Risk factors for cardiovascular death after elective surgery under general anaesthesia

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Summary
A large epidemiological data set was used to identify 115 patients who died from a cardiovascular cause within 30 days of elective surgery under general anaesthesia. For each patient, a control was identified, matched for age (within 5 yr of the patient), sex, operation and consultant. Patients and controls were compared for cardiovascular risk factors in a matched analysis using conditional logistic regression, and a prognostic model was generated. Three risk factors were included in the final model: previous myocardial infarction (odds ratio 3.18 (95% confidence intervals (CI) 1.22–8.28), \( P = 0.018 \)), history of hypertension (odds ratio 1.90 (0.99–3.62), \( P = 0.047 \)) and renal failure (odds ratio 3.56 (1.04–12.10), \( P = 0.043 \)). (Br. J. Anaesth. 1998; 80: 14–19)

Keywords: anaesthesia, general; complications, death; complications, cardiovascular disease; anaesthesia, audit; records, anaesthesia

It is widely accepted that patients suffering from cardiovascular disease represent a particular challenge for the anaesthetist. With modern anaesthesia and perioperative care, major cardiovascular complications after anaesthesia and surgery are uncommon. Forrest and co-workers\(^1\) reported 19 deaths and 23 complications, cardiovascular disease; anaesthesia, audit; cardiovascular risk factors and perioperative cardiovascular complications imply that such studies have to include a large number of patients in order to achieve adequate statistical power. An alternative approach is that of the case-control study. This study design is particularly useful for studying rare outcomes and for examining several risk factors simultaneously. Because most of the available studies are cohort studies it could be argued that they may be subject to some form of systematic bias. A case-control study which achieved similar results to the cohort studies would add weight to the validity of findings from each type of study.

We have used the Oxford Record Linkage Study (ORLS), which is a large epidemiological data set, to conduct a case-control study of risk factors for cardiovascular death after elective surgery under general anaesthesia.

Analysis of a subset of the data taken from the ORLS has been undertaken previously to examine the effects of admission arterial pressure and diagnosed hypertension on cause of death.\(^12\) In this article some of these patients have been included together with more patients from the same data set, but all have been re-analysed with regard to this extended list of variables that we have included in our analysis. Overall, we have included 75 patients from the previous dataset, with 40 additional patients.

Patients and methods
DATA COLLECTION
The Oxford Record Linkage Study (ORLS) covers approximately 1.9 million people within the former Oxford Regional Health Authority area. It includes routine data on all hospital admissions for individuals treated within the study area. All stays in hospital, both in-patients and day cases, are recorded and entered in the database. Patient characteristics and diagnostic data are recorded. All operations are noted and coded. Hospital records are linked to death certificates. For the current study we obtained data on patients who underwent surgery between 1979 and 1990. Patients studied underwent surgery at one of three hospitals in Oxford, or at hospitals in Banbury or Kettering. The choice of hospitals was determined by the availability of case notes in medical records departments for detailed study. The overall population of the study area was approximately 800 000. In the years covered by the study, the SMRs for circulatory disease in general and for ischaemic heart disease in particular were both approximately 88 for men and 93 for women in 1979 and were in the mid-80s for both men and women by 1990.

The ORLS was analysed to identify patients who died within 30 days of anaesthesia and surgery and...
whose death certificates included ICD9 codes (9th International Classification of Diseases) in the range 401–438 inclusive, at any position on the death certificate. The diseases covered by these codes are hypertensive disease (401–405), ischaemic heart disease (410–414), diseases of the pulmonary circulation (415–417), other forms of heart disease (420–429) and cerebrovascular disease (430–438). Patients who died after a pulmonary embolism (code 415.1) were excluded, as were those undergoing cardiac or neurosurgery. It was recognized that there are specific codes available within ICD9 for complications associated with anaesthesia (e.g. 995.4 for shock as a result of anaesthesia). These codes had not been used as certified causes of death on death certificates for any patient in the study population.

