatric and neurological examinations (Priest, Zaks, Yacorzynski, and Boshes, 1957; Lee et al., 1971; Willner, Rabiner, Wisoff, Hartstein, Struve, and Klein, 1976; Willner, Rabiner, Wisoff, Fishman, Rosen, Hartstein, and Klein, 1976; Willner and Rabiner, 1979; Åberg and Kihlgren, 1974, 1977a, b, 1982; Tienari et al., 1982). The usefulness of these measures in such research is apparent, as they are standardized and quantified (Åberg and Kihlgren, 1980). Some writers have observed that neuropsychological measures may reveal marked deficits even when clinical signs and symptoms are at a minimum (Åberg and Kihlgren, 1977a, 1980; Bethune, 1981; Boccalon, 1982). Åberg and Kihlgren (1980) and Bethune (1981) specifically advocate the use of such standardized instruments in the testing of hypotheses concerning new procedures or equipment in open-heart operations.

Rationale for the Present Study

Research in the field of cerebral dsyfunctions occurring after open-heart surgery has established that their high incidence is probably linked in many cases to the effects of air microbubbles (Aberg and Kilhgren, 1982). The hazard of these microbubbles comes with the use of the heart-lung apparatus, specifically the 'lung' or oxygenator. Though earlier studies have compared the bubbler and membrane oxygenators, in terms of postoperative neuropsychological deficits, these studies did not lead to definitive conclusions, mainly because of methodological weaknesses. Findings lacked precision, for example, because of the use of diagnostically mixed cardiac groups and because of the failure to match experimental groups for certain potentially influential variables, such as age, intelligence, education, and sex. The studies by Landis et al. (1974) and Boccalon (1982) did use neuropsychological tests, which are the optimal measures for use in this field of investigation, but the measures chosen were of questionable validity or else were inadequately identified. Also, some subsidiary factors which might have influenced neuropsychological outcomes, for instance, intelligence, education, and mood states, were not accounted for in the analysis of the outcome data. Lastly, previous studies had used oxygenators which were outdated, or which were of different manufacture from those currently in use at the Health Sciences Centre, St. John's, Newfoundland.

Essentially, then, the question of whether the membrane's more sophisticated design would reduce the risk of ischemic damage attributable to gaseous microemboli, and of whether the greater cost of the membrane was justified, remained to be adequately tested.

Method

Subjects

All subjects in this study were admitted to the General Hospital, Health Sciences Centre, St. John's, Newfoundland, for coronary artery bypass grafting (CABG) in the period between July 12, 1984, and March 4, 1985. As this is the only medical centre in Newfoundland and Labrador where this operation is performed, patients come from all parts of the province. Those scheduled for any operation other than CABG were not requested to participate. In the typical case, patients entered hospital approximately 36 hours before the operation. In keeping with the requirements of the Research Ethics Committtee, Health Sciences Centre, patients were approached with the consent form a minimum of 24 hours before surgery (see Appendix for a copy of the consent form). A total of 133 CABG patients were admitted to hospital during the study period, and of this number, 77 signed the consent form. Of the remainder, some were emergency cases, some were not contacted by the experimenter due to scheduling difficulties, and the rest chose not to participate. The mean age of the patients who did not sign the consent form (n=56) was 55.5, range 30-75, while the mean age of the patients who completed all testing was 50.4, range 34-68. The age difference between these groups was significant ($t=2.82$, $df=93$, $p<.01$). There was also a subgroup which agreed to participate initially, but for various reasons did not complete all testing. Of 77 who originally agreed to participate, 4 did not survive the operation, 8 were illiterate and could not complete some tests, and 24 refused to complete some part of the battery either pre- or postoperatively after having signed the consent form. The mean age of this subgroup (n=36) was 59.7, range 44-68, and this meant these patients were also significantly older on average than the group which completed testing ($t=6.01$, $df=70$, $p<0.01$). In addition, those who completed all tests had significantly more years of education (mean 9.6, range 3-16) than those who did not (mean 6.5, range 2-13), $t=4.71$, $df=71$, $p<.01$. In summary, older patients and those who had less education were less likely to participate initially and, if they did participate, were less likely to complete all tests. This tendency, however, may have meant that the experimental hypothesis was more strictly tested, as younger patients with more education might reasonably be predicted to show less postoperative neuropsychological deterioration.

Measures

In the current study, 12 scores were taken from ten measures. In previous reports, few tests had revealed neuropsychological deficits every time they were applied; many were useful in some studies and not in others. It was decided, in the interests of thoroughness, to use a larger rather than a smaller number of measures. All the measures chosen had been sensitive to deficits in earlier studies, except the Rey Auditory Verbal Learning Test, which has never been used in published investigations of postsurgical disturbances (and is discussed below). All were standardized instruments chosen to assess a variety of mental functions and abilities. Each test and its purpose is briefly described here.

