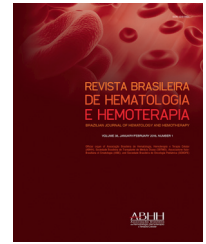




## Revista Brasileira de Hematologia e Hemoterapia Brazilian Journal of Hematology and Hemotherapy

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### Review article

# Economy class syndrome: what is it and who are the individuals at risk?

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#### ARTICLE INFO

##### Article history:

Received 1 September 2016

Accepted 2 May 2017

Available online xxx

##### Keywords:

Economy class syndrome

Air travel

Thromboembolism

Pregnancy

#### ABSTRACT

The term 'economy class syndrome' refers to the occurrence of thrombotic events during long-haul flights that mainly occur in passengers in the economy class of the aircraft. This syndrome results from several factors related to the aircraft cabin (immobilization, hypobaric hypoxia and low humidity) and the passenger (body mass index, thrombophilia, oral contraceptives or hormone replacement therapy, cancer), acting together to predispose to excessive blood coagulation, which can result in venous thromboembolism. Several risk factors, both genetic and acquired, are associated with venous thromboembolism. The most important genetic risk factors are natural anticoagulant deficiencies (antithrombin, protein C and protein S), factor V Leiden, prothrombin and fibrinogen gene mutations and non-O blood group individuals. Acquired risk factors include age, pregnancy, surgery, obesity, cancer, hormonal contraceptives and hormone replacement therapy, antiphospholipid syndrome, infections, immobilization and smoking. People who have these risk factors are predisposed to hypercoagulability and are more susceptible to suffer venous thromboembolism during air travel. For these individuals, a suitable outfit for the trip, frequent walks, calf muscle exercises, elastic compression stockings and hydration are important preventive measures. Hence, it is essential to inform about economic class syndrome in an attempt to encourage Brazilian health and transport authorities to adopt measures, in partnership with the pharmaceutical industry, to prevent venous thromboembolism.

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## Introduction

Venous thromboembolism (VTE) is a clinical condition that involves two related situations, venous thrombosis and

pulmonary embolism.<sup>1</sup> It affects approximately 2–3 people per 1000 individuals per year. VTE is the third cause of death by vascular diseases, only surpassed by myocardial infarction and ischemic stroke. In addition, it is the most common cause of preventable death in hospitalized patients.<sup>2,3</sup>

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<http://dx.doi.org/10.1016/j.bjhh.2017.05.001>

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The term 'economy class syndrome' refers to the occurrence of thrombotic events during long-haul flights, mainly in economy class passengers. This syndrome results from several factors related to the aircraft cabin (immobilization, hypobaric hypoxia and low humidity) and to the passenger (such as obesity, thrombophilia, oral contraceptive use, hormone replacement therapy and cancer), that act together predisposing to excessive blood coagulation, which can result in VTE.<sup>4</sup>

Several risk factors, both genetic and acquired, are associated with VTE. The most important genetic risk factors are natural anticoagulant deficiencies: (1) Deficiency of antithrombin, protein C or protein S; (2) Factor V (FV) Leiden, which is resistant to protein C inactivation; (3) The G20210A mutation in the prothrombin gene, which leads to an increase in gene expression and prothrombin plasma levels; (4) The C10034T mutation in the fibrinogen gene, which produces a variant form of fibrinogen; and (5) Non-O blood group (A, B and AB) as individuals have higher von Willebrand factor and factor VIII plasma levels than O group subjects and have increased risk of thrombosis.

Acquired risk factors include age, pregnancy, surgery, obesity, cancer, hormonal contraceptives and hormone replacement therapy, antiphospholipid syndrome, infections, immobilization and smoking.<sup>5,6</sup>

## Venous thromboembolism and air travel

Data from the Brazilian National Civil Aviation Agency (ANAC) revealed that the number of passengers carried by civil aviation in 2015 surpassed 100 million.<sup>7</sup> Tables 1 and 2<sup>8-10</sup> show the main domestic and international flights in and from Brazil in 2015. The aircraft microenvironment provides very specific conditions, such as reduced oxygen tension, immobilization (in general, people are in tight uncomfortable seats) and circadian dysrhythmia, due to differences in time zones (jet lag).

