Determinants of Neurological Complications with the Use of Extracorporeal Circulation (ECC)

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Introduction

Extracorporeal circulation is currently an ever-changing technology with well-established basic principles. Its effects on the human body are not yet fully defined; likewise, the pathophysiology of several body reactions to this procedure remains a speculation[1].

Because it is a technology in which the principles of normal physiology are not followed, its routine use has encouraged the analysis of associated complications[2,3]. Innumerous researchers report that the deleterious effects of ECC are related to the development of the "Systemic Inflammatory Response Syndrome", characterized by pulmonary, renal, cerebral and cardiac involvement[3-6].

The effect of ECC on the nervous system should be considered. During perfusion, there can be blood pressure elevation, especially in the elderly, who easily develop cerebral edema and hemorrhage. In the presence of hypotension, hypoxia induces tissue damage, this being more severe in the cerebral tissue[1]. Also, ECC may lead to embolic processes with permanent cerebral damage[7].

The advances in the technology of extracorporeal circulation and surgical techniques, anesthesia and postoperative care have contributed to reduce the incidence of undesirable events related to the nervous system[1]. However, neurological complications still occur and are frequently included among the most important events, because they determine survival rates and have a great impact on the quality of life of patients and their families.

Currently, the objective of ECC must go beyond the replacement of cardiopulmonary functions, and should ensure cellular integrity, as well as the structure and function of organs and systems during the time required for the performance of surgeries. To attribute one given alteration to a single procedure is a complex idea; however, some authors classify ECC as an independent variable for the occurrence of neurological dysfunctions[7-9]. Nonetheless, some studies mention other factors as the cause of cerebral lesions, namely: advanced age, severity of disease, anesthetic-surgical procedure, and others[10,11].

Given the frequent use of ECC and the assumption that neurological complications affect the quality of life, it is necessary to consider the evidences of cerebral dysfunction in the management of ECC. Risk factors inherent to ECC and interventions that minimize the incidence and severity of the lesions should also be identified, taking into account the level of safety of this procedure.

Keywords

Extracorporeal circulation/adverse effects; systemic inflammatory response syndrome; cerebrovascular circulation; brain diseases.

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Methods

This is an integrative review on neurological complications caused by the use of ECC. Integrative reviews permit the synthesis and analysis of the scientific knowledge already produced on the subject investigated, meeting the same standards as primary research in terms of clarity and rigor[12]. This type of review permits the analysis of studies that have different methodological approaches, but address the subject at issue. The outcomes of the studies selected in this type of review lead to the construction of a body of knowledge necessary for the technical and scientific improvement of the care provided.

The analysis was based on the classification of strength of evidence elaborated by Stetler et al, who proposed levels for the main sources of scientific evidence[13]. Level I encompasses systematic reviews with meta-analysis, and level VI studies are based on the opinions of experts or of legal or regulatory agencies, as shown in Table 1.

The bibliographic survey of indexed publications was carried out in the period between January 1998 and September 2008, in the following databases: *Literatura Latino-Americana e do Caribe em Ciências de Saúde* (Latin-American and Caribbean Literature on Health Sciences - LILACS), electronic Index Medicus of the National Library of Medicine (MEDLINE), SciELO and Cochrane Library. Reverse search of original articles, which is a study selection method from the references of primary works retrieved in the previous search[14], was also used.

After search in the databases, manuscripts from MEDLINE and LILACS databases were selected and included, based on the following criteria: manuscripts addressing the themes "extracorporeal circulation" and "neurological complications", restricted to the past 10 years, in the Portuguese, English and

Table 1 - **Levels of strength of evidence**

Level of strength of evidence*	Sources of evidence
Level I	Meta-analysis of multiple controlled studies
Level II	Individual experimental study
Level III	Non-randomized, controlled, quasi-experimental study with a single group, with pre and post-test; case-control studies
Level IV	Non-experimental study such as descriptive correlational study, qualitative research or case study
Level V	Case reports or data obtained systematically, with verifiable quality, or assessment programs
Level VI	Opinion of acknowledged authorities (such as nationwide known authors) based on their clinical experience, or an expert committee including their interpretation of information not based on research. This level also includes opinions from regulatory or legal agencies†.

(*)- Level of scientific strength of evidence, as proposed by Stetler et al[13], in 1998.

Spanish languages. One book of acknowledged importance and relevance for this study was also used as a research source.

