

# Cardiopulmonary Bypass - "evidence-based medicine"?

Claus Bartels, MD, on Behalf of the Working Group Extracorporeal Circulation and Mechanical Ventricular Assist Devices of the German Society for Thoracic- and Cardiovascular Surgery

C. Bartels, M.D.

Clinic for Cardiac Surgery, Medical University of Luebeck

Ratzeburger Allee 160, 23538 Luebeck, Germany

Tel.: 0049-(0)451-2108

Fax.: 0049-(0)451-2051

**Abstract:** The purpose of this study was to evaluate the amount and quality of scientific evidence supporting principles that are currently applied for cardiopulmonary bypass (CPB) performance. The scientific data concerning the effectiveness and safety of key principles of cardiopulmonary bypass is insufficient in both amount and quality to serve as a basis for practical, evidence-based guidelines.

## 1 Introduction

The first successful clinical application of cardiopulmonary bypass (CPB) by John Gibbon in 1953, revolutionized cardiac surgical procedures. Today, CPB is routinely used for various cardiac and non-cardiac surgical operations and appears to be a safe procedure. However, the unresolved problems and limitations of CPB are obvious in daily clinical practice. Bleeding disorders, systemic inflammatory reactions, multi-organ failure, neurologic deficits, permanent intellectual impairment and pulmonary dysfunction are only some examples of the hazards of modern CPB.

Improving the quality of medical care by establishing medical practice guidelines has been vigorously promoted by the U.S. health care system [AGF90]. The responsible medical societies have developed practice guidelines based on evidence-based medicine criteria for various procedures [BCL98, EGD99, GCD99, BFC98, BAB00]. Thus a new paradigm of medical practice is emerging. Evidence-based medicine de-emphasizes intuition and unsystematic clinical experience as sufficient grounds for clinical decision making and stresses the examination of evidence from clinical and experimental research [Ev92].

A survey concerning principles of CPB performance was sent to all German centers of cardiac surgery. The obtained results disclosed significant differences regarding CPB performance. As a consequence the "Working Group Extra-Corporeal Circulation and Mechanical Ventricular Assist Devices" of the German Society for Thoracic- and Cardiovascular Surgery tried to develop a consensus document for the clinical application of cardiopulmonary bypass. Forty-eight major principles of CPB were formulated into questions in order to be addressed by a review of the scientific literature.

The issues of interest covered nearly all relevant aspects of CPB, e.g. optimum ACT level for routine CPB or during hypothermic circulatory arrest, anticoagulation management by the use of aprotinin, myocardial protection, technical safety aspects, pump flow rate and/or blood pressure for the different degrees of hypothermia, washout of toxic metabolites from CPB material. In case of clinical studies, the key parameters for scientific evaluation of the investigated principles concentrated on patients clinical outcome, not on surrogate parameters.

Because it is impossible to deal adequately with each of the 48 questions within the scope of a journal article, the topics and our results are presented here in tabular form (Table I). As an example of our methodological approach we selected a sample question (topics 38/39) that will be described in detail in the appropriate sections:

*Sample question: what is the appropriate acid-base management strategy for optimum cerebral protection in adults with respect to moderate resp. deep hypothermia.*

The clinical rationale behind this question: neurologic injury and postoperative cognitive dysfunction appear to be the most frequent complication of CPB procedures. From 1970 to 1973, 8% of patients subjected to CPB died after an neurologic event, by contrast, from 1980 to 1983, 20% of postoperative deaths were related to severe neurologic injury [CLL84]. More recently, a longitudinal assessment of neurocognitive function after CABG was reported [NKP01]. These authors demonstrated an incidence of cognitive decline of 53% at discharge and of 42% after five years.

Although the etiology of postoperative CNS dysfunction in patients subjected to CPB is multifactorial, microgaseous and solid emboli are particularly culpable and seem to be influenced by different brain perfusion rates of pH management.

Scientific and pathophysiologic background:

the ability to control a patients body temperature within a wide range is one of the most important therapeutic modalities made available by the application of CPB. One of the most frequently discussed aspects of clinical hypothermia is the appropriate acid-base management strategy during cooling and re-warming. The term alpha-stat indicates an acid-base management in which the net charge (dissociation) of proteins remains constant as temperature changes. The alternative method is termed pH-stat: maintaining pH value constant at varying temperatures.

