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A Meta-Analysis of Renal Benefits to Pulsatile Perfusion in Cardiac Surgery

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Abstract: Multiple studies have evaluated the efficacy of pulsatile flow during cardiopulmonary bypass (CPB) showing controversial results. Suggested benefits to pulsatile perfusion include reducing the systemic inflammatory response syndrome associated with bypass, decreased need for inotropic support, shortened hospital stay, and superior organ preservation. This study aims to compare prior studies to determine if there is a significant difference in post-operative renal function with pulsatile perfusion compared to non-pulsatile perfusion during cardiac surgery. Studies included in the analysis were identified by searching keywords - pulsatile perfusion, pulse, pulsatile flow, cardiopulmonary bypass, and cardiac surgery. To maintain a homogenous sample, manuscripts were included if they met the following criteria: research was prospective in nature, subjects were human, paper contained documented baseline demographics, outcome data included markers of renal function. A meta-analysis was performed to compare post-op renal function between pulsatile and non-pulsatile perfusion groups. A total of 298 articles were screened. Ten articles met the criteria, of these, 477 patients underwent non-pulsatile perfusion while 708 received pulsatile perfusion during CPB. There was insufficient evidence to show a difference in mean post-operative creatinine or BUN between the groups, however, the pulsatile perfusion group had significantly higher creatinine clearance (standardized difference in means = 2.48, p = .004) and lower serum lactate levels (standardized difference in means = –2.08, p = .012) in the intensive care unit. This study found that there is great variability among pulsatile perfusion research. The methods to create and assess effective pulsatility on bypass varied widely among manuscripts. This analysis suggests that pulsatile perfusion during CPB is beneficial in renal preservation and should be considered. **Keywords:** pulsatile perfusion, pulse, meta-analysis, renal, kidney. *JECT. 2012;44:10–14*

Multiple studies have looked at the efficacy of pulsatile flow during cardiopulmonary bypass (CPB) and show controversial results. Advantages to pulsatile perfusion include a reduction of systemic inflammatory response syndrome and endocrine response associated with bypass, superior organ preservation as seen by better cerebral perfusion, decreased need for inotropic support, better myocardial function, less pulmonary edema and intubation times, greater urine output, and lower lactate levels post bypass (1–6). Disadvantages may include greater hemolysis and gaseous micro emboli production when pulsatile perfusion is used (7,8). The practice of pulsatile perfusion during CPB is accomplished using either an intra-aortic balloon pump, pulsatile roller pump, or a rotational pump, such as the Medos Deltastream (Stolberg, Germany). Pulsatile perfusion is quantified by pulse pressure or energy equivalent pressure (9,10). The energy equivalent pressure takes into account the hemodynamic energy gradient rather than a pressure gradient during each pulse cycle. The purpose of this meta-analysis is to compare prior studies published on the use of pulsatile perfusion during CPB to determine if there is a significant difference in post-operative renal function with pulsatile perfusion compared with non-pulsatile perfusion during cardiac surgery.

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METHODS

A literature search was performed using PubMed, Ovid, and Medline databases. The original keyword search included "pulsatile perfusion," "pulse, pulsatile flow," "cardiopulmonary bypass," and "cardiac surgery." No date restrictions

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were placed on the search. To maintain a homogenous sample, manuscripts were included if they met the following criteria: research was prospective in nature, subjects were human, paper contained documented baseline demographics, and outcomes data included markers of renal function.

The following data were extracted from each study meeting the inclusion criteria: first author, year of publication, study type, number of subjects, method of pulsatile perfusion, demographics data, and outcomes data. Demographics data included preoperative creatinine, preoperative creatinine clearance (CrCl), preoperative blood urea nitrate (BUN), cardiopulmonary bypass (CPB) time, cross clamp time, and mean arterial pressure (MAP) on bypass. Outcome data was retrieved wherever possible on the following variables of interest: intensive care unit length of stay, hospital length of stay, creatinine, CrCl, BUN, systemic vascular resistance (SVR), and serum lactate levels.

A meta-analysis was performed using Comprehensive Meta-Analysis version 2.2 (Biostat, Englewood, NJ) for Windows (Microsoft Corp, Redmond, WA). Data are expressed as standardized difference in mean and standard error. A random effects model was used when heterogeneity of effect sizes was present.

