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Abstract

Introduction: Neuronal tissue is known to be extremely vulnerable to hypoxic insult, which is often one of the very first events resulting in or contributes to ischemic cell death. An increase in oxygen availability may be achieved by infusion of a 3rd generation of PFCs, namely Oxycyte™ (PrimaPharm for Oxygen therapeutics International), a promising synthetic emulsion for increasing brain oxygen tension in patients suffering severe head injury. We measured the increase in ptiO₂ as well as several variables to assess the clinical safety of Oxycyte™.

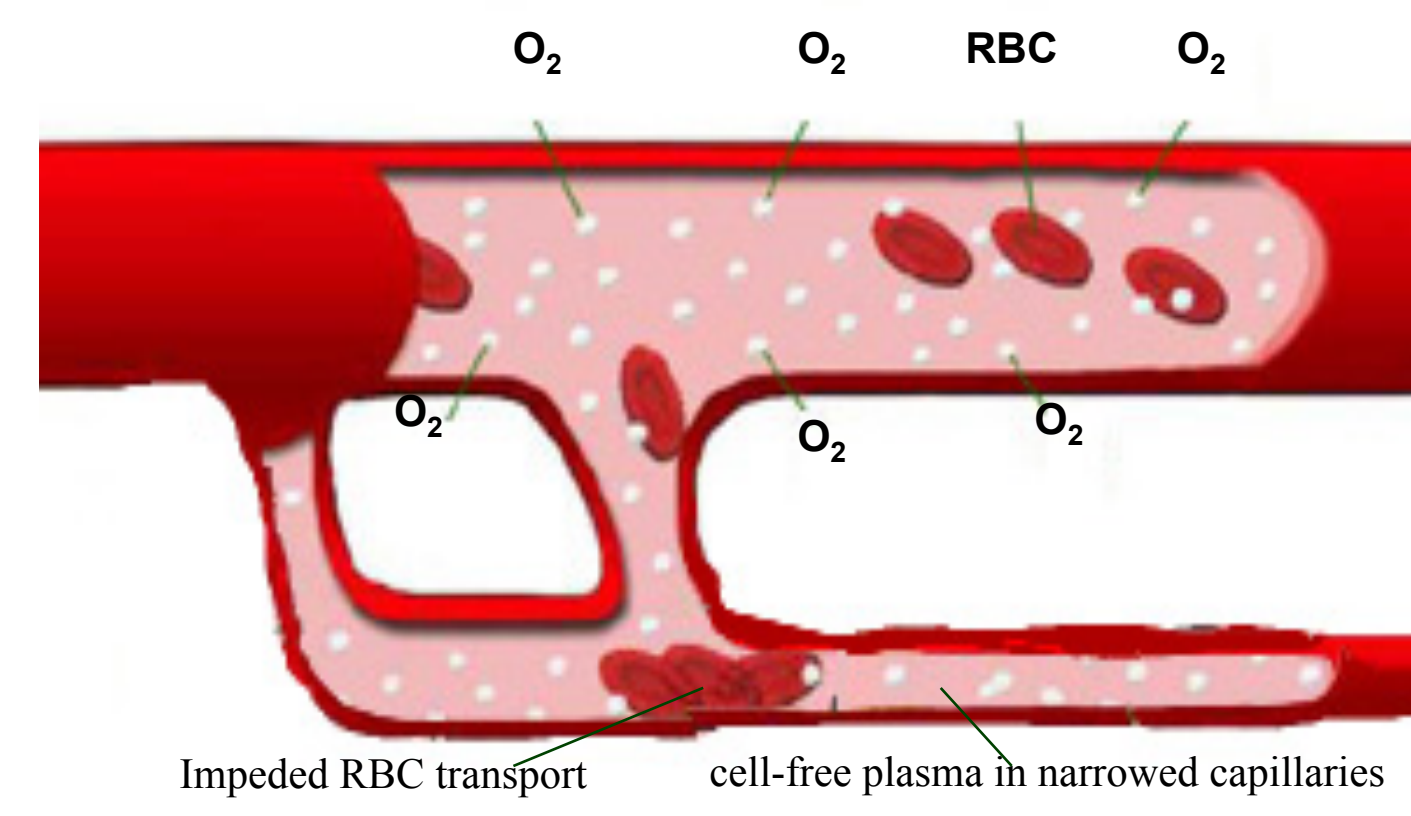
Methods: Nine severe closed head injury patients with an initial GCS score of 3-9 were admitted to the study. Monitoring included CPP, ICP, and cerebral microdialysis, ptiO₂ measurements, CPP-directed blood pressure management, and arterial blood gases. Daily sampling for hematology, blood chemistry and coagulation parameters during days 1-4 after admission, and liver enzymes were measured. The 1st group of 4 patients were administered a FiO₂ of 0.5 starting 4 hours before giving the Oxycyte™ infusion (lasting ~25 min) and maintained for a total of 12 hours, then adjusted according to the blood gas values, while the 2nd group of 4 patients received a FiO₂ of 1.0. The safety data were compared to a matched control group of 36 TBI patients. (in one patient, the Licox PtiO₂ monitor failed)

Results: Immediately after beginning the Oxycyte™ infusion, the ptiO₂ increased to 23 ± 9 mmHg and 27 ± 14 mmHg in the 1st and 2nd group respectively, reaching stable levels at 28 ± 1 mmHg and 28 ± 1 mmHg respectively for 48 hours. The drop in hemoglobin, hematocrit and platelets was more pronounced in the Oxycyte™ group, but the difference was not significant. The liver enzymes remained stable, except for the ALT which increased from 39 ± 16 U/L to 83 ± 20 U/L over 5 days, and the alkaline phosphatase which increased from 185 ± 30 U/L to 699 ± 410 within 7 days. (difference no significant) 2 oxycyte treated patients died, but the remainder (77%) were classified as Good recovery or minimal disability, at 6 months.

Conclusion: The use of Oxycyte™ in patients with severe TBI clearly increased brain oxygenation, and Severe Adverse Events, and Adverse Events were not more frequent than in the controls. A larger phase IIB study has been funded, and will begin in 2008.

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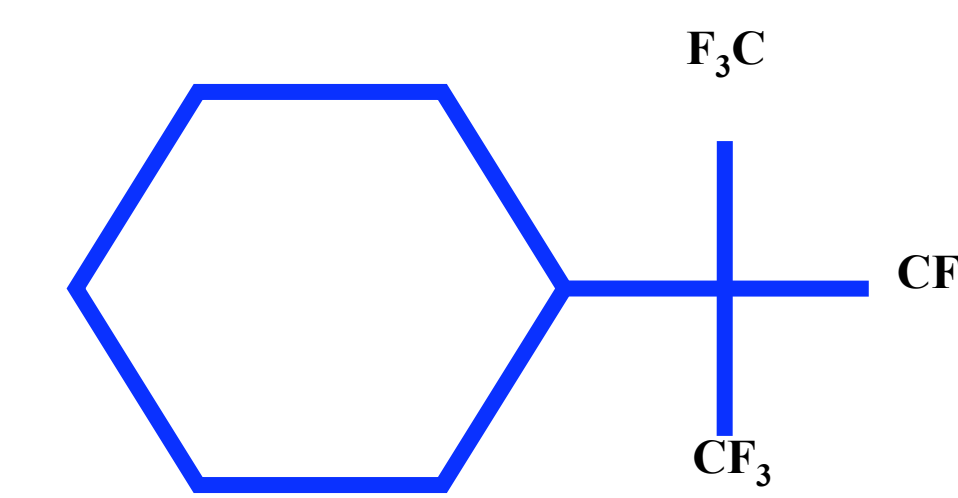
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In areas where RBC flow is excluded, due to capillary narrowing PFCs may be able to continue the delivery of O₂ because of their small particle size (1/35th the size of an RBC, i.e. 0.2 μm), thereby allowing perfusion of those tissues via cell-free plasma. Thus, PFCs offer a new possibility for therapy by perfusing and oxygenating “peri-contusional” brain tissue where capillaries are so narrowed as to obstruct RBC transport.

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- Structure: perfluoro-tert-butylcyclo-hexane (only carbon and fluorine (C₁₀F₂₀)), which is twice as dense as water and boils at 147°C.