When the period of interest was selected, the number of manuscripts was reduced to 20 in the LILACS database and to 184 in MEDLINE. After reading and analyzing the 204 manuscripts selected, we verified that 27 articles directly or indirectly addressed the issues of interest. The full-text articles were ordered through *Biblioteca do Campus Saúde da UFMG* (Health Campus Library, UFMG), the Bibliographic Commutation System, consultation of the Homepage of CAPES Periodicals, and through BIREME (*Biblioteca de Revistas Médicas* - Library of Medical Journals).

In order to facilitate data collection from the studies selected, an instrument containing items for the analysis and synthesis of data from the content of the publications was elaborated, as shown in Box 1. These studies were put in order and were assigned values according to the classification of strength of evidence previously mentioned, considering the prevalence of neurological changes with the use of ECC, the types of complications, and their causal factors. The results extracted from each study were discussed in light of the specific literature.

Results

Sample analysis

The sample comprised one widely referenced book on this theme, one in vitro experimental study, three studies with a case-control design, one quasi-experimental study with a single group with pre and post-test, 14 cohort or case report observational descriptive studies, and eight literature reviews.

The countries with the largest number of publications were the United States of America (30%), Brazil (19%), England (15%), Spain (11%), and Japan (11%). As regards the languages selected, 66.7% of the studies were published in English, 18.5% in Portuguese, and 14.8% in Spanish.

From the introduction of extracorporeal circulation to the present day, there has been no specific time for the increase in the number of publications. In this sample, the distribution of periodicals is practically homogeneous,

Box 1 - **Data collection instrument**

STUDY CARD*- Manuscript nº	
1)Title:...	2)Author: ....
3)Periodical:	4)Year of publication: ....
5) Language:	6) Country: ....
7) Profession/ Titles:	8) Type of publication: ....
9) Study design:	10) [ ] direct [ ] indirect relation to the subject
11) Ethical aspects [ ] Yes [ ] No	12) Relationship between theory and outcomes: ....
13) Bibliographic review [ ] Yes [ ] No	14) Relationship between problem and method: ....
15) Is there an association between the use of ECC and the occurrence of neurological complications? [ ] Yes [ ] No	
16) Description of complications (when reported)	
17) Description of causal factors (when reported)	
18) Positive aspects of ECC	
19) Negative aspects of ECC	
20) Further studies recommended [ ] Yes [ ] No	
21) Scientific Strength of Evidence: [ ] I [ ] II [ ] III [ ] IV [ ] V [ ] VI	

(*) Elaborated by the authors of the present study.

with 14 studies published in the past 5 years, and 13 in the previous 5 to 10 years. This shows the constant interest in the theme, which contributes decisively for the construction of a specific knowledge.

In relation to the authors' professions, four studies directly cited doctors as the authors. The authors of six studies icluded professionals with a doctorate or masters degree. Most of the sample mentioned that their authors were affiliated members of hospital institutions or universities (but did not mention their profession or titles), and 37% of the studies were linked exclusively to universities, 30% only to hospital institutions, 26% to both, and 7% did not mention the authors affiliations.

In the identification of the sources for manuscript search, 81.5% were from MEDLINE and 18.5% were found in the LILACS database.

Among the studies published, no scientific article was produced based on dissertations or theses, and two used an experimental or quasi-experimental design. Although the experiments had some limitations regarding ethical aspects due to manipulable variables, they are technically the studies that best respond to the test of causal hypotheses[15].

As regards the ethical procedure in researches involving humans, six correlational descriptive studies, three case studies and one quasi-experimental study did not mention the ethical aspects of the study. These studies account for 55.5% of the study sample involving humans. The Declaration of Helsinki[16] and Resolution no. 196 of the National Health Council[17] establish that the compliance to ethical principles should be stated in the study protocol, but there is room for the interpretation that this statement is not mandatory in the final text of the studies.

When the whole sample was analyzed, we could observe that the theme of the present study is not specific to periodicals related to cardiovascular surgery or cardiology. Most of the manuscripts were published in general medical and health periodicals and neurology and anesthesiology journals, and this can also hinder a rapid update of knowledge.

In the structural analysis, we observed that only in a few cases the research priorities are not established as recommended. It is important to point out that 100% of the studies provided a background to support their objective and the other phases of the research process. The background was varied, extracted from national and international references, and represented a great part of the sample of the present study.

Neurological complications

Of the 28 studies analyzed, 51.7% are directly related to the occurrence of neurological complications in procedures using extracorporeal circulation, and only one of these studies mentions that this association is relative[18]. The background of all literature reviews and other studies that indirectly refer to the subject at issue showed the possibility of cerebral damage resulting from this procedure.

