Assessing Endothelial Responsiveness After Cardiopulmonary Bypass: Insights on Different Perfusion Modalities

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Objective: **Cardiopulmonary bypass (CPB) exerts several deleterious effects on inflammatory pathways. Most of these can be related to an endothelial insult leading to endothelial dysfunction. To date, the degree of endothelial damage only has been evaluated on a cellular and molecular level, but no studies exist looking at the functional effects of CPB on the endothelium.**

Design: **Previous studies hypothesized a negative effect of continuous flow as opposed to the physiologic pulsatile flow. The aim of the present retrospective study was to investigate how different perfusion modalities during CPB (ie, continuous *v* pulsatile flow) or its avoidance differently impact endothelial function.**

Setting: **Cardiovascular operating room and intensive care unit of a large tertiary University Hospital in Monza, Italy.**

Participants: **Flow-mediated dilatation (FMD) of the brachial artery was assessed in 29 patients undergoing elective myocardial revascularization. Ten patients receiving continuous-flow CPB, 10 receiving pulsatile-flow CPB, and 9 scheduled for beating-heart revascularization were studied.**

Interventions: **Patients were studied at baseline (after induction of general anesthesia), after CPB upon intensive care unit (ICU) admission after surgery, and on the first postoperative day before discharge from the ICU (on average, 24 hours after CPB discontinuation).**

Measurements and Main Results: **The continuous-flow CPB group demonstrated a significant reduction in FMD after CPB, (12.8% ± 9.7% *v* 1.6% ± 1.5%, $p < 0.01$), which lasted up to the first postoperative day (5.9% ± 4.1%). On the other hand, FMD did not change in the pulsatile-flow group (12.5% ± 10.5%, 11.0% ± 7.2%, and 16.6% ± 11.7%, respectively). FMD also was unaffected in the beating-heart group, thus suggesting a direct effect of CPB itself on endothelial function.**

Conclusions: **In conclusion, in this study population of adult patients undergoing elective coronary revascularization, continuous-flow CPB markedly impaired endothelial function, although this was not the case with pulsatile-flow CPB. This study posed the rationale for further investigations on the potential value of FMD to predict cardiovascular events in these patients.**

KEY WORDS: cardiopulmonary bypass, endothelial function, continuous flow, pulsatile flow, flow-mediated dilatation

THE DETRIMENTAL EFFECTS OF cardiopulmonary bypass (CPB) on inflammation pathways have been studied extensively, and a central role of the post-CPB inflammatory response in the pathophysiology of endothelial dysfunction has been emphasized repeatedly.[1–3] Several studies were performed in patients undergoing CPB to assess its pathophysiologic effects on endothelial function, but all investigated the cellular and molecular pathways involved, without a systematic detection of its functional correlates.

In this regard, the in vivo assessment of endothelial responsiveness by measuring the brachial artery hyperemic flow-mediated dilatation (FMD) is now viewed as a useful research tool for assessing cardiovascular evolution in patients with various degrees of cardiovascular risk.[4–9]

An application of the FMD technique in the clinical follow-up of CPB procedures may, therefore, appear appropriate for predicting the risk of future events. Previous studies hypothesized a negative effect of continuous flow as opposed to the more physiologic pulsatile flow. Considering that the major physiologic determinant of endothelium release of vasoprotective mediators is the laminar flow and consequent wall shear stress,[10] the influence of different perfusion modalities during CPB (ie, continuous flow *v* pulsatile flow) on the endothelial reactivity might represent important information concerning potential clinical drawbacks.

Based on these premises, the present pilot investigation was undertaken in a population of adult patients undergoing elective myocardial revascularization, with the aim to evaluate the effects of different perfusion modalities commonly employed in clinical practice on endothelial responsiveness during the postoperative intensive care unit (ICU) period. The authors particularly wanted to investigate the potentially negative effect of continuous-flow CPB on the endothelium and the protective influence, if any, of a more physiologic pulsatile-flow CPB.

METHODS

Study Population and Design

This was a retrospective study on prospectively collected data. All procedures were compliant with the ethical standards of the Helsinki Declaration and conformed to standards currently applied in Italy. All patients gave their informed consent to be enrolled in the study.

Twenty-nine adult patients with normal preoperative FMD, scheduled for elective cardiac surgery, were enrolled according to the following eligibility criteria: Age ≥ 18 years, elective cardiac surgery, isolated coronary artery bypass grafting, and patient's consent to participate in the study. Exclusion criteria

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were: Emergent/urgent surgery other than isolated coronary artery bypass grafting and patient denial. Major cardiovascular risk factors as part of the clinical scenario of surgical patients did not constitute, per se, exclusion from the study.

Of the 29 patients who were enrolled, 10 received continuous-flow CPB (CF-CPB), 10 pulsatile-flow CPB (PF-CPB), while 9 patients underwent beating-heart revascularization (off-pump coronary artery bypass [OPCAB]).

