

Metabolism changes during direct revascularization in moyamoya disease: illustrative case

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BACKGROUND Cerebral revascularization is recommended for patients with moyamoya disease (MMD) with reduced cerebral perfusion reserve and recurrent or progressive ischemic events. The standard surgical treatment for these patients is a low-flow bypass with or without indirect revascularization. The use of intraoperative monitoring of the metabolic profile using analytes such as glucose, lactate, pyruvate, and glycerol has not yet been described during cerebral artery bypass surgery for MMD-induced chronic cerebral ischemia. The authors aimed to describe an illustrative case using intraoperative microdialysis and brain tissue oxygen partial pressure (PbtO₂) probes in a patient with MMD during direct revascularization.

OBSERVATIONS The patient's severe tissue hypoxia situation was confirmed by a PbtO₂:partial pressure of oxygen (PaO₂) ratio below 0.1 and anaerobic metabolism by a lactate:pyruvate ratio greater than 40. Following bypass, a rapid and sustained increase in PbtO₂ up to normal values (PbtO₂:PaO₂ ratio between 0.1 and 0.35) and the normalization of cerebral energetic metabolism with a lactate/pyruvate ratio less than 20 was observed.

LESSONS The results show a quick improvement of regional cerebral hemodynamics due to the direct anastomosis procedure, reducing the incidence of subsequent ischemic stroke in pediatric and adult patients immediately.

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KEYWORDS moyamoya disease; brain metabolism; cerebrovascular circulation; cerebrovascular physiology; hypoxic ischemia; intraoperative monitoring; oximetry

Moyamoya disease (MMD) is a steno-occlusive cerebrovascular disorder characterized by progressive occlusion of the bilateral intracranial internal carotid arteries and the formation of collateral circulation due to hypertrophy and proliferation of the lenticulostriate arteries.^{1,2} Surgical treatment is recommended for progressive or recurrent cerebral ischemic events with reduced cerebral perfusion reserve.^{3–10} Surgical armamentariums can generally be divided into direct and indirect techniques. Both aim to increase collateral blood flow to cortical hypoperfused areas and prevent further ischemic injury using external carotid circulation as the donor supply.^{3,11–20} Advantages of the direct technique using the superficial temporal artery (STA) as the donor vessel and a cortical middle cerebral artery (MCA) branch (M4) as the recipient vessel (STA-MCA direct arterial bypass) versus indirect revascularization are based on the early improvement in regional cerebral hemodynamics and the

immediate reduction in ischemic stroke events.^{21,22} The purpose of our article is to describe the case of a patient with MMD during direct revascularization that shows how surgery rapidly improves brain metabolism using intraoperative microdialysis and brain tissue oxygen partial pressure (PbtO₂) probes.

Illustrative Case

A 37-year-old woman with diagnosed MMD after an ischemic stroke underwent STA-MCA direct arterial bypass and indirect encephaloduromyosynangiosis (EMS) cerebral revascularization surgery. The case is the first of a series proposed for studying metabolic changes in revascularization surgery in patients with chronic cerebral ischemia, both in patients with MMD and in cases of symptomatic carotid occlusions undergoing intra-extracranial bypass. Preoperative

ABBREVIATIONS CSF = cerebrospinal fluid; EMS = encephaloduromyosynangiosis; LPR = lactate:pyruvate ratio; MCA = middle cerebral artery; MMD = moyamoya disease; SBP = systolic blood pressure; STA = superficial temporal artery.

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studies on the patient included (1) brain magnetic resonance imaging with T1- and T2-weighted, fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted sequences to identify ischemic and hemorrhagic lesions; (2) complete cerebral arteriography including both external carotids to define the degree of effect, according to the Suzuki classification²³; and (3) a ^{99m}Tc-single-photon emission computed tomography (SPECT) before and after acetazolamide administration to assess the cerebral vascular reserve status. Figure 1 shows the main neuroimaging studies of the patient.