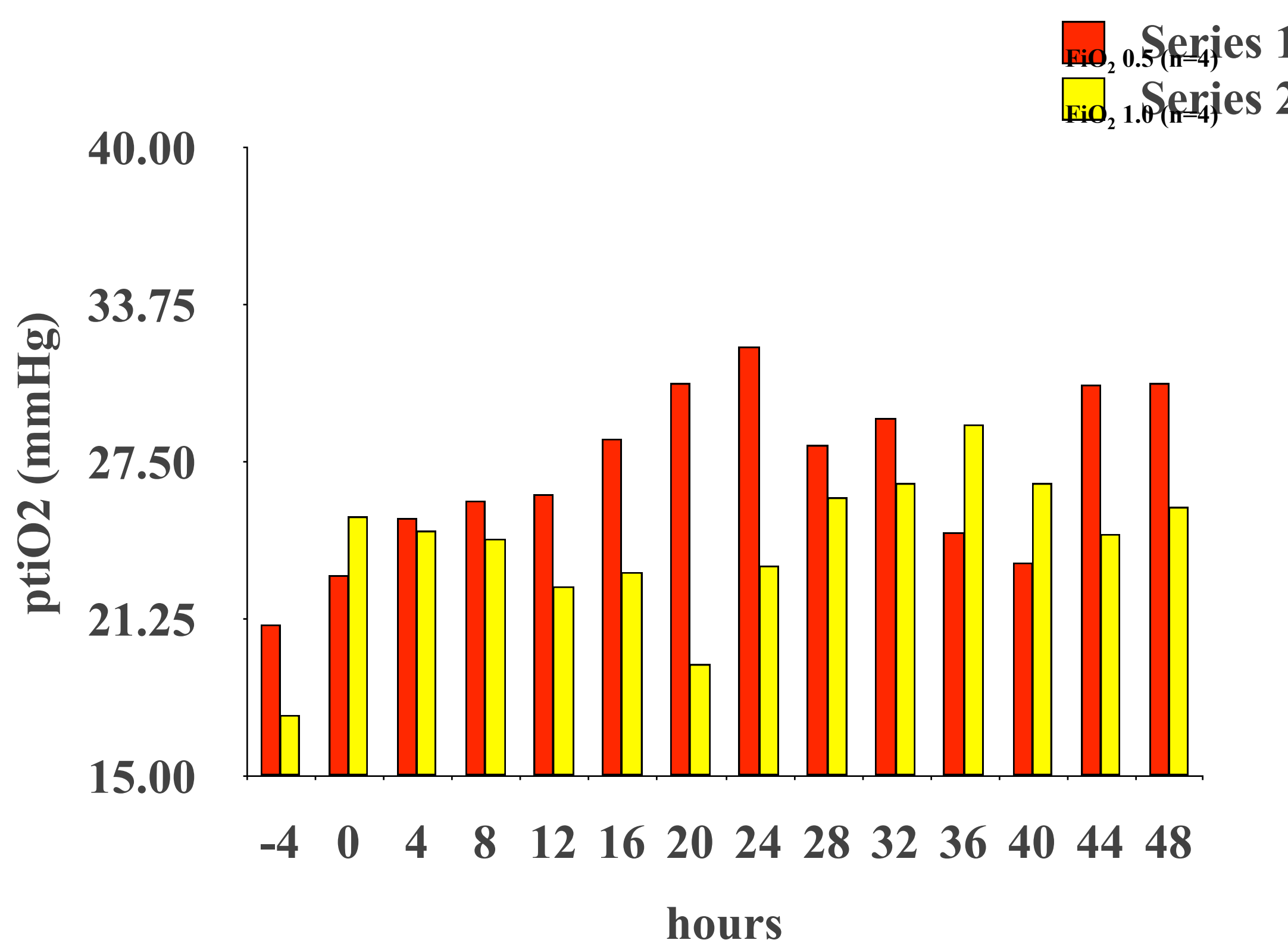
- Carries about 43 ml of oxygen and 196 ml of carbon dioxide per 100ml of PFC, i.e. 5 times more oxygen than haemoglobin.
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- Remains in the circulation for ~20 hours after a single 30 minute rapid infusion.

Materials and Methods

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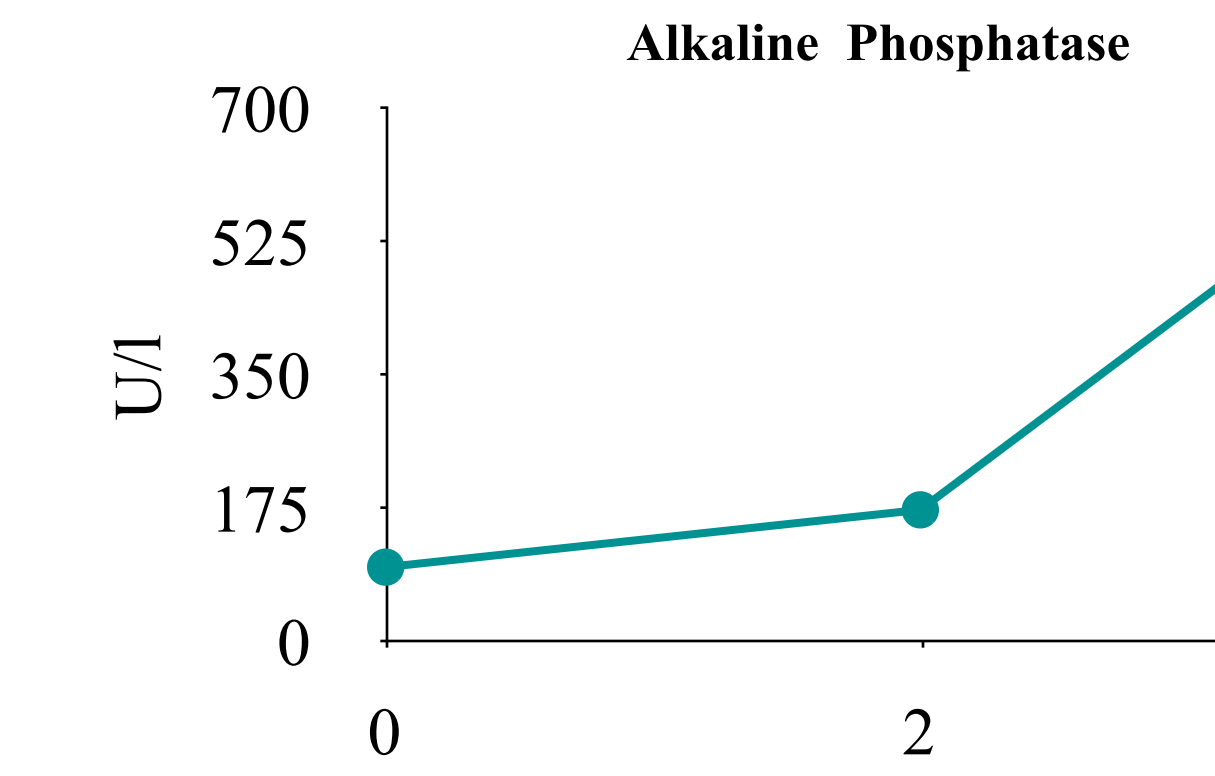
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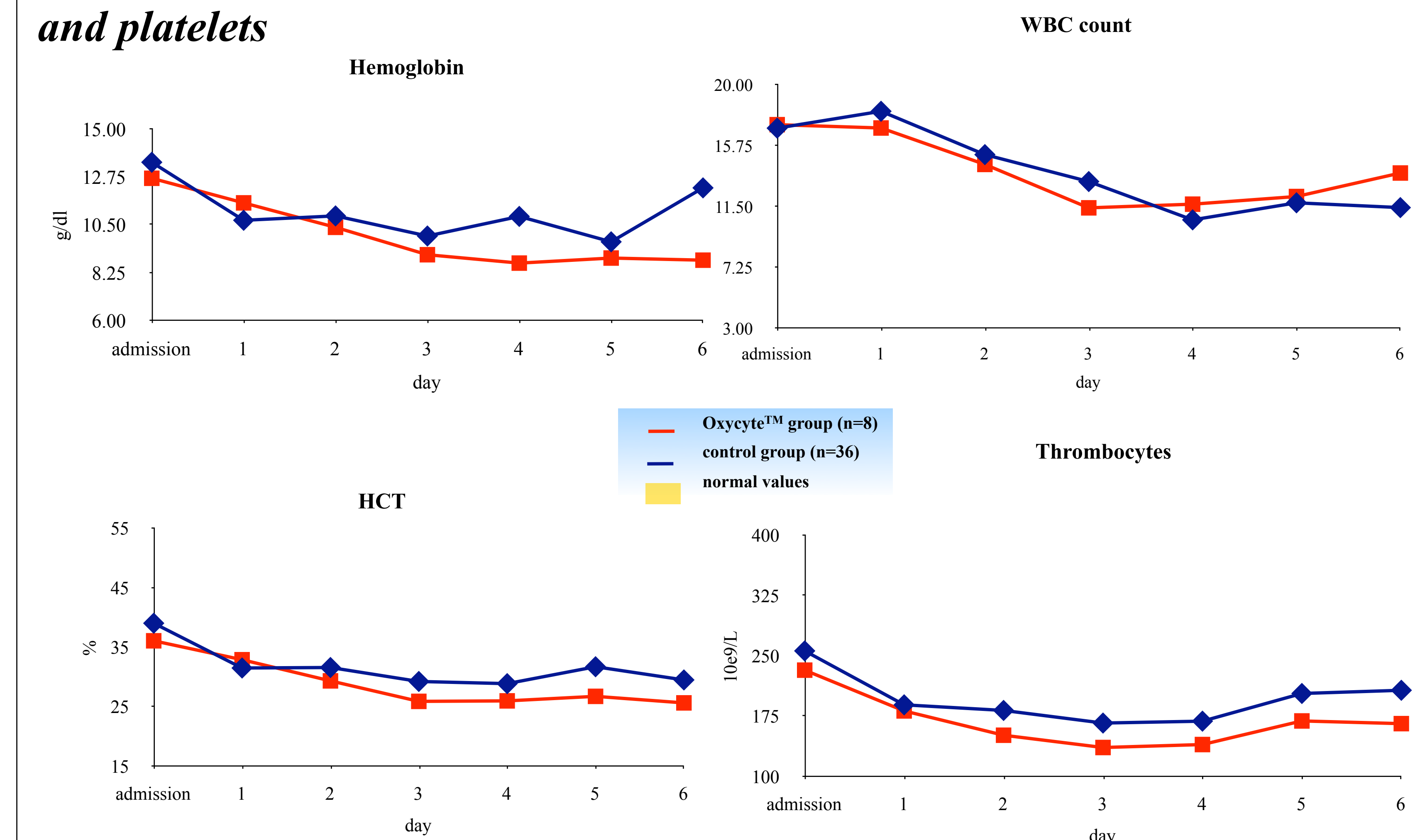
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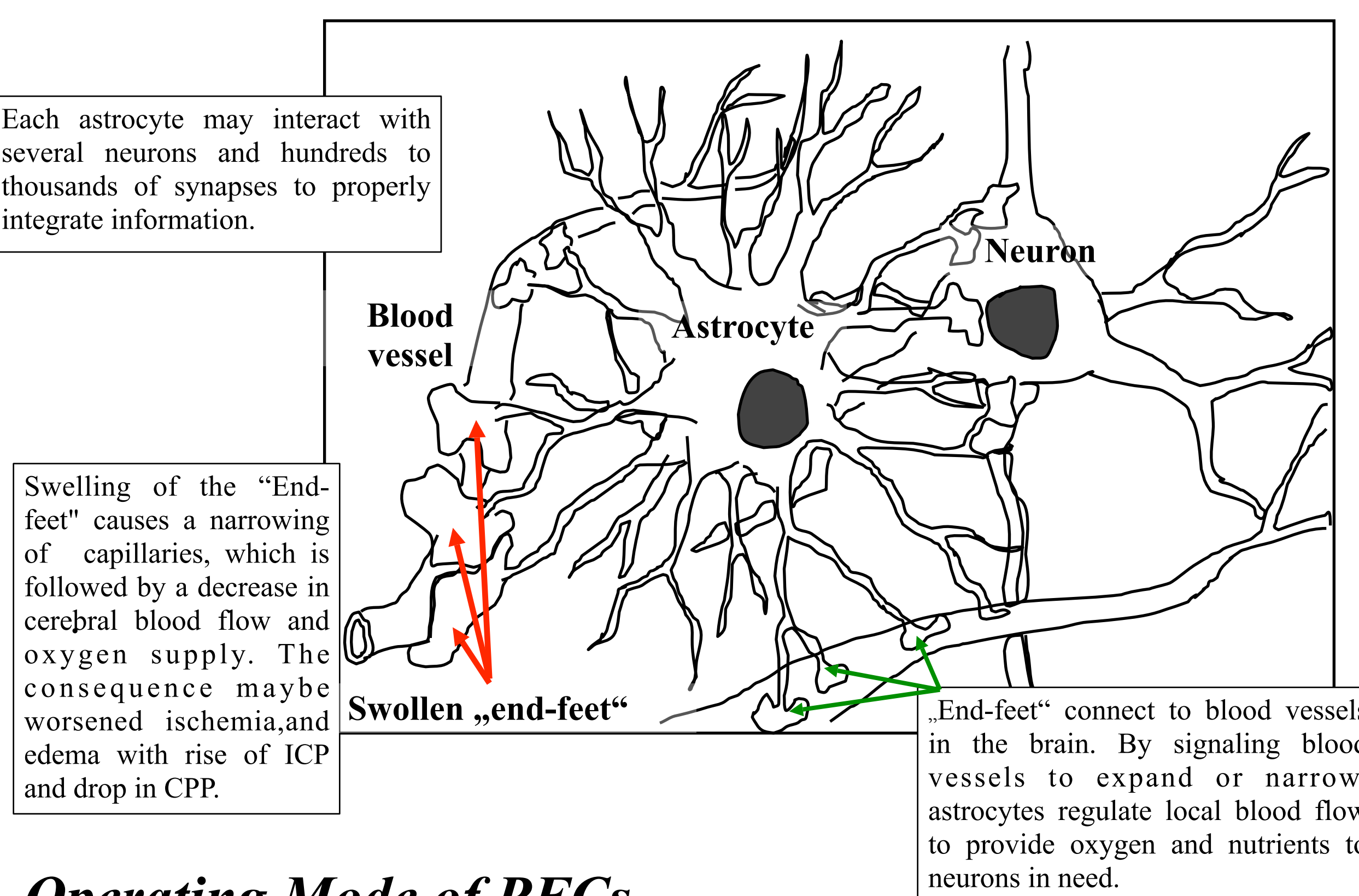
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Conclusions

Oxycyte™ combined with either 50% or 100% O₂ can increase cerebral oxygenation after TBI. Outcome was better, in this