Review Article

Cerebral Perfusion and Cerebral Autoregulation after Cardiac Arrest

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Received 22 November 2017; Revised 28 February 2018; Accepted 3 April 2018; Published 8 May 2018

Academic Editor: Yi Yang

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Out of hospital cardiac arrest is the leading cause of death in industrialized countries. Recovery of hemodynamics does not necessarily lead to recovery of cerebral perfusion. The neurological injury induced by a circulatory arrest mainly determines the prognosis of patients after cardiac arrest and rates of survival with a favourable neurological outcome are low. This review focuses on the temporal course of cerebral perfusion and changes in cerebral autoregulation after out of hospital cardiac arrest. In the early phase after cardiac arrest, patients have a low cerebral blood flow that gradually restores towards normal values during the first 72 hours after cardiac arrest. Whether modification of the cerebral blood flow after return of spontaneous circulation impacts patient outcome remains to be determined.

1. Introduction

The prognosis of cardiac arrest patients is mainly determined by the extent of neurological injury induced by the circulatory arrest. Return of spontaneous circulation (ROSC) does not naturally result in recovery of cerebral perfusion, as cerebral perfusion failure after ROSC is well described in animal models with no-reflow, hypoperfusion, and hyperperfusion. In animals, cerebral blood flow (CBF) ultimately restores towards normal [1]. Human studies have revealed that, in the early phase after cardiac arrest, patients have a low CBF that gradually restores towards normal values during the first 72 hours following the arrest [2–4]. In the first part of this review, the temporal course of cerebral blood flow after ROSC is described. This is relevant, because changes in cerebral blood flow can contribute to secondary brain injury. The second part of this review will focus on cerebral autoregulation after cardiac arrest, because this is an important factor in the development of ischaemia and secondary brain damage.

2. Cerebral Blood Flow after Cardiac Arrest

Cerebral perfusion after resuscitation is characterized by early hyperemia followed by hypoperfusion and, finally,

restoration of normal blood flow. Furthermore, the blood flow is heterogeneous, with areas of no flow, low flow, and increased flow at the level of the microcirculation [5].

2.1. Early Hyperemia (Vasoparalysis) (0–20 min after ROSC). Reduction of vascular tone due to tissue acidosis leads to vasoparalysis [6], which does not respond to changes in blood pressure or CO₂ [7]. Hypoxia-induced vasoparalysis has been demonstrated in rats in the very early phase of cardiac arrest [8] and is suggested to result from an imbalance between vasodilatory and vasoconstrictive mediators in the cerebral circulation, including nitric oxide (NO) [9] and adenosine [10]. There is no direct evidence for this phenomenon *in vivo*. Hyperemia, in combination with brain swelling, can cause increased intracranial pressure, which usually normalizes before the hypoperfusion phase initiates [11]. Antioxidants and polynitroxyl albumin represent therapies that may be of value in the early hyperemia phase [12, 13].

2.2. Hypoperfusion Phase (20 min–12 h after ROSC). The hypoperfusion phase is due to an impairment of the metabolic/hemodynamic coupling mechanisms, and its severity is independent of the duration of ischaemia [14]. We confirmed this lack of a relationship between ischaemia duration and the

severity of hypoperfusion in comatose patients after cardiac arrest (data not published) [15]. During the hypoperfusion phase, the CBF decreases by approximately 50% [16, 17]. Several factors are implicated to play a role, including endothelial damage and an imbalance of local vasodilators (NO) and vasoconstrictors such as endothelin [18]. In this phase, impairment of the autoregulation may further decrease CBF in the setting of low blood pressure. Viable therapies for this hypoperfusion phase have been examined in animal models and include 20-hydroxyeicosatetraenoic acid inhibition by HET0016, nimodipine, and endothelin type A-antagonists [19–23].

2.3. Restoration of Normal Blood Flow (12–72 h after ROSC). Finally, CBF returns to normal, remains low, or increases [24, 25]. In more recent literature, only a return to normal or an increase in CBF is described [2, 26]. Bisschops et al. described a low mean flow velocity in the middle cerebral artery (MFV_{MCA}) on admission, which remained relatively stable during the first day and increased to normal levels at 48 hours [2].

