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Lethal mesenteric ischaemia after cardiopulmonary bypass: a common complication?☆

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Abstract

Objectives: The purpose of the study was twofold: (1) to identify the incidence of acute mesenteric ischaemia (A.M.Isc.) following cardiopulmonary bypass and (2) to identify factors associated with its development. **Methods**: A retrospective review of all autopsy reports from 1st January 1994 to 31st December 2000 was undertaken. Fifty-two patients were identified with acute mesenteric ischaemia at post-mortem following cardiac surgery. Demographic, pre-, intra- and post-operative variables were collected from their case notes. Four age, sex and period matched controls $\{n = 208\ (4 \times 52)\}$ were randomly selected for each case. Conditional logistic regression was used to compare the cases and controls. **Results**: A total of 11,202 patients underwent surgery requiring cardiopulmonary bypass (CPB) during the study period with an overall mortality rate of 3%. The autopsy rate was 95% throughout the study period. From autopsy reports 52 patients (corrected for autopsy rate: 0.49% of group) were identified with A.M.Isc. Comparing controls with A.M.Isc. cases by univariate analysis, significant associations ($P \leq 0.001$) with A.M.Isc. were identified. These included: (1) peripheral vascular disease [15 (7%) vs. 14 (27%)]; (2) intraaortic balloon pump (IABP) use [5 (2%) vs. 22 (42%)]; (3) post-operative renal failure [2 (1%) vs. 32 (61%)]; (4) operation type {coronary artery bypass graft (CABG) alone [143 (69%) vs. 25 (48%)], valve alone [35 (17%) vs. 5 (10%)], valve + CABG [23 (11%) vs. 11 (21%)], major cardiac [7 (3%) vs. 11 (21%)]}; (5) priority of operation {elective [155 (75%) vs. 27 (52%) emergency 52 (25%) vs. 25 (48%)]; and (6) smoking 12 (7%) vs. 9 (17%). CPB and cross-clamp times (minutes) were also significantly different between the groups [median (inter-quartile range (IQR)); 72 (55,96) vs. 100 (76,128) and 39 (30,54) vs. 56 (37,84), respectively]. Neither diabetes 23 (11%) vs. 6 (12%) nor hypertension 102 (49%) vs. 26 (50%) achieved significance ($P < 0.001$). **Conclusion**: The incidence of acute mesenteric ischaemia is 0.49% of all cases undergoing CPB. A.M.Isc. is a common association with death following CPB (11%). It appears to be significantly associated with the presence of peripheral vascular disease, IABP use, the development of post-operative renal failure, operation type and priority, smoking, duration of CPB and cross-clamp time. Surprisingly, it was not linked to general risk factors for vascular disease.

Keywords: Mesenteric ischaemia; Cardiopulmonary bypass

1. Introduction

Acute mesenteric ischaemia (A.M.Isc.) leading to massive infarction of the bowel is a serious life threatening complication following cardiopulmonary bypass (CPB). It is reported to be a rare complication with an incidence of 0.6–2% [1]. The mortality following this complication is extremely high ranging from 70 to 100% [2]. Various pre- and post-operative risk factors for the development of this fatal condition have been proposed [1]. This retrospective review of the autopsy reports of patients dying with A.M.Isc. aims to (1) identify its incidence and (2) identify those patients at particular risk of developing this condition in order to facilitate an early diagnosis, thus optimising treatment and improving its appalling prognosis.

2. Materials and methods

Autopsy reports were reviewed retrospectively from 1st January 1994 to 31st December 2000 to identify patients with ischaemia or infarction of the small and/or large intestine following cardiac surgery using CPB. All patients showing signs of ischaemic bowel in the form of discoloura-

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tion, mucosal necrosis to gangrene was included in the study. Data collected included age, sex, pre-operative creatinine, smoking, operative procedure and priority, cross-clamp time, bypass time, the presence of diabetes mellitus, hypertension, peripheral vascular disease (PVD), post-operative atrial fibrillation and low cardiac output. In addition to the use of intraaortic balloon pump (IABP), inotrope and the need for re-operation for bleeding, and haemofiltration for renal failure were noted as was clinical abdominal findings, findings at laparotomy, and whether mesenteric angiogram was performed. Four age, sex and period matched controls $\{n = 208 \ (4 \times 52)\}$ were randomly selected for each case. Categorical variables are described by frequency (%) and continuous measures by mean (standard deviation (SD)) or median [inter-quartile range (IQR)] for skewed data. Cases and controls were compared using conditional logistic regression for both the univariate analysis and the final model. Significance ($P < 0.05$) was assessed using the likelihood ratio test.

