Review
ARTICLE

TRAVELLER'S VENOUS THROMBOEMBOLISM

A Review of World Literature, a Survey of World Airlines and an Australian Perspective

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ABSTRACT

Venous thromboembolism (VTE) following long distance travel has cost the lives of many travellers. A number of airlines have been successfully served with lawsuits based on their failure to warn the passengers of potential health risks of flying and especially their failure to warn against potential thromboembolism.

Traveller's Venous Thromboembolism (TVTE) is not limited to air travellers and may follow road and rail travel. Most studies have focused on air travel and air travel-related VTE has been called the 'Economy Class Syndrome'. This phenomenon is by no means limited to the economy class passengers and may affect passengers in other cabin classes as well as cabin and flight crew.

The incidence of TVTE is estimated to range from 0.5 to 4 per 10,000 travellers. The most common presenting symptoms are leg pain and swelling but patients may remain asymptomatic. The majority of patients develop symptoms within a week of travel. TVTE may present as deep venous thrombosis (DVT), pulmonary embolism (PE), superficial thrombophlebitis (STP) or various combinations of the three. The most common presentation of travel related DVT is femoropopliteal thrombosis and the most commonly affected leg is the left leg. The main postulated travel related risk factors are immobilisation and cramped conditions of travel, reduced humidity and hypoxia. The majority of patients, however, have multiple personal risk factors in addition to those presumed to be associated with travel. The presence of thrombophilic abnormalities as demonstrated by the authors is the most common risk factor identified in 72% of patients. Other important risk factors include female hormonal supplements, obesity, a past history or family history of VTE, history of recent trauma or surgery, and malignancy. Travel related conditions interact in an additive or even synergistic fashion with the pre-existing personal risk factors to precipitate the thrombotic event. The severity of the final outcome depends on the delicate balance between pro-coagulant and anti-coagulant factors. Clearly, there is a need to identify those travellers who have multiple risk factors. Assessment of passengers' individual risks is essential in providing appropriate advice and prophylactic measures. Airlines can help this process by informing their clients of potential risks of flying and by encouraging travellers to discuss prophylaxis with appropriate physicians especially if personal risk factors are present. This review examines the current state of knowledge regarding TVTE and proposes a set of recommendations.

INTRODUCTION

Venous Thromboembolism (VTE) is a serious disorder which may have a fatal outcome in 1 to 2% of the sufferers.[1] The annual incidence of VTE in Caucasian populations is 1 to 2 per 1000.[2-5] This incidence is age dependant and climbs from virtually zero in children to less than 1 per 10 000 in young adults and 3-5 per 1000 in people over the age of 60 years.[6] A serious disabling long-term consequence of deep venous thrombosis (DVT) is post-thrombotic syndrome which may present with pain, trophic skin changes and ulceration.[7] Approximately 10 to 30% of patients will ultimately develop chronic venous insufficiency after DVT. Fatal pulmonary embolism (PE) occurs in 1-2% of all patients.[3]

International travel has grown substantially over the last twenty-five years and millions of people travel for very long distances. VTE following long distance travel has unfortunately cost the lives of many travellers. This has attracted the public attention and has formed the front-page headlines of many local and foreign newspapers. A number of airlines have been successfully served with lawsuits based on their failure to warn the passengers of potential health risks of flying and especially their failure to warn against potential thromboembolism. This review examines the current state of knowledge regarding Traveller's Venous Thromboembolism (TVTE) and proposes a set of recommendations.

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AIR TRAVEL AND TOURISM

International Air Travel

Long distance trips and travelling to other countries are becoming ever more common and most destinations in the world are readily accessible with international flights. In 1999, an estimated 664 million people travelled to foreign countries. The total scheduled traffic carried by the Airlines of the 185 contracting states of the International Civil Aviation Organization (ICAO) amounted to a total of about 1,560 million passengers. It is estimated that by 2005, more than 2 billion passengers will be carried annually.[8] The expansion of such mass travel in the past forty years has been due to the widespread introduction of longer-range jet aircrafts and engineering and other technical improvements such as introduction of pressurized cabins. At the end of 1999, there were 721 air carriers worldwide providing commercial passenger services. On a regional basis 36% of the total traffic volume (passenger/freight/mail) was carried by North American airlines, followed by European (28%), Asia-Pacific including Australian carriers (7%), Latin American (4%), Middle Eastern (3%) and African airlines (2%).[8] The world's number one tourist destination was France with 73 million short-term arrivals in 1999 followed by Spain (52 million) and the United States (49 million). Australia ranked 32nd receiving 0.7 per cent of the world's tourists.[9]

Australia, International Tourism and Travel

Australia is a large island continent lying between the Pacific and Indian oceans in the Southern Hemisphere. With formation of Queensland and Northern Territory Aerial Services Limited (QANTAS) in 1920 the professional civil aviation began in Australia. During the 1930s, a network of commercial routes was developed worldwide. The early flights from London to Australia took up to twelve days. Nowadays, an average flight from Europe to Australia may take up to 22 hours of flight time interrupted by at least one stopover. Visitors from Asia and Americas enjoy direct flights from their country of origin to Australia. Non-stop flights between Sydney and Los Angeles may take up to 14 hours and direct flights between Sydney and Asian cities of Singapore, Bangkok and Hong Kong take 8 to 9 hours.