Anesthetic Management

Anesthetic management was conducted by one of the authors. Upon arrival to the operating room, the patient underwent noninvasive monitoring, including electrocardiography, noninvasive blood pressure monitoring, and pulse oximetry. General balanced anesthesia was induced with fentanyl (2 µg/kg), propofol (2 mg/kg), and atracurium besylate (0.5 mg/kg). Following orotracheal intubation, end-tidal CO₂, esophageal temperature, central venous pressure, diuresis, Bispectral Index™ (BIS™) Monitoring System (Medtronic Covidien, UK), and continuous blood pressure through the radial artery were routinely monitored. The patient was positioned under a Mayfield skull clamp with a local anesthetic of 1% mepivacaine and 0.25% bupivacaine with

epinephrine (1:200,000) at equal volumes applied to the pin sites. A continuous intravenous perfusion of remifentanyl (0.1–0.2 µg/kg/min), atracurium besylate (0.3 mg/kg/hr), and 0.5 minimum alveolar concentration of desflurane was used to maintain anesthesia. Antibiotic prophylaxis was done with sulfamethoxazole and trimethoprim 1600/320 mg at least half an hour before the surgical incision. The fraction of inspired oxygen (FiO₂) was maintained at 0.5 throughout the surgical procedure. Volume-controlled assisted ventilation of 7 mL/kg tidal volume, with a positive end-expiratory pressure of 5 cmH₂O and a respiratory rate between 12 and 15 breaths per minute to maintain a partial pressure of arterial carbon dioxide (PCO₂) around 35 to 40 mm Hg. Crystalloids with balanced solutions were given intravenously to provide a central venous pressure of at least 5 mm Hg and a pulse pressure variation below 12. The highest preoperative systolic blood pressure (SBP) ± 20 mm Hg was used to maintain intraoperative SBP within range. The normovolemic state was maintained, and hypotensive techniques or hyperosmotic drugs were avoided. The use of vasoactive drugs was not necessary to reach the desired SBP.

Surgical Technique and Monitoring

The patient was positioned supine with the head turned parallel to the floor and fixed using a 3-pin headholder. A linear incision