small study, than expected. Moreover, no important changes in MAP, CPP and ICP after the infusion of Oxycyte™ was seen, and there were no significant differences between the 2 groups, in liver parameters, or Platelets, and hemoglobin, although in both groups, values outside the normal range were seen. the incidence of Severe Adverse Events, and AE's were similar, in both groups. Accordingly, a large Phase IIB study, with 200-300 patients has been funded, and will begin in 2008.

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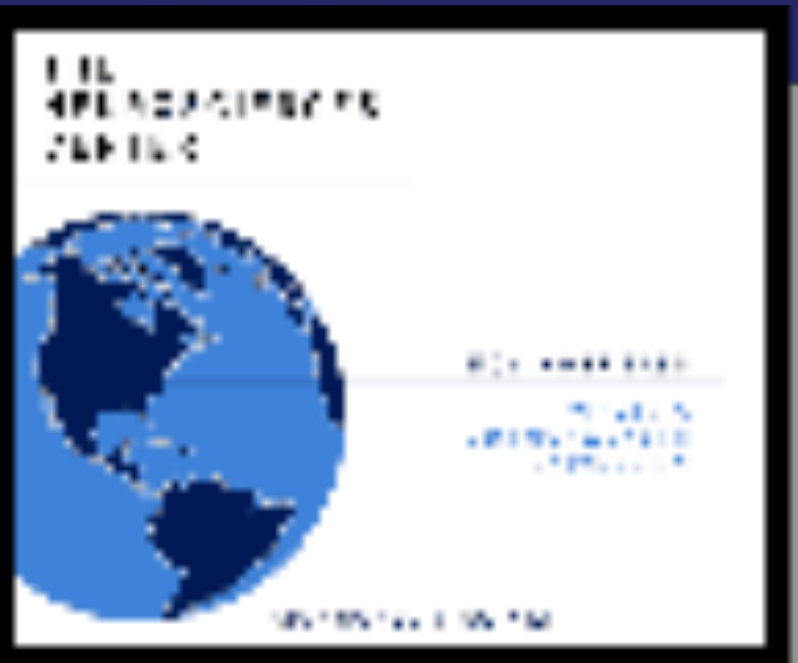
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Perfluorocarbons have the potential to perfuse and oxygenate tissues in contused brain areas, where capillaries are so narrow that red blood cell transport is impeded.