Despite its remote location, Australia receives many international visitors. In the year ending June 2000, 4,651,800 million international visitors arrived in Australia.[10] International visitor arrivals are forecast to increase to 5.3 million in 2001 and 10.2 million by 2010.[11] Most overseas visitors arrive in Australia from Asia followed by Europe (Figure 1). The majority of these visitors (58%) came to Australia for holiday purposes.[11] New South Wales received 58% of visitors followed by Queensland (48%), Victoria (26%), Western Australia (13%), Northern Territory (9%), South Australia (8%), Australian Capital Territory (4%), and Tasmania (2%). Visitors on average see 1.68 States and/or Territories.[9] Including the permanent and long term arrivals, the total number of passengers arriving in Australia in the year ending June 2000 was 8,256,820 (Table 1).[10]

Australians also enjoy travelling overseas. In the same year, the number of outbound short-term resident departures was 3.3 million. This total figure is forecast to increase to 5.2 million by 2010. New Zealand has been the most popular destination for short-term visits followed by the US and the UK (Figure 2).[4] Including the permanent and long term departures of Australian residents and the return of the overseas visitors, the total number of outbound travellers in the year ending June 2000 was 8,165,307 (Table 1).[10] The international travellers were moved to and from Australia by a total of 58 international airlines (Figure 3).[12]

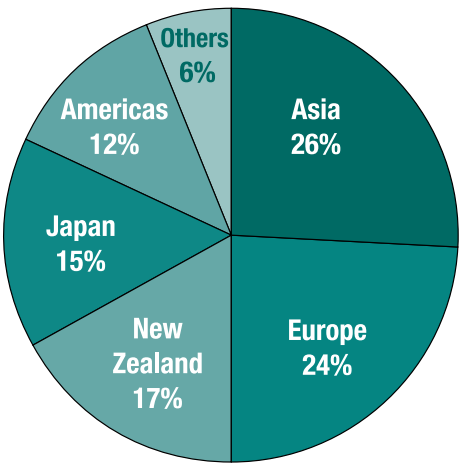

Figure1: *Regional share of short-term visitor arrivals in Australia (Financial year 1999-00)*

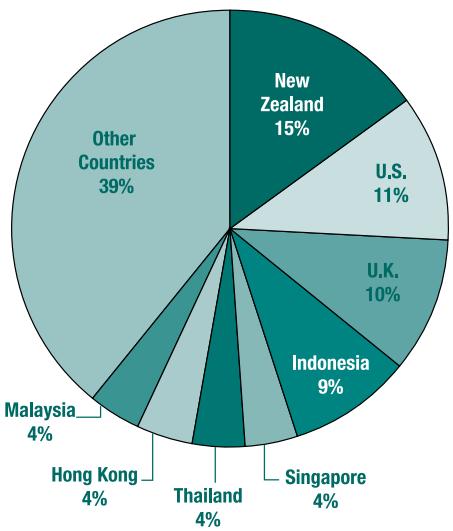

Figure2: *Outbound short term residents travel (Financial year 1999-00)*

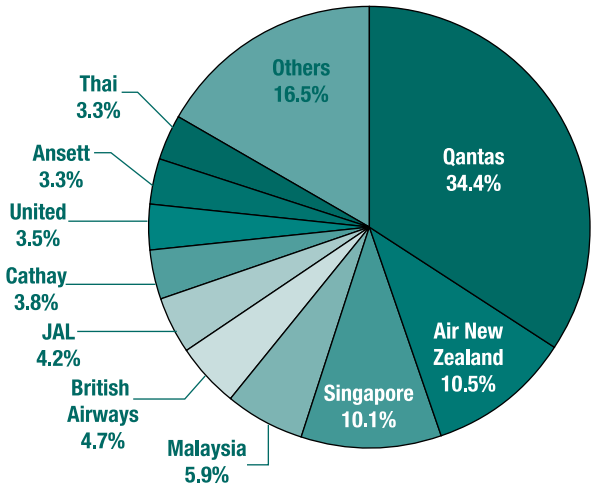

Figure3: *International passengers by major airlines (Financial year 1999-00)*

Considering the internal travel within Australia, in the year 1999, 29.4 million revenue passengers were moved by domestic or regional airlines in Australia. Two domestic airlines (Qantas and Ansett) moved 24.4 million passengers while 35 regional operators carried 5 million passengers to about 200 airports in Australia.[12]

Sydney's Kingsford Smith remains the busiest Australian airport. In the year ending June 2000, a total of 15,209,404 domestic and regional passengers travelled through Sydney Airport which accounted for 29% of the national total. The number of international passengers reached 8,048,190 which formed nearly 50% of the national figure. In total, 23,257,594 passengers used Sydney Airport.[13]