The Trail Making Test (Reitan, 1958), a widely used and sensitive measure of brain injury, (Sterne, 1973; Golden, 1978) is an index of patients' planning ability, and also measures visuomotor speed and concentration. Part A requires subjects to connect consecutive numbers which are scattered randomly on a page; in Part B, the subject is required to draw lines alternately between letters and numbers (1-A-2-B-3-C, etc.). This measure was found to be a useful index of postoperative decline in three studies (Kilpatrick, Miller, Allain, Huggins, and Lee, 1975; Savageau, Stanton, Jenkins and Klein, 1982; Savageau, Stanton, Jenkins, and Frater, 1982). The Figure Rotation measure, (also known as the Spatial Relations subtest from Thurstone and Thurstone's Primary Mental Abilities test, 1963), is a non-constructional indicator of spatial ability. A line drawing of an abstract figure is presented at the beginning of an array, and five other drawings are given, representing the first figure in various orientations. The subject is required to select those figures which, when rotated within a plane, would match the original. This is a comparatively difficult and sensitive test (Swiercinsky, 1978), which has consistently revealed cognitive deficits in open-heart surgery patients tested by Aberg and Kihlgren.

The Figure Rotation test has, also, been used by those authors as an outcome measure in the quality testing of heart-lung equipment (1974, 1977a,b, 1980, 1982).

Three subtests from the Wechsler Adult Intelligence Scale, Revised, were employed (Wechsler, 1981). The Digit Span test measures immediate memory ability by testing the number of digits that can be remembered and repeated in correct forward or backward order. This is a valuable measure of brain injury (DeWolfe, 1971; Woo-Sam, 1971; Golden, 1978) which is especially useful for initial assessments of memory functioning (Lezak, 1976). A number of authors have found that notable declines occurred on this test after open-heart surgery (Gilberstadt and Sako, 1967; Priest et al., 1957; Kilpatrick et al., 1975; Sotaniemi et al., 1981). In the Digit Symbol test (Wechsler, 1981), nine symbols are paired with digits 1-9 in a key printed above the response sheet. The task is to match as many symbols with digits as possible within a time limit of 90 seconds. This test calls for rapid eye movement and short-term visual retention, and is thought by some researchers to be more sensitive to brain injury than any other WAIS subtest (Golden, 1978). The scores of open-heart-surgery patients declined significantly on this test following surgery in four studies (Gilberstadt and Sako, 1967; Priest et al., 1957; Zaks, 1959; Willner, Rabiner, Wisoff, Hartstein, Struve, and Klein, 1976). The WAIS-R Vocabulary Test, which of all the WAIS-R subtests correlates best with overall IQ, (Wechsler, 1981) was given as a short intelligence measure primarily for the purpose of matching experimental groups.

In addition, three separate scores were taken from the Rey Auditory Verbal Learning Test (AVLT) (Rey, 1964; Lezak, 1976). In this test, the subject is read a list of 15 words five times over, and each time is asked to recall as many words as possible in any order. The individual is then tested on a second list, only once, and following this distraction task, is asked to remember as many items as possible from the first list. Of the three scores taken from this test, the first was the total of the items remembered in trials four and five on the first list (REY4+5). This sum indicated the subject's best performance on the initial list before the interference list was presented. Second, the total in trial one was subtracted from that in trial five, as an index of the cumulative learning occurring over the five trials prior to the interference task (REY5-1). Finally, the total number of words recalled in trial five minus the total in trial six, that is, the number of words lost after the presentation of the distraction task, was calculated (REY5-6).

The Rey AVLT was selected to replace the test of new learning, described as a 'delayed recall test,' which was used by Bethune (1980, 1981, 1982; Williams, 1968). In Bethune's test, the subject was required to memorize a set of objects pictured on a card for one minute and then to recall them ten minutes later after undergoing a brief interview and the Digit Span test. Following open-heart surgery, Bethune's patients were retested with the original card and were also tested on a new one, hence 'new learning'. However, a weakness in the procedure is that the subject is given verbal, and then, if necessary, visual hints to help recall the pictures. The correct responses might be divined through association. A sample hint is, 'are you a good listener?,' to which the correct answer is 'ear.' Many might give the correct response simply by producing their first association to the question. It is probable that the scoring method (number of hints required) cannot take sufficient account of wide individual variations in responses to these prompts. The Rey AVLT was selected as a more standardized measure of a similar function.

The Conceptual Levels Analogy Test (Willner, 1971) is a measure of abstract reasoning which has been found in earlier studies (Willner, Rabiner, Wisoff, Hartstein, Struve, and Klein, 1976; Willner and Rabiner, 1979; Willner and Rabiner, 1982) to predict postoperative disturbances and long-term organically based mortality. Subjects answer a series of increasingly difficult analogy questions, such as the following:

Bird-Sings: Dog (Cat, Song, Florida, Barks, Dances)

Tea-Coffee: Piano (Concert, Bugle, Grand, String, Milk)

Also, as noted above, many studies have shown that the patient's mood state can have an important influence on postsurgical mental functioning (Gotze and Dahme, 1980; Tienari et al., 1982; Heller et al., 1970; Kimball, 1969, 1972, 1973). The Spielberger State Anxiety scale (Spielberger, 1966) assesses the subject's anxiety level at the time of testing. Administration of this test gave a measure of the situational anxiety present at the time the subjects took the various tests. The Spielberger Trait Anxiety scale is a measure of anxiousness, not in the situation, but as a character trait, which again, was administered as a way of monitoring the influence of emotional makeup on neuropsychological performances. The Beck Depression Inventory (Beck, Ward, Mendelsohn, Mock, and Erbaugh, 1961) measures feelings of depression which, along with feelings of anxiety, are very common in the pre- and postoperative periods and may influence performance (Gotze and Dahme, 1980; Tienari et al., 1982; Jakubik, 1972; Frank, Heller, and Kornfeld, 1972).

