REVIEW

Treatment of poisoning induced cardiac impairment using cardiopulmonary bypass: a review

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Severe poisoning can cause potentially fatal cardiac depression. Cardiopulmonary bypass (CPB) can support the depressed myocardium, but there are no clear indications or guidelines available on its use in severe poisoning. A review was conducted of relevant papers in the available literature (seven single case reports of both deliberate and accidental ingestion of cardiotoxic drugs and two animal studies). Although CPB is rarely used in the management of poisoning, it may have potential benefits for haemodynamic instability not responding to conventional measures. At present there is insufficient evidence concerning the use of CPB as a treatment for severe cardiac impairment due to poisoning (grade C). This review suggests that in patients with severe and potentially prolonged reversible cardiotoxicity there is potential for full survival with CPB, provided that the patient has not already sustained hypoxic cerebral damage due to resistant hypotension prior to its use.

Acute poisoning is a common presentation to emergency departments, and it accounts for 310 attendances per 100 000 population per year in the UK.[1] An increase in availability of all types of medication, including a number of potentially lethal drugs, resulted in a peak in the 1970s.[2] In 2003, there were 1997 deaths from acute poisoning in England and Wales.[3]

Specific antidotes and conventional supportive measures are not always sufficient to deal with life threatening overdoses. Accidental overdoses in childhood are usually apparent immediately and present early, whereas adult overdose tends to be deliberate and present later,[3] with one or more pharmaceutical agents involved. In severe cases the presentation is of an acutely unstable patient with multiorgan dysfunction. Measures to counteract poisoning include reducing the absorption or enhancing the elimination of the toxin; administering specific antidotes; and supportive resuscitative measures. For many antidepressant, antihypertensive, antimalarial, and antiarrhythmic drugs there are a limited number of effective antidotes or means of extracorporeal elimination (for example, haemodialysis) because these drugs have a large volume of distribution.[4 5] The first signs of toxicity are often cardiovascular, manifesting as arrhythmias and hypotension within 30–120 minutes of ingestion,[5] but severe cardiotoxicity and systemic vasodilation (for example, due to calcium channel blockers) may be resistant to standard measures including vasopressors, inotrope infusions, repeated defibrillation, and pacing.[4 6–10]

Once a drug enters the central circulation and the tissues, it may become essential to maintain circulatory function with supportive therapy. This would permit hepatic detoxification over time[6] while providing reliable tissue perfusion and allowing sufficient antidote circulation.[7] Modalities that may be used include continuous cardiopulmonary resuscitation (CPR; manual or with a mechanical device), balloon counterpulsation, and cardiopulmonary bypass (CPB).[8] Emergency extracorporeal membrane oxygenation (ECMO) may also be used to provide adequate cardiac output and restore vital organ perfusion to allow clearance of the toxic metabolite in question. ECMO is a form of partial CPB used for support of a longer duration of respiratory and/or cardiac dysfunction. It is primarily indicated in patients with such severe ventilation and/or oxygenation problems that they are unlikely to survive conventional mechanical ventilation, and therefore it is differs from CPB.[10] However, CPB provides better cardiac support, stability, and flow rates, although cannulation techniques more often tend to be central rather than peripheral.

There are no clear guidelines available on the use of CPB as a treatment for severe overdose. Moreover, CPB is expensive with numerous technical difficulties. We therefore examined the literature with regard to its to counteract temporary severe cardiac dysfunction use once conventional measures have failed. Our review focused on the following: the overdose drug in question, mechanism of toxicity, patient characteristics, variables related to CPB, clinical outcome, and associated morbidity.

LITERATURE SEARCH

We searched for relevant articles published between 1976 and 2004. We performed a MEDLINE/PubMed search combining the heading ''cardiopulmonary bypass'' with the following keywords: ''overdose'', ''poisoning'', ''intoxication'', ''cardiotoxicity'', and ''accidental ingestion''. The MeSH headings were ''overdose'', ''poisoning'', and ''cardiopulmonary bypass''. Ovid, EMBASE, and the Cochrane database were also searched

Abbreviations: CPB, cardiopulmonary bypass; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation

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with these headings. In addition, the PubMed feature ''related articles'' was used to identify further relevant publications.

DATA EXTRACTION AND VALIDATION OF THE STUDIES

The data of interest were:

- type and dose of drug overdose
- cardiopulmonary bypass variables (time interval between incident and initiation of CPB, total bypass time)
- comorbidities present, other types of treatment undergone by the patient, and associated morbidity and mortality.