Operating Mode of PFCs

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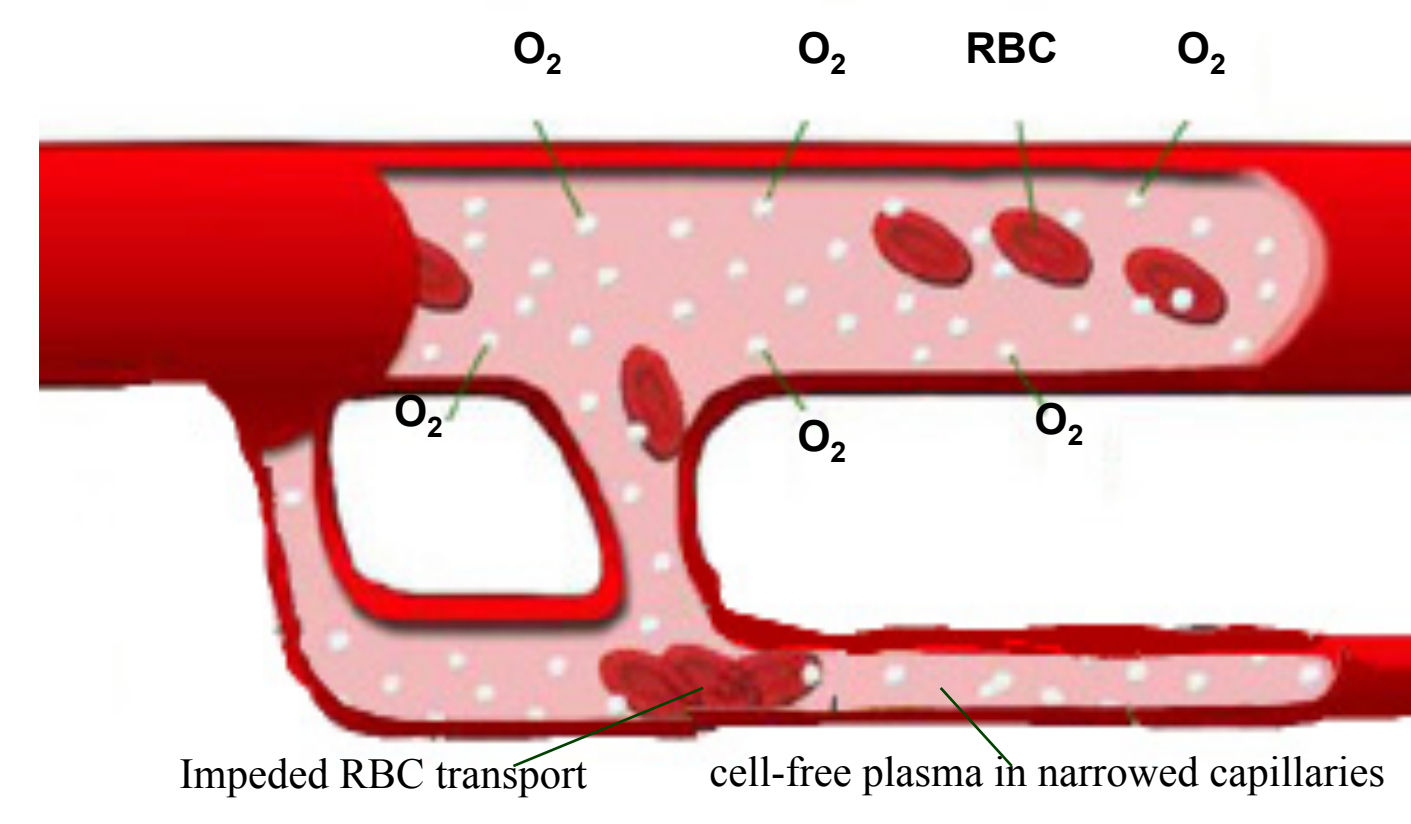
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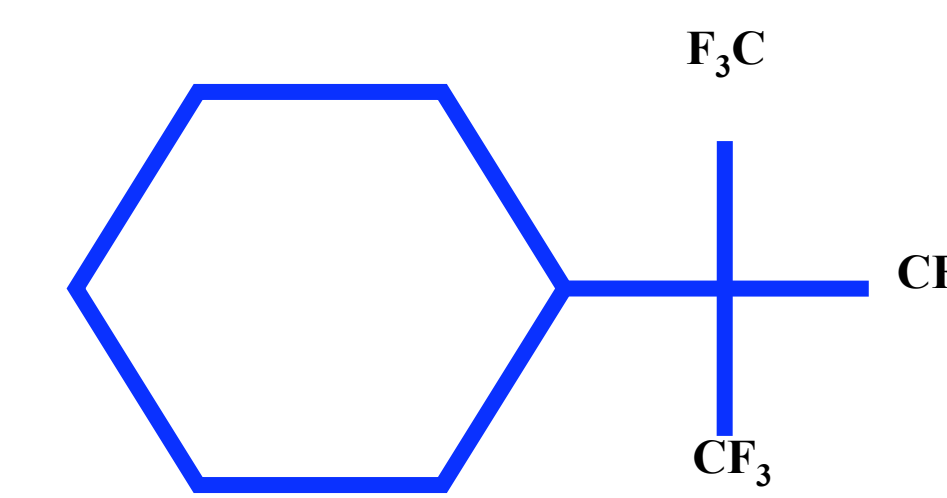
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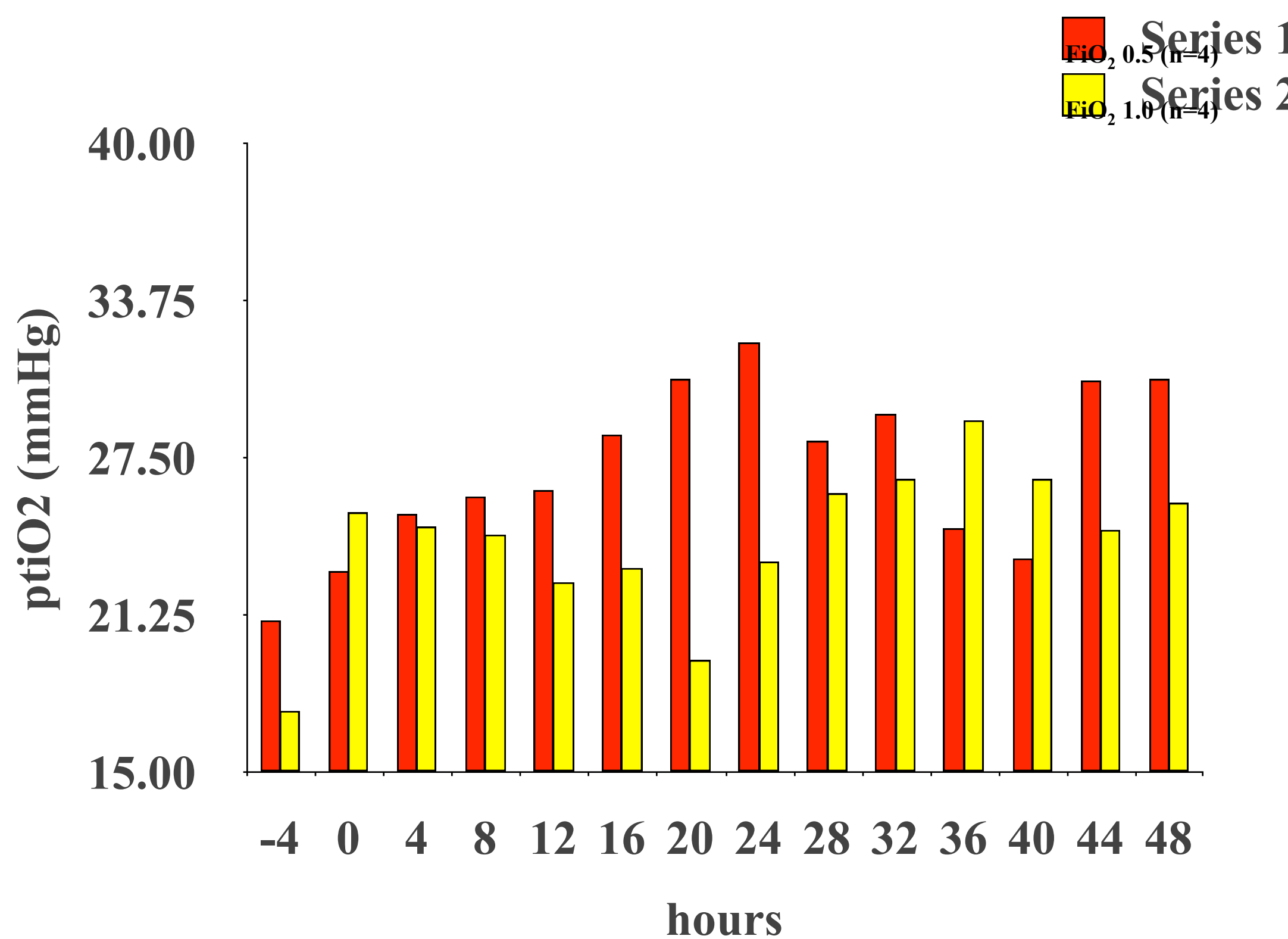
