

Partial Occlusion of the Descending Aorta Increases Cerebral Blood Flow in a Nonstroke Porcine Model

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Key Words

Cerebral blood flow · Cerebral perfusion augmentation · Partial aortic occlusion

Abstract

Background: We studied the effect of partial aortic occlusion on cerebral perfusion and cardiac performance using the intra-aortic NeuroFlo™ catheter. **Methods:** Adult pigs were instrumented to determine cardiac parameters; unique isotope-labeled microspheres were used to determine cerebral blood flow (CBF) before, during and after sequential partial aortic occlusion. **Results:** Six pigs were studied; there was no relevant change in cardiac output, and the desired pressure drop of 10–15 mm Hg across the balloons was achieved. CBF increased significantly with inflation of the suprarenal balloon and remained elevated 90 min after deflation. **Conclusions:** Partial aortic occlusion with the NeuroFlo catheter significantly increased cerebral perfusion without adversely affecting cardiac performance.

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Introduction

Acute ischemic stroke remains a critical health care issue, but treatment options are limited; despite approved drugs for thrombolysis and devices for thrombectomy, a majority of ischemic stroke patients cannot receive these therapies [1]. In addition, recanalization itself is limited as a therapy, as many patients experience only partial recanalization, rethrombosis occurs frequently, and proximal recanalization may increase the risk of hemorrhagic transformation [2]. Improving cerebral blood flow (CBF) to the ischemic tissue by means other than recanalization may avoid some of these limitations yet result in salvage of the ischemic penumbra. Cross-clamping of the abdominal or thoracic aorta has been shown, in both animal models and in clinical studies, to result in blood flow redistribution to the upper torso within minutes [3, 4]. Such studies of aortic manipulation led to the development of the NeuroFlo™ catheter, an endovascular dual-balloon catheter designed to partially occlude the abdominal aorta (fig. 1, CoAxia, Maple Grove, Minn., USA). A pilot feasibility study of NeuroFlo in treating ischemic stroke demonstrated qualitative perfusion augmentation [5, 6]. In addition, a study of patients with symptomatic vasospasm following aneurysm embolization demon-

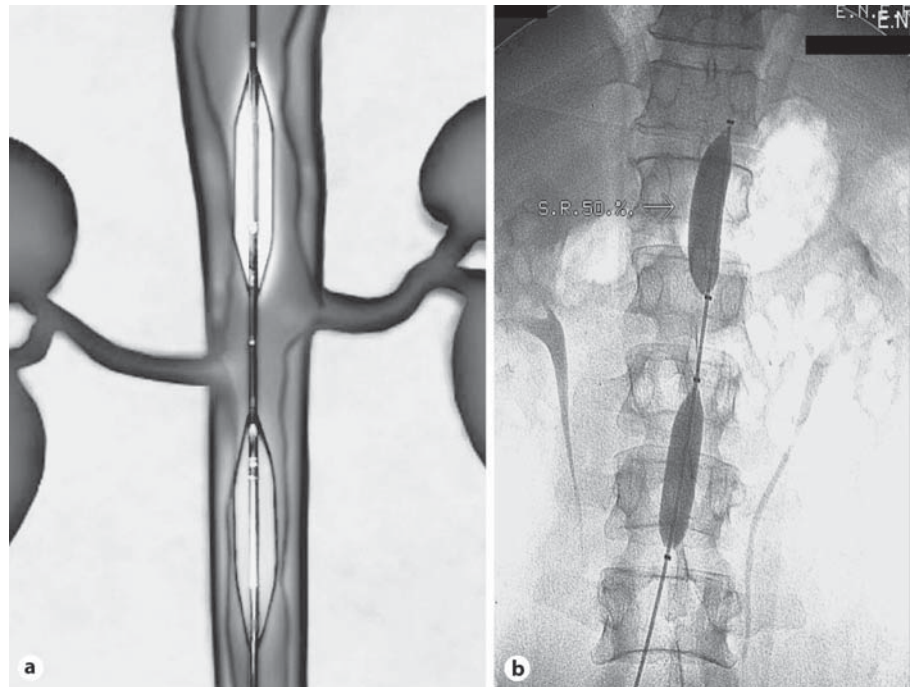


Fig. 1. NeuroFlo device. **a** Intended placement above and below the renal arteries. **b** Fluoroscopic image of the inflated NeuroFlo device.

strated that the NeuroFlo catheter increased blood flow velocities in the middle cerebral arteries, an increase which persisted in the majority of patients more than 24 h after the procedure [7].