Intraoperative measures. During operations, perfusion times were routinely noted by the cardiovascular perfusionists. The measurement of hypotension, however, was less straightforward. In previous studies, 'hypotension' has been defined and measured in many ways. In the present study, intraoperative blood pressure levels were recorded at 5-minute intervals by the medical resident in anaesthesia. Afterwards, graphs depicting the progression of blood pressure readings for each patient were constructed, and the total length of time spent below the safety level of 50 millimeters of mercury (50mmHg) was measured in each case.

Procedure

Once preoperative testing was complete, the patient was assigned to oxygenator Group A or B. The assignment of patients to groups was not a random process, as the subjects were selected for groups in such a way that gender distributions, mean ages, years of education, WAIS Vocabulary scores, and scores on the Conceptual Levels Analogy Test were evenly matched. The author, who was the tester, assigned each individual to a group in accordance with the desire to keep these matching variables equal, but was blind concerning which group, A or B, was associated with each oxygenator. Mean ages in the groups were matched because, as noted, several studies have reported that older patients may be more susceptible to postoperative complications (Javid et al., 1969; Tufo et al., 1970; Stockard et al., 1973; Stockard et al., 1974). Because women tend to experience more difficulties in recovery after open-heart surgery, the small number of women in the current study sample were distributed evenly between the two groups. Further, because performances on several of the neuropsychological outcome measures could be affected by level of education, mean educational achievement in the two groups was matched. An attempt was made to control for intelligence levels through the administration of the WAIS-R Vocabulary test (Wechsler, 1981). Lastly, Willner, Rabiner and associates (Willner, Rabiner, Wisoff, Hartstein, Struve, and Klein, 1976; Willner, Rabiner, Wisoff, Fishman, Rosen, Hartstein, and Klein, 1976; Willner and Rabiner, 1979, 1982) have published evidence which suggests that preoperative scores on the Conceptual Levels Analogy Test (CLAT) may predict postoperative cerebral dysfunctions. Accordingly, mean preoperative CLAT scores in the two groups were equated.

In most cases, preoperative testing could be completed in one session, but sometimes more were required. The cardiovascular perfusionists, who operate the heart-lung machine, were notified before each patient's surgery and would employ the appropriate oxygenator in the operation. Group A underwent cardiopulmonary bypass using a Cobe Membrane Lung (Cobe Labs, Denver, Colorado). Group B, the bubbler group, underwent cardiopulmonary bypass using a Bentley Bio 10 oxygenator (Bentley Labs, Irvine, California). A Shiley Saf-20 arterial line filter (Shiley, Inc., Irvine, California) with 20 micron screen filter was used with this oxygenator to prevent air bubbles created during oxygenation from entering the patient's bloodstream.

Patients underwent the second set of test trials between 5 and 14 days postoperatively. In the typical case, retests began at 7 days and the patient left hospital at 10 days, although there were many variations on this pattern. Because patients were often fatigued and because there were interruptions from many sources, testing was rarely completed in one session. At this test administration, alternate forms were devised for the Rey Auditory Verbal Learning Test (AVLT), the Digit Span, and the Digit Symbol tests. A list of comparable common nouns was selected for the AVLT by the author. In the Digit Span, similar number lists were used, and in the Digit Symbol the sequences of the symbols were altered. At this second administration, 41 patients, 20 in Group A and 21 in Group B, completed the entire test battery.

Six weeks postoperatively, patients returned for a clinic checkup, and this was the occasion for the second postoperative neuropsychological assessment. Alternate forms were again used for the AVLT, Digit Symbol, and Digit Span. However, some patients had checkups at other medical centres, some refused testing, and a few were missed due to schedule changes. As a result, only 30 patients, 14 in Group A and 16 in Group B, completed the full test battery at 6 weeks.

Results

The eight dependent measures employed in this study included the Trail Making test, with parts A and B summed to make a single score, the Figure Rotation test, the Digit Span, the Digit Symbol, the CLAT, and, in addition, the three outcome measures derived from the Rey Auditory Verbal Learning Test: the sum of the words recalled on trials four and five (REY4+5); the index of improvement between trials one and five on the initial word list (REY5-1); and the number of words forgotten after the interference task (REY5-6). Six covariates were assessed at the preoperative trial, and eight at each of the two postsurgical trials. The two new variables, measured during the operation, were hypotension time and bypass time. The total list of covariates comprised age, education, bypass time, hypotension time, and scores on the WAIS-R Vocabulary, State and Trait Anxiety, and Beck Depression scales.

Forty-one patients completed all tests at the first followup session, and of these, 30 completed the battery again at the 6-week session. Of the remaining 11 subjects, several did complete some tests. In these instances, the scores were included in the data file, so that the total number participating at the 6-week followup varied slightly from measure to measure. There were never scores from more than 32 subjects included in the 6-week data for any test.