RESULTS

A total of 298 articles were initially identified by the keyword search. Ten articles met the inclusion criteria (Table 1). In these 10 studies, a total of 708 patients received pulsatile perfusion during bypass and 477 underwent non-pulsatile perfusion.

Table 1. Articles included in meta-analysis.

Article	Pediatrics or Adults	Sample Size (PP/NP)	Method of Pulsatility
Badner et al., 1992 (11)	Adults	27/26	Roller pump
Louagie et al., 1992 (12)	Adults	50/50	Roller pump
Poswal et al., 2004 (13)	Adults	50/50	Roller pump
Onorati et al., 2005 (14)	Adults	20/20	IABP
Alkan et al., 2006 (15)	Pediatrics	25/25	Roller pump
Alkan et al., 2007 (16)	Pediatrics	151/64	Roller pump
Onorati et al., 2007 (17)	Adults	50/50	IABP
Onorati et al., 2009a (18)	Adults	40/40	IABP
Onorati et al., 2009b (19)	Adults	87/71	IABP
Akcevin et al., 2010 (20)	Pediatrics	208/81	Roller pump

PP, pulsatile perfusion; NP, non-pulsatile perfusion; IABP, intra-aortic balloon pump.

The standardized difference in means was used to determine significant difference. There was no significant difference between groups for pre-operative creatinine, CrCl, CPB time, or cross clamp time (Table 2). The on-bypass MAP was significantly lower in the pulsatile group ($p = .03$), however the difference was less than 2 mmHg.

Data did not show a significant difference in means between groups for post-operative creatinine, BUN, or SVR. Post-operative CrCl was significantly greater with pulsatile perfusion (Z = 2.88, standardized difference in means = 2.48, standard error = .86, range .79–4.16, $p < .01$) (Figure 1). There was also a significant reduction in post-operative serum lactate levels with pulsatile perfusion (Z = –2.52, standardized difference in means = –2.079, standard error = .83, range –3.7–.46, $p = .01$) (Figure 2). Studies using an intra-aortic balloon pump to generate pulsatile perfusion had more favorable results than other methods.