The NeuroFlo catheter is currently being studied in the ongoing SENTIS (Safety and Efficacy of NeuroFlo for Treatment of Ischemic Stroke) Trial, a prospective, controlled, randomized, multicenter trial, comparing NeuroFlo treatment alone relative to medical management, for improving neurological outcome in stroke up to 14 h from onset.

Despite anecdotal reports of enhanced cerebral perfusion with the NeuroFlo device in the SENTIS Trial and in other feasibility studies [8, 9], there are no data that provide a quantitative measurement of the effect of partial aortic occlusion on CBF. Using a nonstroke porcine model, we sought to quantify the effect of partial aortic occlusion with the NeuroFlo device on CBF, using microsphere-determined regional blood flow, and to further investigate the effect on cardiac performance. The results should provide the basis for further studies in experimental models and the translation to clinical trials [10].

Materials and Methods

Experimental Design

Female domestic pigs were anesthetized and intubated. A pulmonary artery catheter was placed for determination of cardiac output and pulmonary arterial wedge pressure. The right femoral artery was cannulated with a 9-french sheath to permit NeuroFlo catheter placement, recording of infrarenal (IR) pressure through the sheath side-port, and recording of the suprarenal (SR) pressure through the central lumen of the NeuroFlo catheter. Using a minithoracotomy, the left atrium was cannulated for microsphere injection, and the left mammary artery was cannulated for the microsphere reference blood sample collection. The diameter of the aortic lumen was determined via angiogram above and below the renal arteries to determine the balloon volume estimated to achieve a 70% aortic occlusion.

Hemodynamic measurements were recorded (IR and SR systolic, diastolic and mean pressures, pulmonary arterial wedge pressure, cardiac output and heart rate), and microsphere injections were made at the following time points: (a) baseline (30 min after completion of all instrumentation); (b) 5 min after IR inflation; (c) 5 min after SR inflation; (d) 30 min after balloon inflation; (e) 30 min and (f) 90 min after balloon deflation. Cardiac output was determined by thermal dilution measurement performed in triplicate and averaged. After baseline measurements had been performed and the first microsphere injection performed, the dual-balloon NeuroFlo catheter was inserted through the femoral artery into the aorta as shown in figure 1. The independent IR and SR balloons were sequentially inflated to a volume anticipated to occlude 70% of the aorta and were then adjusted to achieve a pressure drop of 15 mm Hg across the balloons, i.e. to

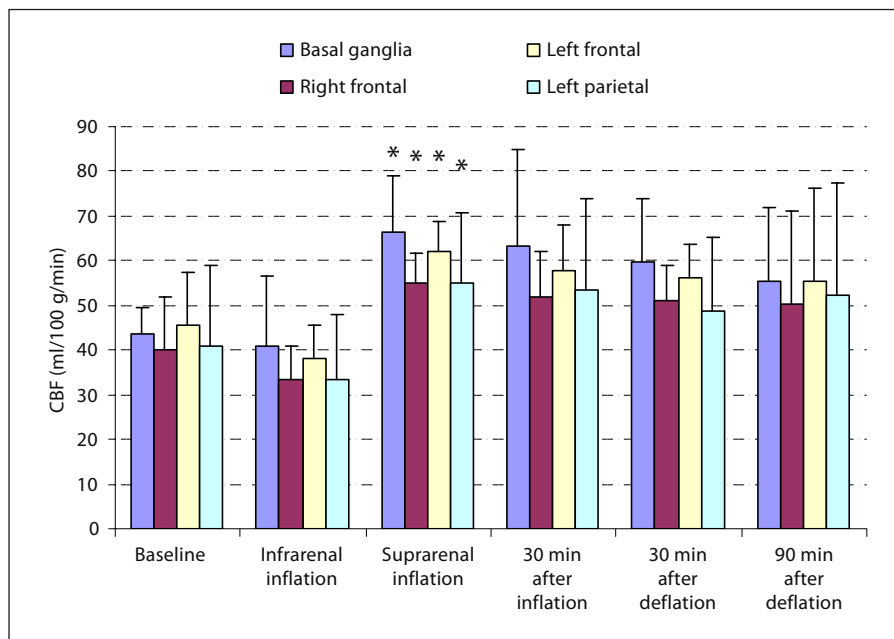


Fig. 2. CBF in the right frontal cortex, left frontal cortex, basal ganglia and parietal regions of the brain. Values shown are means \pm SD; * $p < 0.05$ when compared to baseline with no further subsequent change.

obtain a difference of 15 mm Hg above and below the device. Dual-balloon inflation was maintained for a total of 45 min, and then the device was removed.