Analysis of Raw Scores

Repeated-measures multiple analyses of variance (MANOVAs) were performed on the raw data, before any of the covariates had been accounted for, using the SPSS-X MANOVA program (1983). The main advantage of MANOVA over ANOVA is that MANOVA controls for the possibility that false significances may emerge simply because of the large number of comparison tests performed when there are a number of measures and repeated trials. The factors entered into these MANOVAs were the two groups, the eight outcome measures, and the three test sessions. The initial MANOVA was performed on the data from all three test sessions, and three subsequent MANOVAS were executed on data from sessions one and two only, session one and three only, and sessions two and three only. Before the MANOVA based on scores from only sessions two and three was executed, the variance predictable from the preoperative scores was removed from the total postoperative-score variance by means of multiple regression. The purpose of these subsidiary analyses was to determine how much change occurred within each sub-interval. Only one of all these analyses, performed on data from sessions one and three only, produced significant results. There was an overall interaction between group, test and time ($F=2.59$, $df=7,23$, $p<.05$). To establish which of the individual tests in the battery were responsible for the group, test and time interaction, univariate tests were performed. These analyses revealed significant group x time interactions on the REY5-1 ($F=8.13$, $df=1,30$, $p<.01$) and the

Digit Span (F=6.69, df=1,3, p<.01) tests. Table 1 contains the raw score means for the REY5-1, the REY4+5, and the Digit Span tests. Examination of these means shows that, while the scores of the membrane group were higher preoperatively, the mean score of the membrane group on the REY5-1 fell by 2.34 points between sessions one and three, while that of the bubbler group fell by only .52 points. While scores of both groups had fallen on this measure by the 6-week test session, those of the membrane group had fallen to a significantly greater extent.

There was also a group x time interaction in the Digit Span scores, which presents a rather different pattern. Scrutiny of the means for all three trials shows that while the mean Digit Span scores of the two groups were widely disparate before surgery on this task, most probably because of sampling error, the performances of the two groups were virtually equivalent by the time of the last test session. The group x time interactions obtained on the Digit Span test in several data analyses most plausibly reflect a pattern of regression toward the mean occurring in both groups.

Table 1

Group Means (Raw Scores)

Dependent Measure	Test Session	Membrane Group	Bubbler Group	Difference
REY5-1	Preoperative	5.45	4.62	.83
	1st postoperative	2.95	3.76	-.81
	2nd postoperative	3.11	4.1[illegible]	-.99
DIGIT SPAN	Preoperative	9.9	11.52	-1.62
	1st Postoperative	9.25	10.43	-1.18
	2nd Postoperative	10.55	10.53	.02
REY4+5	Preoperative	18.15	17.62	.53
	1st Postoperative	13.95	16.95	-3.00
	2nd Postoperative	14.17	15.29	-1.12

Analysis of Standardized Residuals

In the subsequent analyses, multiple regression was used to remove variance associated with the eight covariates, leaving residuals. Also, because the various measures had originally been scored according to different scales, (some from 1 to 10, some from 1 to 70, for example) the residuals were transformed into z scores. The residuals, then, are properly called 'standardized residuals'.

The first analysis of standardized residuals was performed on the data from all three test sessions. The top row, middle column of Table 2 presents the significant findings from this analysis. The only interactions to emerge were those between group and test, and between group, test, and time. The results of the associated univariate tests are presented in the top row, right hand column of Table 2. The Table shows that the major changes occurred on the REY4+5, the REY5-1, and the Digit Span tests. (Interactions between group and time for the REY4+5 and the Digit Span measures, though not quite significant, are noted because differences on these measures in each of the three subsequent analyses did attain significance). The interaction between group, test, and time reveals that the pattern of the scores in each group changed in relation to the pattern in the other group on these three measures over test sessions. Mean scores on the two Rey measures, presented in Table 3, reveal that before surgery the performances of the two groups did not differ, but that after the operation the scores of the bubbler group were much better than those of the membrane group. Although Digit Span residual scores were significantly different before surgery ($t=3.24$, $df=38$, $p<.01$), this difference disappeared after surgery. The overall interaction between group and test indicates simply that when the scores on these three measures from all test sessions were summed separately within each group, the group differences were signifcant.

Table 2

Significant Results Obtained in MANOVAs Performed on Standardized Residuals

Testing Sessions Compared	Overall Effects	Univariate Test Results
1, 2, and 3	group x test $p<.05$ group x test x time $p<.05$	REY4+5 $p<.09$ group x time REY5-1 $p<.05$ group x time D. SPAN $p<.09$ group by time
1 and 2	group x test $p<.05$ group $p<.07$	REY4+5 $p<.01$ group x time REY5-1 $p<.06$ group x time D.SPAN $p<.01$ group
1 and 3	group x test x time $p<.05$	REY4+5 $p<.05$ group REY4+5 $p<.05$ group x time REY5-1 $p<.01$ group x time D.SPAN $p<.05$ group x time
2 and 3	group $p<.05$ group x test $p<.05$ test x time $p<.01$	REY4+5 $p<.01$ group REY4+5 $p<.05$ time REY5-1 $p<.05$ group D.SPAN $p<.05$ group

Table 3

Group Means (Standardized Residuals)