CONTROLS

For each patient at least one control was identified. Where possible two controls were identified to allow for the possible non-availability of the medical records of the first control examined. Controls were matched with patients on the following criteria:

- underwent the same operation as the patient,
- under the care of the same consultant as the patient,
- age within 5 yr of the patient,
- same sex as the patient.

When two controls were obtained, one was chosen at random and the notes obtained. If these were unavailable or if the control was excluded for any reason, the notes of the second control were examined.

EXAMINATION OF MEDICAL RECORDS

The medical records of patients and controls were obtained. As required by the local Ethics Committee, we obtained consent to examine the medical records from the consultant caring for each patient during admission for surgery. Where the consultant had died or retired, consent of his or her successor was obtained. The notes were examined in detail by a research nurse. Whenever possible, it was confirmed from the notes that the cause of death given on the death certificate was supported by the medical records. If a patient had clearly not died from a cardiovascular cause, he or she was excluded from the study. Patient data and data on cardiovascular risk factors were collected.

EXPOSURES OR RISK FACTORS

Data were collected on the following risk factors. 1

Treated hypertension, angina and heart failure

A patient was defined as having one or more of these conditions if they had been receiving medication for the condition in question. This was felt to be more reliable than depending on these diagnoses being mentioned in the notes as there was likely to be considerable variation between subjects as to whether systematic enquiry had been made for co-morbidity and as to whether this information was recorded. Drug history is recorded more consistently and can usually be corroborated from drug charts filed in the notes.

Where the term hypertension is used in this article, it refers to treated hypertension. It is important to note that this definition of hypertension was independent of admission arterial pressure.

Previous myocardial infarction, previous cerebrovascular accident, diabetes mellitus, peripheral vascular disease

Patients were considered to have one or more of these conditions if the medical records indicated this to be the case. For these conditions we believed that we could not rely on treatment history to indicate disease. Patients who have suffered a significant myocardial infarction or have peripheral vascular disease may not be receiving cardiovascular medications. Diabetes controlled with diet alone may cause significant end-organ damage.

Renal failure

Patients were said to have renal failure if they had a creatinine concentration > 150 µmol litre⁻¹ at admission for surgery.

DATA HANDLING

A computer database written using Microsoft Access 2.0 was used to store and examine the data. Microsoft Excel 5.0 was used to examine the tables produced by Access. Statistical analysis was performed using Stata version 4.0. Data were exchanged between the various programs using DBMScopy version 5.10.

STRATEGY OF ANALYSIS

Data were examined for errors and inconsistencies and descriptive statistics produced. Crude odds ratios were calculated and the data were examined using McNemar’s test. Where one of the cells in the contingency table had a zero value, exact probabilities were calculated. Because the age difference within pairs could be up to 5 yr, there was potential for residual confounding by age within pairs. It was found that this was best adjusted for by including in the analysis each subject’s deviation from the mean age of that matched pair. Adjustment for age difference within pairs was made using conditional logistic regression and these adjusted odds ratios are reported for each risk factor.

Multivariate analysis was performed using conditional logistic regression, the strata being identified by pair numbers linking the patients and matched controls. The aim was to produce a prognostic equation for perioperative cardiovascular death. Terms which were statistically significant at the 0.05 level using the log likelihood test were included in the final regression equation. We also report the result of the Wald test for each term in the final equation. This test is based on a normal approximation to the log likelihood. Terms which were significant on log likelihood testing were included in the final model, even if not quite significant at the 0.05 level by the Wald test.
As with the analysis for individual risk factors, a term for deviation of each subject from the mean age of that pair was included in the model. It was not possible to examine the main effects of exposures on which the subjects had been matched, that is age, sex, type of surgery and consultant. However, interactions between these exposures and hypertension were examined. Potential interactions between the various risk factors were also examined.

**Results**

We identified 177 patients who died from a cardiovascular cause within 30 days of elective surgery under general anaesthesia; 115 of these patients were selected for further study, together with the same number of individually matched controls. Thirty-seven patients were excluded because the notes of either the patient or the control, or both, were missing. Twenty-five patients were excluded because no matching control could be identified.