VENOUS THROMBOEMBOLISM AND TRAVEL

The possible association between long distance air travel and VTE was first described in 1946 by John Homans, who reported five cases of DVT after prolonged sitting.[14] This included the case of a 54-year-old physician who developed DVT after a 14-hour flight from Boston, USA to Venezuela. He also described two cases of VTE following car travel and suggested the risk was greater if one or two legs rested on a support that could damage the endothelium. Following Homans article several other authors have reported thromboembolic events following long distance trips. Symington and Stack first used the term 'Economy Class Syndrome' in 1977.[15] In 1986, a study by Sarvesaran showed that PE was the second leading cause (18%) of in-flight or post-flight deaths at London's Heathrow between 1979 and 1983.[16] Subsequently, this phenomenon has caused considerable concern with many reports making the association between travel and VTE appearing in international literature on a regular basis.[15-76] Variations in presentation have included subclavian vein

Table 1: *Overseas Arrivals and Departures (Financial Year 1999-00)*

Category of Traveller	Total Movements by State of Intended/Actual Residence								
	NSW	*Vic*	*Qld*	*SA*	*WA*	*Tas*	*NT*	*ACT*	*Total**
Settler Arrival	39,311	19,319	17,286	3,105	11,512	444	471	809	92,272
Long Term Resident Return	33,327	18,462	12,223	3,569	9,243	642	685	1,496	79,651
Long Term Visitor Arrival	59,218	32,945	17,083	4,478	13,774	875	1,278	3,525	133,198
Short Term Resident Return	1,319,108	791,761	502,692	157,699	399,652	30,594	34,167	62,635	3,299,914
Short Term Visitor Arrival	1,945,019	685,956	1,325,930	122,337	443,449	25,114	66,398	36,836	4,651,785
Sub-Total: All Arrivals	3,395,983	1,548,443	1,875,214	291,188	877,630	57,669	102,999	105,301	8,256,820
Permanent Departure	18,217	7,841	7,460	1,666	4,533	391	272	686	41,078
Long Term Resident Departure	30,788	20,208	15,083	4,473	9,118	1,031	686	3,497	84,918
Long Term Visitor Departure	38,390	13,871	9,268	1,859	5,894	247	667	1,649	71,850
Short Term Resident Departure	1,325,893	792,369	506,965	159,032	413,191	31,303	36,046	65,050	3,332,258
Short Term Visitor Departure	1,978,173	671,761	1,302,534	107,779	448,657	30,396	59,398	33,336	4,635,203
Sub-Total: All Departures	3,391,461	1,506,050	1,841,310	274,809	881,393	63,368	97,069	104,218	8,165,307
Total Movements	6,787,444	3,054,493	3,716,524	565,997	1,759,023	121,037	200,068	209,519	16,422,127

*Includes Other Territories and Not Stated. NSW: New South Wales; Vic: Victoria; Qld: Queensland; SA: South Australia; WA: Western Australia; Tas: Tasmania; NT: Northern Territory; ACT: Australian Capital Territory. Source: DIMA Overseas Arrivals and Departures Data (reference10)

thrombosis,[75] phlegmasia cerulea dolens,[77] acute abdomen secondary to occlusive ilio-femoral thrombosis[25], cerebral vein thrombosis[38], and peripheral arterial thrombosis.[70]

How strong is the association between recent travel and VTE? Three case control studies[20, 64, 78] and a randomised trial[79] have addressed this issue so far. In the first case-control study, Ferrari et al found that 39/160 patients with VTE (24.4%) had a history of recent travel compared to 12/160 of the control group (7.5%). In this study, long distance travel (air or surface transport) was found to be associated with an increased risk of VTE (Odds Ratio (OR) 4.0).[20]

In the second case-control study (The Sirius Study), Samana et al found 62/494 cases (12.6%) had a history of long distance travel (air or surface transport) compared to 31/494 control group (6.3%). This study found travel to be associated with an increased risk of deep venous thrombosis (OR 2.3).[78]

The third study, however, could not establish this association.[64] Kraaijenhagen et al examined 186 patients with confirmed VTE and 602 symptomatic patients with a suspected DVT in whom VTE was excluded as controls. This study found that 9/186 patients (5%) in the DVT group had a history of recent travel compared with 43/602 (7%) in the control group. Thus, this study did not show a relation between venous thrombosis and long distance travel (OR 0.7).[64]

This study had a number of limitations, however. Firstly, compared with the first two studies, the number of events and patients exposed to long distance travel were small (9 cases and 43 controls). Secondly, this study used symptomatic patients in whom VTE was excluded as controls to avoid referral bias. It is possible, however, that these patients might significantly differ from a general population control group on a variety of factors including a history of recent travel. Immobility and inactivity of the foot and calf muscle pumps result in swelling.[80-82] Travel-related immobility, therefore, may cause lower leg swelling and pain with no associated VTE. Thus, symptomatic patients with suspected DVT may not be an ideal control group and non-symptomatic healthy members of the general population make a much more appropriate control group for any future studies.