In the study analysis, patient groups at a greater risk for the performance of ECC were identified. Neonates, elderly, hypertensive, diabetic and obese patients, as well as those with history of stroke are known to be more susceptible to the development of neurological complications.

When patients are prospectively evaluated by an expert team using advanced technology, as well as refined and specific tests, neurological alterations, whether temporary or not, can be identified in more than 70% of them[1].

Cognitive impairment is reported in 16 studies of the sample (55%), with an incidence ranging from 2 to 80% of the cases[19-21]. Disorders of the level of attention, wake-sleep cycle, gait and memory; simple disorientation; mild to severe confusion; and psychomotor agitation with more severe psychotic behavior are among the organ dysfunctions reported. These dysfunctions are usually described as diffuse and reversible functional changes (in most of the cases) of the cerebral oxidative metabolism and of transmission, both in the adrenergic and cholinergic pathways[22,23].

The incidence of severe neurological complications such as intracranial hemorrhage in neonates (9.9 to 31%) and adults (3.4 to 18.9%), cerebral death or infarction (11%) is cited in some of the Strength of Scientific Evidence level IV articles[20,24,25].

The occurrence of cerebral dysfunction during the handling of ECC is presumed in the background of some level III or level IV studies; however, these studies did not show this neurological complication in their results due to the sample size or to the insufficient monitoring mechanisms for the analysis of this type of complication[4,26-28].

Sudden onset of painless loss of vision, whether uni or bilateral, diagnosed as "anterior ischemic optical neuropathy" and ocular palsy have been discussed with increasing frequency as complications following surgeries with extracorporeal circulaton[23,25,29]. Ischemic optical neuropathy is a defect in the optical nerve; its pathophysiology is not yet clear, and leads to irreversible loss of vision in most of the cases. Therapeutic attempts have failed. Thus, prophylactic transoperative measures targeting the possible causes, such as prolonged hypotension or catecholamine-induced vasoconstriction, have been suggested as the only means to prevent this complication[29].

Mechanisms of lesion

The mechanisms of brain lesion more frequently reported in the studies were those related to the occurrence of microembolism (17 studies) and low cerebral perfusion (16 studies), corresponding to 63 and 59.3% of the studies describing the development of brain lesions, respectively. Twenty four (89%) out of the 27 studies reported at least one of these events.

These two mechanisms of lesion may precipitate a cascade of cellular biochemical events induced by cerebral ischemia. A scientific evidence level II quasi-experimental study showed that values lower than 40% of oxygen saturation are able to cause cognitive impairment in the patients analyzed, indicating insufficient cerebral circulation for the metabolic demands[19]. Changes in blood flow distribution during the non-physiological state seen in ECC, the patient's individual response to these changes, and the concurrent reduction of pump flow to facilitate surgical repair may adversely affect regional and global cerebral reperfusion[30].

The pathophysiological mechanism of brain damage requires a detailed study. There may be a selective vulnerability to prolonged hypoxia in certain neuronal nuclei of the brainstem[23]. Inadequate oxygen delivery induces cell death due to lack of energy and to the modulation of an excitotoxic response by partially perfused cells. The ischemic cells release a variety of receptors that cause elevation of intracellular calcium and sodium. Simultaneously, glucamate stimulates the receptors that induce the formation of inosol, triphosphate and diacylglycerol, which lead to increased sensitivity of excitatory amines. In the final state, calcium-activated enzymes degrade arachidonic acid, which, together with platelet activating factor, lead to vasoconstriction, vessel occlusion, and thus aggravate ischemia[30].

The brain is subject to continuous exposure to microemboli during ECC. Neurological morbidity and the magnitude of dysfunction are related to the size and number of emboli spread in the cerebral circulation. Emboli are produced by different sources: gaseous microemboli, atheromatous material, and intracardiac thrombi in the cerebral circulation[5,30,31].

Gaseous microembolism is caused by several situations created during the use of ECC: 1) during manipulation of the ascending aorta while clamping and unclamping; 2) flow switch to the left ventricle and aorta; 3) unexpected heart contraction while it is still open, with unclamped aorta; 4) inadequate air removal before reestablishing circulation; and 5) situations of low blood level in the ECC reservoir[5,30,31].

There are strong evidences that microbubbles may also originate from the rapid movement of prosthetic valves, specifically mechanical ones. These generate a local flow of high pressure inclinations that can cause cavitations, especially during closure, thus causing a decompression effect during the cardiopulmonary bypass[31].

