Hypotension during ERCP is common but not a risk factor for post-ERCP pancreatitis

BC Jacobson and DL Carr-Locke

Division of Gastroenterology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

Background

In patients undergoing cardiopulmonary bypass, hypotension is a risk factor for developing acute pancreatitis. Hypotension in animal models can also induce pancreatitis. We sought to determine whether or not relative hypotension during ERCP is a risk factor for developing acute pancreatitis.

Patients and methods

A nested, case-control study reviewed all cases of post-ERCP pancreatitis resulting from ERCPs performed at this institution between May 1993 and May 1998. Post-ERCP pancreatitis was defined as abdominal pain requiring hospitalisation and elevation of serum amylase or lipase more than four times the upper limit of normal 24 hours or more after ERCP. Non-invasive blood pressure measurements were recorded automatically at least every 5 min during ERCP. Hypotension was defined as any systolic blood pressure (SBP) $<$100 mmHg, diastolic blood pressure (DBP) $<$60 mmHg, or mean blood pressure (MBP) $<$80 mmHg. Controls were chosen randomly from ERCPs performed on the same or the nearest day as each index case.

Results

In total, 1854 ERCPs were reviewed from the study period. There were 96 cases of post-ERCP pancreatitis, giving an incidence of 5.2%. The average age of cases was 48 years, while that of controls was 55 years ($p<0.003$). There were no differences between the groups regarding gender, ERCP findings, need for sphincterotomy nor acinar filling on the pancreatogram (acinarisation). At least one episode of hypotension was recorded in 32% of cases and 30% of controls ($p=0.75$). There were no differences between cases and controls comparing mean pre- and intra-procedure SBP, DBP and MBPs, or lowest procedure SBP, DBP and MBP.

Discussion

Episodes of acute hypotension are common during ERCP but are not a risk factor for developing post-ERCP pancreatitis.

Keywords

pancreatitis, endoscopic retrograde cholangiopancreatography, hypotension.

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) has become a commonplace gastroenterological procedure, but post-ERCP acute pancreatitis remains an appreciable source of morbidity. Studies have documented an incidence of pancreatitis between 1 and 5% after diagnostic ERCP and up to 15% after therapeutic ERCP [1–7], although we have previously demonstrated little difference in complications between diagnostic and therapeutic ERCP [8]. A better understanding of the risk factors associated with this complication might provide insight into its cause and suggest strategies for its prevention.

Several variables have already been linked to an increased risk of developing post-ERCP pancreatitis. These are younger age [6], difficulty with cannulation [6,8], presence of (or suspected) sphincter of Oddi dysfunction [4,6], number of contrast injections [1,6,9], acinarisation during injection of contrast [1,6], performance of a pancreatogram [2,8,9], performance of sphincterotomy [6,8] and prior history of post-ERCP pancreatitis [6,8]. Prior history of pancreatitis may, however, correlate inversely with severity of post-ERCP pancreatitis [5]. The use of low osmolar, non-ionic contrast media does not decrease the risk for post-ERCP pancreatitis [10].

Hypotension associated with cardiopulmonary bypass has been shown to cause acute pancreatitis, but it is an

Correspondence to: *BC Jacobson, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA*

uncommon complication occurring in only 0.1–7.7% of such operations [11–17]. The aetiology of pancreatitis in these situations is unknown, but pancreatic ischaemia may be a factor. In animal models, hypotension induced by haemorrhage can result in acute pancreatitis [18]. Hypotension results in diminished blood flow within the pancreatic microvasculature and subsequent tissue ischaemia [18,19]. We sought to determine whether or not hypotension during ERCP is associated with an increased risk of developing subsequent pancreatitis.

Patients and methods

Patients

All cases of post-ERCP acute pancreatitis resulting from ERCP performed at our institution between May 1993 and May 1998 were included in this study. Demographic, clinical, and procedural data about each case were prospectively recorded in our endoscopy centre database. Information recorded included age, gender, indication for procedure, findings during the procedure, types and quantity of sedation used, presence or absence of acinarisation during injection of contrast into the pancreatic duct, performance of sphincterotomy and many other variables. Post-ERCP pancreatitis was defined as abdominal pain requiring hospitalisation and elevation of serum amylase or lipase more than four times the upper limit of normal 24 hours or more after ERCP. Severity of pancreatitis was determined according to a modified grading scale previously defined [3]. Patient follow-up was performed prospectively and captured cases of pancreatitis admitted to our own and other hospitals. Patient follow-up was maintained by subsequent office visits, telephone conversations with patients, and by written or verbal communication with referring physicians. Admissions to outside facilities were also documented in this fashion. Controls were chosen randomly from ERCPs performed on the same or the nearest day as each index case.