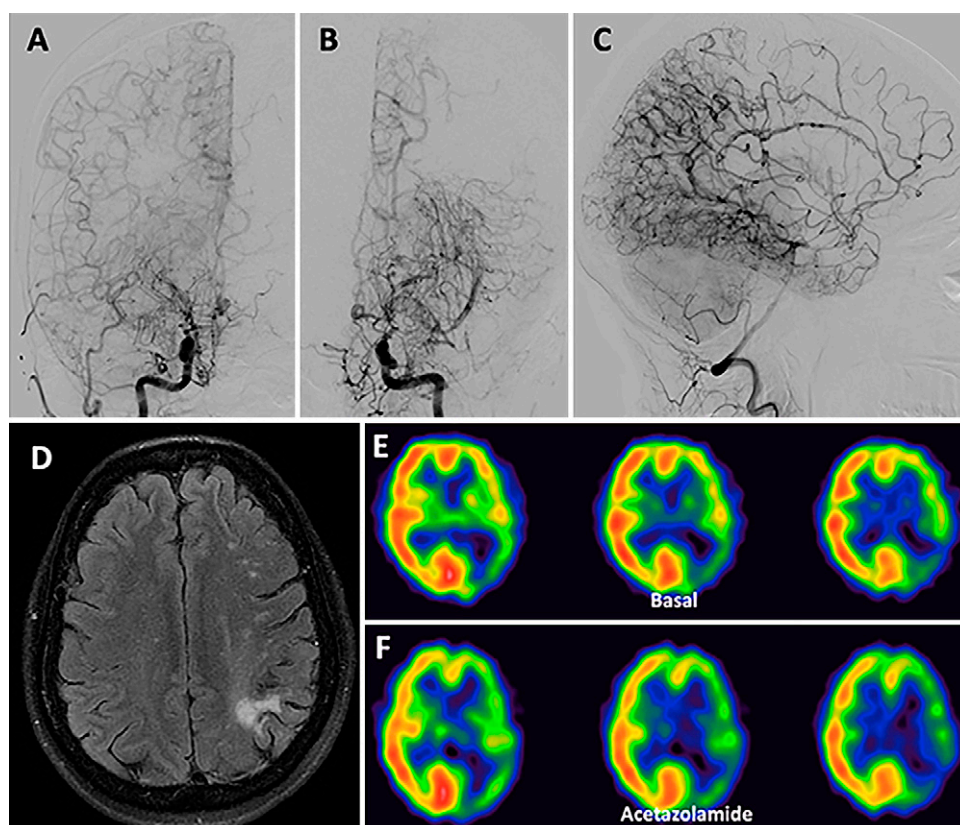


FIG. 1. Angiographic series (A–C) corresponding to the right internal carotid artery, left internal carotid artery, and left vertebral artery, respectively. Note stenosis of both terminal portions of the internal carotid arteries and an abnormal network of collateral vessels corresponding to an angiographic pattern of MMD of Suzuki stage 4. A T2-weighted dark fluid magnetic resonance (MR) slice (D) in which the acute ischemic lesion is detected. Brain single-photon emission computed tomography (SPECT) performed in basal conditions (E) and after the administration of acetazolamide (F). This study shows how the patient is in a pattern of hemodynamic failure.

was made from the zygoma to the superior temporal line over the identified vessel. Once dissected, the STA was left preserved until the recipient vessel was exposed. Subperiosteal dissection and elevation of the temporalis muscle were performed through a linear incision, and a small craniotomy was centered 6 cm above the external auditory canal around the sylvian fissure. Careful dura mater bony dissection and section were performed, preserving the middle meningeal artery. Once the arachnoid plane was accessed, the largest visible cortical vessel was selected as the recipient artery. A polarographic Clark probe (CC1.2 sensor, Integra Neurocare) and a cerebral microdialysis catheter with a 100-kD dialyzing membrane (CMA-71, M Dialysis AB, Solna, Sweden) were inserted in the cortical area adjacent to the M4 recipient vessel between 20 and 25 mm deep, with separation between the 2 probes around 0.5 cm (Fig. 2). The distance between the recipient vessel and the entry point of both catheters was less than 30 mm. The P_{btO_2} :partial pressure of oxygen (PaO_2) ratio was calculated by obtaining 2 arterial blood gas samples, 1 at baseline after steady-state P_{btO_2} readings (1 hr, 30 min after probe implantation) and the second just after completing STA-MCA anastomosis. Both P_{btO_2} and PaO_2 values correspond to the same point in time. To rule out changes related to systemic insults, an abdominal subcutaneous microdialysis catheter was also inserted. The microdialysis catheter was connected to an infusion pump (CMA-107) through which an artificial cerebrospinal fluid (CSF) solution (147 mmol/L NaCl, 2.7 mmol/L KCl, 1.2 mmol/L $CaCl_2$, and 0.85 mmol/L $MgCl_2$) infused at a rate of 0.3 μ L/min. The vials with the microdialysate were renewed every 30 minutes and analyzed with the ISCUSflex microdialysis analyzer. The analytes to be monitored were lactate, pyruvate, glucose, and glycerol. After checking the correct functioning of the implanted catheters and prior proximal placement of a temporary clip, the distal portion of the preserved STA was prepared by removing the connective tissue and adventitia. Next, a sharply angulated incision was made using microscissors to create an opening approximately 3 times the diameter of the recipient M4 branch. Temporary clips were applied to the ends of the recipient artery, and a longitudinal arteriotomy was performed. A 10-0 monofilament suture was then used to perform

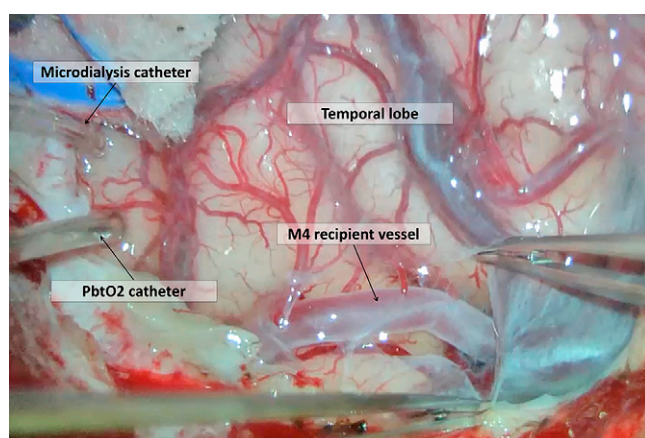


FIG. 2. Intraoperative image obtained with the surgical microscope showing both catheters. The polarographic Clark probe (CC1.2 sensor, Integra Neurocare) and the cerebral microdialysis catheter (CMA-71 catheter, CMA) were inserted 20- to 25-mm deep in the brain area adjacent to the M4 recipient vessel with a separation between the 2 probes around 0.5 cm. The distance between the recipient vessel and the entry point of both catheters was less than 30 mm.

the anastomosis after lumen irrigation with heparinized saline. The anchor sutures were continued through a running technique, initially loosened and later tightened after ensuring that no back wall of the vessel was captured. Finally, temporary clips were removed in the following order: first, the distal M4 branch clip; second, the proximal M4 branch clip; and third, the clip on the STA. The anastomotic patency was assessed by videoangiography using indocyanine green and Doppler ultrasonography.