3. Results

From 1st January 1996 to 31st December 2000 there were 52 patients identified with ischaemic bowel. The autopsy rate was 95% during the study period and remains steady at this level, to date. During the same period 11,202 patients underwent cardiac operations using both normo- and hypothermic CPB. The overall mortality was 3%. The calculated incidence of A.M.Isc. following CPB was therefore 0.49% [(52/11,202)/0.95)]. In 37 of the 52 patients (71%) the pathologist described A.M.Isc. as contributing to death. Eleven percent of deaths in the study period was because of A.M.Isc. In the remaining 15 patients A.M.Isc. was described as a manifestation of a low cardiac output state with multi-organ failure.

There were 24 women and 28 men in the group. The mean age of patients was 70 years ranging from 48 to 88 years. Twenty-five patients had undergone isolated coronary artery bypass graft (CABG), five valve replacement, 11 combined valve and CABG, seven aortic operation and four underwent 'major cardiac operation' (other than the above (Table 1)). Sixteen (30%) patients were re-explored for bleeding following their cardiac surgery and the incidence of post-operative atrial fibrillation in this group was 50%. The onset of abdominal symptoms varied between 1 and 30 days with a median of 3 days. A general surgeon reviewed 16 patients of whom 12 underwent laparotomy. In all cases no re-vascularisation procedure was possible as the entire intestine was found to be gangrenous. In total, 25 patients who did not undergo operation showed frank gangrene of intestine at post-mortem. It was these 37 patients who were described by the attending pathologist to have died due to A.M.Isc. (3.6% of all deaths). Two of the 52 (3.8%) patients showed evidence of vascular occlusion (atheroma) at post-mortem.

Table 1
Patient demography and procedures

Age	Mean 70 years
Sex	24 women and 28 men
Procedure	
CABG	25
Valve replacement	5
Valve + CABG	11
Major cardiac	4
Aortic	7

Univariate analysis revealed (Table 2) that PVD, operative priority, IABP use, post-operative renal failure (requiring continuous veno-venous haemofiltration), procedure type were significantly associated ($P \leq 0.001$) with the development of A.M.Isc. CPB and cross-clamp times (minutes) were also significantly different between groups [median (IQR) controls vs. cases: CPB time, 72 (55,96) vs. 100 (76,128) min; cross-clamp time, 39 (30,54) vs. 56 (37,84) min]. Neither the presence of diabetes nor hypertension was associated with A.M.Isc. (Table 2).

Some of the factors we have considered here are related and so a full multivariate analysis was not possible, as there was insufficient power to detect significant associations. However, two factors analysis did reveal that CPB time was significantly ($P = 0.02$) associated with A.M.Isc. irrespective of the type of procedure. The resulting adjusted odd ratios (95% CI) for type of procedure (all vs. CABG alone) were 0.82 (0.29,2.4) for valve only, 1.9 (0.73,4.9) for valve + CABG and 3.9 (0.98,15) for 'major cardiac operation'. Each additional 10 min of CPB time was associated with an odd ratio (95% CI) of 1.12 (1.01,1.23).

4. Discussion

A.M.Isc. following CPB is, seemingly, a rare event. This clinical impression is supported by our study where an incidence of 0.49% was found. This appears to be lower than that reported by Allen et al. [1] (0.6–2.0%) almost a decade ago. However, 11% of deaths during the study were due to, or associated with, A.M.Isc. In a post-mortem study from this hospital, Goodwin et al. identified that 9.6% of patients after operations involving CPB died because of gastrointestinal complications. Five percent of these patients had intestinal infarction as an unexpected complication at post-mortem [3]. Our study shows that this condition is surprisingly common in death following CPB and may be its cause.

Studies have shown that during hypothermic CPB there is disparity between the mesenteric oxygen consumption and oxygen delivery [4]. Although the reported incidence of non-occlusive A.M.Isc. is around 40% [1], our study suggested this to be of the order of 96%. This is in contrast to the findings following general surgery where arterial embolus is the main cause of mesenteric ischaemia. Coupling this information and the apparently significant association with prolonged CBP time, use of IABP and the development of post-operative renal failure, it is tempt-