Mean age of the patients was 72.6 (range 45–93) yr and that of the controls was 71.3 (43–90) yr. Mean age difference between the patients and controls was 0.63 (std 1.82) yr. Pairs were matched for sex. In 74 (64%) of the pairs the patient and control were male.

Patients and controls were matched for operation. In 29 (25%) pairs, the patient and control underwent abdominal surgery, in 11 (10%) vascular surgery, in 12 (10%) hip replacement surgery and in 63 (55%) pairs other surgery. The other surgery group included patients undergoing endoscopic procedures, including TURP and cystoscopy, in addition to operations such as inguinal hernia repair and Keller’s procedure.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Case exposed/ control exposed</th>
<th>Case unexposed/ control exposed</th>
<th>Odds ratio (exact 95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>25</td>
<td>6</td>
<td>5</td>
<td>79</td>
</tr>
<tr>
<td>Angina</td>
<td>24</td>
<td>7</td>
<td>3</td>
<td>81</td>
</tr>
<tr>
<td>Hypertension</td>
<td>39</td>
<td>15</td>
<td>15</td>
<td>45</td>
</tr>
<tr>
<td>Renal failure</td>
<td>18</td>
<td>4</td>
<td>0</td>
<td>93</td>
</tr>
<tr>
<td>Heart failure</td>
<td>24</td>
<td>9</td>
<td>1</td>
<td>81</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>10</td>
<td>4</td>
<td>18</td>
<td>83</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>13</td>
<td>6</td>
<td>0</td>
<td>96</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>13</td>
<td>14</td>
<td>2</td>
<td>86</td>
</tr>
</tbody>
</table>

**Table 2** Results for individual risk factors. Crude and age-adjusted odds ratios

Among the patients the mean time from operation to death was 8.4 days (median 6 days). Seventy-eight (68%) of the patients died of myocardial infarction or ischaemic heart disease, 23 (20%) died of heart failure and in 14 (12%) patients the cause of death was cerebrovascular accident. The number of concordant and discordant pairs for each risk factor is shown in table 1.

**RISK ASSOCIATED WITH INDIVIDUAL RISK FACTORS**

The crude odds ratios for perioperative cardiovascular death are reported for each risk factor in table 2. Table 2 also gives the odds ratios adjusted for residual confounding by age. After adjustment for residual confounding by age, histories of myocardial infarction, angina, hypertension, renal failure and heart failure were observed to have a significant effect on the risk of perioperative cardiovascular death. The odds ratio associated with a history of myocardial infarction was 4.04 (95% confidence intervals CI 1.60–10.19; P = 0.003). The odds ratio associated with a history of angina was 3.55 (1.48–8.82; P = 0.004). For a history of treated hypertension the odds ratio was 2.53 (1.38–4.69; P = 0.003). The odds ratio associated with renal failure, defined as a serum creatinine concentration >150 μmol litre −1, was 4.23 (1.36–13.20; P = 0.013). For a history of heart failure requiring medical treatment the odds ratio was 2.80 (1.25–6.41; P = 0.014). The odds ratios for a history of peripheral vascular disease, cerebrovascular accident or diabetes mellitus were not statistically significant.

**CONDITIONAL LOGISTIC REGRESSION**

The data were then examined by forward stepwise conditional logistic regression. The final model is reported in table 3.

In the final regression model two risk factors (myocardial infarction and renal failure) were significant at the 0.05 level, and hypertension reached borderline significance at this level. The coefficient adjusting for residual confounding by age was also significant at the 0.05 level and its inclusion had a significant impact on the values of the other regression coefficients. No significant interaction terms were identified.

The coefficient for myocardial infarction in this equation was 1.16 (SEM 0.49), giving an odds ratio of 3.18 (95% CI 1.22–8.28) and a P value of 0.018 by the Wald test. The coefficient for hypertension was 0.64 (SEM 0.33), giving an odds ratio of 1.90 (95% CI 1.00–3.62). The Wald test for the effect of
hypertension was not quite significant at the 0.05 level ($z = 1.95$, $P = 0.052$). The Wald test is based on the normal approximation to the log likelihood. A comparison of the log likelihoods associated with models including and excluding hypertension (log likelihood ratio test) yielded a value of chi-square $= 3.95$, $P = 0.047$, 1 df. Hypertension was therefore retained in the model.

