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Review Article

Pulsatile Perfusion during Cardiopulmonary Bypass: A Literature Review

Aileen Tan, MBBS;* Caroline Newey, MSc;† Florian Falter, MD, FRCA, FFICM, PhD*

**Department of Anaesthetics and Intensive Care, Royal Papworth Hospital, Cambridge, United Kingdom; and the †Department of Clinical Perfusion, Royal Papworth Hospital, Cambridge, United Kingdom*

Abstract: The use of cardiopulmonary bypass (CPB) in cardiac surgery has often been associated with postoperative organ dysfunction. Roller and centrifugal pumps produce non-pulsatile flow (NPF) by default, and this still is the most widely used mode of perfusion. The development of pulsatile pumps has allowed comparisons to be made with NPF. Pulsatile flow (PF) mimics the arterial pulse generated by the heart and is thought to be more physiological by some. This review aims to examine the proposed mechanisms behind the potential physiological benefits of PF during CPB and to summarize the current clinical evidence. MEDLINE and EMBASE were used to identify articles published over a 25 year period from 1995 to 2020. A literature review was conducted to determine the effects of PF on organ functions. A total of 44 articles were considered. Most of the articles published on PF were randomized controlled trials (RCTs). However, there was a wide variation in study methodology, method of pulse generation and how pulsatility was measured. Most of the evidence in favor of PF showed a marginal improvement on renal and pulmonary outcomes. In these studies, pulsatility was generated by an intra-aortic balloon pump. In conclusion, there is a lack of good quality RCTs that can inform on the short- and long-term clinical outcomes of PF. Further research is required in order to draw a conclusion with regards to the benefits of PF on organ function. **Keywords:** cardiopulmonary bypass, pulsatile, perfusion, cardiac surgery. *J Extra Corpor Technol. 2022;54:50–60*

More than one million cardiac surgical procedures are performed each year worldwide (1). The majority of cases are done on cardiopulmonary bypass (CPB), which affords the opportunity to operate in a bloodless field on a quiescent heart, while maintaining systemic perfusion and oxygenation. The use of CPB is not without risk and its use has often been associated with postoperative organ dysfunction. Considerable efforts have been made to identify organ-protective strategies, pulsatile flow (PF) on CPB has been identified as one of them.

Roller and centrifugal pumps produce nonpulsatile flow (NPF) by default, and this still is the most widely used mode of perfusion. However, it is also possible to mimic the arterial pulse generated by the heart, which is thought to be more physiological by some (2). This PF can be generated during CPB by the use of pulsator devices within the circuit (3) or by modifying the arterial pump itself to rapidly accelerate and decelerate, thus generating pulsatility (4). A further method, whereby pulsatility is generated outside of the extracorporeal circuit is through the use of an intra-aortic balloon pump (IABP) (5). There is evidence both in favor of and against PF reducing the systemic inflammatory response and protecting renal, cerebral, pulmonary, hematological, and myocardial function. The 2019 EACTS/EACTA/EBCP guidelines on CPB in adult cardiac surgery recommended that pulsatile perfusion should be considered for patients at high risk of adverse lung and renal outcomes, while recognizing the lack of strong evidence for beneficial effects (6). Concerns that PF modes may also have deleterious effects have persisted, with some evidence that in some CPB circuits, it may increase levels of hemolysis (7). In view of the continuing controversy over the use of PF, this review aims to summarize the suggested physiological mechanisms by which PF may benefit patients, and examine the current clinical evidence surrounding the use of PF during CPB.

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Address correspondence to: Aileen Tan, Royal Papworth Hospital NHS Foundation Trust, Cambridgeshire, CB2 0AY, Cambridge, United Kingdom. E-mail: aileen.tan@nhs.net
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EFFECTS OF PF AND NPF

Under physiological conditions, pulsatility is generated by the beating heart and is an intrinsic feature of the cardiovascular system. This alternating cycle of pressure and flow generates different hemodynamic forces, such as pulse pressure, cyclic shear stress, and cyclic stretch, which are sensed at cellular level and lead to a variety of physiological responses (8,9). The endothelial glycocalyx (EG) is a primary sensor of shear stress and is vital for the production of endothelial nitric oxide (NO) (10). NO maintains endothelial and vascular homeostasis, including regulation of vasomotor tone, vascular permeability and is an important antioxidant (11). Additionally, the EG plays a critical role in modulating inflammatory responses, acting as a physical barrier to leukocyte recruitment and extravasation (12). Loss of pulsatility may induce endothelial injury, demonstrated by EG degradation and shedding, which lasts for up to 3 days after an average of about 100 minutes of NPF bypass (13).