Table 2
Results of univariate analysis

Factors	Category	Controls (%)	Cases (%)	Odds ratio (95% CI)	*P*-value
IAPB	No	203 (98)	30 (58)	1	< 0.001
	Yes	5 (2)	22 (42)	21 (7.4,62)	
Procedure	CABG	143 (69)	25 (48)	1	< 0.001
	Valve	35 (17)	5 (10)	0.9 (0.32,2.5)	
	Valve + CABG	23 (11)	11 (21)	2.7 (1.1,6.4)	
	Major aortic	7 (3)	11 (21)	8.8 (2.9,25)	
PVD	No	193 (93)	38 (73)	1	< 0.001
	Yes	15 (7)	14 (27)	4.9 (2.1,12)	
Renal failure	No	206 (99)	20 (39)	1	< 0.001
	Yes	2 (1)	32 (61)	NA[a]	
Smoking (56 missing)	Never	41 (27)	27 (52)	1	< 0.001
	Ex	99 (65)	16 (31)	0.25 (0.12,0.52)	
	Current	12 (8)	9 (17)	1.14 (0.40,3.2)	
Priority (1 missing)	Elective	155 (75)	27 (52)	1	0.001
	Urgent/emergency	52 (25)	25 (48)	2.7 (1.4,5.0)	
Hypertension	No	106 (51)	26 (50)	1	0.90
	Yes	102 (49)	26 (50)	1.04 (0.55,2.0)	
Diabetes	No	186 (89)	46 (89)	1	0.92
	Yes	23 (11)	6 (12)	1.05 (0.40,2.7)	
Cross-clamp time[b]	Median (IQR)	39 (30,54)	56 (37,84)	1.28 (1.12,1.45)	< 0.001
CPB time[b]	Median (IQR)	72 (55,96)	100 (76,128)	1.19 (1.09,1.30)	< 0.001

[a] Not possible to evaluate due to insufficient numbers.
[b] Odd ratios reported for 10 min increase.

ing to suggest that A.M.Isc. following CPB is due to low mesenteric blood flow following a low cardiac output state. Others have suggested such a mechanism in the past [5,6,7]. What role the use of vaso-active agents have is beyond the scope of this paper as all patients requiring IABP also received inotrope with or without vasoconstrictors (noradrenaline or ADH). A prospective study will be required to tease out this influence. Previous reviews have shown inotropic support in addition to advanced age, emergency operation, use of an IABP, and prolonged bypass time to be significant risk factors for A.M.Isc. [8,9,10]. Our study confirmed a statistically significant association between A.M.Isc. PVD and smoking status.

The operative procedure is clearly important. Why valve replacement alone was not associated with developing mesenteric ischaemia, yet valve plus CABG was, may be due to a shorter time on cross clamp and bypass or due to the presence of generalised atheroma. It is therefore surprising to note that pre-operative risk factors for athero-genesis such as hypertension and diabetes mellitus did not appear to be correlated with A.M.Isc. Furthermore, 96% of our series had no evidence of atheromatous occlusion or stenosis of mesenteric vessels directing us to a conclusion that duration of CPB is the main associated risk factor here. The impact of 12% additional risk with every additional 10 min of CPB is perhaps understandable.

The median time to develop symptoms in our study was 3 days. Delay in initial recognition and diagnosis of mesenteric ischaemia was probably present in most, if not all of our cases and has been reported by others [1]. The delay in diagnosis has been attributed to the state of the patient at risk. Often heavily sedated and ventilated patients are unable to express discomfort and the physical examination is often unrewarding. A persistent and refractory metabolic acidosis (persisting despite efforts to directly correct it with appropriate volumes of bicarbonate infusion), lactic acidosis, hyperkalaemia and lecocytosis are often associated with A.M.Isc. Their presence in a post-cardiac surgical patient with abdominal pain, distention and/or prolonged ileus should raise the possibility of underlying A.M.Isc. [11]. It is likely that only a high index of suspicion in 'at risk patients' will lead to early diagnosis and life saving intervention.

So who are 'the at risk patients'? This study suggests that the 'at risk patient' may be characterised by a current smoking history (odds ratio: 1.14), undergoing emergency surgery (odds ratio: 2.7), that is major cardiac surgery (odds ratio: 8.8) which leads to the use of IABP (odds ratio 21) and (perhaps) further complicated by renal failure requiring haemofiltration.

So what of diagnosis and early intervention? Most of our patients were very ill and were unfit for 'safe' transfer for angiographic imaging. Even though mesenteric angiography is quoted as a gold standard test for diagnosing A.M.Isc. none of our patients underwent this investigation. The use of intra-arterial papavarine infusion in non-occlusive mesenteric ischaemia has been reported [12]. Laparotomy, with an aggressive surgical approach entailing repeated re-exploration has also been reported to be the only way to save these patients. As ever prevention is the best option. Randomised clinical trials and experimental studies show that using dopexamine in hypothermic CPB

reduces gut permeability and increases splanchnic blood flow [13,14,15]. It is reasonable to hypothesise that this single step could significantly reduce the incidence of A.M.Isc.