Haemodynamic monitoring

Non-invasive blood pressure measurements were recorded automatically during ERCP using an Accutor Plus (Datascope Corp., Paramus, NJ). Measurements were taken at least every 5 min in accordance with our institutional policy for conscious sedation. Printouts containing every recorded systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), pulse rate and oxygen saturation were included with the endoscopy report in each patient's medical record. Haemodynamic monitoring typically began several minutes before administration of sedation. Measurements were taken regularly throughout the procedure and continued for several minutes after withdrawal of the endoscope. There are no uniformly accepted blood pressure values that define hypotension. For the purposes of this study we were mainly interested in comparing values between the cases and controls. Based on clinical experience, we chose to define hypotension as any SBP$<$100 mmHg, DBP$<$60 mmHg, or MBP$<$80 mmHg. MBP is calculated by the Accutor Plus according to the formula:

$$\frac{SBP+2(DBP)}{3}$$

Statistical analysis

Mean pre-procedure and intra-procedure SBP, DBP and MBP were calculated for both cases and controls. Mean lowest procedure SBP, DBP and MBP were also calculated for both cases and controls. To determine whether relative declines in blood pressure were a risk for pancreatitis, the mean differences between pre-procedure and lowest procedure SBP, DBP and MBPs were calculated for both cases and controls. Continuous variables were analysed using Student's *t*-test and categorical variables were compared using chi-square analysis or the Fisher's exact test when indicated.

Results

From 1854 ERCPs recorded in our database for the period reviewed, there were 96 cases of post-ERCP pancreatitis for an incidence of 5.2%.

Patient characteristics

Demographic and procedural information was available for all patients studied. Patient characteristics are shown in Table 1. The average age of cases was 48 years, while that of controls was 55 years ($p<0.003$). There were no differences between the groups regarding gender, ERCP findings, need for sphincterotomy, nor acinarisation. A prior history of post-ERCP pancreatitis carried a significant risk for developing post-ERCP pancreatitis with an odds ratio of 4.0 (95% CI 1.52–10.94). However, a prior history of pancreatitis not related to ERCP did not carry an increased risk for developing post-ERCP pancreatitis (O.R. 1.5, 95% CI . 79–2.68).

Table 1. *Patient characteristics*

	Cases	Controls	*p* Value
Number	96	96	
Mean age (years)	48	55	0.003
Male/female	35/61	32/64	NS
ERCP findings (%)			
Normal	21.9	19.8	NS
CBD stones	11.5	18.8	NS
Malignant stricture	12.5	12.5	NS
Chronic pancreatitis	10.4	8.3	NS
Pancreas divisum	6.2	5.2	NS
Sphincter of Oddi dysfunction	7.3	2.1	NS*
Other	30.2	33.3	NS
Biliary sphincterotomy	17 (17.7%)	13 (13.5%)	NS
Acinarisation	5 (5.2%)	8 (8.3%)	NS

*Fisher's exact test

The severity of post-ERCP pancreatitis was mild in 73% of cases, moderate in 23% of cases and severe in 4% of cases. There were no deaths resulting from post-ERCP pancreatitis in this study.

Haemodynamic measurements

Haemodynamic measurements were available for 97% of both cases and controls. At least one episode of hypotension was recorded in 32% of cases and 30% of controls ($p=0.75$). This same incidence of hypotension was observed at each level of severity of pancreatitis. Most episodes of hypotension lasted less than 10 min. Only one patient experienced prolonged hypotension, this being a control patient who had a MBP below 70 mmHg for 50 min. Episodes of hypotension were either treated with intravenous fluid or were simply documented. No patient received pressor support. There were no adverse sequelae that could be attributed to hypotensive episodes. Comparison of haemodynamic measurements between cases and controls is shown in Table 2. There were no differences between cases and controls comparing mean pre- and intra-procedure SBP, DBP and MBPs or lowest procedure SBP, DBP and MBP. Likewise, the mean decline from pre-procedure measurements to lowest procedure measurements was the same between cases and controls.

Since our definition of hypotension may have been too restrictive to detect a difference between cases and controls, we lowered our threshold value for hypotension as a categorical variable to any SBP<90 mmHg, DBP<50 mmHg, or MBP<70 mmHg. Using these values, at least one episode of acute hypotension was observed in 15% of cases and 13% of controls.