The MFV_{MCA} was shown to be similar in survivors and nonsurvivors upon ICU admission [26]. However, in survivors of cardiac arrest, the MFV_{MCA} increases towards normal values in the following 72 hours, whereas a much more pronounced increase in MFV_{MCA} , resulting in an overshoot of CBF, was observed in nonsurvivors [26]. This overshoot is most likely the result of a loss in vascular tone resulting in a decrease in cerebrovascular resistance in these nonsurvivors [26].

Low CBF after cardiac arrest may cause a mismatch between cerebral oxygen demand and supply. A reduction in cerebral metabolism after cardiac arrest has been described in humans and animals [27–31]. In the first 48 hours after cardiac arrest, cerebral oxygen extraction remains normal with a low CBF. This low CBF is not associated with anaerobic metabolism, determined by the jugular venous-to-arterial CO_2 /arterial-to-jugular venous O_2 content difference ratio [32]. The jugular venous CO_2 content significantly decreases after cardiac arrest, suggestive of low CO_2 production due to low cerebral metabolism [32].

In survivors, the MFV_{MCA} is low immediately after cardiac arrest, accompanied by low metabolism, with a gradual restoration towards normal values accompanied by restoration of metabolism. This gradual increase of metabolism in survivors is consistent with recovery of neuronal activity. These results imply that the cerebrovascular coupling is intact in patients with a favourable neurological outcome.

In contrast, in nonsurvivors with cerebral hyperfusion, the cerebral oxygen extraction is strongly reduced, suggesting decoupling of cerebral flow and metabolism in nonsurvivors. This ongoing low metabolism likely reflects irreversible neuronal damage [32].

3. Cerebral Autoregulation following Cardiac Arrest

3.1. Cerebral Autoregulation. Generally, it is assumed that cerebral autoregulation maintains CBF at a constant level

FIGURE 1: Cerebral autoregulation maintains cerebral blood flow at a constant level when the mean arterial pressure is between approximately 50 and 150 mmHg (the plateau phase).

FIGURE 2: More recent data support the opinion that cerebral autoregulation does not maintain constant blood flow through a broad MAP range of 50–150 mmHg, but probably in a smaller range. Cerebral autoregulation is more effective in the range above baseline mean arterial pressure, compared to the range below.

when the mean arterial pressure (MAP) is between approximately 50 and 150 mmHg (the plateau phase) (Figure 1). However, more recent data suggest that cerebral autoregulation maintains constant blood flow in a smaller range [33, 34] (Figure 2). Cerebral autoregulation is more effective in the range above baseline MAP than below baseline MAP [35] (Figure 2).

The upper and lower limits of cerebral autoregulation are not fixed [36]. For example, chronic hypertension shifts these limits up. This adaptation protects the brain against high blood pressure but makes it also more vulnerable to hypoperfusion during periods of hypotension.

Dynamic cerebral autoregulation is clinically more relevant than static autoregulation, because it protects the brain against rapid alterations in blood pressure. Various methods and models are available for estimating dynamic cerebral autoregulation, using both spontaneous and induced fluctuations in blood pressure.

3.2. Cerebral Autoregulation following Cardiac Arrest. Cerebral autoregulation after cardiac arrest has been investigated in various studies. Initially, a linear relationship was demonstrated between MAP and CBF [37], suggesting a completely dysfunctional (static) cerebral autoregulation after cardiac arrest. Static cerebral autoregulation curves were constructed for patients after cardiac arrest by stepwise increasing MAP with vasopressors and simultaneous determination of CBF using TCD [38]. Of the 18 patients after cardiac arrest studied by Sundgreen et al., static cerebral autoregulation was absent in 8 and present in 10 patients. In five out of ten patients with preserved cerebral autoregulation, the lower limit of autoregulation was shifted upwards (range 80–120 mmHg) [38]. In fact, autoregulation may remain intact, but with a narrowed and upward shifted intact zone. This study demonstrated the heterogeneous nature of cerebral autoregulation in cardiac arrest patients.