In a recently published randomised trial, Scurr et al[79] allocated volunteer travellers to wearing or not wearing Class I (20-30 mmHg) graduated compression stockings (GCS). Passengers were included if they were more than 50 years of age, intended to travel economy class with two sectors of at least 8 hour duration within 6 weeks, and consenting to have a venous duplex study before and after the trip. In this study, the reported incidence of DVT was a startling 10% which appears unusually high. This study had a number of limitations. Firstly, only patients above the age of 50 were included. It is known from other studies that the risk of VTE increases with age, from roughly 1 per 10,000 people per year before age of 40 to 1 in 100 per year for those over age of 75 years[2, 3] and the effect of age is marked after the fifth decade but further increases in the sixth and seventh decades.[83] Thus, volunteers over the age of 50 do not represent the general population. Secondly, all thrombi were detected in calf veins by duplex sonography. None of these findings were confirmed with venography and in all these cases the D-dimer[84] results were negative. It is possible, therefore that some of the thrombi were either very small or false-positive findings.[85]

Given the current state of knowledge, definitive conclusions cannot be drawn from the existing data and adequately powered prospective studies are required to further establish and quantify this link.

Incidence

The annual incidence of VTE in Caucasian populations is 1 to 2 per 1000.[2-5] The frequency of TVTE amongst acute VTE cases has been reported to range from 3.2% to 24.4%.[20, 64, 67, 87, 88] The incidence of TVTE in the general population is not known but has been estimated to range from 0.4 to 3 per 10,000.[68] Kesteven reports an incidence of 0.4 per 10 000 per annum in a population in Northeast England.[68] The incidence of VTE amongst travellers is estimated to range from 0.5 to 4 per 10,000 travellers.[68, 73] In a recent study, the incidence of flight-related DVT was estimated to be 1 to 2.5 per 10 000 travellers.[86]

These figures refer to symptomatic patients who sought medical help. The real incidence of TVTE could be much higher as VTE may remain asymptomatic[89] and some symptomatic patients may not present for treatment.

Hirsh and O'Donnell argue that if the relative risk of 3.0 is assumed for an association of long-distance air travel with VTE, and if the annual incidence of symptomatic VTE in the general population is 1 in 1000, the estimated absolute incidence of symptomatic VTE in the month after long distance air travel would be about 1 in 4000.[85]

If it is assumed that the long haul flights average about 8 hours then the annualised rate for the risk of long haul flying is approximately 1 in 10 per year per passenger continuous flying time. It is fallacious, therefore, to compare the risk of VTE per flight with the annual rate of spontaneous DVT. It is also possible that some of the cases of the so-called spontaneous VTE were related to travel the influence of which was not recognised.

Presentation

TVTE may present as DVT, PE, superficial thrombophlebitis (STP) or various combinations of the three (Table 2). The most common presenting symptoms are leg pain and swelling but DVT may remain asymptomatic or present with symptoms of PE or STP.[88] In a recent study by the authors, 98.5% of the patients were symptomatic. We found leg pain to be the most common complaint (76%) followed by swelling (60%), and dyspnoea (26%). There were no leg symptoms in 12% of events.[88]

Most studies have defined the latent presentation time to 4-5 weeks following the travel,[33, 82, 88] however a European consensus conference in 1995 proposed a latent period of 2 weeks.[90] The majority of patients develop symptoms within a week of travel. In the study by the authors, 89% presented within a week of travel with 31% experiencing symptoms during the trip.[88]

Travel-related DVT most commonly presents in the femoropopliteal segment (Table 2).[20, 33, 87, 88] By contrast, Ouriel et al have previously reported the thrombosis of the peroneal vein to be the most prevalent in general VTE population.[91] It has been postulated that the predominance of the popliteal vein thrombosis in travellers is due to compression of the vein by the edge of the seat.[40]

Previous studies of acute VTE have demonstrated that DVT tends to occur more often in the left leg than the right.[91, 92] Consistently, TVTE affects the left leg more commonly (Table 2).[20, 87, 88] It has been postulated that the extrinsic compression on the left common iliac vein from the overlying right common iliac artery may be a contributing factor.[93]

TVTE may present as isolated calf vein thrombosis (ICVT). In the authors' study, ICVT was found in 36%.[88] Previous studies of TVTE have shown incidences of 2.6%[33] and 23%[20] (Table 2). Lower rates of ICVT were reported in earlier studies partially because the posterior tibial vein was the only calf vein that underwent evaluation.[92] Recent studies have shown prevalences ranging from 24% to 34% [94-96] utilising colour flow duplex scanning and 12 to 49% using venography in general VTE populations.[97-100] The clinical significance of ICVT remains controversial. It is generally believed that once proximal propagation occurs, the potential of PE is substantial. Proximal propagation is reported to occur in 4 to 35%[96,101-104] and PE in 0 to 35% of patients with ICVT.[100, 101, 105, 106] In the study by the authors, 25% of ICVT events had an associated PE which formed 31% of all PEs.[88] In a study by Passman et al, 35% of patients with ICVT and respiratory symptoms were found to have PE.[107] These findings emphasise the need for review scanning in 7-10 days to exclude proximal propagation and performing V/Q scans if respiratory symptoms are present.