Table 2. *Haemodynamic measurements**

	Cases	Controls
% SBP<100 mmHg**	17.2	18.3
% DBP<60 mm Hg**	23.7	23.7
% MBP<80 mmHg**	28	28
Mean pre-procedure SBP***	131±20.0	136±20.0
Mean pre-procedure DBP	81±14.2	81±11.1
Mean pre-procedure MBP	100±15.7	102±13.6
Mean intra-procedure SBP	142±19.4	144±21.1
Mean intra-procedure DBP	84±11.8	84±10.2
Mean intra-procedure MBP	106±18.6	108±14.0
Mean lowest procedure SBP	119±22.3	120±22.3
Mean lowest procedure DBP	68±14.7	68±12.2
Mean loweset procedure MBP	89±17.2	89±15.7

*None of the differences is statistically significant

**Per cent of cases or controls in which at least one blood pressure reading fell below the cutoff

***Standard deviation

SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure

Medication usage and hypotension

The total amount of medication used during ERCP did not differ between normotensive patients and those who experienced hypotensive episodes. This statement held true for midazolam, meperidine, fentanyl and glucagon. However, when we examined the timing of hypotensive episodes, 41% occurred within 5 min after administration of either a sedative or glucagon. All medications were associated with at least one episode of hypotension without any particular drug emerging as especially noxious.

Discussion

In this study, we examined the role of relative hypotension during ERCP as a risk factor for post-ERCP pancreatitis. Our incidence of post-ERCP pancreatitis was found to be 5.2% and is consistent with values reported previously in the literature [3–6]. Younger age was found to be a statistically significant risk factor for developing pancreatitis. This finding has been demonstrated in the past [6] with similar age differences. While these mean ages are statistically different, the clinical relevance of the age difference remains unclear. Also demonstrated in this study was an increased risk of post-ERCP pancreatitis in patients with a prior history of this complication.

Regarding haemodynamic measurements, we found that brief episodes of acute hypotension are common during ERCP, occurring during one-third of procedures. Over half of these episodes do not appear related to the administration of sedatives or glucagon. However, hypotension was

not associated with the development of acute pancreatitis or any other adverse sequelae. This finding differs from the published experience following cardiopulmonary bypass and aortic cross-clamping. Fernandez-del Castillo and colleagues prospectively examined 300 patients for pancreatic cellular injury after cardiopulmonary bypass [15]. Eighty patients (27%) demonstrated evidence of pancreatic injury defined as elevated serum levels of amylase and either pancreatic isoamylase or lipase (or both). Of these 80 patients, 23 experienced signs or symptoms potentially attributable to pancreatitis, giving an overall incidence of 7.7%. Postoperative hypotension, defined as a MBP$<$80 mmHg, was noted in 35% of patients experiencing pancreatic cellular injury compared with 7% of patients without injury ($p<0.0001$). Exogenous calcium was also shown to be a risk factor for 'post-pump' pancreatitis. These investigators have subsequently shown that, while hypotension alone causes pancreatitis in rats, the subsequent administration of calcium chloride augments the effects of hypotension and results in a more severe form of organ damage [20].

Christenson and co-workers identified 86 gastrointestinal complications following 3493 cardiac operations [17]. Nine patients (10% of complications) developed acute pancreatitis. In their analysis of variables associated with complications, low postoperative cardiac output emerged as a major risk factor. The authors concluded that splanchnic hypoperfusion and visceral ischaemia represent a common aetiology for the development of gastrointestinal complications, including pancreatitis.

Taking pancreatic hypoperfusion a step further, Gullo and associates [21] characterised the level of pancreatic injury following cross-clamping of the aorta in patients undergoing operation for thoracic or thoracoabdominal aortic aneurysms. Serum levels of amylase, pancreatic isoamylase and lipase were monitored in the perioperative setting. Patients were also assessed postoperatively for clinical evidence of acute pancreatitis. The mean length of cross-clamp time was 44 min. Only one out of the 21 patients studied developed clinically evident pancreatitis: this was a fatal case of necrotising pancreatitis in a woman who had her aorta cross-clamped for 43 min. The remaining patients uniformly demonstrated elevations in serum pancreatic enzyme levels shortly after declamping. A correlation was seen between the duration of cross-clamping and the level of pancreatic enzyme release. This study provides evidence that ischaemia can cause acute pancreatitis, although the severity of ischaemia with cross-clamping of the aorta would presumably be much greater than that from minor hypoperfusion. Ischaemia has also been cited as the cause of pancreatitis in the setting of shock [22], emboli [23,24], transplantation of the pancreas [25], ergotamine poisoning [26] and polyartertitis nodosa [27]. In rats, splanchnic vasoconstriction secondary to phenylephrine can worsen the severity of otherwise mild pancreatitis [28]. This effect can be mitigated by using alpha-adrenergic receptor blockade, which improves splanchnic blood flow. The pathogenesis of ischaemic pancreatitis is suspected to include reperfusion injury and local production of oxygen free radicals [29–33].