NPF is associated with systemic release of catecholamines, vasopressin, and endothelin, as well as increased renin secretion. Together with reduced NO production, this may result in increased systemic vascular resistance and reduced organ perfusion (14–17). Other authors have speculated that NPF may lead to a reduction in Surplus Hemodynamic Energy (SHE, see below) below a critical closing pressure, causing loss of patency within capillaries, thus reducing tissue perfusion (18).

At least in theory, PF avoids the detrimental effects of NPF on the endothelium. A number of animal studies have demonstrated improved blood flow through liver, kidneys, and stomach following cardiogenic shock, when utilizing pulsatile bypass-support (19,20), although a later publication does not support these findings (3).

DEFINITIONS OF PULSATILITY

Pulsatility has traditionally been defined as the arterial pressure pulse (PP) (see Equation 1) (21).

$$\text{PP (mmHg)} = [\text{AoP}_{max} - \text{AoP}_{min}] \quad (1)$$

where AoP_{max} is the maximum systolic pressure (mmHg) and AoP_{min} is the minimum diastolic pressure (mmHg).

An alternative definition of pulsatility is the pulsatility index (PI) (see Equation 2). The PI is a dimensionless parameter, relating maximum and minimum flow to mean flow.

Measuring it requires the use of ultrasound catheters or transonic flow probes and is more difficult to obtain clinically (22).

$$\text{PI} = \frac{V_{max} - V_{min}}{V_{mean}} \quad (2)$$

where V_{max} is the maximum blood flow velocity (cm/sec), V_{min} is the minimum blood flow velocity (cm/sec), and V_{mean} is the mean blood flow velocity (cm/sec).

Although usually sufficient as measures of pulsatility, these equations are inadequate for quantifying the hemodynamic energies associated with different perfusion modes because the generation of PF depends on energy gradients rather than pressure or flow gradients alone (23,24).

The energy-equivalent pressure (EEP) has been proposed as a measurement to calculate differences between steady-state and pulsatile blood flow (see Equation 3). It is based on the ratio between the area under the hemodynamic power curve and the area under the pump flow curve (22).

$$\text{EEP (mmHg)} = \frac{\int Q * P * dt}{\int Q * dt} \quad (3)$$

where Q is the pump flow rate (l/min), P is the arterial pressure (mmHg), and dt is the change in time at end of flow and pressure cycles.

The difference between EEP and mean arterial pressure (MAP) is known as SHE and represents the additional energy in a pulsatile waveform compared with a nonpulsatile one with the same mean pressure and flow (see Equation 4).

$$\text{SHE}\left(\frac{\text{ergs}}{\text{cm}}\right) = 1332 \times [\text{EEP} - \text{MAP}] \quad (4)$$

EEP should be higher than MAP; however, with complete NPF, the values equalize. When this occurs, the SHE also becomes 0, whereas in the normal human heart, the SHE is approximately 10% of the MAP (24,25). It is this energy loss that may compromise microcirculatory flow.

Newer heart–lung machines (HLM) do not rely on having to insert a pulse generator into the circuit but allow perfusionists to apply pulsatile settings to the arterial pump flow by just pressing one button, allowing PF to be used routinely during CPB if so desired. The components of PF comprise

- base flow, or the nonpulsatile component of stroke volume;
- the pulse width, or the percentage of each cycle that is spent in "systole"; and
- the frequency, or number of pulsatile cycles per minute.

Although settings that produce flows with a PP > 15–20 mmHg are considered pulsatile, the waveforms may not resemble those produced by the heart or generate significant SHE levels, and it has been recommended that hemodynamic energy levels be quantified

when investigating the effects of PF (26). Low base flows and smaller pump widths have been reported to generate better pulsatility; however, this requires faster pump accelerations that may increase hemolysis (27). This may be mitigated by using higher cycle frequencies (28). Although pumps that synchronize with ECG do exist, existing research on clinical outcomes focuses on the use of PF solely during the cross-clamp period (29). The components of the extracorporeal circuit may also affect the quality of pulsatility generated. The oxygenator, arterial filter, circuit tubing, and arterial cannula all create resistance and shear stress and may thus not only reduce the hemodynamic energy generated but also increase hemolysis under pulsatile conditions (30,31). Increased pressure drops at the pump inlet and across the oxygenator occur during PF, which may induce the cavitation of air dissolved in solution; it has been noted that roller pumps functioning in pulsatile modes produce an increased number of gaseous microemboli, levels of which are known to affect morbidity and neurological dysfunction (32,33). Performance of the cannula is also affected by PF, with a study employing computation flow dynamics, showing that PF significantly enhanced turbulence, blood velocities, and aortic wall shear stress in blood exiting the cannula (34). However, regulatory requirements currently do not demand that circuit components are tested under PF conditions.