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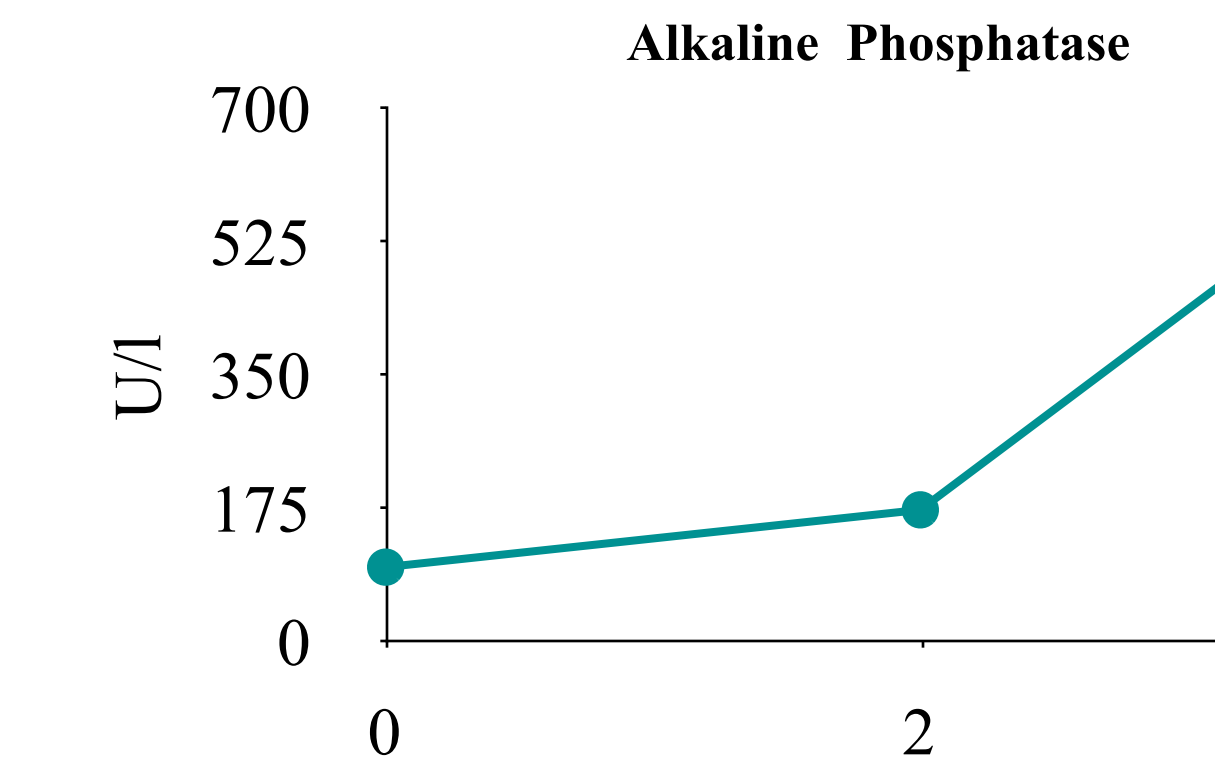
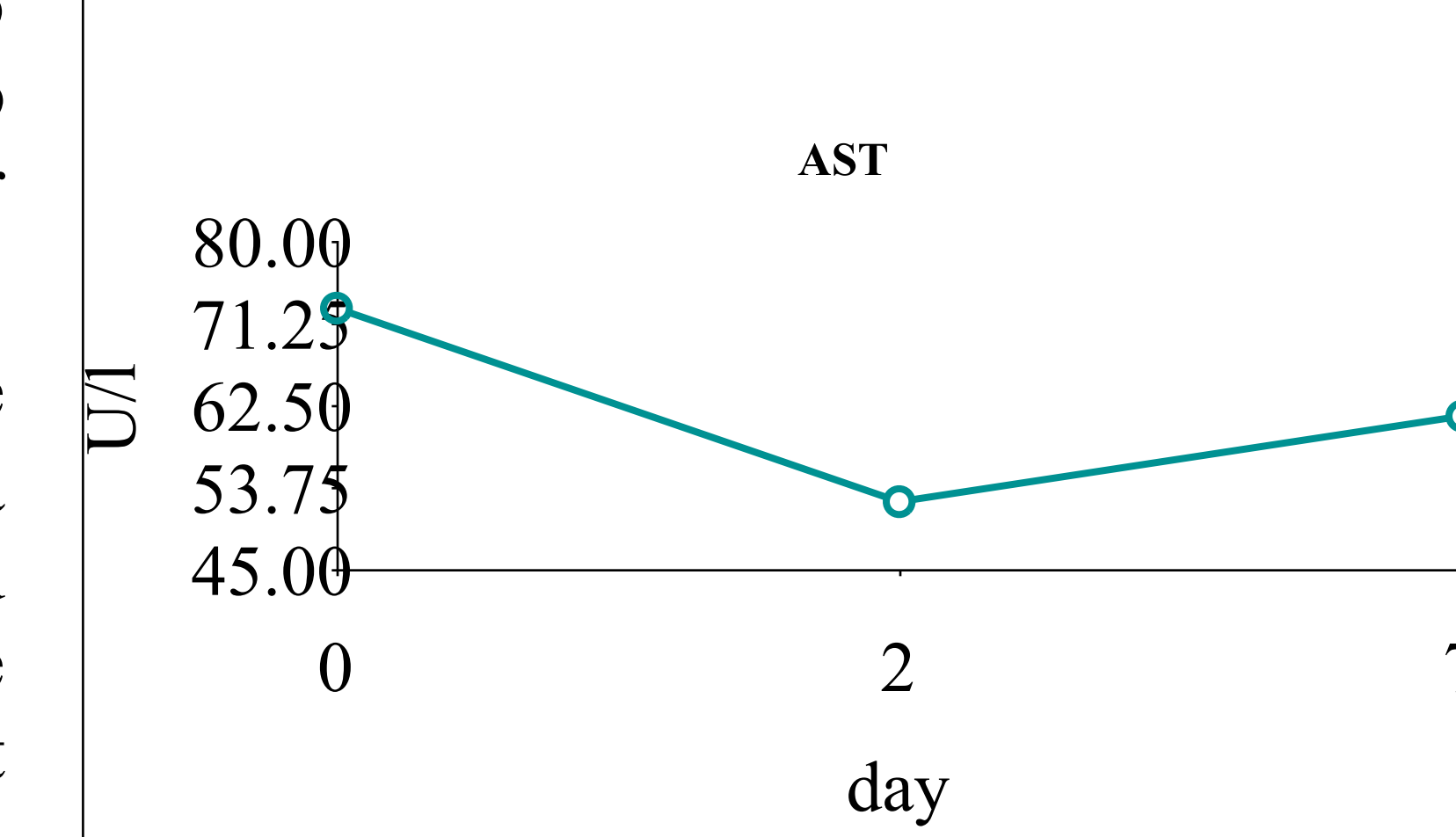
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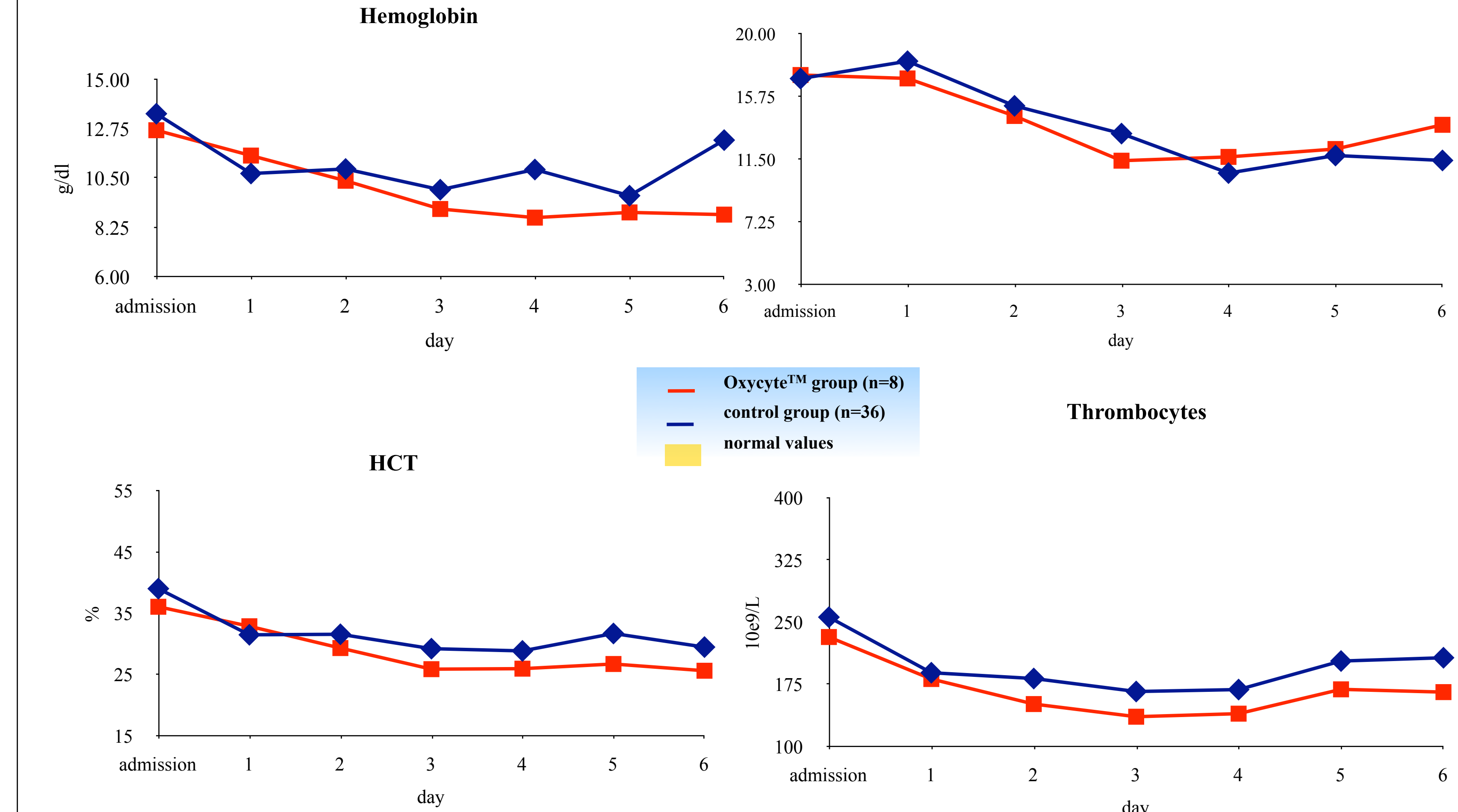