PE is a potentially fatal manifestation of TVTE. In the authors' study, 32% of all events involved PE with no associated mortality.[88] PE has been previously described in association with TVTE (Table 2).[24, 33, 87]

Another manifestation of TVTE is STP which was a feature of 27% of events in the authors' series. The right long saphenous vein (LSV) was the most affected superficial vein (13 %) followed by the left LSV (7%).[88] Half of these events occurred in conjunction with a DVT. 20 to 40% coexistence rate has been previously reported in the general VTE population.[108-110] Clinically, the associated DVT may remain silent and therefore undiagnosed.[108, 111, 112] An 11% progression rate of STP to DVT at a mean time of 6.3 days (range 2 to 10 days) has been reported in general VTE population.[113] STP without a concurrent DVT has also been associated with PE.[113-115] We found two STP events associated with PE one of which had no associated DVT.[88]

***Table 2**: Thromboembolic Presentations in TVTE*

	Parsi (n=64)[88]	Arfvidsson (n=25)[116]	Ferrari (n=39)[20]	Partsch (n=39)[87]	Mercer (n=33)[24]	Eklof (n=44)[33]
STP	27%		-	-		
DVT	80%	100%	97.5%	100%		
PE	33%	36%	2.5%	44.7%		
Breakdown of VTE						
STP only	13%					
DVT only	43%	64%			49%	63.6%
DVT & STP	11%					
PE only	6%				24%	11.4%
DVT & PE	24%	36%			27%	25%
PE & DVT & STP	1.5%					
PE & STP	1.5%					
DVT Involvement by Limb						
Right	33%		41%	41%		
Left	64%		56.5%	59%		
Bilateral	3%		2.5%	-		
DVT Segmental Distribution						
Iliofemoral	20%		5%	15.4%		35%
Femoropopliteal	44.5%		70%	72%		60%
Calf vein	35.5%		23%	13%		2.6%

RISK FACTORS

Generally accepted risk factors for VTE include a past history of VTE, a strong family history of VTE, puerperium, recent immobility, malignancy, recent surgery or trauma, female hormonal supplements including the oral contraceptive pill (OCP) and hormone replacement therapy (HRT), pregnancy and thrombophilic abnormalities. Circumstances associated with long-distance travel by air, road, or rail are believed to expose individuals to a host of conditions which may further increase the possibility of VTE.

TRAVEL RELATED RISK FACTORS

The main postulated travel related risk factors are immobilisation and cramped conditions of travel, reduced humidity and hypoxia.[15, 20, 33] Immobilisation is the only condition which may coexist during train and car trips. These conditions, which may increase the susceptibility of individual passengers to VTE, reflect the current knowledge about the pathophysiology of thromboembolism. In the absence of prospective clinical studies, the association between VTE and these travel related risk factors has remained circumstantial.

Mode and Class of Travel

Most studies have focused on air travel and air travel-related VTE has been provocatively called 'Economy Class Syndrome'. This phenomenon is by no means limited to economy class passengers. In the study by the authors, 90% of VTE events followed air travel while 10% followed road and rail travel. The plane trips included Economy class (72%), Business class (20%), First class (4%), cabin crew (3%) and pilot (1%) (Table 3). Thus, 'Economy Class Syndrome' is clearly a misleading title and should not be used. In the study by the authors, the class of travel did not demonstrate any association with the travelling time. In other words, those who travelled business or first class did not have to travel longer distances to develop thrombosis (p=0.3968). The class of travel also did not demonstrate any association with the number of trips. In other words, those who travelled business or first class did not have to have higher number of trips to develop thrombosis (p=0.2395).[88]

Travel Time and Distance

In the study by Ferrari et al the mean travelling time was 5.7 hours, [20] while Rege et al reported a median travelling time of 7 hours.[65] In the study by the authors, the average cumulative flight time before the first symptoms were noticed was 23 hours and 27 minutes. On average, there

Table 3: *Travel details in TVTE studies*

	Parsi (n=64)[88]	Arfvidsson (n=25)[116]	Ferrari (n=39)[20]	Partsch (n=39)[65]	Mercer (n=33)[24]	Eklof (n=44)[33]
Air	90%	100%	23%	100%	100%	100%
Road	7%		71%	-	-	-
Rail	3%		4%	-	-	-
All Forms of Transport						
Mean Travel Time (h)	23.1		5.7			
Median Travel Time (h)	21.8			7		
Travel Time Range (h)	1.5-55			1-23		5-17
Mean Travelling Distance (Km)	17,008					
Travelling Distance Range (Km)	979-40,422					
Air						
Mean Travel Time (h)	23.4					
Travel Time Range (h)	3-55	5-18				
Mean Travelling Distance (Km)	18,680					
Travelling Distance Range (Km)	1232-40,422					
Economy Class	72%			90%		
Business Class	20%			10%		
First Class	3.6%			-		
Cabin Crew	3.1%			-		
Flight Crew	1%			-		
Car						
Mean Travel Time (h)	23.2					
Travel Time Range (h)	11-44					
Mean Travelling Distance (Km)	2133					
Travelling Distance Range (Km)	979-3958					

were 2 flights of 11 hours 36 minutes duration in a four-week period per thrombotic event. The average travelling time and distance (any form of transport) was 23.1 hours and 17,008 Km (Table 3).[88]

Cramped Seating Conditions and Immobilisation

In 1856, Virchow recognized that VTE may be precipitated by venous stasis secondary to immobility.[117] For many years now, travel related immobility has been considered to be contributing to the venous stasis in the lower limbs. Other conditions similar to long distance travel such as sitting in crowded air-raid shelters in World War II have also been associated with VTE.[118]