Microsphere Injections and Reference Blood Samples

Approximately 14 ml of unique, stable isotope-labeled 15- μ m microspheres (Biopal™, Worcester, Mass., USA) were injected at each time point over 2–5 s via the left atrial catheter. Unique microspheres were used at each injection: (a) baseline – gold; (b) IR inflation – samarium; (c) SR inflation – lutetium; (d) 30 min of inflation – lanthanum; (e) 30 min after balloon deflation – yttrium, and (f) 90 min after balloon deflation – europium. Reference blood samples were collected beginning 15 s prior to microsphere injection and continuing for 2 min at a rate of 4.5 ml/min.

Measurement of Regional Blood Flow

Animals were euthanized with pentobarbital and autopsied. Representative samples of the brain (left and right cerebral cortex, basal ganglia and left parietal region), heart, gut, spinal cord, renal cortex and medulla, and upper and lower extremity muscles were removed, weighed and sent to Biopal for neutron activation and calculation of regional blood flow.

Statistics

Changes in blood flow over time were evaluated using a repeated-measures analysis of variance, accounting for correlation among multiple measurements in pigs over time. Baseline values were included as a covariate in these analyses, which were run both including and excluding the IR time point measurements. The overall change from baseline at subsequent time points was the basis for all reported p values, which were 2-sided with values less than 0.05 deemed significant.

Results

Six pigs completed all study procedures and were included in the analysis. As shown in table 1, there were no significant changes in cardiac output or pulmonary arterial wedge pressure associated with balloon inflation or deflation. There was a statistically significant albeit clinically irrelevant increase in SR mean arterial pressure and systemic vascular resistance, a modest decrease in heart rate, and the IR mean arterial pressure demonstrated the desired pressure decrease of 10–15 mm Hg (compared to SR or systemic pressure) associated with balloon inflation. These changes were seen at SR balloon inflation compared to baseline; no further significant change occurred to the end of the study.

Figure 2 demonstrates that CBF was significantly increased in all tested regions of the brain at SR inflation versus baseline; no other significant changes occurred in other tissue beds, including renal cortex and medulla (fig. 3). The increases in CBF seen with SR balloon inflation represented a 35–52% increase (basal ganglia 52.2%, right frontal cortex 36.2%, left frontal cortex 37%, parietal region 34.8%). Although there was a trend to return to baseline flows, the increased flows were maintained (and statistically unchanged) to 90 min after deflation. All tissue beds in the brain and kidneys showed a modest but insignificant decrease in blood flow after IR balloon inflation when compared to baseline.

Table 1. Hemodynamic changes associated with partial aortic occlusion with NeuroFlo

	Baseline	IR inflation	SR inflation	30 min after inflation	30 min after deflation	90 min after deflation
Heart rate, beats/min	85 ± 17	82 ± 17	80 ± 18 ^a	76 ± 17	74 ± 15	75 ± 12
Cardiac output, l/min	5.5 ± 0.5	5.3 ± 0.4	5.2 ± 0.5	4.9 ± 0.5	5.5 ± 0.5	5.2 ± 0.9
PAWP, mm Hg	9.5 ± 4.2	9.8 ± 4.9	9.9 ± 4.6	9.9 ± 4.9	10.4 ± 4.4	10.4 ± 4.1
SR MAP, mm Hg	70.5 ± 9.5	77.6 ± 14 ^b	77.6 ± 8.5	76.9 ± 7.8	74.8 ± 11.3	71.1 ± 9.3
IR MAP, mm Hg	70.5 ± 9.5	65.4 ± 8.5 ^c	61.9 ± 8.5	67.3 ± 8.7	74.8 ± 11.3	71.1 ± 9.3
SVR, dynes/s/cm ⁻⁵	891 ± 157	1,036 ± 209 ^d	1,052 ± 139	1,110 ± 170	932 ± 128	947 ± 129

PAWP = Pulmonary arterial wedge pressure; MAP = mean arterial pressure; SVR = systemic vascular resistance.

^a Decrease in heart rate at SR inflation compared to baseline ($p = 0.03$); no further significant change.

^b Increase in SR MAP from baseline to balloon inflation ($p = 0.003$); no further significant change.

^c Decrease in IR MAP from baseline to balloon inflation ($p = 0.001$); no further significant change.

^d Increase in SVR from baseline to balloon inflation ($p = 0.02$); no further significant change.