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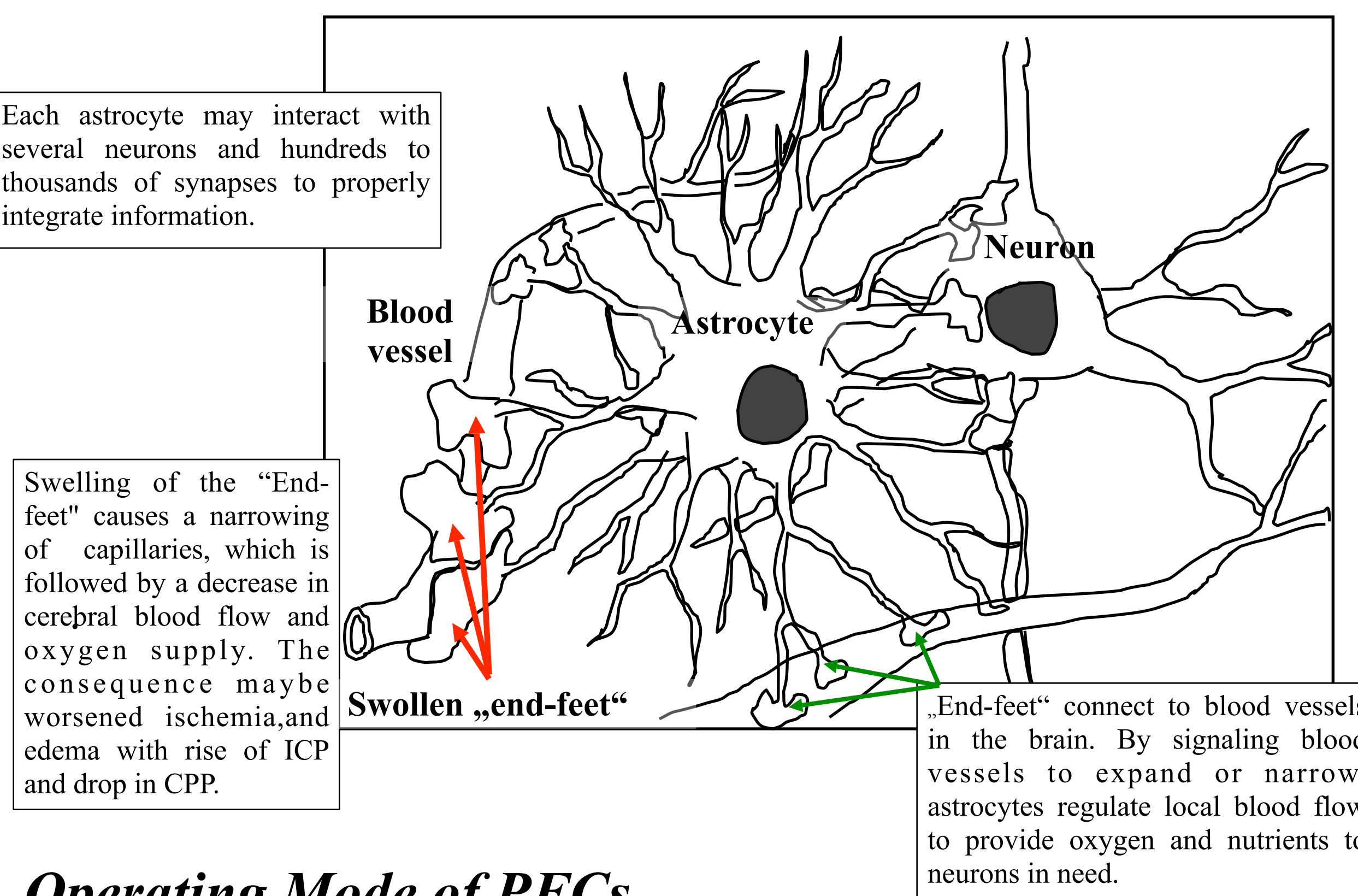
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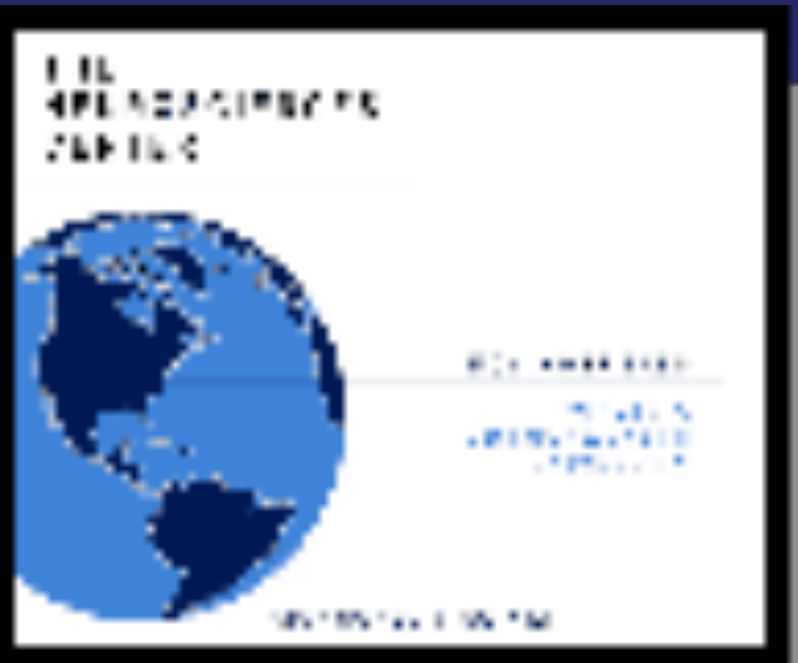
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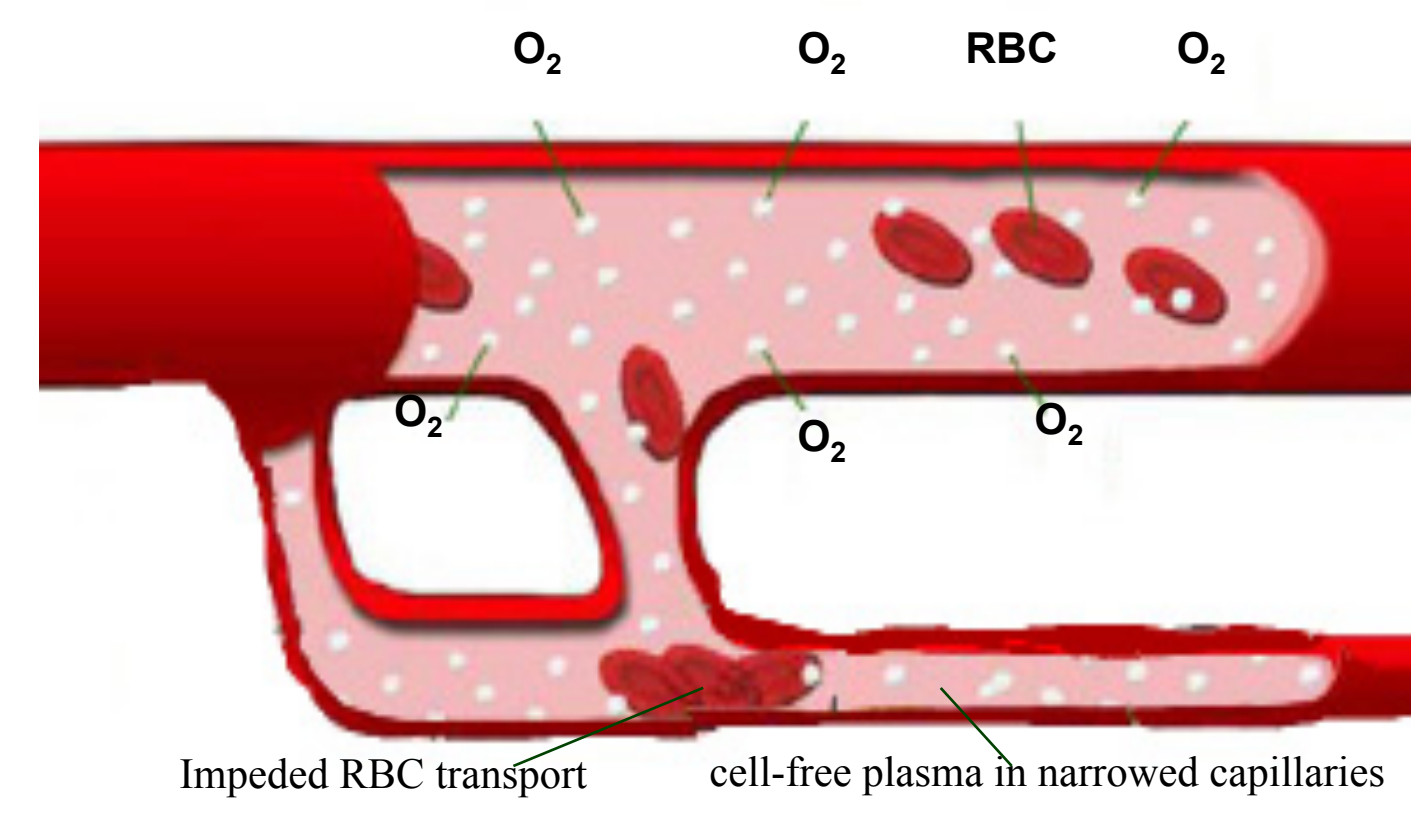