METHODOLOGY

The Embase and Medline databases were searched to identify studies published between 1995 and 2020 in April 2020. The Medical Subject Heading (MeSH) terms and/or text words used were "PF" or "pulsatility" or "pulsatile" and "CPB" or "cardiac surgical procedure" or "cardiac surgery." We included clinical trials, case-control, and cohort studies published in English. Bibliographies of the selected studies were screened for additional eligible papers. We looked at studies comparing the effects of PF and NPF on organ functions both during and after CPB. Pediatric studies and animal studies were excluded.

Studies were screened for eligibility by the three authors. The following variables were extracted from the studies: study population, number of patients, method of generating pulsatility, method of quantifying pulsatility and outcomes. Comparisons were made between PF and NPF in patient groups undergoing cardiac surgery requiring the use of CPB. Methodological quality of all included studies was assessed according to the following criteria: adequacy of randomization and comparability between the intervention group and control group, description of the method of generating pulsatility, outcome measurement, and adequacy of follow-up in clinical trials (see PRISMA chart in Figure 1).

EFFECT OF PF ON ORGAN FUNCTION

Renal

Presumably due to the ease of measuring, urine output is a frequently used parameter in trials comparing PF and NPF. Only one study (35) showed any increase in urine output in the PF group, the remainder reported either lower urine output with PF or no significant difference (36–40).

Serum creatinine or creatinine clearance (CrCl) have also been used for numerous trials comparing different modes of flow. Of four studies utilizing roller pumps (36,38,39,41), only one (38) found a significantly improved CrCl at 48 hours post-CPB with PF, whereas all other studies did not report differences. One study including 46 patients and using centrifugal pumps reported preserved CrCl in the PF group compared to a statistically significant decrease in the NPF group (42). In the same study, patients in the PF group were also found to have lower levels of neutrophil gelatinase associated lipocalin (NGAL) postoperatively. A similar study using centrifugal pumps in 32 patients found no difference in levels of NGAL and other biochemical markers of kidney injury between the two groups (40). One study of roller pumps also investigated levels of NGAL, with lower levels in the PF group where cross-clamp time exceeded 45 minutes (39).

A small number of studies involving roller pumps investigated the effect of pulsatility on renal function and incidence of renal injury (37,43,44). None of these found any difference between NPF and PF, including in a group of patients with preexisting renal dysfunction (44). A recent large, retrospective analysis of incidence of acute kidney injury (AKI) defined by the Kidney Disease: Improving Global Outcomes (KDIGO) criteria following the introduction of PF also failed to show any reduction in risk, even where bypass or aortic cross-clamp time were prolonged (45). KDIGO is widely used as a tool to stratify renal injury (46) and also offers bundles of interventions to improve renal outcomes in medicine (47).

The picture changes when an IABP is used to provide pulsatility. In a series of trials by Onorati et al., patients undergoing coronary artery bypass grafting following preoperative IABP insertion consistently showed improved renal function where the IABP was used to generate PF during CPB (48–52). Subgroup analysis of the larger studies, including up to 500 patients, showed an overall increased eGFR and reduced need for hemofiltration in

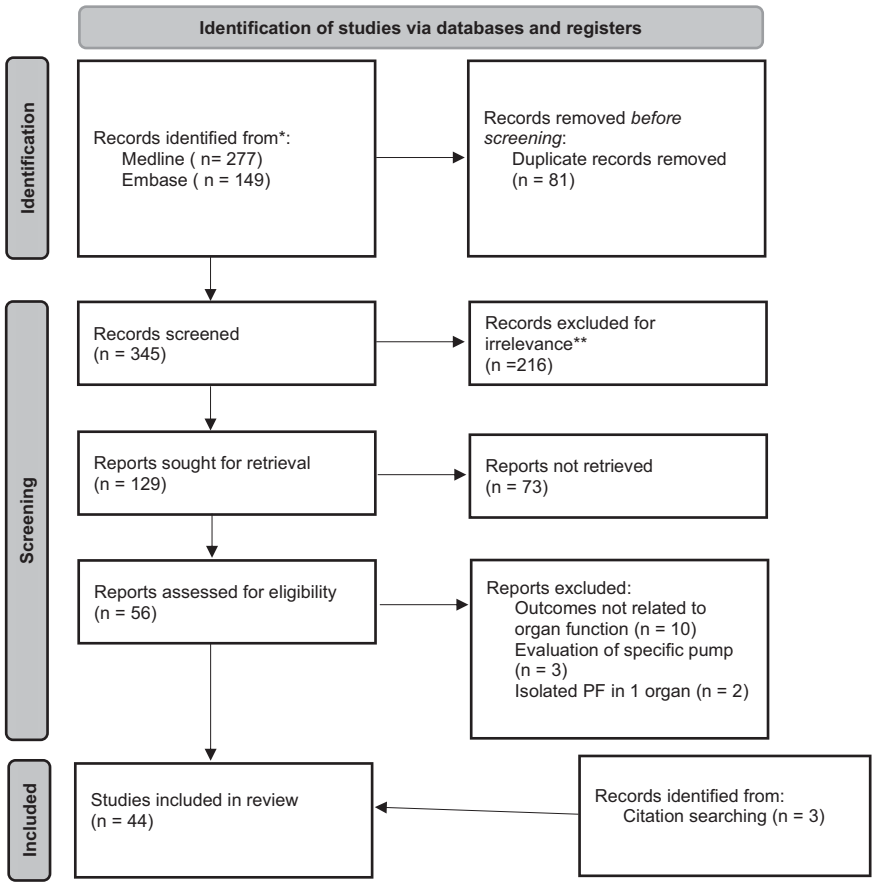

Figure 1. PRISMA flow diagram.