Monitoring Data

Evaluation of cerebral oxygenation differences at baseline and after cerebral revascularization was calculated with the P_{btO_2} : PaO_2 ratio by obtaining 2 arterial blood gas samples, one at baseline at least 45 minutes after probe implantation when steady-state P_{btO_2} readings were reached and a second after STA-MCA anastomosis was completed. Figure 3 shows the graph of pressure monitoring.

Metabolic changes produced during surgery were analyzed with cerebral microdialysis using metabolites related to glucose metabolism to differentiate an aerobic situation of oxidative metabolism of glucose versus an anaerobic situation. We collected glucose, lactate, pyruvate, and the lactate:pyruvate ratio (LPR). Tables 1 and 2 show the results obtained from microdialysis as well as the main parameters related to oxygenation.

Follow-up

The patient recovered postsurgery without incident, and no new neurological deficit was observed. Bypass patency was evaluated with computed tomography angiography the day after surgery and with magnetic resonance angiography 3 months and 1 year after the procedure, revealing preserved blood flow in all cases. No new ischemic events were observed during the follow-up. After being referred to another external center, the patient was lost to follow-up after 14 months.

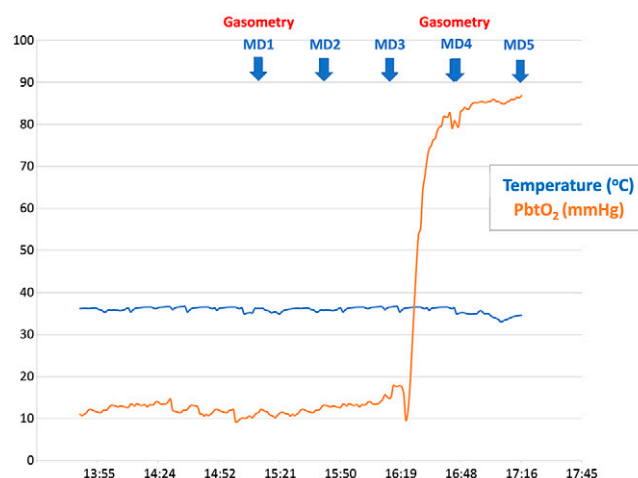


FIG. 3. Pressure monitoring graph. The placement points of the new microdialysis vials (MD) and the blood gas extractions are also represented. Notice how, before performing the anastomosis, the patient presents a hypoxic pattern with P_{btO_2} means below 15 mm Hg (and a P_{btO_2} : PaO_2 ratio < 0.10). After revascularization, P_{btO_2} shows a rapid and sustained rise with parameters within normoxia (P_{btO_2} > 15 and P_{btO_2} : PaO_2 ratio between 0.1 and 0.35).

TABLE 1. Results obtained from microdialysis

Time	Pyruvate-Subcutaneous (μM)	Pyruvate-Subcutaneous (mM)	Lactate-Subcutaneous (mM)	Glycerol-Subcutaneous (μM)	Glucose-Subcutaneous (mM)	LPR-Subcutaneous	Pyruvate-Cerebral (μM)	Pyruvate-Cerebral (mM)	Lactate-Cerebral (mM)	Glycerol-Cerebral (μM)	Glucose-Cerebral (mM)	LPR-Cerebral	Perfusion Rate
15:15	75.16781949	0.075167819	1.321525054	143.7008869	4.69949479	17.5809949	57.2830289	0.05728303	2.43975347	50.6319057	4.119628143	42.59120921	0.3
15:45	114.3669963	0.114366996	2.316195716	151.1654204	1.32899341	20.2523087	79.2462244	0.07924622	1.73901895	34.1940373	3.812596745	21.94450225	0.3
16:15	114.0366518	0.114036652	2.202825327	146.9463593	0.90295766	19.3168187	54.5596255	0.05455963	1.87705891	45.8731446	3.250270073	34.40380845	0.3
16:45	174.8266296	0.17482663	1.323590001	159.8502291	0.80236227	7.57087181	113.765003	0.113765	1.34055779	11.6618236	1.794819292	11.78356925	0.3
17:15	184.4831875	0.184483188	2.188978729	143.06637	0.85528018	11.8654646	279.603398	0.2796034	1.43814459	18.0240854	3.721968227	5.143479342	0.3

Notice how the LPR initially shows parameters compatible with anaerobic metabolism (LPR > 40), which presents a clear improvement after revascularization.

