Open Peer Review on Qeios

REVIEW ARTICLE

The In Vivo Erythrocyte Sedimentation Rate (ESR) Test: Pandemic Reemergence of Robin Fåhraeus's "Fibrin Coagula"?

Donald Forsdyke[1]

1 Queen's University

Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.

Abstract

In the pre-antibiotic era, infections were usually more frequent and serious than today. In those times, Fåhraeus reported an *in vivo* simulation of the clinical erythrocyte sedimentation rate test that was normally carried out *in vitro* with freshly drawn blood. This led him to propose an explanation for the finding of long white strips ("fibrin coagula") within the blood vessels of those who had died from infections. The surge of serious infections in pandemic times has likely kindled a reemergence of the phenomenon.

Donald R. Forsdyke[a,*]

Department of Biomedical and Molecular Sciences, Queen's University, Kingston, Ontario, Canada K7L3N6

[a] ORCID iD: 0000-0002-4844-1417

[*] Email: forsdyke@queensu.ca

Keywords: aggregation, blood, coronavirus, pandemic, rouleaux, sedimentation.

Introduction

As with the thermometer, the erythrocyte sedimentation rate (ESR) test can act as a non-specific indicator of pathologies, especially those related to infections (e.g., with SARS-CoV-2) [1]. As part of the innate immune response there are changes in serum proteins that correlate with the aggregation of red blood cells to form "piles of coins" (rouleaux), which settle more rapidly than non-aggregated cells [2]. Rouleaux do not form in normal serum unless it is slightly concentrated or is preheated to generate albumin polymers [3]. The red cells themselves play a relatively passive role. When mixed, those from different species form distinct homoaggregates [4][5]. The aggregation may be the manifestation of more

profound molecular-level pro-aggregation changes that occur in infections [6][7][8].

Materials and Methods

The intercell linkage being weak, rouleaux do not normally form in vivo in the flowing blood of a sick person. Thus, a column of freshly drawn blood is held stationary in vitro in a vertical tube. The length of the upper plasma layer that appears as the rouleaux settle is measured. Since blood clots rapidly when exposed to a glass surface, it is citrated.

Results

The phenomenon was studied a century ago by the Swedish physician-scientist Robin Fåhraeus (1888-1968), whose doctoral thesis was formally published in 1921 [9]. He predicted that the phenomenon would be observed in vivo if the blood flow were slowed (perhaps in an aneurysm) or if the heart stopped pumping (as after death). Furthermore, being in vivo, in the short term no anticoagulant would be required. His simple experiment with two tourniquets is shown in Figure 1. After the experiment the tourniquets were quickly removed. Had this not been done, there would be the possibility of eventual intravascular clotting so generating a long fibrous white upper strip above the red erythrocyte sediment below.

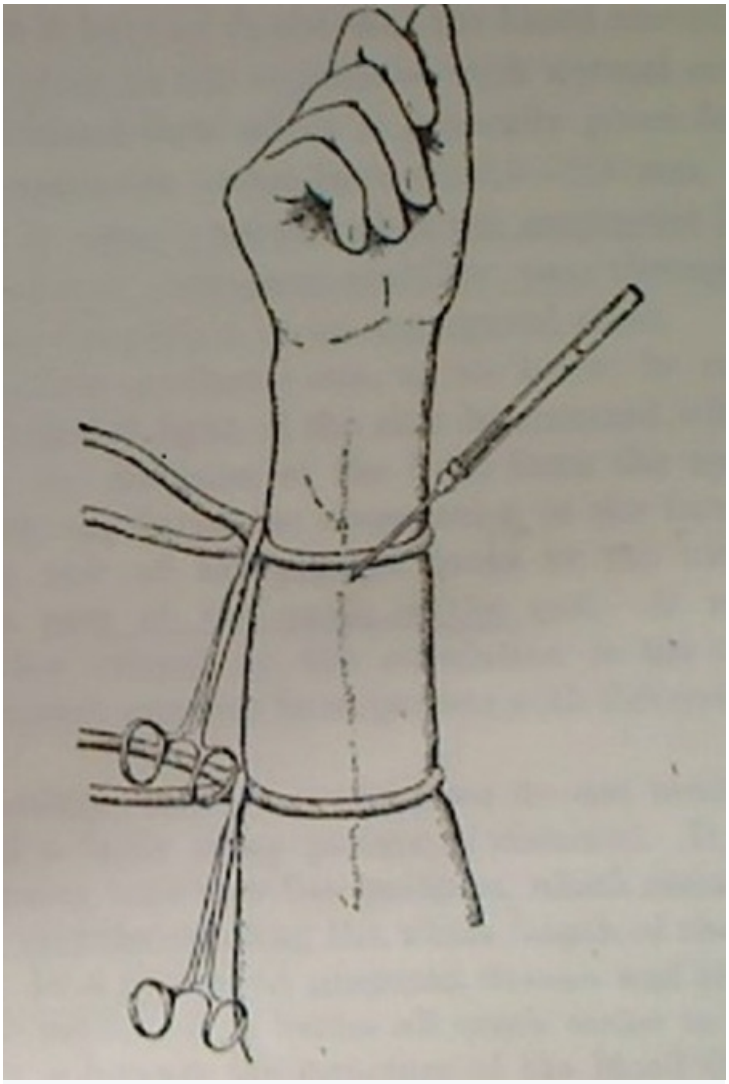

Figure 1. A sick person rests their elbow on a table with their forearm elevated. Fåhraeus ties two rubber tourniquets round the forearm, one low and one high. The high one, near the hand, stops the venous return and the lower one near the elbow prevents the blood draining out of the vein. In other words, he is simulating, in vivo, the ESR test normally carried out with a vertical glass tube. He has occluded a forearm vein, so the blood is not agitated as when it is circulating. Shortly thereafter, he puts a needle into the top of the occluded vein. Out comes pure plasma, free of red blood cells. With a healthy subject, rouleaux *do not form*, and he then withdraws red blood (plasma plus red blood cells). Reproduced from chapter 6 of [9].