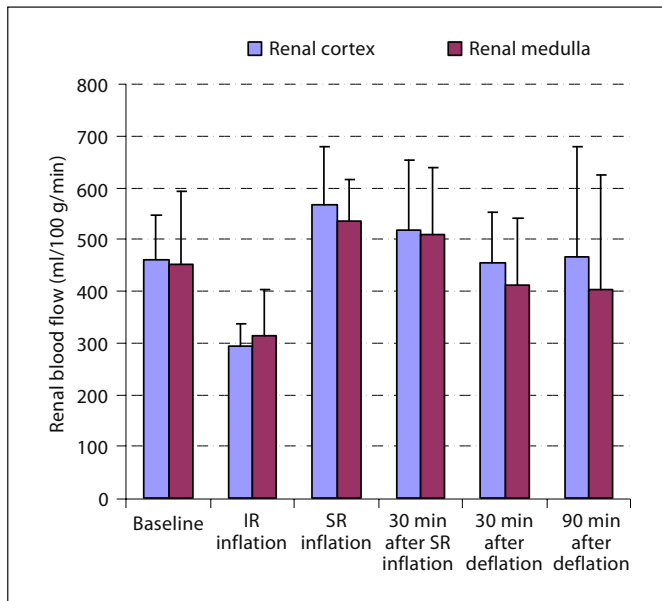


Fig. 3. Renal blood flow in the cortex and medulla before, during and after partial aortic occlusion with the NeuroFlo device.

Discussion

These data demonstrate that partial aortic occlusion with the NeuroFlo catheter increases CBF by 35–50%, and that this increase, presumably due to diversion of a portion of the cardiac output, is largely maintained to 90 min following balloon deflation. The effect appears to be

focused on CBF, as significant changes in blood flow were not seen in other tissue beds including the kidneys. In addition, this 30–50% increase in CBF was accomplished with only modest and arguably clinically irrelevant changes in cardiac parameters. Although the changes in heart rate (6% decrease from baseline), SR mean arterial pressure and systemic vascular resistance (a 10% and a 16% increase over baseline, respectively) achieved statistical significance, all values remained well within normal physiological limits. Further studies should be performed to elucidate the significance of these changes in patients with compromised cardiac function. However, it is likely that patients with mild cardiac dysfunction would tolerate the modest change in systemic vascular resistance induced by transient partial aortic occlusion; caution is appropriate in the selection of patients for this application.

Increasing CBF to treat ischemic stroke by means other than recanalization of the occluded artery has been attempted clinically in a variety of ways, including induced hypertension, hypervolemia and hemodilution. The effect of increased systemic blood pressure (either permissive or active hypertension) on CBF may be limited by cerebral autoregulation and may have deleterious cardiac effects [11, 12], since autoregulation is impaired in the first days after ischemic stroke [13].

A recent study by Ogoh et al. [14] supported the concept that CBF in humans increases as cardiac output increases. These researchers found a linear relationship between cardiac output and middle cerebral artery velocity at rest and during exercise, indicating that the cerebral vasculature is capable of accepting increased flow [14].

Although increasing cardiac output with hemodilution or hypervolemia should theoretically increase CBF, neither has demonstrated clinical success in randomized, controlled studies, and use of either therapy may be limited by the associated decreased oxygen-carrying capacity (hemodilution) and increased myocardial work (hypervolemia) [12]. In our porcine model, total cardiac output was not altered, but the proportion directed to the brain was increased. Because the increase in CBF in our study was achieved with minor effects on cardiac parameters, it appears that it is possible to increase cerebral perfusion using partial aortic occlusion without risking major alterations in cardiac performance.

The clinical implications of this study are intriguing. If partial aortic occlusion can increase cerebral perfusion to the ischemic penumbra, it may reduce infarct volume. In a study of embolic stroke in a rat model, Noor et al. [15] demonstrated that a 60-min period of partial aortic occlusion, with or without tissue-type plasminogen activator infusion, reduced final infarct volume, returned matrix metalloprotease levels to normal and reduced perfusion deficit without increasing hemorrhage rate.

Study Limitations and Conclusions

This study was not performed in a stroke model, and it remains to be shown that partial aortic occlusion can improve flow within and salvage the ischemic penumbra. Second, this study was concluded 90 min after balloon deflation, so the absolute duration of increased blood flow is not known. Finally, all animals studied had normal cardiac function; the cardiac effects of partial aortic occlusion may be different in the setting of cardiac compromise. However, this demonstration that partial aortic occlusion increases CBF by diversion of cardiac output provides encouragement for further clinical studies, including the ability of partial aortic occlusion to improve perfusion of the ischemic brain during acute stroke.

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