Discussion

Available published data recommend surgery in patients with MMD with progressive or recurrent cerebral ischemic events with reduced cerebral perfusion reserve.^{1,3–8,11–13,16–19,24–27} Operative techniques aim to increase the collateral blood flow to hypoperfused cortex and prevent further ischemic injury by using the donor supply from the external carotid circulation and can be divided into direct and indirect types.^{3,11–20} Our standard of treatment combines direct and indirect revascularization, adding the benefits of rapid revascularization and the delayed but sustained revascularization of EMS.^{13,14,18,19} Our results, following those of other authors,^{13,14,18,19,21,22} show the advantage of the quick improvement in regional cerebral hemodynamics created by direct revascularization compared with indirect revascularization, and thus promptly reducing the incidence of ischemic stroke in pediatric and adult patients with MMD. The results obtained in this patient show us how direct revascularization not only improves tissue oxygenation quickly, as we had already demonstrated in previous work by our group, but also suggests improvement at an energetic metabolic level, by getting it to change from an anaerobic metabolism to an aerobic metabolism.

Intraoperative Monitoring of Brain Oxygen and Hypoxic Thresholds

Since Jödicke et al.²⁸ published their pivotal paper, the threshold of 15 mm Hg for PbtO₂ has been commonly used as the most sensitive threshold and highest positive-predictive value for detection of irreversible intraoperative damage ischemia. Nevertheless, high PaO₂ ventilation parameters can artifactually increase PbtO₂ during surgery compared with normal breathing. To avoid it, an intraoperative hypoxia threshold PbtO₂:PaO₂ ratio below or equal to 0.10 was already proposed by our group in a previous paper.²⁹ Thus, we considered a hypoxic pattern to be present when brain tissue oxygen (PtiO₂) was below or equal to 15 mm Hg and/or the PbtO₂:PaO₂ ratio was below or equal to 0.10.

Intraoperative Cerebral Microdialysis

The metabolic changes produced in the brain in a situation of acute ischemia analyzed by cerebral microdialysis have been widely studied in recent years, thanks in part to the motivation produced by the spectacular results obtained with decompressive craniectomy in malignant infarction of the MCA. However, the study of the brain's energy state through cerebral microdialysis during revascularization of a brain subjected to a situation of subacute/chronic cerebral ischemia like this together with MMD and its modifications during surgery has not been previously described to date.

Metabolites related to glucose metabolism are crucial to differentiate an aerobic situation of oxidative metabolism of glucose versus an anaerobic situation. Glucose, lactate, pyruvate, and LPR were cited as the most clinically relevant biomarkers to understand the cerebral energetic metabolic situation.³⁰ In a normal-oxygen situation, glucose uptake by both neuronal and glial cells undergoes oxidation via glycolysis to form 2 pyruvate molecules. However, in situations of inadequate oxygen delivery, the brain uses lactate as an alternative fuel via the tricarboxylic acid cycle.^{31,32}

In recent years, better technology has made it possible to manage microdialysis at the patient's bedside, a revolutionary monitoring technique historically only feasible in an animal experimentation laboratory.