Ameloot et al. showed that (dynamic) cerebrovascular autoregulation, determined by the moving correlation coefficient between MAP and the ratio of oxygenated versus deoxygenated hemoglobin (COX), was not preserved in one-third of postcardiac arrest patients [39]. Disturbed autoregulation was associated with unfavourable outcome [39, 40]. A MAP below the optimal autoregulatory range during the first 48 hours after cardiac arrest was associated with worse outcomes compared to patients with higher blood pressures [41].

The relationship between brain tissue oxygen saturation and MAP can also be used to determine the optimal MAP in individual patients after cardiac arrest. The feasibility of this technique to obtain real-time values for optimal MAP was demonstrated in a small prospective cohort study [42]. The optimal MAP for patients after cardiac arrest in this study was found to be 75 mmHg. In a retrospective study, Ameloot estimated the optimal MAP in patients after cardiac arrest to be 85 mmHg in patients with preserved autoregulation and 100 mmHg in patients with disturbed autoregulation [39].

Taken together, these results emphasize the importance of accurate blood pressure control in patients after cardiac arrest. Larger prospective cohort studies are required to establish the value of a tailored blood pressure targeted therapy versus conventional blood pressure targets.

The CBF changes after cardiac arrest. The critical closing pressure (CrCP) is a reliable method to quantify characteristics of the cerebrovascular bed and is defined as the lower limit of arterial blood pressure below which vessels collapse and flow ceases [43, 44]. Immediately following cardiac arrest, CrCP was shown to be high, accompanied by increased cerebrovascular resistance [26]. The CrCP decreased in the first 48 hours after admission towards normal values [26]. The CrCP was significantly higher in patients who survived compared to those who deceased [26]. Apparently, vasoactive tone was lost in patients with unfavourable outcome, resulting in reduced cerebrovascular resistance and a subsequent-increased CBF. In contrast, vasoactive tone and cerebral blood flow velocities returned to normal values in patients with favourable neurological outcome.

In addition, immediately following cardiac arrest, spontaneous variability of MFV was found to be low [15]. MFV variability increased to normal values in patients who survived,

whereas it further decreased in patients who did not survive after cardiac arrest [15]. It is plausible that these changes are the consequence of the associated severe brain damage, resulting in impaired control of intrinsic myogenic vascular function and autonomic dysregulation. These changes in spontaneous fluctuations in MFV imply changes in dynamic cerebral autoregulation after ROSC.

Bisschops et al. showed a preserved cerebrovascular reactivity to fluctuations in PaCO₂ during mild therapeutic hypothermia after cardiac arrest [2]. Previously, Yenari et al. demonstrated a preserved cerebrovascular reactivity to changes in PaCO₂ under normothermic conditions in patients after ROSC [45]. This emphasizes the importance of strict control of blood gas values during mechanical ventilation in cardiac arrest patients, because secondary neurological damage as a result of cerebral ischaemia could be prevented by avoiding iatrogenic hypocapnia.

4. Conclusion

CBF is low after cardiac arrest and returns towards normal values in patients that ultimately survive. In patients with severe postanoxic encephalopathy disturbed autoregulation, loss of normal vascular tone, and increased CBF may contribute to the development of secondary brain damage, ultimately leading to fatal brain injury.

The changes in CBF after cardiac arrest may be regarded merely as a feature of severe primary brain damage resulting from ischaemia and reperfusion injury. Alternatively, they may contribute to the development of secondary brain damage. Whether modulation of the CBF after ROSC, for example, by maintaining MAP at optimal autoregulation ranges, impacts the outcome of these patients remains to be determined.

In addition, differences between CBF in the microcirculation are poorly understood and deserve more attention.

Conflicts of Interest

The authors declare no conflicts of interest.

