

Peripheral vascular resistance and angiotensin II levels during pulsatile and non-pulsatile cardiopulmonary bypass*

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ABSTRACT The effects of pulsatile and non-pulsatile cardiopulmonary bypass (CPB) on levels of peripheral vascular resistance and plasma angiotensin II (AII) have been studied in 24 patients submitted to elective cardiac surgical procedures. Twelve patients had conventional non-pulsatile perfusion throughout the period of CPB (non-pulsatile group), while 12 had pulsatile perfusion during the central period of total CPB, using the Stockert pulsatile pump system (pulsatile group). There were no significant differences between the groups in respect of age, weight, bypass time, cross-clamp time, or in mean pump flow or mean perfusion pressure at the onset of CPB. Peripheral vascular resistance index (PVRI) and plasma AII levels were measured at the onset of total CPB and at the end of total CPB. In the non-pulsatile group PVRI rose from 19.6 units to 29.96 units during perfusion. In the pulsatile group PVRI showed little change from 20.89 units to 21.45 units during perfusion ($P < 0.001$). Plasma AII levels (normal < 35 pg/ml) rose during perfusion from 49 pg/ml to 226 pg/ml in the non-pulsatile group. The rise in the pulsatile group from 44 pg/ml to 98 pg/ml was significantly smaller than that in the non-pulsatile group ($P < 0.01$). These results indicate that pulsatile cardiopulmonary bypass prevents the rise in PVRI associated with non-pulsatile perfusion, and that this effect may be achieved by preventing excessive activation of the renin-angiotensin system, thus producing significantly lower plasma concentrations of the vasoconstrictor angiotensin II.

The physiological superiority of pulsatile perfusion over conventional non-pulsatile cardiopulmonary bypass (CPB) has been acknowledged for many years, though acceptably reliable pulsatile pump systems have not, until recently, been widely available. We have, in previous studies, reported our initial experience using the Stockert pulsatile pump system in clinical cardiac surgical procedures, and have shown that this system produces acceptable pulsatile arterial flow with a low index of haemolysis (Maxted *et al*, 1978; Taylor *et al*, 1978a) and have shown its metabolic superiority in comparative studies of pituitary-adrenal stress responses (Taylor *et al*, 1978b, 1978c).

Previous studies have commented not only on the metabolic advantages but also on the fact that pulsatile perfusion appeared to prevent the pro-

gressive rise in peripheral vascular resistance (PVR) associated with non-pulsatile CPB (Mandelbaum and Burns, 1965; Dunn *et al*, 1974; Hoar *et al*, 1976; Stinson *et al*, 1977). Although this haemodynamic difference with pulsatile CPB is well recognised, the mechanism for the change in PVR pattern has not been identified.

In recent studies the role of the renin-angiotensin system, and particularly the substance angiotensin II (AII) in the generation of the vasoconstriction associated with open-heart surgery, has attracted considerable interest. Angiotensin II is a powerful vasoconstrictor (Folkow *et al*, 1960; Sancetta, 1960; Oelkers *et al*, 1975) and a previous study showed a pronounced rise in plasma AII levels during non-pulsatile CPB (Taylor *et al*, 1977). A subsequent study showed a highly significant correlation between the rise in PVR during non-pulsatile CPB and the quantitative rise in plasma AII levels (Taylor *et al*, 1979a). Increased

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plasma renin activity has also been reported during non-pulsatile CPB by Favre *et al* (1976) and Roberts *et al* (1977).

The present study was designed to investigate the effects of pulsatile and non-pulsatile CPB on both peripheral vascular resistance and plasma AII levels in patients undergoing cardiopulmonary bypass during open-heart surgery.

Patients and methods

Twenty-four adult patients admitted for elective open-heart operations were arbitrarily allocated to pulsatile or non-pulsatile study groups. In the pulsatile group seven patients had valve replacements and five had coronary artery bypass grafting. In the non-pulsatile group six patients had valve replacements and six had coronary artery bypass grafting.

The preoperative and operative details for both groups are shown in table 1. There were no significant differences between the groups in respect of age, weight, body surface area, core temperature on bypass, mean perfusion pressure, or mean pump flow at the onset of CPB. Total bypass time and aortic cross-clamp times were also similar. A standard anaesthetic regimen was used in all cases—that is, induction with sodium pentothal and maintenance with nitrous oxide, oxygen, and intravenous morphine. A Temptrol bubble oxygenator was used in all cases, and a 40 μ Ultipor screen filter was placed in the arterial return line. The bypass circuit was primed with 2 litres Ringer’s lactate solution. The Stockert cardiopulmonary bypass pump was used in both groups, according to the following protocol:

Non-pulsatile group—Pump in non-pulsatile mode throughout the period of perfusion.

Pulsatile group—Pump in non-pulsatile mode

until left ventricular ejection ceased. Thereafter, pump in pulsatile mode, at 72 pulses/min until left ventricular ejection restarted. Pump reverted to non-pulsatile mode until end of perfusion.

The pump flow in both groups was maintained on the calculated flow of 2.2 l m⁻²/min and the haematocrit maintained between 20 and 25%.

