



LETTER

Oxygen, the Link between Intracranial Aneurisms Disruption and the Atmospheric Environment?

Thierry Patrice, MD, PhD*

Nantes University Hospital, University of Nantes, France



*Corresponding author: Thierry Patrice, MD, PhD, Nantes University Hospital, University of Nantes, France

The general purpose of research either clinical or basic is to describe links existing between an identified disease and its whole environment from the surrounding tissues and the patient, to his ecosystem. From this point of view berry aneurisms are extremely interesting: They develop from normal tissues, their cause is largely unknown, and their evolution is barely predictable but dramatic in case of disruption. Subarachnoid hemorrhage (SAH) from a ruptured aneurysm accounts for around 5% of all strokes. It has a high rate of mortality comprised between 40 and 60% according to studies and among survivors between 30 and 70% will suffer from heavy deficits [1,2]. The classically described patient's profile is woman in her 50's without any noticeable medical history, discovered lying on the floor in late afternoon by her husband coming back home. In addition SAH occur less frequently at night and seem to be so more frequent at some period of time that a number of studies had been published aimed at finding a link between SAH and meteorological conditions extending to moon phases, tides or even typhoons. Results had been disappointing providing opposite results, particularly when involving large multicentric cohorts, patients being recruited all over a wide territory, the whole being inconclusive despite the strong feeling that patients seemed more likely gathered some weeks or months. SAH being a pretty negative event most studies tried naturally to correlate with a "bad weather" event as depressions are associated with wind and rain, as indicated by the barometer's needle. In addition atmospheric oxygen (O_2) partial pressure (pO_2) needs to be calculated as it varies with atmospheric pressure, temperature and relative humidity and therefore values and variations appear only unfrequently in papers.

Living on the French Atlantic shore in Brittany and familiar with both the weather analyses and oxidative stress we found [3] that disruptions occurred mainly at the very end of a several days period of anticyclonic conditions: Atmospheric pressure above 1010 hPa, low relative humidity and a relatively high atmospheric pO_2 were all changing very mildly, resulting in a relatively lower pO_2 . SAH also occurred more frequently in spring and autumn and between 6 am and 12 pm, nearly never during night hours. One must consider these oceanic weather changes as a quasi-experimental model of what happens inland and of course not as a coastal specificity. Inland weather changes are more difficult to evidence, which is the main cause of controversial results published for years, as they are most often issued from temperature differences between the ocean and the coast and then progressively decrease. Oxygen is also largely produced from ocean photosynthesis. Finally patients with a SAH do not appear at all to be free of heavy diseases and one cannot exclude the hypothesis that in a number of cases that might play a role as great as classically described risk factors themselves i.e. smoking or obesity [4]. In fact meteorological conditions at time of disruption differed in patients without recorded diseases from those with a heavy medical past: Variations of pO_2 were 3 times more than for patients without any known disease. Aneurisms disruption appears thus to be dependent to a certain extent on conditions external to patients. However the question remains to know whether it is a mild decreased oxygen pressure or a high one persisting for a long while which is directly responsible for the disruption. Considering that only a limited number of SAH occur at low atmospheric pressure we would rather consider the effects of a high pO_2 for a long while as being the main cause.

Diseases with a link with weather conditions are not so frequent. They mostly are virus or parasite-related and temperature or humidity often acts through their relative impact on a vector i.e. a mosquito. However climate changes stimulate the quest for a possible influence of temperature not only on infectious diseases but also chronological ones from cancers to COPD [5-9]. In these cases, weather influences oxygen availability to patients. Oxygen solubility in water increases when temperature decreases and for a salinity of 0.9/00 it doubles between 30 and 0 °C [10]. O₂ transfer from air to erythrocytes thus varies. In normal persons there are systemic mechanisms likely to regulate O₂ transfers, i.e. heart frequency and blood pressure, but it is quite possible that these would not be operating in case of localized disturbance i.e. a saccular berry aneurysm, if no significant systemic signal is generated. In such aneurysms the blood stream is not laminar but heterogeneous, being hyper coagulating and viscous in some areas, these corresponding to a low partial oxygen pressure and a high level of Reactive Oxygen Species and pro necrotic factors [11-16]. Clotting needs O₂ and at the same time consumes O₂ and anti-oxidative proteins, leading to various cascades of inflammatory disorders, eventually catalyzed by heme degradation [17-19]. A high O₂ pressure that would have no effect normally would allow coagulation followed by initial steps of necrosis to develop till an irreversible step.

One could thus propose, as a hypothesis, the following sequence of events: in a saccular aneurism thrombosis initiated during a high pO₂ over consumes O₂ and simultaneously leads to an overproduction of ROS. The both cooperate and lead to a necrotic process involving the aneurism wall and blood irruption all around contributing again to an additional ischemia. This sequence of events could be independent on the aneurysm size, dependent on the anti-oxidative defenses available, thus dependent on the patient's general health status and triggered by a change in O₂ concentration likely to be transferred from atmosphere and lungs to the aneurysm wall. A little atmospheric change might then have heavy consequences as being amplified by local necrotic processes already "pre-positioned" and could then provoke the wall disruption. In addition most hypothesized mechanisms likely to explain aneurysm disruption i.e. pressure changes, shear stress, vorticity and of course ischemia could be directly related or associated to the pO₂ changes we suspect to act as a final trigger.

Such an O₂ related approach is not only theoretical but could have practical consequences when an unruptured aneurism is diagnosed but patient waiting for an endovascular treatment. Of course many other studies should be performed and focused on O₂ changes at the aneurism location in relation to environmental conditions, assays far out of range from a single research team. If we are right, exerting a close and active survey

of patients with an UIA or even maintaining optimal conditions of pO₂ in a specially designed room within patient's house could help overtaking risky days and allow at a low cost a safe issue.

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