TABLE 2. Main parameters related to oxygenation as well as oximetry parameters

Time	PbtO ₂ (mean)	PbtO ₂ :PaO ₂	Glucose Arterial (mg/dL)	Lactate (mM)	PaCO ₂ (mmHg)	PaO ₂ (mmHg)	ctHb (g/dL)	pH	FiO ₂	SBP	DBP
15:15	11.61	0.052	112	1.69	37.4	221.5	12.4	7.284	0.55	129	78
15:45	12.71								0.55		
16:15	17.8								0.55	115	68
16:45	80.01	0.345	107	1.61	39.5	231.8	11.4	7.24	0.55	109	67
17:15	86.4								0.55		

ctHb = total hemoglobin concentration; DBP = diastolic arterial blood pressure; FiO₂ = fraction of inspired oxygen; PaCO₂ = partial pressure of carbon dioxide. Notice how PbtO₂ and the PbtO₂:PaO₂ ratio initially show parameters compatible with anaerobic metabolism (PbtO₂ < 15 mm Hg and PbtO₂:PaO₂ ratio < 0.1), which presents a clear improvement after revascularization (PbtO₂ > 15 mm Hg and PbtO₂:PaO₂ ratio between 0.1 and 0.35).

The microdialysis catheter simulates the function of a blood capillary, continuously sampling the cerebral extracellular space by a process of diffusion of analytes with a molecular weight that allows their diffusion through the pores of the catheter. With this technique, a 0.62-mm-diameter catheter is inserted into the brain, surrounded by a semipermeable membrane that allows the passage of molecules smaller than 100 kD, and is continuously perfused with a micropump and a solution identical to that of the CSF.

The microdialysate, collected in microvials, is analyzed by an enzymatic system at the patient's bedside, through which it is possible to continuously monitor lactate, pyruvate, glucose, urea, glycerol, and glutamate. Different studies have shown this technique's high sensitivity and specificity for the early detection of anaerobic metabolism. The reference values used today are those obtained from Reinstrup et al.³¹ in a series of 9 patients who underwent surgery for large tumors in the posterior fossa. Persistent high LPRs (LPR > 25 or > 40) indicate metabolic dysfunction of the brain's energy state.^{32,33}

The only precedent in intraoperative monitoring with microdialysis was published by Mendelowitsch et al. in 1997.¹⁵ They described a patient with chronic cerebral ischemia due to MMD secondary to sickle cell anemia, who underwent cerebral revascularization techniques. In this case, pyruvate levels were not presented, nor was the LPR. The presurgical metabolic pattern of the extracellular space showed a decreased pH and elevated glutamate levels. In this case, both parameters were corrected rapidly after cerebral revascularization.

Observations

Intraoperative monitoring of the metabolic profile using analytes such as glucose, lactate, pyruvate, and glycerol during cerebral artery bypass surgery for MMD-induced chronic cerebral ischemia has not been previously described. The PbtO₂:PaO₂ ratio at baseline and after revascularization was used to analyze cerebral oxygenation. As previously described, we consider the PbtO₂:PaO₂ ratio rather than absolute PbtO₂ as a better index for hypoxia detection due to the possible PaO₂ increase during surgical mechanical ventilation (e.g., when patients are under mechanical ventilation).²⁹ Our patient presented a baseline situation of severe tissue hypoxia confirmed by a PbtO₂:PaO₂ ratio below 0.1. Following bypass, the patient showed a rapid and sustained increase in PbtO₂, which reached normal values (PbtO₂:PaO₂ ratio between 0.1 and 0.35).

In the same way, before performing the anastomosis, cerebral microdialysis confirmed an anaerobic metabolic pattern characterized by an LPR greater than 40. Cerebral anastomosis, as with oxygenation, showed a rapid improvement in metabolism, obtaining

values of normality typical of a highly metabolized aerobic. Microdialysis analysis before anastomosis displayed anaerobic metabolism with an LPR greater than 40 and later normalization after the anastomosis with LPR values under 20.

Lessons

STA-MCA direct arterial bypass offers quick improvement in regional cerebral hemodynamics, thereby immediately reducing the incidence of subsequent ischemia. The bypass results in a very rapid resolution of tissue hypoxia, which has never been previously described. It also offers an immediate change in the metabolic situation, as has been shown by cerebral microdialysis, going from an anaerobic metabolism to an aerobic metabolism.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Arian, Calvo-Rubio. Acquisition of data: Arian, Chocron, Santos, Gándara. Analysis and interpretation of data: Arian. Drafting of the article: Arian, Chocron, Calvo-Rubio. Critically revising the article: all authors. Reviewed submitted version of the manuscript: Arian, Chocron, Calvo-Rubio, Gándara. Approved the final version of the manuscript on behalf of all authors: Arian. Administrative/technical/material support: Arian, Calvo-Rubio, Santos. Study supervision: Arian.

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