During prolonged periods of immobility, the foot and muscle pumps of the lower legs are inactive which results in stagnation of blood in the venous sinuses and subsequent oedema. Noddeland and Winkel have demonstrated a significant difference between the swelling of the foot with normal leg activity (0.33 ml/100ml.h) and sitting (0.71 ml/100ml.h).[80] A study by Benigni et al [81] demonstrated an average increase of 26 cm^3 ($p<0.001$) or 3.7% in leg volume after a flight of minimum 4 hours duration. Consistently, Lowe et al have demonstrated an increase in the leg volume in simulated 12-hour flights and that stockings prevented this rise in volume.[82]

Blood velocity may also be affected by posture. From supine to sitting the venous blood flow is reduced by two thirds and from supine to standing by half.[15] It has been hypothesized that the decreased venous flow velocity while sitting may cause venous distension.[119] Electron

Table 4: *Typical Seat Pitch in Cabin Classes of Various Airlines**

Airline	Aircraft	Route	Seat Pitch (inches)		
			Economy	Business	First
Air New Zealand	B 747-400	International (Syd-LAX)	33-34	50	60
	B 767-300	Syd-NZ	34	50	-
	B 767-200	Syd-Pacific Island	34	50	-
	B 737-300	Syd-NZ	31-33	36	-
Alitalia	MD-11	International	33	55	-
American	B 777	International (LAX-London)	33-35	50	89
	B 767-200		31-32	40	55
Ansett Australia	B 747-400	International	31-34	57	-
	B 767-200	Domestic	32	42	-
	A 320-211		32	36	-
	146-200	Perth-Darwin	34	37	-
British Airways	B 747-400	International	31	40	62
	A 320, 319	Europe	31	34	Bed
Continental	B 737	Cairns-Guam-Macronesia	31	Combined 38	
Delta	B 767- 300	International and LAX to NY	30-33	40-41	60
Emirates	B 777	International (Syd-Dubai)	34	46	63
JAL	B 747	International (Syd-Tokyo)	33-34	48-50	None
KLM	B 747-400	International	31	60	-
Lufthansa	B 747	Sing/Bangkok- Frankfurt	31-32	40	61
Malaysian	B 747-400	International	32	50	72
	B 777		34	50	72
	A 330-300		32-33	40	60
Northwest	B 747 400	Syd-Sing-Amsterdam	31	46-51	-
Qantas	B 747-400	International	31-32	50	Bed
	B 737	Domestic	31-32	37	-
	B 767-200		31-32	39	-
	B 767-300		31-32	50	-
	B 747-400	Syd-Perth	32	50	Bed
Singapore Airlines	B 747-400	Syd-Sing-London	32	52	78
	B 777	Syd-Sing	32	50	60
South African	B 747-SP, (-200)	International, (Johannesburg-Perth)	34	45	83
Thai	B 777	Syd-Bangkok	32	47	-
United	B 747-400	International	31	48	60
	B 747-200	US Domestic, Hawaii	31	38	55
	B 747-400	US East Coast, Asia	31	48-50	61
Virgin	B 737	Domestic	30	-	-

*Information correct at the time of survey and subject to change. Syd: Sydney; LAX: Los Angeles; Sing: Singapore; NY: New York; NZ: New Zealand; B: Boeing; A: Airbus. Adapted from reference 88 with permission.

microscopic studies have shown endothelial damage following venous distension.[120]

As we discussed earlier, travel-related DVT presents most commonly as femoropopliteal thrombosis. Compression of popliteal vein at the edge of the seat following prolonged periods of sitting is believed to contribute to stasis.[40] The popliteal vein also develops transverse rippling in seated position. This may be damaging to the endothelium and cause sufficient alteration of flow to facilitate the formation of thrombus.[44]

Seat Pitch and Cabin Space

'Seat pitch' refers to the distance between identical fixed points on the seat and the seat ahead. Seat pitch measurement is used to calculate how many rows of seats fit into a certain section of the aircraft making no allowance for the thickness of the seat back or reclination of the front seat. We conducted a survey of international and domestic airlines and found the seat pitch to range from 30 to 35 inches in the economy class (average 34 inches) and 38 to 60 inches in the business class (average 45.5 inches)(Table 4).[88] If the seat back is two inches thick, a seat pitch of 28 inches is the bare minimum that the UK safety regulations permit.[121] Seat design and configuration are clearly important in determining the amount of space available to passengers. Although the issue of space is more relevant to economy class passengers, lack of mobility concerns all passengers including those travelling in cars and coaches as well as passengers travelling business or first class.

