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Viral respiratory tract infections increase platelet reactivity and activation: an explanation for the higher rates of myocardial infarction and stroke during viral illness

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Recently, much information has accrued demonstrating the close interaction of inflammation, atherosclerosis and thrombosis [1]. Several case–control studies have repeatedly confirmed the common clinical observation that respiratory tract infections often shortly precede or accompany acute ischemic strokes or acute myocardial infarctions [2–5]. A large population based case-series study found a relative risk ratio of 4.95 for acute myocardial infarction in the first 3 days following respiratory tract infections [5]. Influenza is recognized as a major risk factor for the occurrence of acute ischemic cardiovascular events in the elderly population. Epidemiologic evidence consistently proves a decrease in cardiovascular mortality following vaccinations with influenza [6]. Thus far limited data are available on the changes in platelet aggregation during common viral respiratory tract infections, that are most commonly due to rhinovirus and coronavirus infections (40–65% of cases combined) [7].

In the present study, subjects ($n = 17$, eight males, nine females) with presumed viral upper respiratory tract infections presenting with bronchitis, pharyngitis, rhinitis or sinusitis were recruited among hospital employees and at outpatient clinics. Patients with suspected bacterial infections receiving antibiotic therapy or taking non-steroidal anti-inflammatory agents, aspirin, thienopyridines, and warfarin were excluded.

Peripheral venous blood samples were obtained at the time of the viral infection and 6 weeks after enrolment. Platelet surface receptor expression was determined by flow cytometry using monoclonal antibodies against CD41a (Glycoprotein IIb/IIIa) and CD62P (P-selectin) as previously described [8]. Platelet aggregation was determined using a Chronolog Lumi-Aggregometer as previously described [9]. Platelets were stimulated at 37 °C with adenosine diphosphate (ADP) at concentrations of 1, 5 and 20 μM. Platelet aggregation was expressed as the maximal percent change in light transmittance from baseline, using platelet poor plasma as a reference.

Eight healthy volunteers (six males, two females) served as controls. The mean age of patients with viral infection was 35 years (range 24–62), and the mean age of controls was 30 years (range 23–42).

Platelet reactivity was higher during viral upper respiratory tract infection as measured by low dose (1 μM) ADP-induced aggregation [45 ± 28% vs. 26 ± 21% after 6 weeks ($P = 0.0098$) and 22 ± 8% in the control group ($P = 0.006$)] (Table 1). Similarly, P-selectin expression was higher during times of viral infection with 2.3 ± 0.8% of platelets CD62 positive vs. 1.8 ± 0.5% after 6 weeks ($P = 0.017$) and 1.7 ± 0.4% in the control group ($P = 0.03$). There were no significant differences in P-selectin expression and aggregation between 6 weeks post-infection and the control group.

Our study suggests that subjects suffering from the 'common cold' exhibit increased platelet reactivity and activation. We

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Table 1 Platelet aggregation and p-selectin expression in subjects during infection, at 6-week follow-up and in controls

	During infection*	Six-week follow-up*	*P*-value†	Controls*	*P*-value‡
1 μM ADP-induced aggregation (%)	45 ± 28	26 ± 21	0.0098	22 ± 8	0.006
5 μM ADP-induced aggregation (%)	76 ± 15	76 ± 18	0.61	73 ± 5	0.55
20 μM ADP-induced aggregation (%)	76 ± 8	76 ± 10	0.99	72 ± 7	0.24
P-selectin (% of CD62 positive platelets)	2.3 ± 0.8	1.8 ± 0.5	0.017	1.7 ± 0.4	0.03

*Values represent mean ± SD.
†*P*-values for paired Wilcoxon ranked-sum test between infection and 6-week follow-up.
‡*P*-values for Student's *t*-test between subjects with infection and control group.

demonstrated that platelets were more sensitive to a lower dose of an important agonist (1 μM ADP), but did not demonstrate any difference in their maximal aggregation induced by higher doses (5 and 20 μM ADP). The finding of increased P-selectin expression is consistent with the presence of activated platelets in the peripheral venous circulation during viral illness. Our data support the concept of a systemic pro-aggregatory state during or shortly after viral infections as postulated by earlier studies. Changes in coagulation, platelet aggregation, lipid metabolism, smooth muscle spasm, plaque composition, and alteration of endothelial function have been postulated as a mechanism underlying this observation [2–5].

P-selectin expressed on platelets upon activation plays a pivotal role in platelet-monocyte aggregation formation and inflammation [10]. P-selectin is essential in controlling platelet rolling at sites of vascular injury and enhances local thrombus formation by cytokine and tissue factor release from monocytes [10]. Circulating activated platelets exacerbate atherosclerosis in mice deficient in apolipoprotein E, an effect that was reduced when using P-selectin-deficient platelets, thus underlining the importance of P-selectin in platelet-dependent inflammation [11]. Also higher levels of activated platelets have been consistently documented in acute myocardial infarction, congestive heart failure, microangiopathic diabetes mellitus, and stroke. The source of the activated platelets documented in our study remains unclear.

Our study is limited by the relatively small sample size. Also our findings need to be repeated in sets of patients with multiple risk factors or documented coronary disease, who are at greatest risk for future ischemic events. These studies may help to determine the role of additional prophylactic platelet inhibition in patients with viral upper respiratory tract infections and documented cardiovascular disease.

In conclusion, our study demonstrates that viral respiratory tract infections are associated with increased platelet reactivity and activation. These findings support a pro-aggregatory state that may contribute to the higher rates of myocardial infarction and stroke as shown by epidemiologic studies.

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