Dependent Measure	Test Session	Membrane Group	Bubbler Group
REY4+5	Preoperative	.013	-.012
	1st Postoperative	-.464	.420
	2nd Postoperative	-.418	.507
REY5-1	Preoperative	.127	-.121
	1st Postoperative	-.228	.207
	2nd Postoperative	-.320	.388
DIGIT SPAN	Preoperative	-.431	.410
	1st Postoperative	-.305	.276
	2nd Postoperative	-.032	.036

With little variation, these main findings--the postsurgical superiority of the bubbler group on the two Rey measures, and the preoperative difference on Digit Span scores which disappeared postoperatively--were also obtained in the next three analyses. The second analysis of residuals differed from the first in that data from only two test sessions, the preoperative and the first postoperative, were included. Results (shown in the second row, middle column of Table 2) revealed overall group and group x test effects, meaning that although the groups did differ on the Rey measures and the Digit Span, there was no interaction of group differences with test sessions. However, the univariate test results showed that on the REY4+5 and the REY5-1 measures the scores of the bubbler group were higher than those of the membrane group after surgery ($F=7.51$, $df=1,39$, $p<.01$; $F=3.64$, $df=1,39$, $p<.06$). The group effect associated with the Digit Span test reflects the preoperative difference in group means on this measure.

The third MANOVA and the associated univariate tests were based on data from sessions one and three only. Results of these analyses (presented in the third row, middle column of Table 2) showed that at the 6-week followup, the performance of the bubbler group was superior on the two Rey measures (REY4+5: $F=5.16$, $df=1,29$, $p<.05$; REY5-1: $F=7.66$, $df=1,29$, $p<.01$), and that differences in the scores of the two groups had almost disappeared on the Digit Span test ($F=4.81$, $df=1,30$, $p<.05$).

The fourth and final MANOVA, in which the groups were compared across the two postoperative (1 and 6-week) trials, was more complex. First, the preoperative scores of all measures, including those of the covariate measures, were partialled out from all postoperative scores on those measures, irrespective of group membership; that is, the pre-measures were themselves treated as covariates. The resulting residuals reflected 'pure' postoperative responses, with the variance attributable to preoperative scores removed. This procedure left an initial set of standardized residuals. Then, as in the previous analyses, the effects of the original eight covariates were removed from the dependent measures through multiple regression, and these residuals were again standardized.

In this way, the MANOVA was based only on postoperative outcome scores, from which preoperative data and the covariate measures had b[illegible]tialled out. The only significant results were the interactions between group and test ($F=2.91$, $df=1,28$, $p<.05$), test and time ($F=3.6$, $df=7,22$, $p<.01$) and the main effect of group ($F=4.44$, $df=1,28$, $p<.05$). The group x test interaction reflected the higher scores of the bubbler group on the REY4+5 and the REY5-1, and the higher scores of the membrane group on the Digit Span test (means in Table 4). The test x time interaction indicated that large changes occurred between test sessions on some measures when the two groups were treated as a single sample. Univariate test results were similar to those obtained in all previous analyses, with the exception of the REY4+5 time effect, ($F= 4.28$, $df=1,28$, $p<.05$), which indicated a large between-sessions difference on this

Table 4

Group Means: Residuals Obtained When Pre-measures and Covariates Were Partialled Out

Dependent Measure	Test Session	Membrane Group	Bubbler Group
REY4+5	1st Postoperative	-.194	.655
	2nd Postoperative	-.408	.033
REY5-1	1st Postoperative	-.281	.367
	2nd Postoperative	-.355	.359
DIGIT SPAN	1st Postoperative	.026	-.377
	2nd Postoperative	.413	-.124

measure when the groups' scores were combined.

The analyses of the standardized residuals affirmed the results of the raw-score analyses, and expanded those conclusions. They revealed that the postoperative performance of the bubbler group was significantly superior on the REY4+5 measure, as it had also been on the REY5-1 measure in both raw data and residual analyses. This was not surprising, since each of these measures assesses in a different way the extent of new learning which has taken place by the fifth trial on the Rey AVLT.

Whereas the raw score means for both groups on the two Rey measures decreased postoperatively, (Table 1) the mean residual scores of the bubbler group (Table 3) appear to have improved. Some caution must be exercised in interpreting these residuals, in that no absolute improvement occurred in these instances. Two covariates, hypotension time and bypass time, were partialled out from postoperative but not preoperative scores, and the introduction of these factors caused a change in the pattern of postoperative means. Simply put, these residual means affirmed the lack of a significant decline in the bubbler group's performance on the Rey measures after surgery. This conclusion was strengthened by repeated-measures analyses performed separately on the raw scores of each group. These analyses produced significant decreases in mean REY4+5 and REY5-1 scores over the three test sessions in the membrane group ($F=13.53$, $df=2,16$, $p<.01$; $F=14.31$, $df=2,16$, $p<.01$), whereas decreases over the three sessions in the bubbler group were not significant.

Also, residual scores on the Digit Span test in Table 4 seem to favor the membrane group, while the raw scores suggest the opposite pattern. However, this reversal is an artifact which arises from the fact that the groups' scores were quite divergent before surgery. When the preoperative scores were partialled out from the postoperative scores, the removal of the large original difference led to an apparent pattern of reversal. In consequence, it is difficult to draw conclusions from this finding.