patients with preoperative Stage 3 Chronic Kidney Disease (CKD) (49,51).

A meta-analysis (53) analyzed 10 prospective clinical trials with 1,185 patients, including results from IABP-generated PF. The authors concluded that there was significant heterogeneity in effect sizes, but that PF resulted in lower lactate levels ($p = .012$) and higher postoperative CrCl ($p = .004$); although interestingly, there was no difference in serum creatinine levels. They also noted that the results from studies where an IABP was used were more favorable.

Another meta-analysis by Nam et al. (54) evaluated nine randomized trials involving 1,372 patients, which also included pump and IABP-generated pulsatility studies. The authors concluded that 1) levels of NGAL and incidence of renal failure were not affected by the type of flow, 2) a beneficial effect on postoperative serum creatinine levels ($p < .00001$) was only demonstrated where effective pulsatility, defined by SHE > 10% of MAP, was seen, and 3) CrCl was higher ($p < .0001$) and the incidence of AKI lower ($p < .00001$) when PF was used, although the incidence of renal failure was the same between groups.

Pulmonary

Most of the positive pulmonary outcomes were seen in studies that used an IABP to generate PF. Better PaO_2/FiO_2 ratio and chest radiograph severity scores were seen in the PF group as compared to the NPF group up to 48 hours postoperatively in these studies (49–51,55). Better lung compliance was also seen in the PF group up to 8 hours postoperatively (49–51,55). Higher postoperative oxygen tension-based indices, such as the alveolar to arterial oxygen tension differences ($P[A\text{-}a]O_2$), arterial oxygen tension to alveolar oxygen tension ratio (PaO_2/PAO_2), PaO_2/FiO_2 ratio, and respiratory index, were only achieved with PF in two out of four studies involving a centrifugal or roller pump (41,56–58). Two (57,58) out of three (56–58) of these studies reported a lower pulmonary vascular resistance with PF 15 minutes after the administration of protamine.

Only studies involving IABP-generated PF showed a shorter duration of mechanical ventilation in the PF group when compared to NPF (41,43,49–51,56,57,59). They also showed a reduction in the need for postoperative noninvasive ventilation (49–51). These results are in agreement with a meta-analysis conducted on the pulmonary effects of PF (60). It was noted that several

studies did not report if PF provided effective pulsation, defined by EEP or SHE (37,41,56,58). When analysis was restricted to studies with effective pulsatility, PF was seen to be reducing the duration of mechanical ventilation by a mean difference of 3.96 days (95% CI: −5.85 toe4 −2.08).

Splanchnic/Hepatic

Only studies with IABP-generated PF achieved significantly improved transaminases, lactate dehydrogenase (LDH), and bilirubin levels postoperatively compared to NPF (49–52). Intra- and postoperative serum lactate levels, however, were significantly lower when PF was generated with either IABP or roller pump (7,41,49–52,55,61).

Splanchnic blood flow and tissue oxygenation were investigated only in studies involving roller pumps and with conflicting results. Sezai et al. (41) showed no difference in blood flow through hepatic tissues between PF and NPF, whereas Mathie et al. (62) and Ohri et al. (63) demonstrated that PF resulted in improved gastric mucosal blood flow compared to NPF. This effect lasted from 10 minutes after commencing CPB until 60 minutes after weaning (41). Hamulu et al. showed that gastric mucosal pH was lower in the NPF group both during and after CPB, whereas it remained unchanged in the PF group (64).

Cerebral

Studies assessing postoperative cognitive dysfunction are difficult to compare because neither test battery nor time or interval of testing were standardized. Although all studies used roller pumps to generate pulsatility, outcomes were remarkably varied. Öztürk et al. found no difference in Mini Mental State Examination between patients after PF and NPF on postoperative day 3 (65). Conversely, Aykut et al. used the Montreal Cognitive Assessment test and found a statistically significant improvement in scores 1 month postoperatively in the PF group (66). This was in agreement with a study by Murkin et al. that also found significantly improved scores in both neurologic and cognitive function in the PF group at 7 days and 2 months postoperatively using the Western Perioperative Neurological Scale and subtests of the Wechsler Memory Scale, Adult intelligence Scale and Grooved Pegboard Test (67).