Alpha-stat will result in lower cerebral flow compared to pH-stat. Intact cerebral auto-regulation has been demonstrated in humans following alpha-stat strategy at temperatures from 21° to 29° [GRM84]. In contrast, cerebral auto-regulation was abolished, and it varied, depending on cerebral blood flow, when pH-stat was used [Mu87]. In deep hypothermia the normal vascular responses are lost and cerebral blood flow is dependent on the perfusion pressure with uncoupling of flow and metabolism. During moderate hypothermia the variations in PCO<sub>2</sub> between the different acid-base managements are only minor and do not seem to be clinically relevant [BTN90]. In contrast, difference in PCO<sub>2</sub> during deep hypothermia approaches 80mm HG between the two acid-base strategies. The increased cerebral blood flow associated with pH-stat may increase the risk of micro-emboli, cerebral edema, or high intra-cranial pressure. On the other hand increased brain perfusion may result in improved cerebral cooling prior to circulatory arrest.

This paper has two main aims:

- to summarize the results obtained regarding the scientific quality of the reviewed publications and
- to determine the scientific basis of currently applied CPB principles.

## **2 METHODS**

We did a systematic search of the Medline database for Medical Subject Headings referring to the various principles of CPB in the last 20 years. The appropriate selection, combination and use of the Medical Subject Headings were cross-checked by two other members of our working group to ensure as complete a search as possible.

### **2.1 Step 1**

Scientific level of the reviewed literature

All abstracts of articles identified by the search were reviewed by at least four members of the working group. Papers were selected for further review if one or more of the following criteria was met:

- articles available in English, French, Italian or Spanish language
- randomized study design
- control group available
- Editorials and reviews in peer reviewed journals
- meta-analyses
- the same criteria were applied to in-vitro studies and animal studies

All reference lists were checked for publications missed in the Medline search.

### **2.2 Step 2**

The scientific quality of the manuscripts was assessed by at least four members of the working group regarding structure and content.

Manuscripts were selected for further review if they included:

- A background review of the subject
- explicit statement of objectives
- a detailed description of type and selection of subjects/ procedures
- a detailed description of applied methods
- a description of quantitative methods
- a comparison with alternative technologies/ procedures
- a detailed description of clinical endpoints

All manuscripts that did not meet these criteria were checked for further important information, in which case they were also selected for review. If no manuscript fulfilled the mentioned criteria, manuscripts of lesser scientific quality were selected for review. Papers were excluded if:

- study results summarized in high quality reviews selected for evaluation of their scientific level
- the same data had evidently been published twice
- the statistical methods were inadequate
- the selection of subjects/ procedures was inadequate

### **2.3 Step 3**

According to the methodological rigour the selected manuscripts were classified according to their scientific level:

Level I: Investigations yielding clear evidence that a given procedure or treatment is useful and effective (large randomized prospective trials with low false-positive (alpha) and low false-negative (beta) errors, high-quality meta-analysis)

Level II: Investigations that do not provide clear scientific evidence about the usefulness/efficacy of a procedure or treatment e.g. small sample size, lack of randomization

Level III: Investigations that do not provide scientific evidence about the usefulness/efficacy of a procedure or treatment e.g. trials without appropriate controls

Level IV: In-vitro or animal studies, non-systematic reviews

All in-vitro and animal studies selected for inclusion in the study were classified as Level IV without respect to the scientific design, number and quality of interventions or statistical methods. This approach was chosen in view of limited application of in-vitro and animal study results to the clinical situation.

The level of scientific evidence assigned to each paper was cross-checked by two other members of the working group. Any disagreements were resolved by consensus. For all manuscripts the adequate use of statistical methods was critically assessed and discussed with collaborating medical statisticians.

### **2.4 Step 4**

Classification of the scientific evidence on CPB principles

After all relevant manuscripts had been graded with respect to their scientific level, the investigated principle (procedure or treatment) was classified according to a modification of the AHA/ACC guidelines for scientific evidence [BCL98, GCD99, BAB00].

Class I: Principle for which there is clear evidence and/or scientific agreement that a given procedure or treatment is useful and effective

Class II: Principle for which there is conflicting scientific evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment

Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy of a procedure or treatment

Class IIb: Usefulness/efficacy is less well established by evidence/opinion for a procedure or treatment

Class III: Principle for which there is no sufficient scientific evaluation about the usefulness/efficacy of a procedure or treatment, in-vitro studies and animal studies

If a cardiac surgeon is to be convinced to critically assess his daily practice, more is generally required than advantages achieved by means of surrogate parameters. Therefore, we gave priority to studies analyzing different techniques or procedures with respect to patients clinical outcome, e.g. mortality, morbidity, special organ function, transfusion requirements, length of stay at the ICU and overall hospital time (see Table I).