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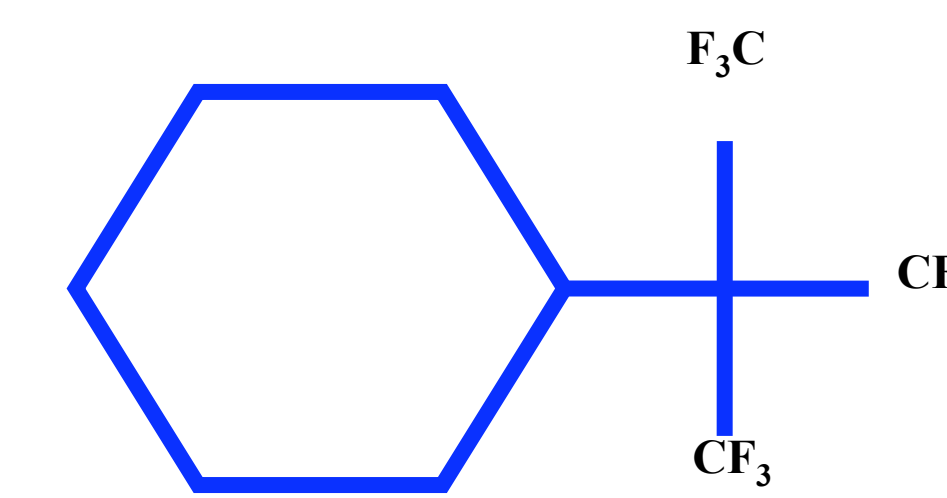
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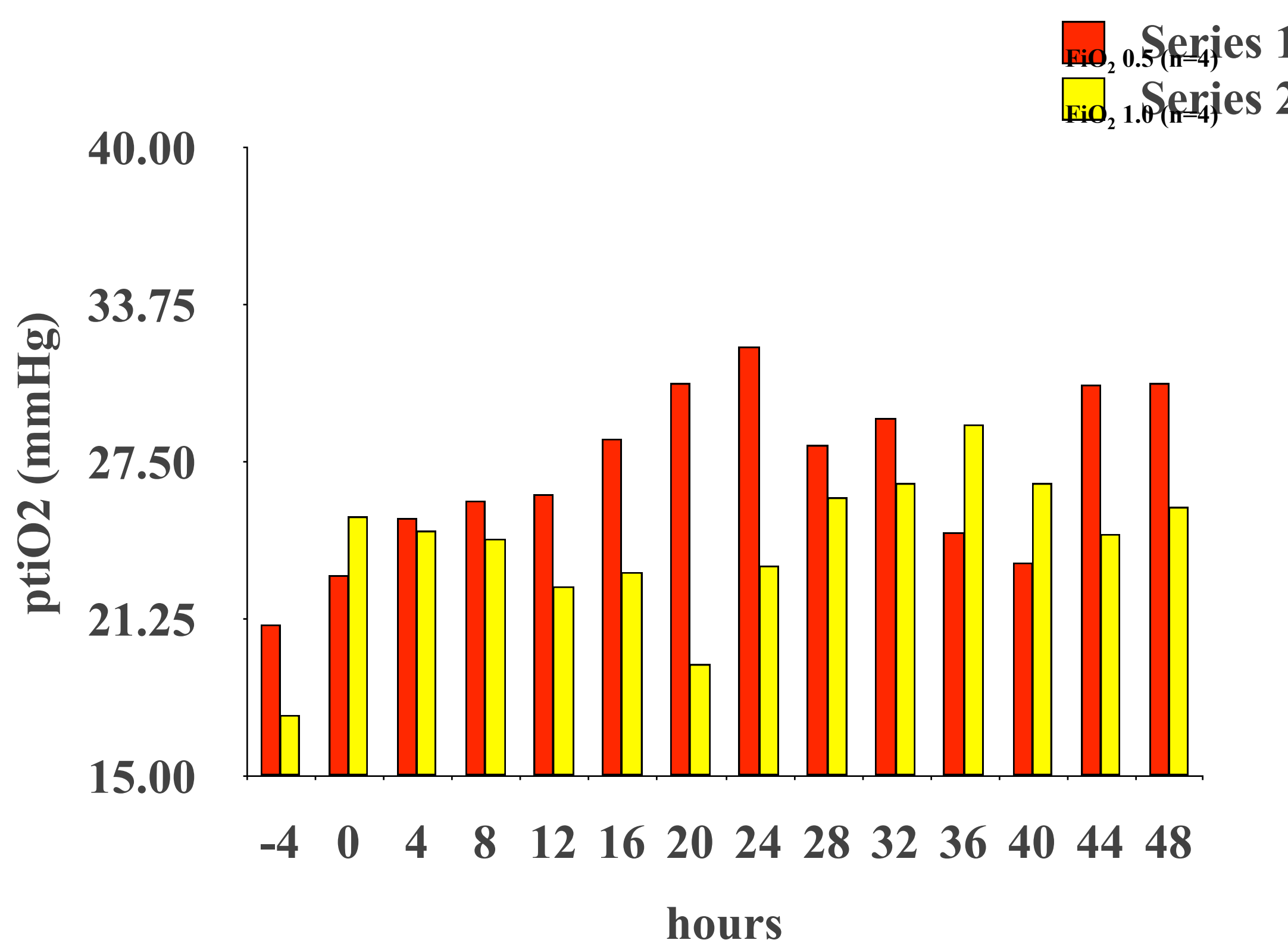
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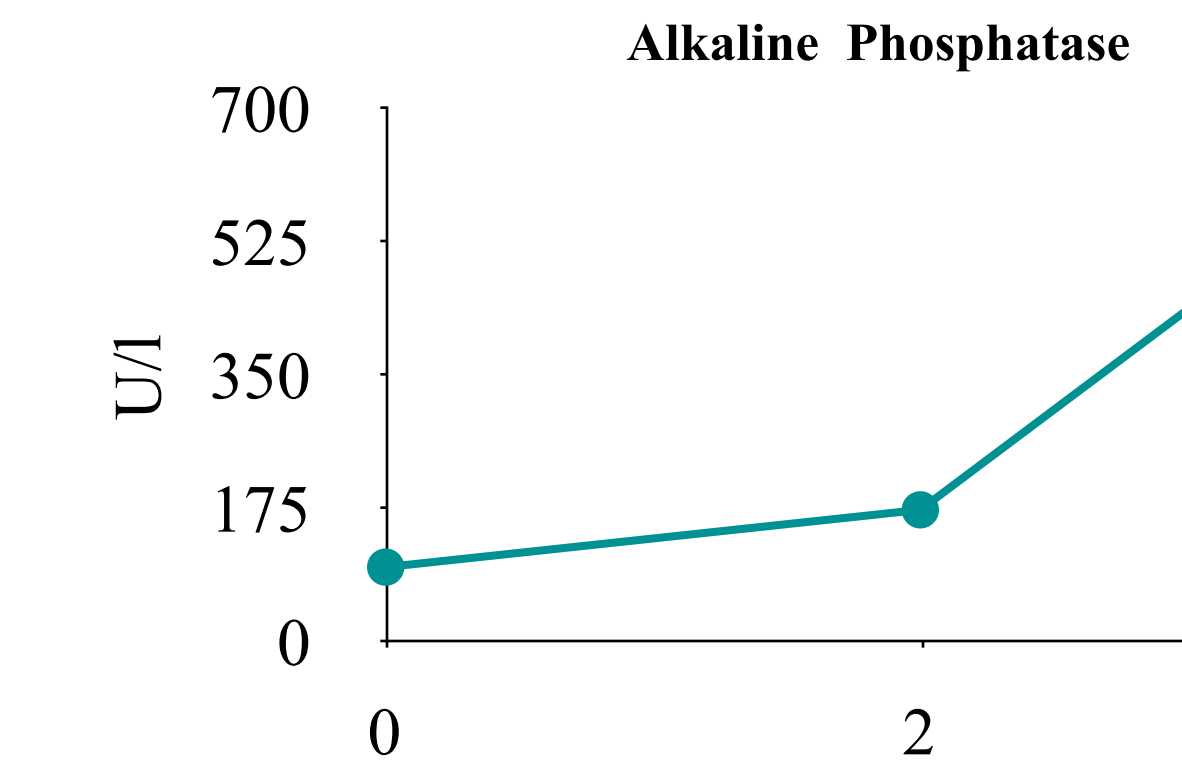