Covariate Interactions

In order to assess the impact of each of the covariates, MANOVAs were used to compare the correlations of each covariate with the performance of each group on each measure at each trial. For instance, one such MANOVA tested whether education was correlated with CLAT scores at first followup to a greater extent in group A than in group B. It should be noted that in five of the instances presented in Table 5, education or vocabulary correlated negatively with postoperative scores in the membrane group, and that these correlations differed significantly from the corresponding positive correlations in the bubbler group. The implication here would be that although the groups were originally matched for years of education and vocabulary scores, patients in the membrane group were less able to draw on these resources postoperatively than those in the bubbler group. Education and vocabulary, incidentally, were significantly correlated with each other at all three trials ($r=.75$, $r=.69$, $r=.70$). The conclusion that the membrane group was less able to use these resources postsurgically would tend to support the study's main finding, that postoperatively the bubbler group performed more effectively on the two Rey AVLT measures. However, no single covariate interaction directly involved the measures which were otherwise of most importance, the Rey AVLT or the Digit Span.

Table 5

Correlations between outcome measures and covariates which differed significantly between groups

Variables	Test Session	Correlation, Membrane Group	Correlation, Bubbler Group
Trail Making Test/ Education	1st Postoperative	-.03	.58 ($p<.01$)
Trail Making Test/ Vocabulary	1st Postoperative	-.09	.51 ($p<.01$)
CLAT/ Trait anxiety	1st Postoperative	.46 ($p<.05$)	-.32
CLAT/ Education	1st Postoperative	-.38 ($p<.05$)	.71 ($p<.01$)
Trail Making Test/ Education	2nd Postoperative	-.43 ($p<.05$)	.10
Digit Symbol/ Education	2nd Postoperative	-.42	.10

In the present study, several neuropsychological measures were used in an attempt to assess cognitive deficits known frequently to occur after coronary artery bypass grafting. Though discussion up to this point has focussed on deficits occurring differentially in the two oxygenator groups, it is worth asking whether, in any absolute sense, any patients could be said to have shown important declines in postoperative mental ability as measured by these tests.

Separate repeated-measures analyses performed on the scores of each group revealed that whereas the performance of the membrane group declined significantly over all three test sessions on the REY4+5 and the REY5-1 measures, decreases were not significant in the bubbler group. The postoperative decline in the membrane group, then, is the proper focus of attention. Whereas scores in the membrane group fell by an average of 4.2 words on the REY4+5 test 1 week postoperatively, and regained only .22 words at 6 weeks, those in the bubbler group dropped by only an average .67 words at 1 week, and an additional 1.66 words at 6 weeks. On the REY5-1, the scores of the membrane group fell by an average 1.5 words at 1 week and and regained only .17 words at 6 weeks, whereas those of the the bubbler group declined by only .86 words at 1 week, and subsequently improved by .34 words. It is clear that the membrane group suffered a distinct loss in learning ability which remained in evidence 6 weeks after surgery.

Discussion

The major finding of the study was that the bubbler group performed more effectively than the membrane group on two measures from the Rey Auditory Verbal Learning Test at both postoperative test sessions. This finding may be understood to mean that, after surgery, the bubbler group displayed abilities for learning and storing new information which were superior to those of the membrane group. There is, then, some evidence that the bubber is the preferable oxygenator for use. However, one cannot state without qualification that the bubbler was the superior device, for two reasons: First, the number of subjects was relatively small, and second, followups did not extend beyond six weeks.

The finding that patients' scores fell significantly on one test and not on others is not an unusual one in research on cognitive deficits occurring after open-heart surgery. While the sensitivity of new learning was demonstrated in the current study, other findings have shown that a variety of abilities may be affected, including abstract reasoning (Willner et al., 1982), visuospatial organization (Aberg and Kihlgren, 1982), and short-term memory (Kilpatrick, 1975; Gotze and Dahme, 1980). In a major international study currently under way, a number of cognitive functions, including new learning, are being assessed (Willner, personal communication, 1984). Few writers have directly addressed the problem of variability among conclusions, beyond alluding to the lack of methodological comparability which exists between studies.

Several have also expressed the view, widely held, that dysfunctions occurring after open-heart surgery have many causes. It is understood that, by implication, these dysfunctions may take many forms (Kornfeld et al., 1978; Dubin et al., 1979; Gotze et al., 1980; Katz, 1980; Willner et al., 1979).

The present study has led to certain practical conclusions which have much potential value for future studies in this field. In particular, it has provided some valuable indications concerning which variables would most profitably be followed up in future investigations. There are also special points to be made concerning the CLAT, Figure Rotation, hypotension and bypass time, and mood measures.

<u>The Importance of Learning and Memory</u>

In this investigation, measures of learning and memory were of central importance. The Rey AVLT, clearly, should be used in future studies. Findings from this test were robust, and were obtained in analyses based on both the standardized residuals and the raw data. Other studies have also obtained notable findings with tests of new learning. Bethune (1980), for example, administered a delayed recall task to a subset of valve patients in his sample who showed mild neurological signs after surgery. These patients performed adequately when relearning pictures they had seen before the operation, but had difficulty in recalling newly presented pictures. It appeared that their capacity for acquiring new information was impaired, even though retention of previously learned information was adequate. Two other studies have found that verbal learning tests comparable to the Rey AVLT were sensitive to postoperative deficits, though in neither study were these among the most prominent findings. Sotaniemi et al. (1981) used the Learning Test (Weckroth, Tienari, and Airikkala, 1975), in which 12 words are learned by rote, and found that scores correlated highly with neurological outcome. Also, Juolasmaa et al. (1981) found that, after surgery, more than 20% of the sample showed impairment on the Paired Associates subtest of the Wechsler Memory Scale (Wechsler, 1945), a test whose difficult items can be said to constitute a test of new learning. The present report is not the only one, then, to suggest that the learning of new information may be particularly vulnerable to the stress of the open-heart operation.