Articles reporting on the same patients were excluded. For each study we noted the first author, year of publication, and study type. The validity of the studies was also taken into consideration by assessing the source and strength of the evidence using the US Preventative Services Task Force method[12]:

- Grade A—there is good evidence to support the recommendation
- Grade B—the strength of evidence is ''fair''
- Grade C—there is insufficient evidence to conclude for or against.

SEARCH RESULTS

The search produced a total of 16 articles, and these were reviewed for relevance. One case report was excluded as ECMO was used instead of CPB[13] and another was excluded as intoxication with digoxin was described in a case involving the use of CPB.[11] Therefore a total of 15 articles were reviewed.[4–7 9 10 14–22] We were unable to identify controlled trials of any type in the literature on the subject of treatment of overdose using CPB. Of the 15 relevant articles identified, 7 were case reports,[4–7 9 18 21] 2 were animal studies,[19 20] 2 were letters[17 22] and 4 were reviews of current management of overdoses,[10 14–16] which were not felt to be pertinent to a formal review of current literature. The seven case reports were about both deliberate and accidental ingestion of cardiotoxic drugs, including flecainide, verapamil, diltiazem, digoxin, and prajmalium bitartrate, and one iatrogenic intravenous injection of bupivacaine.

OVERDOSE AND USE OF CPB IN EXPERIMENTAL ANIMAL STUDIES

Larkin *et al*[19] in 1992 performed a prospective randomised controlled trial in pigs and showed successful application of CPB to support the circulatory collapse secondary to an infusion of amitsiptyline. Refractory cardiotoxicity and hypotension in the control group led to accumulation of the tricyclic antidepressant in the intravascular space. In the CPB supported group perfusion to the brain and heart was maintained as well as hepatorenal blood flow to permit ongoing drug clearance. Freedman *et al* in 1982[23] achieved similar successful supportive CPB resuscitation following lidocaine administration in dogs. The results were encouraging.

The main drawback of these studies is that CPB was started very early compared with in humans, so that the timeframe chosen is not clinically applicable. In practice it takes longer to determine if a patient is truly refractory, and it would definitely take longer to arrange CPB.

OVERDOSE AND USE OF CPB IN HUMANS (CASE REPORTS)

The seven case reports were of three males and four females; one patient was a boy aged 2 years and the remainder were

Table 1 Patient demographics and presentation details for the case reports included in the present review

Authors	Drug	Dose (mg)	Sex	Weight (kg)	Age (years)	Other agents taken at time of overdose	Comorbidity	ECG findings prior to CPB
Holzer *et al* (1999)[6]	Verapamil	4800–6400	M	60	41	1 g diclofenac, 1 g thiamine, 5 mg vitamin B_{12}, 6.25 mg timolol; unknown quantity of vitamin B_6	None	Idioventricular escape rhythm, PEA
Corkeron *et al* (1999)[4]	Flecainide	4000	F	Not given	20	Alcohol, unknown amount of paracetamol	Asthma, PSVT	Broad complex tachycardia, PEA
Berhringer *et al* (1998)[7]	Digoxin	10	M	Not given	79	Nil	Not given	Idioventricular escape rhythm, fast atrial fibrillation, PEA
Yasui *et al* (1997)[5]	Flecainide130	Unknown	F	Not given	20	Nil	Not given	Idioventricular escape rhythm, agonal rhythm
Hendren *et al* (1989)[9]	Verapamil SR	1440	M	13.5	2	Nil	None	First degree heart block, third degree heart block
Pasic *et al* (2000)[18]	Prajmalium bitartrate	320	F	Not given	25	Nil	Not given	Bradycardia, PEA, ventricular fibrillation
Long *et al* (1989)[21]	Bupivacaine	75	F		27	Nil	None	Ventricular fibrillation

F, female; M, male; PEA, pulseless electrical activity; PSVT, paroxysmal supraventricular tachycardia; SR, slow release.

Table 2 Treatment, cardiopulmonary bypass details, and outcome of patients in the case reports included in this review