References

- [1] P. Safar, "Cerebral resuscitation after cardiac arrest: research initiatives and future directions," *Annals of Emergency Medicine*, vol. 22, no. 2, part 2, pp. 324–349, 1993.
- [2] L. L. A. Bisschops, C. W. E. Hoedemaekers, K. S. Simons, and J. G. Van Der Hoeven, "Preserved metabolic coupling and cerebrovascular reactivity during mild hypothermia after cardiac arrest," *Critical Care Medicine*, vol. 38, no. 7, pp. 1542–1547, 2010.
- [3] G. Buunk, J. G. Van Der Hoeven, M. Frölich, and A. E. Meinders, "Cerebral vasoconstriction in comatose patients resuscitated from a cardiac arrest?" *Intensive Care Medicine*, vol. 22, no. 11, pp. 1191–1196, 1996.
- [4] V. Lemiale, O. Huet, B. Vigué et al., "Changes in cerebral blood flow and oxygen extraction during post-resuscitation syndrome," *Resuscitation*, vol. 76, no. 1, pp. 17–24, 2008.
- [5] B. Iordanova, L. Li, R. S. Clark, and M. D. Manole, "Alterations in Cerebral Blood Flow after Resuscitation from Cardiac Arrest," *Frontiers in Pediatrics*, vol. 5, 2017.