The Rey AVLT is more suitable for measuring new learning than Bethune's delayed recall test, not only because it is better standardized, but because it provides multiple scores; these reflect the degree of improvement over repeated trials, the maximal performance attained after repeated trials, and the effects of a distraction list. It is worth remarking that the Rey's sensitivity in identifying learning and memory impairments has recently received increased attention in the neuropsychological literature. Mungas (1983) showed that AVLT results clearly differentiated several subgroups of brain damaged and psychiatric patients according to the degree of memory and learning impairment in each group. Amnesics, who suffer primary learning impairment, performed especially poorly on the Rey. Rosenberg, Ryan, and Prifitera (1984) found that the AVLT scores of memory-impaired psychiatric and neurological patients were much poorer than those of patients whose memory was not impaired.

Another measure which could be used to assess new learning would be the difficult items from the Paired Associates subtest in the Wechsler Memory Scale, in which unrelated word pairs are presented over repeated trials. Findings with these items might well affirm the results obtained here with the Rey test. Note, however, that without alternate forms for this measure or for the Rey AVLT, new learning cannot truly be assessed.

Also, though Digit Span scores in the present investigation appear to have followed a pattern of regression toward the mean, this test should be used again in future studies, in the interests of greater certainty. Another reason is that authors have reported postoperative deficits occurring on this index of short-term memory more than on any other test in the literature (Gilberstadt and Sako, 1967; Priest et al., 1957; Kilpatrick et al., 1975; Sotaniemi et al., 1981). Learning and memory, as measured by the Rey test and the Digit Span, may well be among the cognitive functions most likely to be affected by the open-heart procedure.

Results Obtained with the CLAT

Willner, Rabiner, and associates (Rabiner, Willner, and Fishman, 1975; Willner, Rabiner, Wisoff, Hartstein, Struve, and Klein, 1976; Willner, Rabiner, Wisoff, Fishman, Rosen, Hartstein, and Klein, 1976; Willner and Rabiner, 1979; Rabiner and Willner, 1980; Willner and Rabiner, 1982; Rabiner, Willner, and Detmer, 1982) have published a number of studies in support of their hypothesis that some heart disease patients may incur cognitive deficits well before surgery because of diminished blood flow to the brain. These authors have also published evidence to support the theory that these preoperative deficits are early warning signs whose presence can reliably predict both psychopathological and neurological disorders occurring in the early postoperative period, and also symptoms and mortality over the long term. These researchers used Willner's Conceptual Levels Analogy Test to assess the presence of what they have termed the Psychopathology and Cognitive Disorder (PCD) Syndrome in patients about to undergo open-heart operations. Their research showed that, in a sample of 64 patients, those with very low scores were significantly more likely to suffer inhospital pathology and organically related symptoms and death over a five-year period than were subjects with normal scores.

Though the CLAT was used in the current study, no significant findings were associated with this test. A plausible explanation is that the mean years of education (9.61) and Vocabulary scores (preoperative mean scaled score of

8.2) in the current sample were lower than those in Willner's population (mean 11.0 years education, mean Vocabulary score 10.5) (Rabiner et al., 1975). In an earlier publication, Willner observed that patients at the medical centre from which his subjects were drawn were of "considerably above average" intelligence (Willner and Struve, 1970, p. 432). Willner further claims that because the words used in the CLAT's test items never exceed a fourth grade level of difficulty, this test measures 'pure' abstract reasoning ability in any subject who possesses that much education or more.

However, in the present investigation, CLAT scores correlated positively and significantly with Vocabulary scores at all three trials, with education at the first postoperative trial, and nearly significantly with education at the first postoperative trial. Essentially, then, patients with less education and weaker vocabulary skills also had poorer powers of abstract reasoning as assessed by the CLAT. This test may be of less utility with poorly-educated populations, whose low scores probably reflect inexperience with problems of reasoning rather than organic deficit. Particularly low scores on the CLAT would more plausibly suggest organic injury in a middle-class population with good educational background and vocabulary ability. Though the current sample had only 1.39 fewer mean years of education than Willner's sample, the two groups were sociologically very different. Willner's was a middle-class suburban (Long Island, New York) population, while the current sample had a strong representation from rural areas, in a province (Newfoundland) where mean Verbal I.Q.

scores have been shown to fall below the national average (Burnett, Beach, and Sullivan, 1963). As a general rule, it has been shown that rural subjects obtain poorer scores than their urban counterparts on standard intelligence tests (Vernon, 1979). Use of the CLAT may be more appropriate with populations of least average verbal intelligence.