The coefficient for renal failure was 1.27 (SEM 0.63). This translated to an odds ratio for renal failure of $3.56$ (95% CI 1.04–12.18). The Wald test for the coefficient for renal failure was significant at the 0.05 level ($z = 2.02$, $P = 0.043$).

**Discussion**

**FINDINGS**

When adjustment was made for residual confounding by age, but not for other confounding factors, five risk factors were found to be significantly associated with cardiovascular death within 30 days of anaesthesia and surgery. These were previous myocardial infarction, history of angina, history of hypertension, history of renal failure and history of heart failure. In the conditional logistic regression model derived by stepwise regression, myocardial infarction and renal failure were found to be significant risk factors ($P < 0.03$), with hypertension at a borderline level of 0.052.

It was found that angina made a significant contribution to the regression model if a history of myocardial infarction was not included in the equation. When a history of myocardial infarction was included in the model the term for angina ceased to be significant. That is to say, most of the risk caused by ischaemic heart disease could be accounted for by the term for myocardial infarction.

Much of the heart failure reported in this population was probably a result of ischaemic heart disease or hypertension. The absence of heart failure in the final regression model may be accounted for by the inclusion of terms for myocardial infarction and hypertension. In the absence of these terms, heart failure made a significant contribution to the model.

Failure to find a perioperative risk associated with diabetes mellitus is difficult to explain. It may be that there was a bias in the recording of the cause of death in diabetics, such that some perioperative cardiovascular deaths of diabetics were coded as being caused by diabetes rather than by a cardiovascular event.

**METHOD OF ANALYSIS**

A predictive or prognostic equation, such as the one reported here, is useful for identifying patients at risk. However, a distinction should be made between predictive and explanatory models. A predictive equation aims to predict outcome on the basis of the patient’s exposure to risk factors, but it does not necessarily give an accurate impression of the importance of individual risk factors. An explanatory equation is intended to give the best possible estimate of the effect of one or more risk factors. The distinction can be illustrated using the current data. There is a complex interaction between various cardiovascular risk factors. One risk factor may lie on the causal pathway for the effect of another. For example, hypertension has a role in the pathogenesis of ischaemic heart disease and patients with hypertension are more likely to have suffered myocardial infarction. A history of myocardial infarction may account for some of the perioperative cardiovascular risk associated with hypertension. Our prognostic equation included both hypertension and myocardial infarction. Adjustment for myocardial infarction may reduce the effect of hypertension. Thus the regression coefficient for hypertension may not reflect the full impact of hypertension on risk.

**COMPARISON WITH OTHER STUDIES**

For the most part, our findings were similar to those of other workers. Many studies, including those of Goldman and colleagues, Larsen and colleagues and Fowkes and colleagues, have identified an association between previous myocardial infarction and perioperative cardiovascular complications. An association between renal impairment and adverse outcome has also been demonstrated in other studies.

There are some interesting contrasts with other studies. The effect of a history of hypertension on adverse outcome is not clearly established. Pryor, Roberts, Meloche and Poës demonstrated associations between poorly controlled hypertension, intraoperative cardiovascular instability and myocardial ischaemia. The multicentre study of general anaesthesia conducted in North America found an association between preoperative hypertension and perioperative bradycardia, tachycardia and hypertension. Browner, Li and Mangano identified an association between history of hypertension and mortality after major non-cardiac surgery. In contrast, hypertension was not found to be a significant risk factor on multivariate analysis in the studies of Foster and colleagues, Pedersen, Eliasen and Henriksen, Larsen and colleagues or Goldman and colleagues.

We found heart failure to be a risk factor on univariate analysis, but not after adjusting for other risk factors. Other studies have found heart failure or poor left ventricular function to be a risk factor for adverse outcome on multivariate analysis.