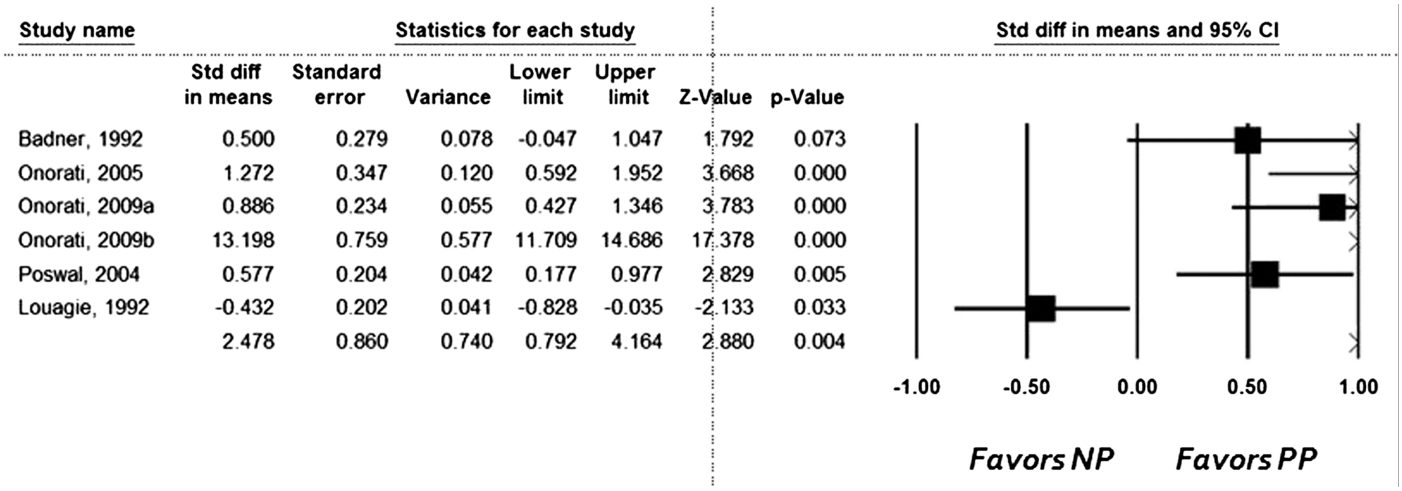
DISCUSSION

There are many physiologic alterations that occur during bypass that can lead to renal dysfunction including exposure of blood to a foreign surface, hemodilution, hypothermia, and non-pulsatile blood flow. During CPB, hemodilution is often used to reduce homologous blood requirements and decrease blood viscosity, while hypothermia is used to protect organs by lowering oxygen consumption, thus allowing for decreased perfusion flows during hypothermia (21). Hypothermia and hemodilution tend to act as opposing forces in relation to blood viscosity. Similarly, as hemodilution decreases oxygen-carrying capacity, hypothermia decreases oxygen demand. An animal study, by Utley et al., comparing the effects of hypothermia and hemodilution on blood flow, oxygen delivery, and renal function found that both hypothermia and hemodilution decrease MAP, reduce blood flow in the outer and inner renal cortex, and decrease oxygen delivery to the kidneys (22). Hemodilution was also found to increase urine output, thus being somewhat beneficial to kidney function.

Table 2. Demographic data.

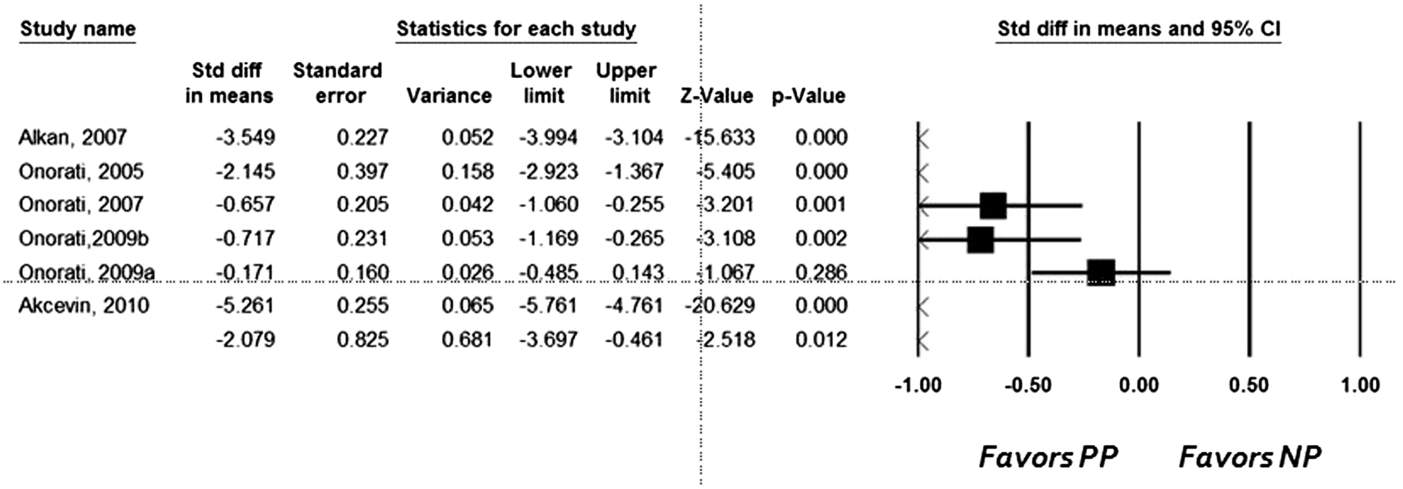
	PP (mean)	NP (mean)	Standardized Difference in Means	Standard Error	Significance
Pre-op Creatinine (mg/dL)	.83	.85	–.01	.07	NS
Pre-op CrCl (mL/min)	70.6	70.1	–.3	.26	NS
CPB Time (min)	103.65	104.23	.11	.1	NS
XC Time (min)	65.33	64.95	.32	.24	NS
MAP (mmHg)	67.4	69.2	–.99	.46	.03

PP, pulsatile perfusion; NP, non-pulsatile perfusion; XC, cross clamp; NS, not significant.



Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Badner, 1992	0.500	0.279	0.078	-0.047	1.047	1.792	0.073
Onorati, 2005	1.272	0.347	0.120	0.592	1.952	3.668	0.000
Onorati, 2009a	0.886	0.234	0.055	0.427	1.346	3.783	0.000
Onorati, 2009b	13.198	0.759	0.577	11.709	14.686	17.378	0.000
Poswal, 2004	0.577	0.204	0.042	0.177	0.977	2.829	0.005
Louagie, 1992	-0.432	0.202	0.041	-0.828	-0.035	-2.133	0.033
	2.478	0.860	0.740	0.792	4.164	2.880	0.004

Figure 1. Meta-analysis results for postoperative CrCl. The standardized difference in means is represented as PP-NP, where PP = pulsatile perfusion, and NP = nonpulsatile perfusion.



Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Alkan, 2007	-3.549	0.227	0.052	-3.994	-3.104	-15.633	0.000
Onorati, 2005	-2.145	0.397	0.158	-2.923	-1.367	-5.405	0.000
Onorati, 2007	-0.657	0.205	0.042	-1.060	-0.255	-3.201	0.001
Onorati,2009b	-0.717	0.231	0.053	-1.169	-0.265	-3.108	0.002
Onorati, 2009a	-0.171	0.160	0.026	-0.485	0.143	-1.067	0.286
Akcevin, 2010	-5.261	0.255	0.065	-5.761	-4.761	-20.629	0.000
	-2.079	0.825	0.681	-3.697	-0.461	-2.518	0.012

Figure 2. Meta-analysis results for postoperative serum lactate levels. The standardized difference in means is represented as PP-NP, where PP = pulsatile perfusion, and NP = nonpulsatile perfusion.

Non-pulsatile perfusion may impact the kidney more than other organs because renin secretion is increased with non-pulsatile perfusion, which increases SVR during bypass and causes redistribution of intra-renal blood flow (23–25). Many studies have shown an increase in renin secretion during non-pulsatile flow, probably due to decreased renal pulse pressure stimulating the release of renin (26). This has a pronounced effect on the kidney and can lead to acute renal insufficiency or failure.

Other physiologic effects of non-pulsatile blood flow include release of catecholamines, vasopressin, and local tissue vasoconstrictors, resulting in vasoconstriction and increased afterload (27). It is suggested that there is a decrease in vasomotor reflexes in the aortic arch and carotid sinus with non-pulsatile perfusion, which may be a cause of increased SVR. Increases in SVR are also thought to occur due to the increased synthesis and release of endothelin by the vasculature onto smooth muscle cells (28). It is suggested that the release of endothelin may be associated with absence of pulsatile perfusion, as well as decreased pulmonary flow, stress of surgery, and thromboxane release from activated platelets (29). Other authors suggest that an increase in SVR may be caused by a decrease in hydraulic energy with non-pulsatile perfusion. This may cause loss of patency in the microcirculation of small arterioles and precapillary sphincters (30), which decreases perfusion and gas exchange at the capillary level. As a result, some ischemia occurs, which is represented by increased lactate levels and acidosis. Increased afterload has an additional deleterious effect on the heart as the cross clamp is removed and the left ventricle attempts to pump against increased SVR (31,32). Some studies show

improved cardiac function in patients with pulsatile perfusion compared with non-pulsatile perfusion (33).

Studies suggest that increased serum lactate levels during and after bypass are an independent predictor of morbidity and mortality after pediatric and adult cardiac surgery (34,35). Prior studies have shown a decrease in tissue oxygen pressure and an increase in lactate levels with non-pulsatile perfusion (36). We hypothesized that when peripheral perfusion and organ perfusion on bypass is improved by implementing pulsatile perfusion, the tissues will be able to extract more oxygen and thereby produce less lactate. This study suggests that pulsatile perfusion provides a benefit to renal function compared with non-pulsatile perfusion as seen by decreased lactate levels and increased CrCl in the pulsatile perfusion group.

There were several limitations to this study. Studies included used different modalities of pulsatile perfusion, both pediatric and adult studies were used, and quantification of pulsatile perfusion was not always reported. The studies used in this meta-analysis did not follow the same hypothermia (28–33°C) or homologous blood transfusion protocols, which may have influenced the final outcome. However, within the analysis there was approximately an even number of patients in the pulsatile and non-pulsatile groups represented from each study. Additionally, publication bias always exists, with researchers tending to publish positive results more often than insignificant findings.

CONCLUSION

This study found that pulsatile perfusion results in greater creatinine clearance and reduced post-operative lactate levels compared with non-pulsatile perfusion, suggesting that pulsatile perfusion is beneficial in renal preservation and increases oxygen delivery to the tissues. In the studies included in this meta-analysis, patients received pulsatile or non-pulsatile perfusion without regard to their individual risk for renal failure. We hypothesize that selected patients at a high risk for renal failure following cardiopulmonary bypass may especially benefit from the use of pulsatile perfusion to maximize renal blood flow.

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