Table I contains a brief version of the questions formulated concerning CPB principles, scientific level of reviewed manuscripts, selected clinical endpoints and their classification based on the scientific evidence. In case no scientific papers were available for a specific question not available (n.a.) was indicated.

Table III depicts the selection of keywords, their combination and the number of articles identified in connection with our sample question regarding acid-base management in adults.(cf. Introduction)

### **3 RESULTS**

A total of 33.000 articles identified was retrieved. 1.500 manuscripts fulfilled the criteria for the first step of selection procedure. The 225 manuscripts with the best scientific evidence available were classified according to the level of their scientific evidence on the basis of of their methodological rigour.

Table I depicts the scientific level of the evaluated literature.

Many studies showed methodological problems, e.g. imprecise study design or inappropriate statistical methods. As a result most of the classified papers showed divergent results regarding individual principles of CPB performance. Thus, the scientific evidence regarding CPB principles could not be conclusive in these cases.

## 4 DISCUSSION

Since its first successful clinical application in 1953, the CPB technique has revolutionized cardiac surgery. Today, CPB is routinely used for various cardiac and non-cardiac surgical operations with good clinical results. So far no systematic review of the available literature has been undertaken to determine the amount and quality of scientific information. On the basis of our scientific evaluation of the current literature on 48 principles of CPB, not a single condition was of sufficient scientific merit to conclude that we were dealing with a principle "for which there is clear evidence and/or scientific agreement that a given procedure or treatment is useful and effective".

Ideally, for each procedure or intervention there should be direct and clear evidence from one or more studies that relate the application of this procedure (compared with specified alternatives) to the health outcomes of interest of a specific patient. However, rapid changes in medical practice, ethical considerations and practical reasons make this desirable principle of patient care impossible to achieve. Thus, the limited scientific evaluation of current medical practice represents a general phenomenon and not one that is specific to the cardio-thoracic surgical community.

Discussion of our sample question:

What is the appropriate acid-base management for optimal cerebral protection in adults with respect to moderate resp. deep hypothermia?

The study design and content of 124 articles identified were reviewed. For 42 original contributions the scientific value was assessed. Six manuscripts were selected for classification of the scientific evidence on the question as to which pH-management strategy should be used for moderate hypothermia in adults [BTN90, Mu95a, Mu95b, VPC95, Pa96, PSR86]. Although study design and statistical evaluation revealed some shortcomings, 5 of the contributions achieved scientific level II [BTN90, Mu95a, Mu95b, VPC95, Pa96]. From this the conclusion could be drawn that alpha-stat is associated with a decreased incidence of postoperative cerebral dysfunction without negative affection of other organs in adult patients subjected to moderate hypothermia and prolonged CPB time [Mu95a, Mu95b, VPC95, Pa96]. This conclusion contrasted with data reported by Bashein et al. [scientific level II] [BTN90]. However, they used bubble oxygenators without arterial filters in their study, which may imply significant influencing factors. On the basis of the manuscripts selected for review, the scientific evidence of this CPB principle was classified as IIa. Postoperative cerebral dysfunction is obviously affected by underlying patients co-morbidity. Thus, whether our conclusion can be applied to patients with preexisting cerebro-vascular disease or uncontrolled hypertension remains unclear and the scientific background is lacking. Therefore, we do not believe, that our conclusion can be used as a general recommendation. This demonstrates that basic elements of CPB performance do not meet EBM criteria.

As for the question which pH-management should be applied to adults undergoing deep hypothermic arrest no valid scientific valuable data currently exist. We selected this example to demonstrate that there is a pressing need to apply EBM principles to CPB performance.

Thousands of publications cover the issue of CPB performance. However, the quality of most papers in other medical journals do not meet basic scientific criteria [WGC86].

After examining the quality of medical knowledge, other authors reported that only 15 percent of medical interventions are supported by solid scientific evidence [EB88]. Although the quality of statistical analysis has improved and the application of more complex statistical procedures has increased during the last decades, imperfect study design and inadequate analysis remain an unresolved problem [A180]. Papers now report larger numbers of analyzed cases than previously, yet the use of methods that aim to control type I error is rare [Sm92]. True randomization requires exact evaluation of inclusion and exclusion criteria prior to a strata or blocked randomization protocol. In many publications the term 'randomized' is used for clinical trial although the investigation applied systematic allocation [A180]. This condition limits the scientific value of the study a priori. For a scientific evaluation of CPB principles more concise study designs and appropriate statistical evaluation seem to be mandatory.