- [6] S. Takagi, L. Cocito, and K.-A. Hossmann, "Blood recirculation and pharmacological responsiveness of the cerebral vasculature following prolonged ischemia of cat brain," *Stroke*, vol. 8, no. 6, pp. 707–712, 1977.
- [7] N. A. Lassen, "The luxury-perfusion syndrome and its possible relation to acute metabolic acidosis localised within the brain," *The Lancet*, vol. 2, no. 7473, pp. 1113–1115, 1966.
- [8] S. Kwon Lee, P. Vaagenes, P. Safar, S. William Stezoski, and M. Scanlon, "Effect of cardiac arrest time on cortical cerebral blood flow during subsequent standard external cardiopulmonary resuscitation in rabbits," *Resuscitation*, vol. 17, no. 2, pp. 105–117, 1989.
- [9] S. A. Humphreys and M. C. Koss, "Role of nitric oxide in post-ischemic cerebral hyperemia in anesthetized rats," *European Journal of Pharmacology*, vol. 347, no. 2-3, pp. 223–229, 1998.
- [10] V. M. Sciotti and D. G. L. Van Wylen, "Increases in interstitial adenosine and cerebral blood flow with inhibition of adenosine kinase and adenosine deaminase," *Journal of Cerebral Blood Flow & Metabolism*, vol. 13, no. 2, pp. 201–207, 1993.
- [11] K.-A. Hossmann, "Reperfusion of the brain after global ischemia: Hemodynamic disturbances," *Shock*, vol. 8, no. 2, pp. 95–101, 1997.
- [12] M. D. Manole, L. M. Foley, T. K. Hitchens et al., "Magnetic resonance imaging assessment of regional cerebral blood flow after asphyxial cardiac arrest in immature rats," *Journal of Cerebral Blood Flow & Metabolism*, vol. 29, no. 1, pp. 197–205, 2009.
- [13] E. L. Cerchiari, T. M. Hoel, P. Safar, and R. J. Scلابassi, "Protective effects of combined superoxide dismutase and deferoxamine on recovery of cerebral blood flow and function after cardiac arrest in dogs," *Stroke*, vol. 18, no. 5, pp. 869–878, 1987.
- [14] P. Blomqvist and T. Wieloch, "Ischemic brain damage in rats following cardiac arrest using a long-term recovery model," *Journal of Cerebral Blood Flow & Metabolism*, vol. 5, no. 3, pp. 420–431, 1985.
- [15] J. M. D. van den Brule, E. J. Vinke, L. M. van Loon, J. G. van der Hoeven, and C. W. E. Hoedemaekers, "Low spontaneous variability in cerebral blood flow velocity in non-survivors after cardiac arrest," *Resuscitation*, vol. 111, pp. 110–115, 2017.
- [16] E. Kagstrom, M. L. Smith, and B. K. Siesjo, "Local cerebral blood flow in the recovery period following complete cerebral ischemia in the rat," *Journal of Cerebral Blood Flow & Metabolism*, vol. 3, no. 2, pp. 170–182, 1983.
- [17] P. Safar, W. Stezoski, and E. M. Nemoto, "Amelioration of Brain Damage After 12 Minutes' Cardiac Arrest in Dogs," *JAMA Neurology*, vol. 33, no. 2, pp. 91–95, 1976.
- [18] D. A. Dawson, H. Sugano, R. M. McCarron, J. M. Hallenbeck, and M. Spatz, "Endothelin receptor antagonist preserves microvascular perfusion and reduces ischemic brain damage following permanent focal ischemia," *Neurochemical Research*, vol. 24, no. 12, pp. 1499–1505, 1999.
- [19] J. S. B. Shaik, S. M. Poloyac, P. M. Kochanek et al., "20-Hydroxyeicosatetraenoic Acid Inhibition by HET0016 Offers Neuroprotection, Decreases Edema, and Increases Cortical Cerebral Blood Flow in a Pediatric Asphyxial Cardiac Arrest Model in Rats," *Journal of Cerebral Blood Flow & Metabolism*, vol. 35, no. 11, pp. 1757–1763, 2015.
- [20] W. A. Kofke, E. M. Nemoto, K.-A. Hossmann, F. Taylor, P. D. Kessler, and S. W. Stezoski, "Brain blood flow and metabolism after global ischemia and post-insult thiopental therapy in monkeys," *Stroke*, vol. 10, no. 5, pp. 554–560, 1979.
- [21] P.-Y. Gueugniaud, P. Gaussorgues, F. Garcia-Darennnes et al., "Early effects of nimodipine on intracranial and cerebral perfusion pressures in cerebral anoxia after out-of-hospital cardiac arrest," *Resuscitation*, vol. 20, no. 3, pp. 203–212, 1990.
- [22] H. Krep, G. Brinker, W. Schwindt, and K.-A. Hossmann, "Endothelin type A-antagonist improves long-term neurological recovery after cardiac arrest in rats," *Critical Care Medicine*, vol. 28, no. 8, pp. 2873–2880, 2000.
- [23] M. Forsman, H. P. Aarseth, H. K. Nordby, A. Skulberg, and P. A. Steen, "Effects of Nimodipine on Cerebral Blood Flow and Cerebrospinal Fluid Pressure After Cardiac Arrest," *Anesthesia & Analgesia*, vol. 68, no. 4, pp. 436–443, 1989.
- [24] F. Sterz, Y. Leonov, P. Safar et al., "Multifocal cerebral blood flow by Xe-CT and global cerebral metabolism after prolonged cardiac arrest in dogs. Reperfusion with open-chest CPR or cardiopulmonary bypass," *Resuscitation*, vol. 24, no. 1, pp. 27–47, 1992.
- [25] M. N. Shalit, A. J. Beller, M. Feinsod, A. J. Drapkin, and S. Cotev, "The blood flow and oxygen consumption of the dying brain," *Neurology*, vol. 20, no. 8, pp. 740–748, 1970.
- [26] J. M. D. van den Brule, E. Vinke, L. M. van Loon, J. G. van der Hoeven, and C. W. E. Hoedemaekers, "Middle cerebral artery flow, the critical closing pressure, and the optimal mean arterial pressure in comatose cardiac arrest survivors—An observational study," *Resuscitation*, vol. 110, pp. 85–89, 2017.
- [27] J. E. Beckstead, W. A. Tweed, J. Lee, and W. L. Mackeen, "Cerebral blood flow and metabolism in man following cardiac arrest," *Stroke*, vol. 9, no. 6, pp. 569–573, 1978.
- [28] B. Bein, E. Cavus, K. H. Stadlbauer et al., "Monitoring of cerebral oxygenation with near infrared spectroscopy and tissue oxygen partial pressure during cardiopulmonary resuscitation in pigs," *European Journal of Anaesthesiology*, vol. 23, no. 6, pp. 501–509, 2006.
- [29] E. Edgren, P. Enblad, Å. Grenvik et al., "Cerebral blood flow and metabolism after cardiopulmonary resuscitation. A pathophysiologic and prognostic positron emission tomography pilot study," *Resuscitation*, vol. 57, no. 2, pp. 161–170, 2003.
- [30] E. Mörtberg, P. Cumming, L. Wiklund, and S. Rubertsson, "Cerebral metabolic rate of oxygen (CMRO₂) in pig brain determined by PET after resuscitation from cardiac arrest," *Resuscitation*, vol. 80, no. 6, pp. 701–706, 2009.
- [31] E. Mörtberg, P. Cumming, L. Wiklund, A. Wall, and S. Rubertsson, "A PET study of regional cerebral blood flow after experimental cardiopulmonary resuscitation," *Resuscitation*, vol. 75, no. 1, pp. 98–104, 2007.
- [32] C. W. Hoedemaekers, P. N. Ainslie, S. Hinssen et al., "Low cerebral blood flow after cardiac arrest is not associated with anaerobic cerebral metabolism," *Resuscitation*, vol. 120, pp. 45–50, 2017.
- [33] C. K. Willie, Y.-C. Tzeng, J. A. Fisher, and P. N. Ainslie, "Integrative regulation of human brain blood flow," *The Journal of Physiology*, vol. 592, no. 5, pp. 841–859, 2014.
- [34] C. O. Tan, "Defining the characteristic relationship between arterial pressure and cerebral flow," *Journal of Applied Physiology*, vol. 113, no. 8, pp. 1194–1200, 2012.
- [35] R. Aaslid, M. Blaha, G. Svir, C. M. Douville, and D. W. Newell, "Asymmetric dynamic cerebral autoregulatory response to cyclic stimuli," *Stroke*, vol. 38, no. 5, pp. 1465–1469, 2007.
- [36] S. Strandgaard and O. B. Paulson, "Cerebral autoregulation," *Stroke*, vol. 15, no. 3, pp. 413–416, 1984.
- [37] H. Nishizawa and I. Kudoh, "Cerebral autoregulation is impaired in patients resuscitated after cardiac arrest," *Acta Anaesthesiologica Scandinavica*, vol. 40, no. 9, pp. 1149–1153, 1996.