Discussion

Fibrin coagula

Fåhraeus extensively cited 19th century literature, which included slowing the blood flow in the back of the eye and watching the red cells attempting, but not succeeding, in forming rouleaux. Thus, rouleaux formation would likely begin in

vivo *within minutes* of the death of a someone undergoing an immune response to foreign antigen. Much later, in vivo clotting would occur. Indeed, in pre-antibiotic times, when *severe infections* were both *more common and more serious*, autopsies frequently revealed long white fibrous intravascular clots ("fibrin coagula," that could correspond to the erythrocyte-free plasma). Much of this work was later summarized both in detail [10], and more broadly [11].

Reemergence in pandemic times

While vaccination saved many lives, during the COVID-19 pandemic there were many unaccounted "excess deaths" [12], some of which may have reflected unrecognized cryptic factors [13]. Adding to such alarms, over the period of the pandemic, embalmers internationally have regularly observed white fibrous clots like the fibrin coagula. As reported to online interviewers and journalists, they are as mystified as are the physicians they consult, who appear unaware of the early history. Fibrin clots in blood vessels were independently noticed in 2022 by pathologist Arne Burkardt and colleagues [14], who declared them "a mystery" in their autopsy reports of their recently vaccinated subjects [15]. The first of several postings by a UK interviewer in 2024 garnered over a million visits in the first week [16].

Phenomenon with broad implications

Fortunately, as suggested here, the phenomenon is *not* "new." Furthermore, whether the antigen has been acquired through natural infection or artificially (through vaccination, as some opposed to vaccination are suggesting) is *not* known. Apart from this, as Fåhraeus suspected in 1939 [11], the aggregation-promoting property of serum may exemplify a more broadly based phenomenon, with important implications for immunological diseases. For example, acting entropically, pyrexia would be expected to promote many molecular aggregations, both extracellularly and intracellularly. Building on subsequent ESR studies [2][3][4][5], we hopefully continue Fåhraeus's work [6][7][8].

Statements and Declarations

Conflict of Interest

I declare no conflict of interest.

Funding

No external funding was received for the preparation of this paper. Funding sources for the author's works are detailed in the corresponding references.

References

1. ^ *Lapić I, Rogić D, Plebani M. Erythrocyte sedimentation rate is associated with severe coronavirus disease 2019*

(COVID-19): a pooled analysis. Clin Chem Lab Med 2020; 58:1146–1148.

2. [a, b]*Forsdyke DR, Ford PM. Rouleau formation as a measure of the phase-separating ability of plasma. J Theor Biol. 1983;103:467–472.*
3. [a, b]*Forsdyke DR, Palfree RGE, Takeda A. Formation of erythrocyte rouleaux in preheated normal serum: roles of albumin polymers and 1ysophosphatidylcholine. Can J Biochem. 1982;60:705–711.*
4. [a, b]*Sewchand LS, Canham PB. Induced rouleaux formation in interspecies populations of red cells. Can J Physiol Pharm. 1976;54:437–442.*
5. [a, b]*Forsdyke DR, Ford PM. Segregation into separate rouleaux of erythrocytes from different species: evidence against the agglomerin hypothesis of rouleaux formation. Biochem J. 1983;214:257–260.*
6. [a, b]*Forsdyke DR. Entropy-driven protein self-aggregation as the basis for self/not-self discrimination in the crowded cytosol. J Biol Sys. 1995;3:273–287.*
7. [a, b]*Forsdyke DR. Lymphocyte repertoire selection and intracellular self/not-self discrimination: historical overview. Immunol Cell Biol. 2015;93:297–304.*
8. [a, b]*Forsdyke DR. Aggregation-prone peptides from within a non-self protein homoaggregate are preferred for MHC association: historical overview. Scand J Immunol. 2023;97:e13306.*
9. [a, b]*Fåhraeus R. The suspension stability of the blood. Acta Med Scand. 1921;55:3–228.*
10. [^]*Fåhraeus R. The suspension stability of the blood. Physiol Rev. 1929;9:241–274.*
11. [a, b]*Fåhraeus R. The erythrocyte-plasma interface and the consequences of their diminution. Lancet 1939;234:630–635.*
12. [^]*Mostert S, Hoogland M, Huibers M, Kaspers G. Excess mortality across countries in the Western World since the COVID-19 pandemic: 'Our World in Data' estimates of January 2020 to December 2022. BMJ Pub Health. 2024;2:e000282.*
13. [^]*Forsdyke DR. Cryptic late-onset myocarditis after coronavirus vaccination. FASEBJ. 2024;38:e23814.*
14. [^]*Burkhardt A. Pursuing the mystery of 'clots' from Covid vaccination. Second Arzte Symposium im Bruker Haus, 18th Sept, 2022. Available at: https://open.lbry.com/@shortXXvids:e/Prof-Burkhardt-Mystery-Clots:e (Accessed 29 August 2024).*
15. [^]*Orient JM. Negative evidence: postmortem examinations of post-COVID-19 vaccine fatalities. J Amer Phys Surg. 2022;27:35–41.*
16. [^]*Campbell J. White clots common. 8th Feb. 2024 https://www.youtube.com/watch?v=4rAoqhTUU0g (Accessed 29 August 2024).*