#### Limitations of the study

Dickersen and co-workers examined the sensitivity and precision of Medline searches for randomized trials [DSL94]. They concluded that although the indexing terms available for searching Medline have improved, the sensitivity 'still remains unsatisfactory'.

For this study the appropriate use, selection and combination of Medical Subject Headings were cross-checked by two other members of our working group. In addition, currently available monographs dealing with the issue of CPB were reviewed for missing publications. All original contributions and reviews retrieved in our search were also checked for missing papers. However, we cannot exclude the possibility that important contributions failed to come to the authors' attention.

In contrast to the Task Force Committee of the AHA and ACC, our purpose in undertaking this investigation could not be the development of guidelines for CPB performance, for the following reasons:

1. Our Working Group Extra-corporeal Circulation does not have the logistic and personal requirements available to the AHA/ACC committees.
2. For most CPB principles the scientific background is not conclusive enough to allow general recommendations. Therefore, recommendations should be based on a consensus of numerous experts opinion on CPB in combination with a review of the literature.

We encourage our colleagues to improve the clinical results achievable with the application of CPB by expanding our limited knowledge of current practice using the criteria evidence-based medicine. The scientific quality of CPB performance would improve if the societies of cardio-thoracic surgeons could initiate large, prospective, randomized trials evaluating clinical CPB performance.

David Eddy, professor of health policy and management at Duke University, who began his medical life as a cardio-thoracic surgeon, became a leader in the field of evidence-based medicine and trained other physicians to achieve consensus for medical practice, stated in 1991: "Get doctors to understand how much they need reliable information. What could be worse than two millennia spent making life and death decisions with inadequate information?"

## 5 Tables

**Table I: Summarized results**

Subject	Scientific level of literature				Parameters determining clinical outcome	Class
	I	II	III	IV		
<b>Technical equipment</b>						
1. Centrifugal vs roller pump	0	4	1	0	sp, trans, vent, icu	IIb
2. Pulsatile vs non-pulsatile perfusion	0	5	7	0	sp, mort, mi, morb,neur	IIb
3. Heparin-coated surfaces	0	5	3	0	sp, trans, vent, icu, hosp, mort, morb, neur, arr; mi, vent,	IIb
4. Toxicity of PVC	0	0	2	0	sp	III
5. Closed vs open cardiomy reservoirs	0	1	2	1	sp, trans, icu, hosp	III
6. Arterial filter systems	0	0	6	0	sp, neur	III
7. Autotransfusion vs cell separation	0	1	1	1	sp, trans	IIb
<b>Preparation of CPB</b>						
8. Volume substitution prior to CPB	0	4	0	0	sp, trans	III
9. Priming in adults	0	10	1	0	sp, trans	IIb
10. Priming in infants and neonates	0	0	3	2	sp, trans,	IIb
11. Application of Aprotinin	3	1	2	0	sp, re, trans, mi, mort, all, byp	IIa
12. Additive drugs in priming solution	0	4	0	2	sp, cvi, vent	III
13. Temperature of priming solution	na	na	na	na		III
14. Perfusion volume	na	na	na	na		III
15. CO <sub>2</sub> rinsing of arterial filters	na	na	na	na		III
16. Protection of tubes by connectors	na	na	na	na		III
<b>Performance and supervision of CPB</b>						
17. How should ACT be measured	0	2	0	3	sp	IIa
18. Other coagulation parameters besides ACT during CPB	0	5	7	0	sp, trans	III
19. Level of ACT during CPB	0	3	2	0	sp, trans	IIb
20. Level of ACT for hemodilution during CPB	0	1	1	2	sp, trans	III
21. Level of ACT using Aprotinin during CPB	1	1	0	1	sp, byp	III
22. Level of ACT using Aprotinin in dhca	0	1	3	0	sp, trans, rf	III
23. Heparin administration	0	1	0	0	sp, trans	III
24. Heparin resistance	0	0	3	0	sp	IIb
25. ATIII deficiency	0	0	3	0	sp, trans	IIa
26. Protamine application	0	2	2	0	sp, trans	IIb
27. Effects of priming solution on platelet function	0	2	0	0	sp, trans	III
28. Effects of oxygenator type on platelet function	0	1	4	0	sp, trans	III
29. Effects of pump type on platelet function	0	2	1	0	sp	III
30. Platelet-rich plasmapheresis and transfusion	0	3	0	0	sp, trans	III