Normothermic bypass was used in both groups, and myocardial protection was achieved using topical hypothermia and the injection of a cardioplegic solution into the aortic root. Measurements of peripheral vascular resistance index (PVRI) and plasma AII were obtained on full pump flow at the onset of total CPB when left ventricular ejection ceased (CPB 1 sample) and on full flow at the end of total CPB before left ventricular ejection restarted (CPB 2 sample). The pump flow at these times was therefore non-pulsatile in both groups. Peripheral vascular resistance index (PVRI) was calculated according to the formula:

$$PVRI \text{ (Index Units)} = \frac{MAPB - CVP}{CO \div BSA}$$

MABP = Mean arterial blood pressure (mm Hg)

CVP = Central venous pressure (mm Hg)

CO = Cardiac output (l/min)

BSA = Body surface area (m²)

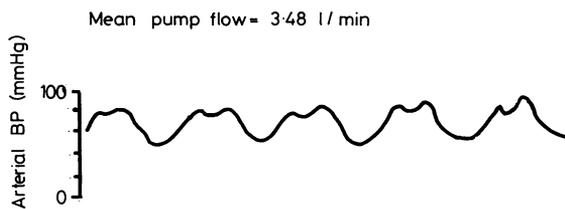
As the measurements were made on total bypass, the cardiac output was considered to be the bypass pump output, the pump having been previously calibrated to an accuracy of ±3%. Body surface area was obtained from height-weight nomograms. Arterial blood pressure was measured via a radial artery cannula and central venous pressure from a superior vena caval cannula inserted at the start of operation. An example of the typical radial artery wave-form achieved with the Stockert pump in the pulsatile mode is shown in the figure.

Plasma AII was measured by the radio-immunoassay technique of Dusterdieck and

Table 1 Preoperative and operative details in pulsatile and non-pulsatile groups (Mean ± SEM)

	Non-pulsatile	Pulsatile	t	p
Age (yr)	46.80 ± 3.20	45.30 ± 4.10	0.2884	< 0.8
Weight (kg)	67.30 ± 4.90	65.20 ± 5.10	0.2969	< 0.8
Body surface area (m ²)	1.71 ± 0.24	1.69 ± 0.28	0.0542	> 0.9
<i>Perfusion details</i>				
Core temp (°C)	36.80 ± 0.9	36.60 ± 0.7	0.1754	> 0.9
Mean arterial pressure (mm Hg)	65.60 ± 3.2	60.20 ± 2.8	1.2700	< 0.3
Mean pump flow (l/min)	3.75 ± 0.5	3.71 ± 0.4	0.0625	> 0.9
Total bypass time (min)	92.30 ± 9.0	88.20 ± 7.8	0.3443	< 0.8
Cross-clamp time (min)	47.30 ± 5.5	51.30 ± 7.4	0.4338	< 0.7

$$kPa = \frac{mm \text{ Hg}}{7.5}$$



Radial artery pressure wave-form in patient on total cardiopulmonary bypass using pulsatile mode of Stockert pump system. Mean pump flow = 3.48 l/min.

McElwee (1971). The antibody used in the radioimmunoassay cross-reacted 100% with (Ileu⁵)—AII and 100% with the (Ileu⁵) analogues of its C-terminal heptapeptide, hexapeptide, and pentapeptide fragments. The antibody cross-reacted less than 0.6% with (Ileu⁵)—angiotensin I. All values were corrected for a recovery of 83%. Statistical analyses were carried out using Student's *t* test.

Results

The levels of peripheral vascular resistance index are shown for both groups of patients in table 2.

Table 2 *Peripheral vascular resistance index values in pulsatile and non-pulsatile groups (Mean±SEM)*

Patient group	CPB1	CPB2	ΔCPB
Non-pulsatile group (n=12)	19.60±0.9	29.96±1.4	10.36±0.8
Pulsatile group (n=12)	20.89±0.8	21.45±0.9	0.56±0.7
t value	1.0713	5.1132	9.2191
P	<0.3	<0.001	<0.001

CPB1=Measurement at onset of total cardiopulmonary bypass.
 CPB2=Measurement at end of total cardiopulmonary bypass.
 ΔCPB=Change in peripheral vascular resistance during total cardiopulmonary bypass.

In the non-pulsatile group PVRI rose during perfusion from 19.6 units±0.9 SEM to 29.96±1.4 SEM at the end of total CPB. The rise in PVRI during perfusion (ΔCPB) was 10.36 units±0.8 SEM.

In the pulsatile group, PVRI levels at the onset of CPB were identical with those in the non-pulsatile group. There was, however, no significant rise in PVRI levels by the end of the period of perfusion. CPB 1 levels were 20.89 units±0.8 SEM and CPB 2 levels were 21.45 units±0.9 SEM. ΔCPB for PVRI was 0.56 units±0.7 SEM in the pulsatile group.

Comparison of PVRI levels between the groups indicates that both the CPB 2 levels and ΔCPB are highly significantly less in the pulsatile group, compared to the non-pulsatile group (*P*<0.001).