In this study we failed to find an association between hypotension and post-ERCP pancreatitis. The study may be limited by the number of cases available for consideration. We acknowledge that the incidence of hypotension-associated pancreatitis is very low. However, the cause of post-ERCP pancreatitis is multifactorial. Our concern was that the insult of hypotension during ERCP might be synergistic with the well-established risks conferred by manipulation of the pancreas or papilla.

Another limitation is the duration of hypotension associated with ERCP. Most episodes of hypotension lasted less than 10 min. It is possible that more prolonged hypotensive episodes would have resulted in more cases of post-ERCP pancreatitis. In addition, because the automated blood pressure monitoring occurred at 5-min intervals, transient episodes of hypotension lasting less than 5 min may have been missed. It is quite possible therefore that the true incidence of hypotension during ERCP is higher than the rate that we observed in this study.

The use of non-invasive blood pressure monitoring raises certain concerns. Spurious results may arise from patient movement or changes in position. Review of the individual records allowed us to verify that drops in blood pressure were (1) accompanied by compensatory increases in heart rate, (2) accompanied by a coincident decrease in heart rate consistent with increased vagal tone, or (3) verified by repeat measurements taken in a timely manner. After reviewing the haemodynamic records, nine cases and six controls had hypotensive episodes that may have been spurious. Excluding these cases would lower the overall incidence of hypotension during ERCP to 22% from 30%.

In conclusion, there was quite a high incidence of acute, self-limited hypotension during ERCP. Unlike the situation with cardiopulmonary bypass or cross-clamping of

the aorta, hypotension during ERCP does not appear to be associated with post-procedure pancreatitis.

Acknowledgement

This paper was presented in part at Digestive Diseases Week, May 1999, Orlando, Florida, USA.

References

1 Zimmon DS, Falkenstein DB, Riccobono C *et al.* Complications of endoscopic retrograde cholangiopancreatography: analysis of 300 consecutive cases. *Gastroenterology* 1975;**69**:303–9.

2 Bilbao MK, Dotter CT, Lee TG *et al.* Complications of endoscopic retrograde cholangiopancreatiography (ERCP): a study of 10,000 cases. *Gastroenterology* 1976;**70**:314–20.

3 Sherman S, Lehman GA. ERCP- and endoscopic sphincterotomy-induced pancreatitis. *Pancreas* 1991;**6**:350–67.

4 Sherman S, Ruffolo TA, Hawes RH *et al.* Complications of endoscopic sphincterotomy: a prospective series with emphasis on the increased risk associated with sphincter of Oddi dysfunction and nondilated bile ducts. *Gastroenterology* 1991;**101**:1068–75.

5 Chen YK, Abdulian JD, Escalante-Glorsky S *et al.* Clinical outcome of post-ERCP pancreatitis: relationship to history of previous pancreatitis. *Am J Gastroenterol* 1995;**90**:2120–3.

6 Freeman ML, Nelson DB, Sherman S et al. Complications of endoscopic biliary sphincterotomy. *N Engl J Med* 1996;**335**:909–18.

7 Deans GT, Sedman P, Martin DF *et al.* Are complications of endoscopic sphincterotomy age related? *Gut* 1997;**41**:545–8.

8 Vandervoort J, Tham TCK, Wong RCK *et al.* Prospective analysis of risk factors for pancreatitis after diagnostic and therapeutic ERCP. *Gastrointest Endosc* 1996;**43**:A440.

9 Lintott IH, Rothwell J, Axon ATR. Acute pancreatitis following endoscopic retrograde cholangiopancreatography. *Clinical Radiol* 1983;**34**:543–6.

10 Johnson GK, Geenen JE, Bedford RA *et al.* A comparison of nonionic versus ionic contrast media: results of a prospective, multicenter study. *Gastrointest Endosc* 1995;**42**:312–6.

11 Rose DM, Ranson JHC, Cunningham JN *et al.* Patterns of severe pancreatic injury following cardiopulmonary bypass. *Ann Surg* 1984;**199**:168–72.