It is important to note that in a small study such as this, especially when dealing with an unusual problem (incidence <1%) the opportunity for error is high. It is probably such a mechanism that led to our observation that patients with a current smoking history were significantly at risk of A.M.Isc. yet being *an ex-smoker* (compared to non-smoker) appeared protective! However, it is also well known that patients are unreliable reporters of their own smoking history.

In conclusion we believe A.M.Isc. following CPB not to be a rare condition. Although the incidence is of the order of 0.5% this is in the setting of a very low incidence of major complications for this well-rehearsed surgery. In addition A.M.Isc. was associated with 11% of total deaths in the study period and incremented in 3.6%. It is gratifying to find that the incidence of A.M.Isc. in this study falls below the range reported 9 years ago by Allen et al. [1] despite an accepted increase in risk to life for patients undergoing surgery with CPB with time. There is a weight of circumstantial evidence suggesting abdominal complications after CPB is due to a low cardiac output state. A high index of suspicion in 'at risk patients' may lead to earlier diagnostic imaging, consequently aggressive intervention and so towards a future where A.M.Isc. carries a less malign prognosis. This study suggests the 'at risk patient' is principally characterised by a current smoking history (odds ratio: 1.14), undergoing emergency surgery (odds ratio: 2.7), that is major cardiac surgery (odds ratio: 8.8) which leads to the use of IABP (odds ratio 21.0) and (perhaps) further complicated by renal failure requiring haemofiltration. Further studies are required to identify a more appropriate inotrope in high-risk patients with the intention of reducing the incidence of A.M.Isc. or ideally preventing it. The low incidence of A.M.Isc. demands that such a study be multicentre and ideally prospective and randomised.

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Appendix A. Conference discussion

Mr N. Roberts (*Leicester, UK*): We presented a paper on Monday looking at this condition as well and identified slightly different risk factors, and in our study we looked at patients who actually managed to survive rather than just those patients that died. And the mortality when this condition was taken to theater within six hours was 48%, meaning that more than half of the patients actually survived with this condition if taken to theater early. So are you sure you have identified the risk factors accurately only by looking at dead patients and not looking at those who survived?

Mr Venkateswaran: We do have survivors in our institution. I think in the last seven-year period total survivors were less than 10. We did have a problem in actually tracing all of them from our database. So in order to give accurate numbers, we just selected only the patients who actually died so that we can give just the actual figures rather than giving any wrong figures. That is why we didn't include those survivors.

Dr G. Wimmer-Greinecker (*Frankfurt, Germany*): Do you do autopsies to all of your patients in the U.K., and secondly, how do you handle the situation, if you have a suspicious abdomen in your department, because the number of 11 laparotomies seems very low to me?

Mr Venkateswaran: For your first question, the autopsy rate following hospital death varies between the institutions, but in Papworth Hospital it is a routine that every in-hospital death within the first 30 days or any patient who dies after operation where the cause of it is not known, or even if you know the cause of death and you want to confirm it, we do have a hospital postmortem performed.

For your second question, only 11 patients underwent laparotomy, yes. Most of those patients were still intubated and ventilated, and all of them, I didn't have that slide because of the time, all these patients showed characteristic findings in the form of persistent metabolic acidosis and increasing lactic acidosis in spite of being on a filter, being dialyzed, and by the time the general surgeons came and saw these patients, they were extremely sick; they had balloon pumps and enormous doses of inotropes. So even though we had the suspicion of mesenteric ischemia in mind, with the consultation of the general surgeons, we decided not to operate, and from

the time of diagnosis, within six to eight hours, these patients succumbed to the disease. But only 11 patients gave any chance of going to the theater, and in those patients we just found out it was massive infarction.

Dr A. Franco-Cereceda (*Stockholm, Sweden*): Just two short questions. Firstly, what do you think is the cause of these events, is it embolization or is it hypoperfusion?

And secondly, related to that, have you tried to correlate your findings with pharmacological treatment of the patients postoperatively? For instance, in Great Britain I believe that norepinephrine is used quite frequently.

Mr Venkateswaran: For your first question, it is obviously not due to thromboembolism. That is what I wanted to tell the audience, that mesenteric ischemia following cardiopulmonary bypass is due to a low cardiac output, low-flow phenomena rather than thromboembolism or occlusion. Now, it is clearly seen in our patients that they all have a long cardiopulmonary bypass time. It is basically because they are unable to come off bypass, they have low cardiac output, a poor heart, they require a large dose of inotropes, balloon pump, and the studies have shown that low cardiac output and low flow causes intense mesenteric vasoconstriction. So that answers your first question.

Next, we know that use of intraarterial papaverine infusion and use of dopexamine as an inotrope helps in mesenteric vasodilatation, and even though there are only a few reports, a large prospective randomized study has to be done to prove the benefit of these drugs in preventing this complication.