		Cardiopulmonary bypass								
Author	**Drug**	**Time to CPB (h/min)**	**Details**	**Flow (l/min)**	**Time on CPB (h)**	**Cardiac arrest duration (h)**	**Supportive measures during CPB**	**Complications**	**Time of first recovery (h)**	**Outcome**
Holzer *et al* (1999)[6]	Verapamil	8.10 from OD 3.5 from admission	Femoral cannulation	3.5 for 80 min then 3	5.5	3.8 after CPB initiated	Dopamine, theophylline, adrenaline, dobutamine infusions, charcoal 50 g	None	288 after OD first neurological reaction	Full recovery to active lifestyle
Corkeron *et al* (1999)[4]	Flecainide	5.15 from OD 5.0 from admission	Femoral cannulation	5	30	Not noted	CVH	Coagulopathy femoral nerve palsy, femoral DVT, renal impairment	6 after CPB, started responds to pain 11.25 after OD	Full recovery to active lifestyle
Berhinger *et al* (1998)[7]	Digoxin	5.17 from OD 0.37 from admission	Femoral cannulation	3 later reduced to 0.2	4	1.4	Anti-Fab 10×80 mg dopamine and adrenaline infusions, and activated charcoal repeated defibrillation	Not stated	None	Died 12 days after OD with ARDS and septic shock.
Yasui *et al* (1997)[5]	Flecainide	2.5 after OD 2 after arrival	Femoral cannulation	4	10	No arrest	Not specified	Haemorrhage at site of cannulation	None	Brain damage and renal failure, died 10 days later
Hendren *et al* (1989)[9]	Verapamil SR	12.45 after OD 9.45 after arrival	Not given	Not given	3.75	2 after starting CPB	Continued dopamine, amrinone, adrenaline, calcium gluconate infusions.	Severe hypotension 4 h after CPB stopped	None	Died 28 hours 30 minutes after OD
Pasic *et al* (2000)[18]	Prajmalium bitartrate	1.30 from OD	Ascending aorta cannulation	Not given	16.75	0.92	Forced diuresis, ultrafiltration. haemoabsorption with charcoal filter, gastric lavage, inotropes, inhaled nitric oxide, IABP	None	Not given	Mild ataxia, discharged 35 days later
Long *et al* (1989)[21]	Bupivacaine	1.75 from OD	Femoral and atrial	4.5	2.75	Not noted	DC cardioversion, AV sequential pacing, inotropes	Mild left leg dysaesthesia	Not given	Full recovery

ADR, adrenaline; ARDS, acute respiratory distress syndrome; CCU, coronary care unit; CVH, continuous venous haemofiltration; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; OD, overdose; PEG, percutaneous ethylene glycol; PSVT, paroxysmal supraventricular tachycardia; SR, sustained release.

20 to 79 years (table 1). All the patients had ingested antiarrhythmic drugs either deliberately or accidentally and had early signs of cardiovascular instability on presentation. Somewhat surprisingly only two patients[4 6] had ingested a cocktail of medication, which included a non-steroidal anti-inflammatory drug and β-blockers[6] and an unknown quantity of alcohol and paracetamol.[4] Prolonged cardiovascular instability (including arrhythmias varying from heart block to fast atrial fibrillation) combined with lack of response to conventional resuscitative measures prompted use of CPB. Four patients had experienced cardiac arrest prior to CPB and the remainder had arrhythmias (both first and second degree heart block).

Therapeutic measures included activated charcoal and gastric lavage (table 2), as well as liberal use of inotropic agents. More invasive measures included haemofiltration and ultrafiltration. Bolus drug doses and infusions (dopamine, adrenaline, calcium gluconate) failed to restore adequate circulation until CPB was initiated.[4 5] A specific antidote (digoxin specific Fab antibody) was administered during CPB in the patient with digoxin overdose. Time from overdose to CPB ranged from 1 hour and 30 minutes to 12 hours and 45 minutes (child with accidental overdose).

Four patients had percutaneous femoral cannulation and one had the ascending aorta cannulated. One patients was started on femoral but then had atrial cannulation to increase the flow of CPB. Duration of CPB ranged from 2.75 hours to 30 hours with an mean of 10.4 hours. Four patients required CPR, the longest time was in a survivor who required 3.8 hours of CPR. The overall average for the four patients was two hours.

Direct complications of CPB included coagulopathy (one patient); femoral nerve palsy (two patients); femoral deep vein thrombosis (DVT) in the patient who received 30 hours of CPB; haemorrhage at the cannulation site (one patient); and severe hypotension four hours after CPB cessation (one patient). In three patients no subsequent complications were reported.

With regard to outcome three patients died. These included those with overdoses of digoxin, flecainide, and verapamil. In two of these patients the duration of CPB was short (four hours and three hours and 45 minutes), although the 20 year old patient with flecainide overdose had an agonal rhythm and prolonged hypotension before 10 hours of CPB. The 2 year old child, who had the longest delay to CPB, died after 3 hours and 45 minutes of CPB; a comment was made in the case report that the device used did not permit prolonged support. The mean time of CPB of those who died was 5.9 hours with an mean time to presentation of 2.7 hours (30 minutes, 3 hours, and 3 hours 48 minutes).