The three studies available reached different conclusions about the effect of PF on the rate of cerebrovascular accidents (CVA). One study found that patients with cerebrovascular stenotic lesions—≥75% stenosis or multiple premorbid cerebral infarctions—undergoing aortic surgery showed a lower incidence of CVA up to 54 months postoperatively when having had PF compared to a control group of patients with no significant cerebral lesions undergoing NPF (68). Conversely, Murkin et al. found no significant difference in the rate of CVA between PF and NPF in a similar cohort (37). A retrospective study even concluded that PF was an independent predictor for CVA after correcting for differences in demographic factors between groups with a stepwise logistic regression analysis (odds ratio of 1.91 [95% CI: 1.11–3.30]), propensity scoring (odds ratio of 2.22 [95% CI: 1.13–4.37]), and risk stratification (69). While the authors did not discuss possible mechanisms behind it, the increase in turbulent blood flow due to the creation of cyclic shear stress and stretch with PF may be a contributing factor.

Studies were in agreement, however, that the type of flow did not make a difference to near-infrared spectroscopy (NIRS) measured cerebral oxygenation, regardless of whether an IABP or roller pump was used (70,71).

Three studies using roller pumps showed no significant difference in S-100β protein and neuron-specific enolase as markers of cerebral injury (65,72,73).

Hematological

Studies investigating hemocoagulative responses to IABP-generated PF reported less derangement of hemoglobin and coagulation profile with PF. Patients undergoing PF had a slightly higher red blood cell count and significantly a higher hematocrit and platelet count in the first 48 perioperative hours compared to NPF patients. They also showed significantly less activation and consumption of the coagulation system (lower INR and aPTT levels) and less activation of the fibrinolytic system (higher fibrinogen and antithrombin-III activity, lower D-dimer levels). It was also noted that patients undergoing PF rapidly recovered normal fibrinolytic activity by 12 hours postoperatively (49–51,74). There were no differences between the flow mode groups with regards to hemoglobin, hematocrit, platelet count, and coagulation profile both intra- and postoperatively when a roller pump was used to generate PF (7,35,38,58).

Studies looking at chest drainage and transfusion requirements had conflicting results (38,40,43,49–51,61,74), with PF only achieving significantly lower chest drainage and transfusion requirements postoperatively when generated with an IABP (49–51,74).

It is difficult to conclude if PF resulted in a greater extent of hemolysis when compared to NPF, independent of the use of roller or centrifugal pumps. The method of generating PF varied among the studies, with two utilizing a centrifugal pump for both PF and NPF (40,75), two utilizing a roller pump for PF and a centrifugal pump for NPF (41,76), and two using a roller pump for both PF and NPF (35,58). Only one of the two studies that used a roller pump for both PF and NPF reported a significantly higher free plasma hemoglobin level that steadily increased during CPB in the PF group as compared to the NPF group (35,58). Red blood cell elongation index postoperatively was also not significantly

different between the flow mode groups when a centrifugal pump was used (40). A more recent study that used roller pumps to generate PF reported significantly higher heme and globin levels in the PF group (7). This study reported a significant increase in systolic pressure (190 mmHg vs. 257 mmHg, $p < .0001$) and pressure amplitude (34 mmHg vs. 152 mmHg, $p < .0001$) measured in the CPB circuit postoxygenator and suggested this as the mechanism for increased hemolysis.

Microcirculation and Inflammation

Studies looking at neutrophil activation produced conflicting results. Only studies that used an IABP showed a consistently lower white blood cell count with PF from the time of aortic cross-clamp release until 48 hours postoperatively (49,51,55,74). Studies that looked at biochemical markers of neutrophil activation also yielded conflicting results. Hyde et al. measured serum levels of complement receptor type 3 post-CPB up to 24 hours postoperatively and found no statistically significant difference between flow mode groups when a roller pump was used (77). Conversely, Driessen et al. found lower levels of plasma elastase bound to α1-proteinase inhibitor in the PF group 1 hour postoperatively, suggesting that the PF causes less neutrophil activation (56).

The vast array of biochemical markers used in the studies makes it exceedingly difficult to arrive at a conclusion about the effect of PF on inflammatory activation. Lower levels of endothelin-1 and IL-8 were seen post-CPB and until 18 hours postoperatively in a roller pump-generated PF group when compared to a centrifugal pump-generated NPF group (41,76). Bayram et al. found no difference in postoperative levels of IL-6, IL-8, and Tumor Necrosis Factor α (TNF-α) when comparing PF and NPF using roller pumps (73). Levels of IL-6, Vascular Endothelial Growth Factor (VEGF), and TNF-α at intensive care unit (ICU) admission were also similar between groups when a centrifugal pump was used (75). With IABP-generated PF, results varied depending on the inflammatory cytokine being investigated (49,51,59,78). Levels of IL-2, IL-6 (49,78), VEGF, and monocyte chemotactic protein-1 (51,59,78) were lower in the PF group just before release of the aortic cross clamp and until 48 hours postoperatively, although the difference in the levels of IL-2, IL-6, and IL-8 did not reach statistical significance in two studies (59,78). The same studies demonstrated that PF is associated with higher levels of the anti-inflammatory cytokine IL-10 at the end of surgery and up to 48 hours postoperatively (49,59,78).