Cabin Altitude and Hypoxia

Air travellers may be at a higher risk of VTE as they experience mild hypoxia during the ascent. The flying altitude for most commercial aircrafts is 26,000 to 42,000 feet. Concord is an exception as it flies at an altitude of 50,000 to 60,000 feet. At an altitude of 35,000 feet, the atmospheric pressure decreases from its sea level of 760 mmHg to 176 mmHg. The ideal aircraft should maintain its cabin pressure at the equivalent of ground level throughout the flight. This is not mechanically possible, as it requires a much stronger aircraft structure to maintain the pressure gradient. As a compromise, aircraft cabins are pressurised so that the cabin pressure is maintained at the equivalent of around 5,000-8,000 feet altitude irrespective of the cruising altitude.[71]

Arterial oxygen pressure is normally 98 mmHg at the sea level but it falls with increasing altitude.[34] Modern Boeing 747-400 and Boeing 777 have a cabin altitude of about 5000-6000 feet which may lead to an arterial oxygen pressure of 70 mmHg in a healthy individual.[122] Studies performed in hypobaric chambers with an inside ambient pressure of 75.8 kPa (equivalent of a cabin altitude of 8000 feet), have shown that the alveolar pO2 drops to only 59 mmHg and the mean oxygen saturation of haemoglobin reaches 90% after 30 minutes of exposure.[119, 123, 124] Passengers may therefore suffer from a rapid relative hypoxia especially during take off. This becomes even more relevant if a particular passenger has pre-existing respiratory compromise due to cardiac or pulmonary disease.[125] Oxygen deprivation can tip the delicate pro-coagulant/anti-coagulant balance to favour coagulation. A number of studies have identified enhanced expression of plasminogen activator inhibitor 1 (PAI-1) suppressing fibrinolysis under conditions of low oxygen tension.[126-128] The decreased fibrinolysis enhances hypercoagulability. Hypoxia is also known to produce endothelial activation and/or injury[129] and within the valve cusps may lead to endothelial malfunction and shedding.[130] Finally, the consequent release of endothelium derived relaxing factor can cause relaxation of venous walls which results in venous stasis.[128]

Compounding Effects of Sleep, Immobility and Hypoxia

Simons et al have demonstrated lower oxygen saturations (80%) at cabin altitudes of 8000 feet in those who were dozing off.[71] This can be explained by the prohibiting effects of drowsiness, cramped conditions, and immobility on proper respiratory activities. Also, the low cabin pressure causes gastrointestinal distension which might limit the downward movement of the diaphragm. Once, these individuals were stimulated to respire properly, the oxygen saturation levels increased.[71] Hypoxemia also leads to vasodilatation and increased capillary permeability which combined with the effect of immobility results in oedema. Sleeping in the seats in a sitting position may further increase the risk of compression of, and damage to the popliteal vein.[37] In the study by authors, about 40% of patients slept more than 50% of the trip duration while sleeping tablets were used in 14% of the events.[88]

Reduced Humidity and Haemoconcentration

Relative humidity (RH) is the percentage of water vapour in air at a given temperature. At cruising altitudes, air is delivered to the cabin at less than 1% RH. As cabin air is re-circulated, more water vapour adds to the cabin air by cabin occupants and other cabin activities. The cabin RH averages around 10-15% within a range from 5%-35% depending on aircraft type, cabin configuration and passenger load.[131] The fall in cabin RH from at least 47% to 11% occurs within 30 minutes of takeoff.[132]The low RH is thought to be beneficial to the aircraft structure and equipment by limiting corrosion and growth of micro-organisms.

The low RH is thought by some to contribute to pronounced fluid loss, haemoconcentration and dehydration. Carruthers et al[133] demonstrated a reduction in urine output during air travel with an increase in urine osmolality. The resulting haemoconcentration may contribute to VTE. Simons and Krol[71] showed an increase in mean plasma and urine osmolality in healthy people exposed for 8 h to a simulated flight at an altitude of 8 000 feet and 8-10% humidity. The increase in mean plasma osmolality indicates dehydration. This view has been

challenged by Nicholson et al[134] who showed that the maximum possible increase in fluid loss over an 8 h period in a zero humidity environment is around 100 ml and that the plasma osmolality shows no change at all. They conclude that there is no evidence that exposure to a low humidity environment can lead to dehydration.[122, 134] The average insensible fluid loss during an intercontinental flight has been estimated to be 84 ml/hr.[37] Clearly, more studies are needed to establish the importance of cabin humidity and its effect on dehydration.

Travel Variables and the Severity of Presentation

In the study by the authors, there was no association between travel related variables and the severity of thrombotic presentation (STP vs. DVT vs. PE).[88] The total travel time or distance showed no correlation with the severity of presentation. In other words, those patients who travelled longer did not have more severe thrombosis (time: p=0.71, distance: p=0.59). The class of travel also did not demonstrate any association with the severity of presentation. In other words, those who travelled business or first class did not have less severe thromboses (p=0.38). Presentation time also showed no correlation with the severity of presentation. In other words, those patients who presented earlier did not have more severe thromboses (p=0.2757)

PATIENT-RELATED RISK FACTORS

Thrombophilia

Thrombophilia may be defined as an increased tendency to thrombosis due to hereditary or acquired deficiency of coagulation inhibitors or fibrinolysis factors. With the current status of knowledge and sensitivity of laboratory methods, at least one genetic defect is found in about 70% of the families with thrombophilia.[135] These hereditary thrombophilic abnormalities have been identified in up to 50% of patients presenting with a first episode of VTE.[1] The predominant genetic factors predisposing to thrombosis are Factor V Leiden (FVL) mutation which may result in abnormal resistance to Activated Protein C (APCR) and Prothrombin gene (G20210A) mutation (FII-GA).[136-139] Other less common genetic defects include deficiencies in protein C, protein S, and antithrombin.[140-144]

The important role of thrombophilic abnormalities in pathogenesis of TVTE was first investigated by Lord et al[72] in 1993. In 1999, the predominant presence of thrombophilic abnormalities was demonstrated for the first time by the authors in 72% of patients with TVTE (Table 5, Figure 4).[74, 88]

Activated Protein C Resistance

The most common thrombophilic abnormality in the authors' study was APCR found in 47%.[74, 88] APCR is highly prevalent (20 – 60%) in patients with VTE.[145-148] This abnormality has been previously reported in association with TVTE.[30] APCR could be acquired or inherited.