Plasma AII levels for both groups of patients are shown in table 3 (normal levels=<35 pg/ml). In the non-pulsatile patients plasma AII levels at the onset of CPB were somewhat raised at 49 pg/ml±15 SEM. As in our previous studies, plasma AII levels rose considerably during non-pulsatile CPB to 226 pg/ml±40 SEM. The mean rise in AII levels during bypass (ΔCPB) was therefore 177 pg/ml±33 SEM. In the pulsatile group plasma AII levels at the onset of CPB did not differ significantly from the CPB 1 levels in

Table 3 *Plasma angiotensin II levels (pg/ml) in pulsatile and non-pulsatile groups (Mean±SEM)*

Patient group	CPB1	CPB2	ΔCPB
Non-pulsatile group (n=12)	49±15	226±40	177±33
Pulsatile group (n=12)	44±9	98±16	54±14
t value	0.2858	2.9711	3.4313
P	<0.8	<0.01	<0.01

CPB1=Measurement at onset of total cardiopulmonary bypass.
 CPB2=Measurement sample at end of total cardiopulmonary bypass.
 ΔCPB=Change in plasma AII level during total cardiopulmonary bypass.

the non-pulsatile group. The rise in AII levels during the period of pulsatile CPB to a CPB 2 level of 98 pg/ml±16 SEM was significantly smaller than that found in the non-pulsatile group. The mean rise in AII levels during pulsatile bypass was 54 pg/ml±14 SEM. Statistical evaluation of the plasma AII levels showed significantly lower actual levels (*P*<0.01) and change in levels (*P*<0.01) in the pulsatile flow patients.

Discussion

The results of the present study indicate that pulsatile cardiopulmonary bypass prevents the rise in peripheral vascular resistance associated with non-pulsatile CPB. In addition, the pronounced rise in plasma AII levels occurring during non-pulsatile perfusion is not seen during pulsatile CPB.

Our findings are in agreement with several previous studies that have investigated the haemodynamic responses to pulsatile and non-pulsatile perfusion. McMaster and Parsons (1938) showed a significant reduction in lymph and capillary flow during non-pulsatile perfusion, and a return to normal when pulsatile flow was reintroduced. Similar results were found by Matsumoto *et al* (1971). A progressive rise in peripheral vascular resistance during non-pulsatile perfusion has been reported by several authors; again, the vasoconstriction was not seen during pulsatile perfusion (Shepard and Kirklin, 1969; Trinkle *et al*, 1969; Dunn *et al*, 1974). The present study, using the Stockert pulsatile system, confirms the prevention of progressive vasoconstriction during pulsatile perfusion.

The increase in vascular resistance during non-pulsatile perfusion has previously been linked to the release of vasoconstrictive agents into the circulation during non-pulsatile flow. Many *et al* (1969) reported increased plasma renin levels during non-pulsatile perfusion of the kidneys.

Favre *et al* (1976) and Roberts *et al* (1977) have subsequently confirmed the presence of raised plasma renin activity during non-pulsatile CPB. The demonstration of a pronounced rise in plasma AII levels during non-pulsatile CPB (Taylor *et al*, 1977) and the subsequent study correlating the rise in AII levels with the quantitative rise in peripheral vascular resistance (Taylor *et al*, 1979a) have focused attention on AII as a possible major causative factor in the vasoconstriction associated with non-pulsatile CPB. The present study has clearly shown that the prevention of excessive rises in PVRI produced by pulsatile CPB is associated with significantly lower levels of AII during the period of pulsatile CPB. It is not yet clear whether pulsatile perfusion acts directly on the kidney, reducing renin-activation, as suggested by the work of Many *et al* (1969), or whether pulsatility exerts a secondary effect on renin release via a neuroendocrine reflex pathway. Further studies are planned to elucidate the precise mechanism of renin release during non-pulsatile and pulsatile perfusion.

We have previously postulated a potential vicious circle (Taylor *et al*, 1977) whereby renin-angiotensin activation, associated with non-pulsatile CPB, produces a high plasma AII level which in turn increases PVR, with a consequent increase in left ventricular work. The prevention of excessive renin-angiotensin activation and undue rise in the plasma AII level would therefore seem to be advantageous in cardiac operations, where left ventricular efficiency is already prejudiced by co-existing cardiac disease and the period of myocardial ischaemia during aortic cross-clamping. Recent studies by Roberts *et al* (1978) and Taylor *et al* (1979b) have indicated that specific treatment to reduce plasma AII levels in the early post-bypass period is associated with a consistent fall in PVR and a consistent rise in cardiac output.

Prevention is, however, more acceptable than cure, and pulsatile CPB, in addition to its metabolic superiority previously reported, has, in the present study, been shown to keep PVR and plasma AII levels significantly lower than corresponding levels during non-pulsatile perfusion. These effects cannot be attributed to altered total flow or pressure, since mean pump flow and mean perfusion pressure were not significantly different at the onset of perfusion in both groups. It seems certain that pulsatility per se exerts a significant metabolic and haemodynamic effect, and that the routine use of a suitable pulsatile pump system of low haemolysis characteristics will be associated

with significant improvement in metabolic and haemodynamic response patterns in patients during open heart surgery.

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