Cerebral dysfunction is also intrinsically related to the intra-abdominal pressure (IAP). IAP elevation may lead to renal, circulatory, respiratory and nervous system failure. A decrease in venous blood return from the central nervous system (CNS) results in cerebral venous hypertension and consequent intracranial hypertension, cerebral edema and infarction. High intra-abdominal pressure increases pulmonary pressure and central venous pressure (CVP); therefore we can presume that increased CVP influences CNS homeostasis[32].

Despite the innumerous risk factors related to ECC, we should consider that the mechanism of brain lesion is complex and frequently influenced by independent causes such as extremes of age, previous history of cerebrovascular diseases, hypoxia, severity of disease, use of bicarbonate and vasopressor and inotropic drugs, and urgency of the surgery[23,24,33,34].

The systemic inflammatory response syndrome (SIRS) is also considered a potential factor for postoperative complications, especially pulmonary, renal, hematologic and neurological complications. The pathophysiological mechanism of this process is described in only a few studies of this sample, and is related to the use of ECC and influenced by several factors. However, it is important to point out that the development of SIRS also occurs in other off-pump surgical procedures[35-37].

The mechanical stress of ECC causes important changes in the formed elements during the switch in the blood flow regimen. In this process, many interleukins are released, with IL-8 being more active in the CNS. IL-8 suffers the action of endothelin, attracting polymorphonuclear cells activated by the humoral and cellular responses, which are responsible for brain injury due to ischemia and reperfusion[38,39].

The synchronization of the central nervous system with the initiation of extracorporeal circulation is unknown, but essential for the understanding of the pathophysiological mechanisms of the development of these neurological complications[40].

Strategies for brain protection

Several strategies have been used to reduce the neurological changes associated with extracorporeal circulation. The use of glucocorticoids; anesthetic agents; barbiturates; membrane oxygenators; hyperbaric chambers; hypothermia; hemofiltration; heparin-coated circuits; and maintenance of temperature, pH and blood volume have been recommended in the literature[1,5,30].

The brain protection effect of hypothermia is relative. Hypothermia permits the duration of cardiac arrest to be prolonged, by decreasing the need for oxygen in the brain, thus preventing neurological damage. On the other hand, deep hypothermia requires longer total duration of ECC, and is considered a risk factor for permanent neurological damage. In addition, hypothermia facilitates hemoconcentration and increased blood viscosity, which can lead to alterations in platelet function, thus promoting cerebrovascular damage. Temperatures ranging from 12 to 28^{o} C are considered safe according to some studies[1,23].

Monitoring mechanisms are also suggested for the prevention and reduction of the extent of brain damage, because they permit an early diagnosis of possible changes, particularly in patients who are prone to neurological injury during ECC[28,32]. In the study analysis, the monitoring mechanisms more commonly cited were those that obtain data on intracranial pressure, CVP, IAP, and imaging methods such as electroencephalogram, uni and bilateral sonography and transcranial Doppler.

In addition to the monitoring mechanisms, the development of safety devices is essential for ECC. Arterial line filters have become popular for their ability to remove microemboli and large air emboli with the same efficacy in the case of perfusion accidents.

Whitaker et al's study with a case-control design, strength of scientific evidence level III, define cognitive impairment as a reduction in the neurological performance in nine tests administered to a sample of 110 patients divided into two groups that used different ECC filters. The results of this study showed that both filters were efficient in removing macro and microemboli during perfusion, with similar outcomes in relation to the occurrence of cognitive dysfunction[41].

The beneficial effect of brain protection of CO_2 insufflation into the operative field, in the event of air entering the venous line of ECC, was demonstrated by Martens et al in an in vivo experimental study classified as scientific evidence level II. Since CO_2 is more soluble than room air, flow interruption or occlusion in the cerebral arteries is presumably decreased when CO_2 is the blocking gas. This method is being increasingly used in open cardiac surgeries and especially minimally invasive heart valve surgeries[42].

Another frequently used method is retrograde cerebral perfusion (RCP), in which oxygenated blood is pumped retrogradely through the superior vena cava. This method has advantages over conventional techniques, because it helps maintain uniform hypothermia by using a different method of perfusate administration. It also has a mechanism of oxygen and metabolic substrate supply, and acts in the removal of toxic metabolites and carbon dioxide, in addition to preventing cerebral embolization with air, atheromatous plaques, thrombi or other cell and tissue debris[43].