- [38] C. Sundgreen, F. S. Larsen, T. M. Herzog, G. M. Knudsen, S. Boesgaard, and J. Aldershvile, "Autoregulation of cerebral blood flow in patients resuscitated from cardiac arrest," *Stroke*, vol. 32, no. 1, pp. 128–132, 2001.
- [39] K. Ameloot, C. Genbrugge, I. Meex et al., "An observational near-infrared spectroscopy study on cerebral autoregulation in post-cardiac arrest patients: Time to drop 'one-size-fits-all' hemodynamic targets?" *Resuscitation*, vol. 90, pp. 121–126, 2015.
- [40] P. Pham, J. Bindra, A. Chuan, M. Jaeger, and A. Aneman, "Are changes in cerebrovascular autoregulation following cardiac arrest associated with neurological outcome? Results of a pilot study," *Resuscitation*, vol. 96, pp. 192–198, 2015.
- [41] J. K. Lee, K. M. Brady, S.-E. Chung et al., "A pilot study of cerebrovascular reactivity autoregulation after pediatric cardiac arrest," *Resuscitation*, vol. 85, no. 10, pp. 1387–1393, 2014.
- [42] M. S. Sekhon, P. Smielewski, T. D. Bhate et al., "Using the relationship between brain tissue regional saturation of oxygen and mean arterial pressure to determine the optimal mean arterial pressure in patients following cardiac arrest: A pilot proof-of-concept study," *Resuscitation*, vol. 106, pp. 120–125, 2016.
- [43] A. C. Burton, "On the Physical Equilibrium of Small Blood Vessels," *American Journal of Physiology-Legacy Content*, vol. 164, no. 2, pp. 319–329, 1951.
- [44] R. C. Dewey, H. P. Pieper, and W. E. Hunt, "Experimental cerebral hemodynamics. Vasomotor tone, critical closing pressure, and vascular bed resistance," *Journal of Neurosurgery*, vol. 41, no. 5, pp. 597–606, 1974.
- [45] M. Yenari, K. Kitagawa, P. Lyden, and M. Perez-Pinzon, "Metabolic downregulation: A key to successful neuroprotection?" *Stroke*, vol. 39, no. 10, pp. 2910–2917, 2008.