12 Haas GS, Warshaw AL, Daggett WM *et al.* Acute pancreatitis after cardiopulmonary bypass. *Am J Surg* 1985;**149**:508–15.

13 Rattner DW, Gu Z-Y, Vlahakes GJ *et al.* Hyperamylasemia after cardiac surgery: Incidence, significance, and management. *Ann Surg* 1989;**209**:279–83.

14 Huddy SPJ, Joyce WP, Pepper JR. Gastrointestinal complications in 4473 patients who underwent cardiopulmonary bypass surgery. *Br J Surg* 1991;**78**:293–6.

15 Fernandez-del Castillo C, Harringer W, Warshaw AL *et al.* Risk factors for pancreatic cellular injury after cardiopulmonary bypass. *N Engl J Med* 1991;**325**:382–7.

16 Lefor AT, Vuocolo P, Parker FB *et al.* Pancreatic complications following cardiopulmonary bypass: factors influencing mortality. *Arch Surg* 1992;**127**:1225–31.

17 Christenson JT, Schmuziger M, Simonet MF *et al.* Postoperative visceral hypotension the common cause for gastrointestinal complications after cardiac surgery. *Thorac Cardiovasc Surg* 1994;**42**:152–7.

18 Mithofer K, Fernandez-del Castillo C, Frick TW *et al.* Increased intrapancreatic trypsinogen activation in ischemia-induced experimental pancreatitis. *Ann Surg* 1995;**221**:364–71.

19 Kerner T, Vollmar B, Menger MD *et al.* Determinants of pancreatic microcirculation in acute pancreatitis in rats. *J Surg Res* 1996;**62**:165–71.

20 Mithofer K, Warshaw AL, Frick TW *et al.* Calcium administration augments pancreatic injury and ectopic trypsinogen activation after temporary systemic hypotension in rats. *Anesthesiology* 1995;**83**:1266–73.

21 Gullo L, Cavicchi L, Tomassetti P *et al.* Effects of ischemia on the human pancreas. *Gastroenterology* 1996;**111**:1033–8.

22 Warshaw AL, O'Hara PJ. Susceptibility of the pancreas to ischemic injury in shock. *Ann Surg* 1978;**188**:197–201.

23 Redha F, Uhlschmid G, Ammann RW *et al.* Injection of microspheres into pancreatic arteries causes acute hemorrhagic pancreatitis in the rat: a new animal model. *Pancreas* 1990;**5**:188–93.

24 Sakorafas GH, Tsiotos GG, Bower TC *et al.* Ischemic necrotizing pancreatitis: two case reports and a review of the literature. *Int J Pancreatol* 1998;**24**:117–21.

25 Fernandez-Cruz L, Sabater L, Gilabert R *et al.* Native and graft pancreatitis following combined pancreas-renal transplantation. *Br J Surg* 1993;**80**:1429–32.

26 Deviere J, Reuse C, Askenasi R. Ischemic pancreatitis and hepatitis secondary to ergotamine poisoning. *J Clin Gastroenterol* 1987;**9**:350–2.

27 Flaherty J, Bradley EL. Acute pancreatitis as a complication of polyarteritis nodosa. *Int J Pancreatol* 1999;**25**:53–7.

28 Klar E, Rattner DW, Compton C *et al.* Adverse effect of therapeutic vasoconstrictors in experimental acute pancreatitis. *Ann Surg* 1991;**214**:168–74.

29 Sanfey H, Bulkley GB, Cameron JL. The pathogenesis of acute pancreatitis: the source and role of oxygen-derived free radicals in three different experimental models. *Ann Surg* 1985;**201**:633–9.

30 Chardavoyne R, Asher A, Bank S *et al.* Role of reactive oxygen metabolites in early cardiopulmonary changes of acute hemorrhagic pancreatitis. *Dig Dis Sci* 1989;**34**:1581–4.

31 Schoenberg MH, Buchler M, Gaspar M *et al.* Oxygen free radicals in acute pancreatitis of the rat. *Gut* 1990;**31**:1138–43.

32 Schoenberg MH, Buchler M, Beger HG. Oxygen radicals in experimental acute pancreatitis. *Hepatogastroenterology* 1994;**41**:313–9.

33 Menger MD, Bonkhoff H, Vollmar B. Ischemia-reperfusion-induced pancreatic microvascular injury: an intravital fluorescence microscopic study in rats. *Dig Dis Sci* 1996;**41**:823–30.