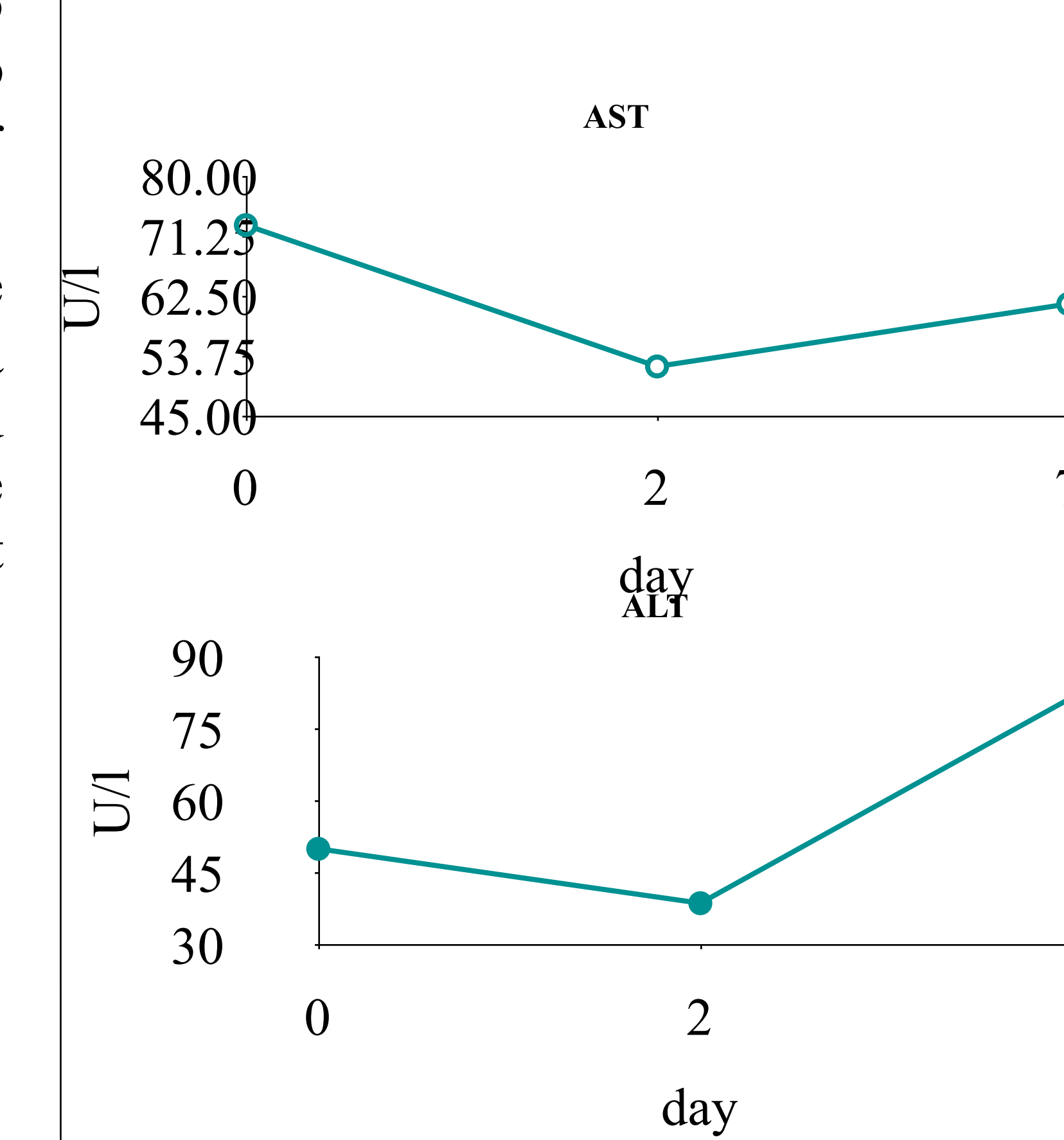
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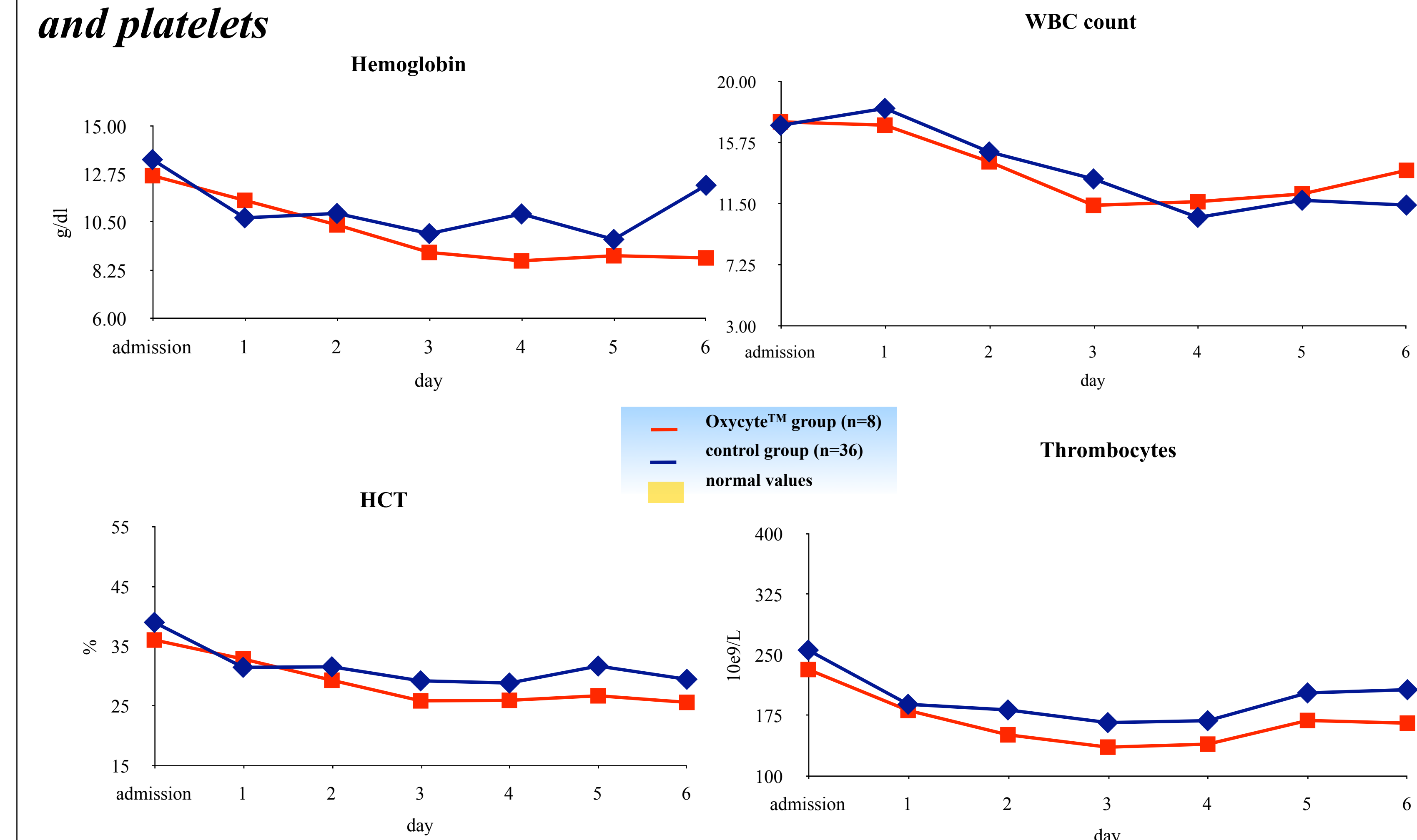
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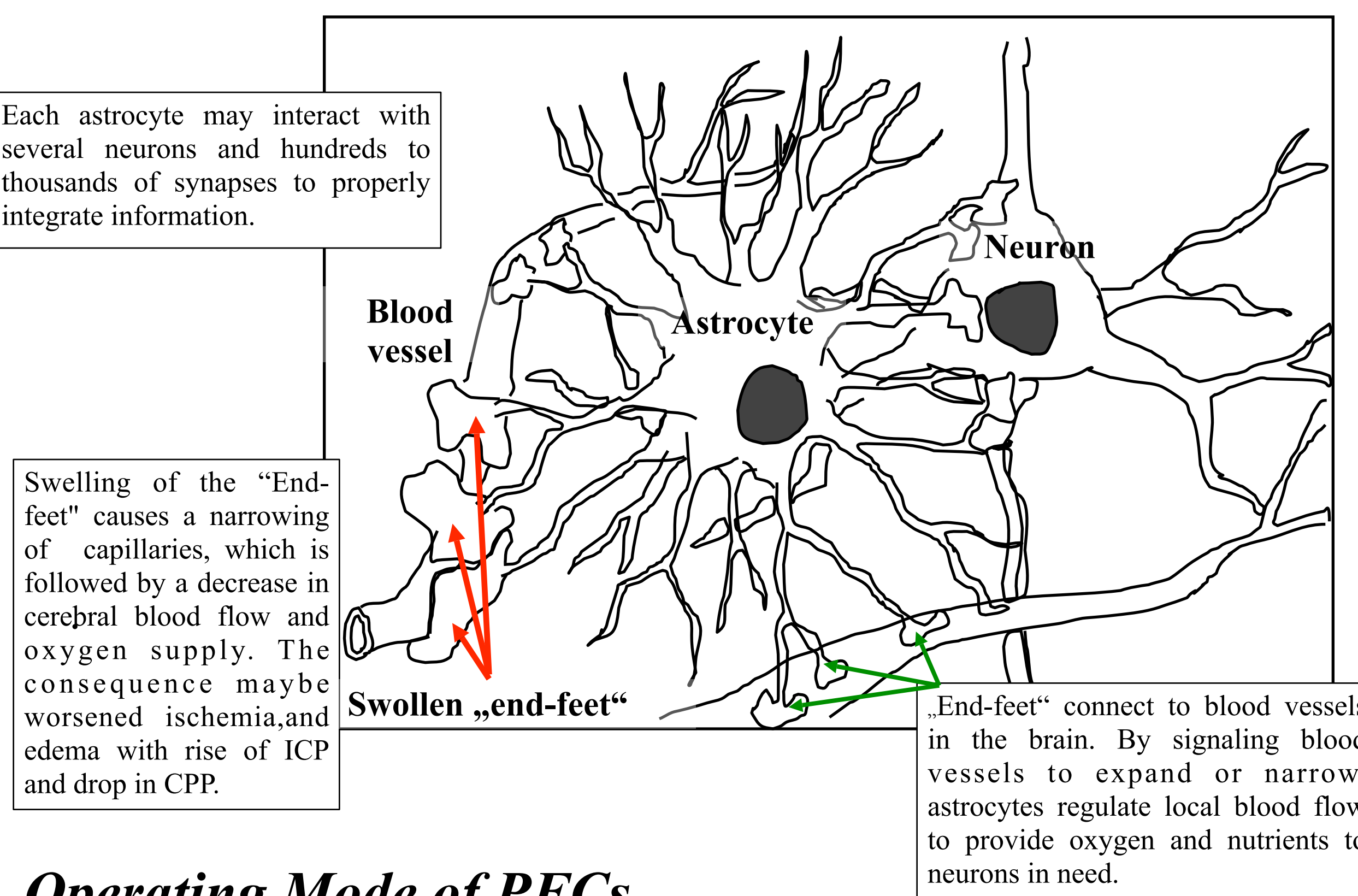
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