Studies investigating the effect of type of flow on endothelial-derived products used roller pumps to generate PF. Although higher levels of endothelin (79), prostacyclin (79), nitrite, and nitrate (62) were seen intraoperatively with PF, the difference reached statistical significance for nitrite only in one study (80).

Several studies investigating microvascular perfusion used sublingual orthogonal polarization spectral imaging. PF from centrifugal pumps showed higher postoperative flow indices (75). However, when using a roller pump, only three (61,75,81) out of four studies (61,75,81,82) showed a higher proportion of normally perfused vessels in the PF group during CPB and up to 48 hours postoperatively.

In their systematic analysis, Hoefeijzers and colleagues (83) pointed out that the timing of assessments may contribute to the difference in outcomes. Studies that showed improvements in microvascular perfusion with PF took their samples after ICU admission (61,75,81), whereas the negative study made the assessment after only 10 minutes of PF (82).

Cardiovascular

Studies investigating cardiac performance after bypass are also heterogeneous in their methodology. Not only do they use different pumps and pulse generation, but the majority did not maintain MAP within similar limits in the flow mode groups (38,41,49,50,58,78).

In studies utilizing IABPs to generate pulse, the type of flow did not make a difference to the amount of vasoconstrictors and inotropes used intraoperatively (49,51,59,78). This is in contrast to the results of a roller pump study, which showed that fewer patients in the PF group required intraoperative inotrope support (35).

All studies agreed, however, that the type of flow has no effect on cardiac output both intra- and postoperatively (38,52,58,61,63,75,78,81).

Studies involving IABP-generated pulse are largely in agreement that PF does not have a beneficial effect on clinical outcomes such as incidence of new onset atrial fibrillation (59,78) and perioperative myocardial infarction (MI) (41,49,50,55,74) when compared to NPF (84). Only one study, which used roller pumps, found a significantly lower rate of MI and requirement for mechanical support with an IABP in the PF group (37). Postoperative markers of myocardial injury, such as Troponin I (41,50,52,55,74,78) or creatinine kinase (58), were similar between the flow mode groups.

Length of Stay

Studies were largely in agreement that the type of flow did not have an effect on length of hospital stay (40,41,43,51,52,55,56,59,65,74,78). Only three studies showed a significantly shorter length of hospital stay in the PF group (43,49,55).

Mortality

No significant difference in mortality was reported between flow mode groups in all (41,43,51,52,55,59,65,69, 74,78) but one study (37). In a randomized controlled trial involving 316 patients, Murkin et al. showed that the

overall in-hospital mortality was 2.8%, with eight out of the nine deaths occurring in the NPF group (5.1% vs. .6%, $p = .018$) (37). However, the analysis was not risk adjusted.

The sample size in most studies was <100 patients and they reported no mortalities (41,51,52,65,74,78).

The findings are similar to what was reported in a systematic review by Alghamdi et al. Six out of eight studies in that meta-analysis were rated as poor quality because they were underpowered to detect a mortality difference (85).

APPRAISAL OF EVIDENCE

The evidence evaluating the effect of PF during CPB is conflicting and studies are heterogenous, a fact that was noted in the three meta-analyses available on the subject (53,54,60). Forty-four studies were included and analyzed in this literature review, and are summarized in Table 1. There was a wide range of study designs, ranging from retrospective observational studies to prospective observational studies and randomized controlled trials.

The sample size of studies analyzed in this systematic review ranged from 14 to 1,959 patients. The majority of the studies did not include a sample size calculation and, hence, were not adequately powered to achieve statistical significance for their primary outcome. Only three studies by Elbers et al. and Onorati et al. (59,78,82) were powered to look at microcirculatory outcomes. Similarly, only studies by Kawahara et al., Murkin et al., and Ozturk et al. (65,67,70) were powered to look at neurological outcomes. Onorati et al. published one study that was powered to detect a difference in CrCl as a primary outcome (50).

The majority of RCTs did not report the method of randomization used. Few studies, such as the RCT by Murkin et al. (37,67), stratified patients by surgeons to account for differences in surgical technique. Very few studies included a comparison of significant baseline demographics to assess patients' risk. There is uncertainty whether intraoperative characteristics such as the duration of CPB time and aortic cross-clamp time are comparable between study groups.