**Table 1 – Major domestic flights of Brazil in 2015.**

Route	Passengers (millions)	Mean flight time
São Paulo (CGH) – Rio de Janeiro (SDU)	4.05	1 h
São Paulo (CGH) – Brasília (BSB)	2.23	1 h 45 min
São Paulo (GRU) – Salvador (SSA)	2.2	2 h 20 min
São Paulo (GRU) – Porto Alegre (POA)	2.02	1 h 35 min
São Paulo (GRU)–Recife (REC)	1.98	3 h 30 min
São Paulo (CGH) – Belo Horizonte (CNF)	1.82	1 h 20 min
São Paulo (CGH) – Porto Alegre (POA)	1.7	1 h 35 min
São Paulo (CGH) – Curitiba (CWB)	1.52	1 h 00 min
São Paulo (CGH) – Brasília (BSB)	1.35	1 h 45 min
Rio de Janeiro (GIG) – Salvador (SSA)	1.34	2 h 15 min
Total	20.21	

**Table 2 – Major international flights from Brazil in 2015.**

Destination	Passengers (millions)	Mean flight time <sup>a</sup>
USA	5.38	11 h
Argentina	3.07	2 h 50 min
Portugal	1.54	11 h
Chile	1.41	4 h
Spain	0.98	12 h
France	0.97	14 h
Germany	0.84	15 h
Peru	0.65	5 h 30 min
Uruguay	0.62	2 h 40 min
United Kingdom	0.59	12 h
Italy	0.50	12 h

<sup>a</sup> Flight time departing from the city of São Paulo.

These factors may disturb the passenger's health, causing fatigue, anxiety and nausea.<sup>11,12</sup>

The first cases of VTE associated with air travel were reported in 1954, and since then, other cases have been described.<sup>4</sup> The vast majority of victims suffer pulmonary embolism and/or deep vein thrombosis, but cases of subclavian vein thrombosis,<sup>13</sup> cerebral vein thrombosis,<sup>14</sup> stroke and arterial thrombosis<sup>15</sup> have also been reported.

The actual incidence of VTE in air travel is unknown. It is difficult to arrive at an estimation given that this condition may be asymptomatic or may develop days or even weeks after the flight.<sup>16</sup> In a cohort of healthy subjects, the absolute risk of VTE on flights lasting more than 4 h was 1 in 6000.<sup>17</sup> A meta-analysis<sup>18</sup> involving 14 studies reported 4055 cases of VTE in trips lasting up to 8 h. These studies included both air and overland trips with the follow-up time after the journey ranging from two to eight weeks. The relative risk of VTE was 2.8 [95% confidence interval (95% CI): 2.2–3.7] and at each increment of 2 h in travel time, there was an approximate 18% increase in the risk of VTE. Considering only air travel, this risk increased to 26%, suggesting a cumulative effect of flight time in the genesis of VTE.

MacCallum et al.<sup>19</sup> demonstrated that on flights lasting less than 4 h, the risk of VTE is approximately two times higher compared to non-traveler subjects [odds ratio (OR): 2.20; 95% CI: 1.29–3.73] and remained high in the four subsequent weeks. In long-haul flights (greater than 12 h as one or more flights), the risk of VTE is around three times higher (OR: 2.75; 95% CI: 1.44–5.28). After 12 weeks, no time-flight effect was observed in the occurrence of thrombotic events.

A number of factors associated both to the aircraft or passengers have been singled out as responsible for triggering VTE.<sup>20</sup> Stasis and hypercoagulability, two components of Virchow's triad, have a crucial role in the occurrence of thromboembolism in flights.<sup>18</sup>

The factors associated with the aircraft include:

- Hypobaric hypoxia: The hypoxia caused by reduced air pressure in the aircraft cabin contributes to VTE. At sea level, normal atmospheric pressure is 760 mmHg, which corresponds to a partial oxygen pressure of 159 mmHg. Under these conditions, oxygen saturation in healthy individuals is 95%. In the cockpit of an aircraft at flight altitude,

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