requirements						
31. Desmopressin acetate and transfusion requirements	0	4	0	0	sp, trans	IIb
32. Indicators for platelet transfusion	0	1	3	0	sp, trans	III
33. Patient selection for tranexamic acid or epsilon aminocaproic acid treatment	0	5	3	0	sp, mi, cvi, pe, dvt, trans	IIb
34. Dosage of tranexamic acid or epsilon aminocaproic acid	0	2	0	0	sp, trans, cvi, dvt, mi	IIb
35. Effects of tranexamic acid or epsilon aminocaproic acid on bleeding	1	5	0	0	sp, trans, mi, cvi, mort	
a) in elective patients						IIb
b) in patients with increased risk of bleeding					sp, trans, cvi, mi, dvt	IIb
36. pH-strategy during DHCA in pediatric cardiac surgery	0	1	2	2	sp, con, vent, icu, neur	IIa
37. pH-strategy during moderate hypothermia in pediatric cardiac surgery	na	na	na	na		III
38. pH-strategy during dhca in adult cardiac surgery	na	na	na	na		III
39. pH-strategy during moderate hypothermia in adult cardiac surgery	0	5	1	0	sp, mort, mi, cvi, arr, rf, neur, vent, icu	IIa
40. Myocardial protection	0	7	3	1	sp, mort, mi, cvi, rf, icu, vent	III
41. Optimum core temperature	0	10	1	0	sp, mort, mi, cvi, neur, re, trans, lco	III
42. Optimum temperature gradient	0	0	0	2	sp	III
43. Optimum mean arterial perfusion pressure and flow	0	2	4	0	sp, neur, mort, mi, cvi, qual	III
44. Selective cerebral perfusion	0	0	5	1	sp, mort, neur	III
45. Efficacy of different methods of selective cerebral perfusion	0	0	5	1		III
<b>Documentation, quality assurance, personal resources</b>						
46. Automatic data documentation	0	0	5	6	na	III
47. Quality assurance	0	0	3	11	na	III
48. Perfusionist's education	0	0	6	0	na	III

\* Classification of the scientific evidence of examined principle  
na: no scientific publication available

**Table II: Abbreviations used in Table I**

<b>Abbreviations</b>	
trans	transfusion requirements including coagulation factors
mort	mortality
morb	morbidity
mi	perioperative myocardial infarction
neur	neurologic/cognitive dysfunction
byp	bypass graft occlusion
rf	renal failure
cvi	cerebrovascular insult
pe	pulmonary embolism
dvt	deep venous thrombosis
con	convulsion
arr	arrhythmia requiring treatment
lco	low cardiac output
re	rethoracotomy for bleeding
vent	ventilation dependence
icu	ICU stay
hosp	hospital stay
all	allergic shock
sp	surrogate parameter
qual	quality of life
DHCA	deep hypothermic cardiac arrest

**Table III: Keyword selection for the sample question**

<b>keyword 1</b>	<b>keyword 2</b>	<b>articles identified</b>
pH	0	226167
pH management		1481
pH management	cardiopulmonary bypass	80
pH management	extracorporeal circulation	95
pH management	heart-lung-machine	0
pH management	cerebral blood flow	57
pH management	temperature	146
pH management	hypothermia	97
pH management	hypothermic cardiac arrest	1
pH management	hypothermic circulatory arrest	14
pH management	cardiac surgery	26
pH management	heart surgery	59
pH-stat	0	483
pH-stat	cardiac surgery	15
pH-stat	heart surgery	29
pH-stat	extracorporeal circulation	53
pH-stat	cardiopulmonary bypass	58

pH-stat	heart-lung-machine	1
pH-stat	circulatory arrest	15
alpha-stat	0	139
alpha-stat	cardiac surgery	24
alpha-stat	heart surgery	56
alpha-stat	extracorporeal circulation	100
alpha-stat	cardiopulmonary bypass	104
alpha-stat	heart-lung-machine	1
alpha-stat	circulatory arrest	22

## 6 Acknowledgement

We acknowledge the expert review of our manuscript by Dr. Dagmar Luehmann, Department of Epidemiology, Medical University of Luebeck.

The reference list of the papers classified according to their scientific level can be found in the internet at our homepage: [www.herzchir.mu-luebeck.de](http://www.herzchir.mu-luebeck.de).