Four patients made recovery to active lifestyle including one who experienced mild ataxia, presumably secondary to cerebral ischaemia. The mean time to presentation of these patients was 1.7 hours (range 15 minutes to 3 hours 5 minutes) and included the two longest durations of CPB (16.75 hours and 30 hours). In comparison to those who died, these patients had a much longer mean time of CPB at 17.4 hours.

DISCUSSION

This review provides insufficient evidence for or against the use of CPB as an effective treatment for severe cardiac impairment due to poisoning (grade C). We only managed to find cases reports of patients who subsequently underwent CPB. The lack of comparative studies is clearly due to firstly, the gravity and rarity of the clinical situation, and secondly, the nature of case report studies—that is, to present favourable outcomes from invasive procedures. Thus one would assume there have been cases of unsuccessful attempts which remain unreported. There may also be patients undergoing successful resuscitation with conservative measures only, therefore any conclusion from a literature review such as this is likely to be subject to publication bias.

Although in general such cases may be more common, case reports of severe cardiotoxic drug ingestion are uncommon, and in those reported there is a marked variation between the treatment regimens employed. CPB has successfully been used after cardiac insults, including cardiothoracic surgery and prolonged cardiac arrest, and for severe hypothermia unresponsive to more conventional measures.[6 24 25] However, uncertainty remains with regard to the management and indications for using CPB in severe drug overdose.

To date there are no systematic evaluations of prognostic indicators and treatment modalities for severe cardiotoxicity due to poisoning. All the patients in the case reports we reviewed received active comprehensive treatments and interventions on arrival to the hospital, with comprehensive investigations and monitoring. Of particular note were cardiac activity, episodes of prolonged hypotension prior to CPB, acidosis, and end-organ damage.

Many of the initial supportive measures, including inotropic agents and pacing, were noted to be ineffectual until CPB had been initiated.[5 13 18] As has been suggested, the efficacy of standard measures may improve as ingested drug serum levels decline. This decline may not simply be a reflection of the volume dilution when on bypass. Pharmacokinetic studies[26] suggest that rapid redistribution, and hence the noted fall in drug serum levels during supportive CPB, is assumed to be a reflection of drug metabolism and hepatic detoxification.[27] Despite poor biochemical markers, including abnormal liver function tests and the presence of coagulopathy, supportive treatment can still lead to full recovery.

The question arising is how long CPB should be continued in such patients and whether central or percutaneous bypass is preferable. The half-life of the drug ingested has correlated in some cases with the duration of CPB and the expected drop in levels to within the therapeutic range.[5 17 27] However, it is necessary to take into consideration the continued absorption of drug from the gut, which may be delayed by the presence of ileus. Improvement in antidote circulation is an additional benefit of CPB; Fab fragments have been reported to have a clinical effect by one hour after the end of the infusion, and with CPB previously refractory ventricular fibrillation was terminated within 30 minutes of the infusion.[7] We found only one case of open CPB (which was successful); in the remainder the percutaneous femoral approach was used. The latter does not require the chest to be opened and can be performed in the presence of ongoing external chest compression. Five patients treated by this route had a mean delay from cardiac arrest to CPB of just less than 80 minutes; three of these patients had distal circulatory compromise, of which one required a fasciotomy.[17]

Severe intoxication with antiarrhythmic drugs manifests early with cardiovascular instability and is subsequently often rapidly fatal.[28] Due to the rapid decline, and the nature of the ingestion not always being apparent, the number of patients who would potentially benefit from more invasive interventions is likely to be higher than is seen. Indeed the lack of equipment and expertise to carry out CPB may well be a limiting factor.

CONCLUSIONS

There is currently insufficient evidence to recommend CPB routinely in acute severe drug ingestion showing signs of cardiovascular insufficiency despite administration of conventional rescue measures. It is a potentially useful treatment modality because it provides adequate tissue perfusion—both

supporting the vital organs and permitting ongoing drug metabolism and antidote circulation. For CPB to be applicable in an emergency setting the femoral percutaneous route is relatively easier to initiate but a pre-primed, portable system needs to be developed to encourage and promote its application. Its use should be considered despite poor clinical and biochemical parameters, prolonged cardiac arrest, and delayed presentation as there is the potential for survival. However, a risk to consider is that patients may have already incurred significant hypoxic brain damage prior to initiation of CPB. Urgent and safe clinical assessment of candidates for CPB as a treatment for poisoning induced cardiotoxicity is therefore essential.

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