Comparing studies is difficult as many use different pulse generators despite investigating the same outcomes. While the majority used roller pumps (7,37–39, 43–45,58,61,65–67,71,80,82,86), there are plenty of studies done with centrifugal pumps (40,42,56,57,75). Surprisingly, there are three studies comparing PF generated using a roller pump with NPF generated using a centrifugal pump (41,76,77). Where reported, the pulse frequency ranged from 50 to 80 beats per minute, with many studies not detailing the specifics of pulse generation.

The studies utilizing IABPs were done by the same group of authors from the same institution in Catanzaro, Italy, between July 2003 and February 2010 (48–52,55,59, 74,78), introducing a high probability of bias particularly considering the methodology and unclear randomization. The patients included in the studies were recruited at the same center and over the same time period and it therefore seems likely that there may be at least some overlap in the data between the different studies. The fact that an IABP is generally only inserted preoperatively in the sickest and most at risk patients (87–89) is very likely to cause a degree of selection bias; a recent meta-analysis of preoperative IABP use demonstrated that this may reduce short-term morbidity and mortality in high-risk coronary revascularization (90), introducing the potential for a high level of bias in these studies. We contacted the authors for clarification, but unfortunately did not receive a reply.

A number of these studies were included in the three meta-analyses of PF. While two stated that they excluded overlapping data (54,60), the other did not (53). In the absence of independent studies demonstrating a benefit for IABP-generated PF, these results are not compelling.

Few studies (40,49,51,57,82) reported the EEP or SHE, which is known to more accurately quantify hemodynamic energies associated with blood flow (91). Where pulse pressure was used to indicate pulsatility, this ranged from 15 to 45 mmHg (35–37,41,43,44). It is possible that studies that failed to show the beneficial effect of PF did not provide an adequate amount of pulsatility. Studies utilizing an IABP reported on significantly higher SHE generated with PF and this could be a plausible mechanism for why it is associated with better outcomes than pump-generated pulsatility. This may be due to damping by the CPB circuit components, estimated to reduce SHE levels by up to 80% (27). In contrast, the invasive nature of an IABP may prevent this energy loss. As mentioned previously, preoperative IABP insertion is generally reserved for the sickest and highest risk patients. The rate of complications associated with IABP has been reported to be as high as 50% (92), which makes it unviable as a routine intervention for pulse generation during CPB in low-risk patients.

Outcomes were not always reported adequately in studies. This ranged from not clearly defining primary and secondary endpoints, to not clearly stating the time period over which the outcome was being studied. Hoefeijzers et al. hypothesize in their systematic review that the heterogeneous outcomes may be due to humoral or inflammatory responses to CPB. The fact that they take time to manifest could account for the variation in results between studies measuring the same outcomes, but doing so at different points (83).

Table 1. Summary of the studies included in the review.