Further Methodological Considerations for Future Studies

Unfortunately, in the current research, the Figure Rotation test, whose utility has been apparent in the valuable work of Aberg and Kihlgren, (1974, 1977a,b, 1980, 1982) was incorrectly administered. Instructions indicating that subjects' performances were to be timed did not come into the author's possession until after data collection had begun. Although no findings of note were associated with this test, then, these results are inconclusive. As the research of Aberg and Kihlgren has consistently confirmed the sensitivity of this measure, and because the instrument was not properly used in this study, it had best be tried again in future undertakings.

When mood states were assessed, neither the Spielberger State and Trait Anxiety Scales or the Beck Depression Inventory suggested that anxious or depressed feelings markedly or consistently influenced performance. Scores rarely surpassed the median of the possible range and never indicated clinically serious emotional states. This is not to say, however, that these states never occurred in the study sample; sometimes patients remarked informally that they were more emotionally affected by their situation than responses on these scales had indicated. It is possible that many middle-aged males in hospital for open-heart operations did not want to reveal significant anxiety or sadness to an unfamiliar researcher, even on a pencil-and-paper test. These mood states might have been more accurately assessed by means of a sensitively conducted standardized interview.

Hypotension time was significantly and positively correlated, in both groups, with Trail Making, REY4+5, and REY5-1 scores, at the third test session only ($r=.34$, $.43$, and $.49$). This finding, which contradicted expectations, implies that decreases in blood pressure did not constitute a risk variable for these patients. It should be noted, however, that the blood pressures of only four patients fell into the potentially severe range below 40mmHg, that in no cases did pressures fall below 35mmHg, and that only one patient spent more than 5 minutes (10 minutes) at 35mmHg. In short, severe hypotension did not occur and was not a hazard in this sample. Bypass time, on the other hand, did correlate negatively in both groups with REY4+5 scores at sessions one and three ($r=-.17$, $p>.05$; $r=-.29$, $p<.05$). The range of bypass times in this sample (12-148 minutes) was reasonable for current surgical practice. While this was not a strong finding concerning the harmfulness of long perfusion times, this variable should continue to be accounted for in future analyses.

Conclusions

The primary finding of this study was that the bubbler group performed more effectively than the membrane group on two measures from the Rey Auditory Verbal Learning Test at 1 week after surgery, and that this result remained true at the 6-week followup. On the basis of this finding, it can be concluded with confidence that the bubbler when used with an appropriate filter is no more hazardous for use than is the membrane oxygenator.

In the larger context, this study has helped to confirm the usefulness of neuropsychological tests for research in this field. It shows that psychometric tests can profitably be used as the sole outcome measures in research on post-CABG dysfunctions. Use of such instruments leads to better standardization of measures within studies and allows for greater comparability between studies. Their use will also help to ensure that future studies of deficits occurring after open-heart surgery will continue to achieve both methodological soundness and clinically useful findings.

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Consent Form

As you may know, during your bypass operation, blood is channeled out of the body from one side of your heart; it goes into the heart-lung machine, and then gets channeled back into your body on the other side of your heart. At this hospital, two types of 'lung,' or oxygenator, are used in the heart-lung machine. Both types of 'lung' are used equally often. After the stress of your operation there will be a normal period of recovery before you are fully yourself again. We are testing patients' moods and alertness before and after surgery to see if there is a difference in how quickly patients recover full alertness and functioning with either of the two 'lungs.' Should you agree to participate in the study, you will be assigned at random to one of the two types of oxygenator-lungs we are comparing. Whether or not you participate in the research project, you will be receiving exactly the same medical care as all other patients. If you agree to participate, you will be requested to fill out two questionnaires concerning your mood and feelings at the time, and to try some tasks of skill and attention. This will take a total of about one to one and a quarter hours, on three different days: first, on the day before surgery, once again a week later, and then when you come for medical checkup in six weeks. The goal of the research project is simply to gain information, which may be used in the future treatment of patients, but which will not alter your treatment in any way. YOUR PARTICIPATION IN THIS STUDY IS ENTIRELY VOLUNTARY AND YOU MAY WITHDRAW AT ANY POINT. IF YOU DO NOT PARTICIPATE, OR IF YOU WITHDRAW, YOUR TREATMENT WILL NOT BE AFFECTED IN ANY WAY AND NEITHER WILL YOUR RELATIONSHIP WITH YOUR DOCTOR. ALL INFORMATION WILL BE KEPT CONFIDENTIAL. This project is being carried out by Mr. Graham Walsh, C.C.P., operator of the heart-lung machine on the heart surgery team, and Mr. Simon Hearn, Master's student in Psychology, Memorial University. It has been approved and supported by Drs. Kevin Melvin and Victor Aldrete, heart surgeons at the General Hospital, Health Sciences Centre. Mr. Simon Hearn will administer the assessment tests of skill and alertness. His work is supervised by Dr. Catherine Penney, Department of Psychology, Memorial University. If you have any questions, feel free to ask. If you would like some time to consider this request, or to discuss it with family or friends, that will be fine. As a final note, you may find that the tests are somewhat enjoyable, and that they help to pass your time in hospital. If you get fatigued, just say so, and you can take a break. We would be very grateful for your help in this research. If you would like to participate, please sign on the line below:

Name:____________________

Date:____________________