Discussion

Extracorporeal circulation is a widely used technology today. An average of 1,200,000 cardiac procedures using extracorporeal circulation is performed worldwide every year. In the United States alone, approximately 700,000 cardiac surgeries are performed per year[44]. In Brazil, approximately 40,000 operations using extracorporeal circulation are performed every year[45]. The forecast is that these figures will be higher in the future, in function of the unfulfilled needs of the population[1].

Extracorporeal circulation is a technical procedure influenced by the use of numerous mechanical devices and by variable patient responses. The lack of standardization of the techniques and materials used in ECC is observed in the variations of perfusate formulations, intraoperative monitoring systems, techniques of administration of cardioplegia, and oxygenators used in the circuits. This can lead to transoperative events that will directly affect patient recovery after surgery.

The safety of patients using ECC is a key issue in the studies. However, today few studies describe the incidents commonly associated with ECC. Mejak et al[45] evaluated 671,290 cardiac procedures performed during two years in 797 hospitals using extracorporeal circulation. In their study, 4,882 incidents were recorded, corresponding to one event in every 138 perfusions.

The study identified the 10 more common occurring incidents: 1st) protamine reactions; 2nd) coagulation problems; 3rd) water pump failure; 4th) air in the circuit; 5th) clots in the circuit; 6th) arterial dissection; 7th) oxygenator defects; 8th) oxygenator switch; 9th) mechanical pump failure; and 10th) pump failure and consequent use of cranks[45].

In addition, in this research, some patients developed stroke, classified as a serious injury. Other less frequent incidents, albeit serious, were massive air embolism (23 incidents and 6 deaths) and 11 incompatible transfusions (two deaths). The rate of incidents resulting in serious injury or death was one in every 1,482 perfusions. This figure means that there have been advances since the 1980's, when this rate was one in every 1,000 procedures[45].

Preventive measures to reduce the incidence of complications were suggested in some of the studies selected. However, the importance of the quality of the work performed by the surgical team during surgery should be emphasized. Experience shows that the incidents occurring in the operation theater are those that define the final outcome of the surgical treatment. The role of the postoperative care is important, but, at the same time, relative, because it is frequently unable to reverse serious changes resulting from a surgical procedure inadequately performed.

A cardiovascular surgery team comprises many multidisciplinary members, its core being essentially formed by a surgeon, anesthesiologist and perfusionist. The overall team supervision, as well as the interaction with the other specialists, in all circumstances, falls to the surgeon[1]. However, it is not reasonable to expect that the surgeon can, at the same time, perform the surgery and supervise the activity of another professional, whose performance the life of the patient depends on.

The participation of perfusionists in the safety of ECC cannot be disregarded. These professionals play a key role in the safety of ECC procedures, whether by means of the equipment and devices they control, or by their direct action[1]. In addition, lack of attention on the part of any team member during the procedure, whether due to negligence or to exhaustion from excessive work hours, may be the origin of very serious incidents.

Hospitals providing this type of procedure and teaching institutions should create a joint system able to offer continuing education, as well as other mechanisms to encourage improvements in the health care provided. However, no safety device can replace regular communication between team members, from the planning phase to the execution and termination of the procedure. ECC is determined by the teamwork and this should be based on cohesion among all professionals that take part in the procedure.

Conclusion

Based on the judicious analysis of the data obtained, we can conclude that ECC brings with it the cerebrovascular risks commonly expected in major surgeries. However, its peculiarities significantly facilitate the occurrence of neurological complications, thus justifying the theoretical background describing this correlation that is frequently found in articles on this subject.

The methodology applied for study selection did not include the analysis of the neurological complications in the perioperative period not related to the use of ECC, because it partly deviates from the scope of this study. Therefore, it is important to point out that this study identifies the occurrence of neurological complications and the main mechanisms responsible for brain injury influenced by ECC, according to the sample studied.

The specificities of ECC found in this study that contribute to the incidence of neurological lesions due to ischemia and reperfusion are:

- changes in blood flow distribution;
- prolonged hypoxia partly caused by the use of ECC, which intensifies a cascade of events inducing more vasoconstriction;
- SIRS induced by the release of inflammatory mediators after mechanical stress on the formed elements during the switch in the blood flow regimen;

- microembolism of atheromatous debris, intracardiac thrombi and air.

Microembolism may result from several situations concerning the management of ECC that have been previously mentioned.

After collection and analysis of the sample studied, we consider that the effects of ECC on the human body, among which are those determining the neurological complications, are still not fully understood. Further pathophysiological studies are necessary to consolidate this area of knowledge and permit the development of techniques able to reduce the incidence and extent of the neurological lesions.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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