All patients were monitored before induction of general anesthesia, with an arterial catheter and a central venous catheter, for hemodynamic evaluation and blood sampling. General anesthesia was induced following institutional protocols with midazolam, 0.1 mg/kg, fentanyl, 4-6 μg/kg, and propofol, 2-3 mg/kg, and neuromuscular blockade was obtained with cisatracurium, 0.15-0.2 mg/kg.

FMD was evaluated at 3 time points (after the induction of general anesthesia, after ICU admission, and on the first postoperative day before ICU discharge to the ward (about 24 hours after CPB discontinuation).

Vascular Studies

Imaging studies of the brachial artery with a high-resolution ultrasound 11-MHz linear-array transducer (Kontron Imagic, France) were performed according to standard procedures.[11] Anatomic landmarks were noted on the clearest view of the artery, the skin was marked, and the transducer was held in position by a stereotactic clamp. Images were obtained by the same investigator throughout the study. The maximal change in diameter of the brachial artery during reactive hyperemia created by an inflated cuff (50 mmHg above systolic pressure for 5 minutes) on the forearm was used to assess vasodilation. Arterial diameter was measured in millimeters, coincident with the R waves on the electrocardiogram, for 6 cardiac cycles, and the 6 measurements were averaged. An individual who was blinded to the sequence evaluated the vasodilator response from repeated studies; images were stored in a video format and then analyzed with image analysis software. Flow velocity was assessed by pulsed Doppler, with the range gate (1.5 mm) in the center of the artery. The cuff was inflated for 5 minutes and then rapidly deflated. A 90-second scan was obtained immediately after deflation. Blood flow was calculated by multiplying the velocity-time integral of the Doppler flow signal by the cross-sectional area of the vessel and heart rate. FMD was calculated as the absolute and percent [(reactive hyperemia – baseline)/baseline × 100] maximal increase in diameter during reactive hyperemia compared with baseline (Fig 1).

Surgical Procedures

A Jostra HL30 heart-lung machine (Maquet Cardiopulmonary AG, Hirrlingen, Germany) with roller pumps was used in all cases, a cardiac index of 2.6 L/min/m^2 was maintained in all patients and, when pulsed flow was administered, a fixed rate of 80 beats/min with an augmentation of 50%, generating a sinusoidal flow pattern, was applied throughout aortic cross-clamping. At the end of surgery, patients were transferred to the cardiac ICU under general anesthesia.

Statistical Analysis

Data were analyzed with commercially available software (SPSS 17, SPSS Inc., Chicago, IL), by means of univariate ANOVA. Tukey's HSD test was used for post-hoc analysis. A t-test for independent measurements was used to compare CPB and cross-clamp times; p values below 0.05 were considered as significant. Data are reported as mean ± standard deviation, unless otherwise specified.

RESULTS

Table 1 reports the baseline characteristics of patients allocated to the 3 perfusion modalities. The 3 populations were homogenous for age and no statistical differences were noted in hemodynamics and cardiovascular risk factor distribution or in the preoperative use of medications with a known effect on endothelial function.

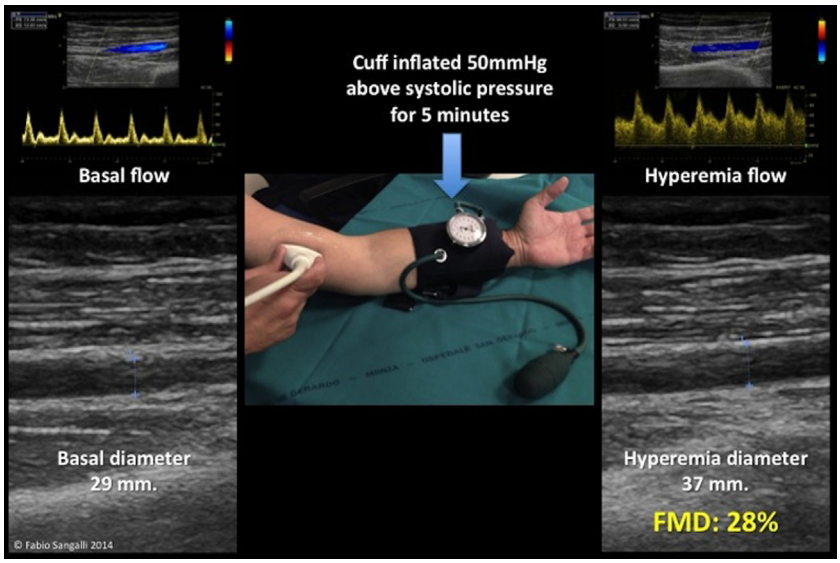

Fig 1. Schematic representation of the flow-mediated dilatation study protocol (see text for details).