## Reference List

- [AGF90] Audet AM, Greenfield S, Field M. Medical practice guidelines: current activities and future directions. *Ann Intern Med* 1990; 113:709-14
- [AI80] Altman DG. Statistics in medical journals: developments in the 1980s. *Stat Med* 1991; 10:1897-913
- [BAB00] Braunwald E, Antman EM, Beasley JW et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). *J Am Coll Cardiol* 2000; 36:970-1062
- [BCL98] Bonow RO, Carabello B, de Leon AC, Jr. et al. Guidelines for the management of patients with valvular heart disease: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). *Circulation* 1998; 98:1949-84
- [BFC98] Biller J, Feinberg WM, Castaldo JE et al. Guidelines for carotid endarterectomy: a statement for healthcare professionals from a Special Writing Group of the Stroke Council, American Heart Association. *Circulation* 1998; 97:501-9
- [BTN90] Bashein G, Townes BD, Nessly ML et al. A randomized study of carbon dioxide management during hypothermic cardiopulmonary bypass. *Anesthesiology* 1990; 72:7-15
- [CLL84] Cosgrove DM, Loop FD, Lytle BW et al. Primary myocardial revascularization. Trends in surgical mortality. *J Thorac Cardiovasc Surg* 1984; 88:673-84
- [DSL94] Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews [see comments]. *BMJ* 1994; 309:1286-91
- [EB88] Eddy DM, Billings J. The quality of medical evidence: implications for quality of care. *Health Aff Millwood* 1988; 7:19-32

- [EGD99] Eagle KA, Guyton RA, Davidoff R et al. ACC/AHA guidelines for coronary artery bypass graft surgery: executive summary and recommendations : A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1991 guidelines for coronary artery bypass graft surgery). *Circulation* 1999; 100:1464-80
- [Ev92] Evidence-Based Medicine Working Group. Evidence-based medicine. A new approach to teaching the practice of medicine. *JAMA* 1992; 268:2420-5
- [GCD99] Gibbons RJ, Chatterjee K, Daley J et al. ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: executive summary and recommendations. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Chronic Stable Angina). *Circulation* 1999; 99:2829-48
- [GRM84] Govier AV, Reves JG, McKay RD et al. Factors and their influence on regional cerebral blood flow during nonpulsatile cardiopulmonary bypass. *Ann Thorac Surg* 1984; 38:592-600
- [Mu87] Murkin JM, Farrar JK, Tweed WA, McKenzie FN, Guiraudon G. Cerebral autoregulation and flow/metabolism coupling during cardiopulmonary bypass: the influence of PaCO<sub>2</sub>. *Anesth Analg* 1987; 66:825-32
- [Mu95a] Murkin JM, Martzke JS, Buchan AM, Bentley C, Wong CJ. A randomized study of the influence of perfusion technique and pH management strategy in 316 patients undergoing coronary artery bypass surgery. I. Mortality and cardiovascular morbidity. *J Thorac Cardiovasc Surg* 1995; 110:340-8
- [Mu95b] Murkin JM, Martzke JS, Buchan AM, Bentley C, Wong CJ. A randomized study of the influence of perfusion technique and pH management strategy in 316 patients undergoing coronary artery bypass surgery. II. Neurologic and cognitive outcomes. *J Thorac Cardiovasc Surg* 1995; 110:349-62
- [NKP01] Newman MF, Kirchner JL, Phillips-Bute B et al. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. *N Engl J Med* 2001; 344:395-402
- [Pa96] Patel RL, Turtle MR, Chambers DJ, James DN, Newman S, Venn GE. Alpha-stat acid-base regulation during cardiopulmonary bypass improves neuropsychologic outcome in patients undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 1996; 111:1267-79
- [PSR86] Prough DS, Stump DA, Roy RC et al. Response of cerebral blood flow to changes in carbon dioxide tension during hypothermic cardiopulmonary bypass. *Anesthesiology* 1986; 64:576-81
- [Sm92] Smith R. The ethics of ignorance [editorial] [see comments]. *J Med Ethics* 1992; 18:117-8,134
- [VPC95] Venn GE, Patel RL, Chambers DJ. Cardiopulmonary bypass: perioperative cerebral blood flow and postoperative cognitive deficit. *Ann Thorac Surg* 1995; 59:1331-5
- [WGC86] Williamson JW, Goldschidt PG, Colton T. The quality of medical literature: an analysis of validation assessments. In: Bailar JC, Mosteller F, editors. *Medical uses of statistics*. 1986.