In trying to understand these differences it must be...
remembered that the various studies examined different populations in different locations, and that the study designs and methods of data collection varied. Goldman and co-workers, and Larsen and colleagues, studied patients more than 40 yr of age undergoing both elective and emergency non-cardiac surgery.\textsuperscript{5, 6} Fowkes and colleagues\textsuperscript{7} examined outcome after all 108 878 anaesthetics given in Cardiff between 1972 and 1978. Pedersen, Eliasen and Henriksen studied all patients undergoing anaesthesia in one hospital over a 1-yr period, no lower or upper age limit being specified for the inclusion of patients.\textsuperscript{8, 10} Browner, Li and Mangano studied US veterans aged 38–89 yr undergoing major non-cardiac surgery.\textsuperscript{11} Shah and colleagues studied patients who were more than 70 yr of age or known to have cardiac disease.\textsuperscript{3} The observations of Forrest and co-workers were made in the context of a multicentre, randomized study of four different anaesthetic agents.\textsuperscript{2} Also, the end-point used varied from study to study. We took cardiovascular death as an end-point. In the study by Shah and colleagues, the end-points were identified by review of the medical records and included angina, myocardial infarction, heart failure and cardiac death.\textsuperscript{3} Goldman and colleagues\textsuperscript{6} used adverse cardiovascular events as identified by the study observers and confirmed on diagnostic testing, while Foster and co-workers\textsuperscript{8} used cardiovascular events reported to the CASS registry. Given these differences, the relative consistency of the different studies is encouraging, while the fact that there are some differences both between the studies and between our findings and those of other workers is not surprising. These differences may result in part from random error or in part from real differences between the populations studied.

**Weaknesses of the Study**

Patients in this study were selected from the Oxford Record Linkage Study on the basis of a cardiovascular cause of death recorded in any of the sections of their death certificate. It is well established that diagnoses recorded on death certificates often do not reflect the true cause of death.\textsuperscript{12} Using the medical records it was possible to identify patients who had suffered a series of surgical and medical complications before death, and it appeared that a diagnosis of heart failure or cardiac arrest had been seized upon to simplify an otherwise very complex picture. Many of these misdiagnoses could be identified from the medical records and such patients were excluded. It is possible, however, that in some cases a diagnosis of cardiovascular death was mistakenly taken at face value.

The research nurse who examined the medical records could not be blinded to the patient/control status of subjects as outcome was usually clearly recorded in the notes. The question therefore arises of possible observer bias in the recording of data on hypertension. This problem was addressed by the use of a data collection tool which demanded specific responses to a series of questions rather than asking more general questions about the observer’s impression of the course of events.

It could be argued that this study was overmatched in the manner described by Rothman.\textsuperscript{18} That is, the matching criteria were demanding and it proved impossible to match 25 subjects, so reducing the efficiency of the study. Matching on type of surgery was probably justified in that this is a potential confounder which has many categories and is difficult to quantify more simply. Matching on consultant may also be justified. Matching on age was probably necessary to avoid the possibility of identifying controls who were appreciably younger than the patients. It would have been possible to control for age in the analysis and at the same time gain information on the association between age and adverse outcome. Frequency matching would have been sufficient. The effect of sex could possibly have been controlled in the analysis. Without matching on sex, information could have been gained on the effect of sex on perioperative risk. Finally, matching on date of surgery would have been useful and was attempted, but led to the loss of a large number of pairs through failure to match.

**Conclusions**

Our study is consistent with previous work in identifying myocardial infarction and renal failure as risk factors for perioperative cardiovascular complications. Unlike some previous studies, we did not identify heart failure as a risk factor on multivariate analysis. In this study, where data were examined by multivariate analysis, hypertension achieved a significance level of $P = 0.052$ for adverse outcomes. Although univariate analysis of this dataset and that of our previous publication suggested a strong association between hypertension and adverse outcome, such a statistical approach does not take into account other confounding factors.

It may be argued that further work is justified. Cross-sectional studies or further case-control studies would provide a means of studying this problem without the substantial resources needed for a major cohort study. However, it must be remembered that the overall risk of death after anaesthesia and surgery is low.\textsuperscript{2} The impact of cardiovascular risk factors is greatest in populations in which the underlying risk is greatest, such as in vascular and other major surgery. It is towards such groups that future investigations should be directed.

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**References**