Author, Year	Study Type	Study Size	Adequate Randomization	Comparability of the Two Groups	Intervention Clearly Defined	Outcomes Clearly Defined	Measurement Validity and Reliability	Follow-Up Adequacy	Sufficiently Powered
Level I Evidence (large RCTs with clear-cut results)									
Ozturk et al., 2016 (65)	RCT	40	Yes	Uncertain	No	No	Yes	No	Yes, for cognitive function
Serraino et al., 2012 (51)	RCT	501	Yes	Yes	Yes	Yes	Yes	Yes	No
Murkin et al., 1995 (37,67)	RCT	316	Yes	Yes	No	Yes	Yes	Yes	Yes, for cognitive dysfunction
Elbers et al., 2011 (82)	RCT	16	Yes	Uncertain	Yes	Yes	Yes	Yes	Yes, for perfused vessel density
Kawahara et al., 1999 (70)	RCT	22	No	Yes	No	Yes	Yes	Yes	Yes, for internal jugular venous oxygen saturation
Onorati et al., 2009 (78)	RCT	40	Yes	Yes	No	Yes	Yes	Yes	Yes, for perioperative changes of MCP-1
Onorati et al., 2009 (49)	RCT	158	Yes	Yes	Yes	Yes	Yes	Yes	No
Onorati et al., 2010 (59)	RCT	40(60)	Yes	Yes	No	Yes	Yes	Yes	Yes, for cytokine levels
Onorati et al., 2009 (50)	RCT	80	Yes	Yes	No	Yes	Yes	Yes	Yes, for creatinine clearance
Level II Evidence (small RCTs with unclear results)									
Onorati et al., 2007 (48)	RCT	100	Yes	Yes	No	Yes	Yes	Yes	No
Ademir et al., 2012 (39)	RCT	85	Yes	Yes	No	Yes	No	Yes	No
Milano et al., 2015 (42)	RCT	46	Yes	Uncertain	Yes	Yes	Yes	Yes	No
Knothe et al., 1995 (79)	RCT	20	No	Uncertain	No	Yes	Yes	Yes	No
Koning et al., 2012 (75)	RCT	34	No	Uncertain	No	No	Yes	Yes	No
Lanzarone et al., 2009 (80)	RCT	18	No	Uncertain	No	Yes	Yes	Yes	No
Mathie et al., 1996 (62)	RCT	24	No	No	No	Yes	Yes	Yes	No
O' Neil et al., 2018 (81)	RCT	20	No	Yes	No	Yes	Yes	Yes	No
Ohri et al., 1997 (63)	RCT	24	No	Uncertain	No	Yes	Yes	Yes	No
O' Neil et al., 2012 (61)	RCT	20	No	Yes	No	Yes	Yes	Yes	No
Onorati et al., 2005 (52)	RCT	40	Yes	Yes	No	Yes	Yes	Yes	No
Onorati et al., 2006 (55)	RCT	50	Yes	Yes	No	Yes	Yes	Yes	No
Onorati et al., 2008 (74)	RCT	96	Yes	Yes	No	Yes	Yes	Yes	No
Orime et al., 1999 (76)	RCT	18	No	Yes	No	Yes	Yes	Yes	No
Poswal et al., 2004 (38)	RCT	100	No	Uncertain	No	Yes	Yes	Yes	No
Sezai et al., 2005 (41)	RCT	24	No	Uncertain	No	Yes	Yes	Yes	No
Song et al., 1997 (35)	RCT	70	No	Uncertain	No	No	Yes	No	No
Tarcan et al., 2004 (58)	RCT	19	No	Uncertain	No	No	Yes	Yes	No
Kusch et al., 2001 (72)	RCT	21	No	Yes	No	Yes	No	Yes	No
Aykut et al., 2013 (66)	RCT	148	No	Yes	No	Yes	No	No	No
Driessen et al., 1995 (56)	RCT	38	No	Yes	No	Yes	Yes	Yes	No
Engels et al., 2014 (57)	RCT	37	No	Yes	Yes	Yes	Yes	Yes	No
Gu et al., 2011 (40)	RCT	32	No	Yes	Yes	Yes	Yes	Yes	No
Hamulu et al., 1998 (64)	RCT	20	No	Yes	No	Yes	Yes	Yes	No
Hyde et al., 1997 (77)	RCT	14	Yes	Yes	No	Yes	No	Yes	No
Level III Evidence (cohort and case-control studies)									
Farid et al., 2016 (44)	Cohort	132	–	No	No	[38]	Yes	Yes	–
Takahara et al., 2000 (68)	Cohort	261	–	No	No	No	Yes	Yes	–
Tan et al., 2020 (7)	Cohort	62	–	Yes	No	Yes	No	No	–
Baraki et al., 2012 (43)	Cohort	1,959	–	No	No	No	Yes	Uncertain	–
Bayram et al., 2012 (73)	Cohort	32	–	Yes	No	Yes	Yes	Yes	–
Grubhofer et al., 2000 (71)	Cohort	14	–	Uncertain	No	Yes	Yes	No	–
Level IV Evidence (historical cohort and case-control studies)									
Coulson et al., 2020 (45)	Observational, retrospective	2,489	–	Yes	No	Yes	Yes	Yes	–
Tovedal et al., 2016 (86)	Observational, retrospective	20	–	Uncertain	No	No	Yes	No	–
Abramov et al., 2003 (69)	Observational, retrospective	1,820	–	No	No	No	Yes	Yes	–

MCP-1, monocyte chemotactic protein-1.

CONCLUSION

Although there is some indication that the use of PF during CPB may improve renal and pulmonary function, the effect on clinical outcomes appears to be marginal. Over the past decade, continuous-flow ventricular assist devices (CF-VADS) have replaced pulsatile devices (PF-VADS) for both long-term and short-term circulatory support. Although there are calls for renewed efforts to develop small, durable, and fully implantable PF-VADS (93), it is widely accepted that continuous-flow pumps are similarly effective as pulsatile ones (94). Moreover, much of the evidence in favor of PF comes from trials where pulsatility was generated by an IABP. Whether this suggests a particular benefit for a particular patient group or that an IABP provides sufficiently high levels of SHE to produce clinically detectable effects is

unclear. Extrapolating the results from these trials to a general cardiac surgical population and recommending the routine use of PF during CPB cannot be justified. However, based on the current evidence, it is safe to conclude that PF is noninferior to NPF.

Outcomes with NPF have steadily improved over the last years. It is unclear if routine PF can add value to our clinical practice and to the patient experience. What will be useful for clinicians is for future research to focus on identifying possible patient subgroups who may benefit from PF.

Further research into the physiology underlying PF is required to design suitable study protocols. A minimal reporting standard for studies involving PF has to be set to make outcomes comparable. These need to be in place to conduct good-quality randomized controlled and adequately powered trials that are able to inform on short- and long-term clinical outcomes.

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