APCR and FVL mutation- Inherited APCR in most patients is due to a single point mutation in factor V gene leading to a G to A substitution at the nucleotide position 1691.[148-152] This mutation causes substitution of glutamine for arginine at amino acid position 506 (FV R506Q) rendering factor V resistant to proteolytic down regulation by APC. This mutation is found in 3-5% of Northern European populations,[148, 153-155] 2% of Southern Europeans[154-157] and not found in Blacks or Asians.[157-162] In the study by the authors, 34% of all patients demonstrated a mutation in factor V, 30% heterozygous and 4% homozygous.[88] Case control studies suggest a five to tenfold increased risk of VTE associated with heterozygosity and 50-100-fold with homozygosity.[148, 163, 164] FVL mutation is also a risk factor for cerebral vein thrombosis[165] and STP[166] but not for retinal vein thrombosis.[167] This mutation is thought not to be a risk factor for primary PE.[168, 169] A number of recent reports have associated this mutation with purpura fulminans.[170-175]

APCR without FVL mutation- This phenotype is a risk factor for VTE,[176] a prominent predictor for advanced atherosclerosis and arterial disease[177] as well as severe arterial thrombosis.[178] In the study by the authors, APCR was not associated with FVL mutation in 15% of patients.[88] Consistently, in general VTE population, 20% or more of all APCR cases do not carry the FVL mutation.[163] Acquired APCR is associated with pregnancy, oral contraceptive pill (OCP), elevated factor VIII levels, and circulating anti-phospholipid antibodies (APA). APA inhibit the inactivation of factor Va by APC and react with APC: protein S: phospholipid complex. This suggests these antibodies can selectively down regulate the expression of anticoagulant activities of the Protein C pathway.[179]

Prothrombin Gene Mutation (FII-GA)

This mutation involves a G to A substitution at nucleotide 20210 in the 3'-untranslated region of the prothrombin gene. It is associated with elevated plasma prothrombin levels and a 2.8-fold increased risk of VTE in both sexes and all age groups.[139, 166] The A20210 allele is present in 5 to 7% of general VTE patients and in 1 to 4% of healthy controls which makes it the second most common genetic risk factor for VTE.[139, 180, 181] Several reports have demonstrated that the combined mutation of FII-GA and FVL is associated with higher risks of VTE.[182-185] This mutation also interacts strongly with the OCP and protein S deficiency but surprisingly not with protein C deficiency.[186] In the study by the authors, 24% of patients were heterozygotes for this mutation.[74] 5 patients (11%) also had a FVL mutation, one patient (2%) had an associated protein S deficiency. 36% of the pre-menopausal female patients on the OCP also demonstrated this genetic mutation.[88]

Antiphospholipid Antibodies (APA)

APA are found in 1-5% of the general population and in 50% of patients older than 80 years.[187, 188] Thrombotic events are reported in approximately 30% of patients with APA.[189, 190] These include both arterial and venous thromboembolic events.[191-194] VTE accounts for about two thirds of the thrombotic events and arterial thrombosis for

the other one-third with cerebral arterial thrombosis as the most common arterial complication.[189, 190, 195] APA which are present in 15-20% of all VTE events. In the study by the authors, 8% of patients had APA with lupus anticoagulants in 2% and anti-cardiolipin antibodies in 6%.[74] Lupus anticoagulants confer a 9-fold increased risk of VTE.[191]

Protein S and Protein C deficiencies

Protein S (PS) is a non-enzymatic cofactor of APC in the inactivation of cofactors Va and VIIIa. PS is inherited in an autosomal dominant manner with two genes on chromosome 3 and more than 70 mutations described.[141] PS deficiency accounts for only 1% of thrombotic events in the population with a relative risk of 2.[1] In the study by the authors, 3 patients (7%) had PS deficiency.[74, 88] Individuals with PS deficiency may also have a predisposition to arterial thrombosis.[196]

Protein C (PC) is a vitamin K-dependent inhibitor of factors Va and VIIIa. In the study by the authors, 4.8% of patients had deficiency of PC.[74] Hereditary PC deficiency is inherited in an autosomal dominant manner with over 160 mutations described.[197] Heterozygosity for PC deficiency is associated with a seven-fold increased risk of VTE.[198, 199] It is found in 0.3% of healthy individuals.[200, 201] The attributable risk for the overall thrombosis incidence is only 1 to 2%.[1]

Protein C and S levels are reduced by vitamin K deficiency, liver failure, and therapeutic anticoagulation with warfarin.[202] Protein S circulates bound to C4b binding protein and the active form, free protein S should be

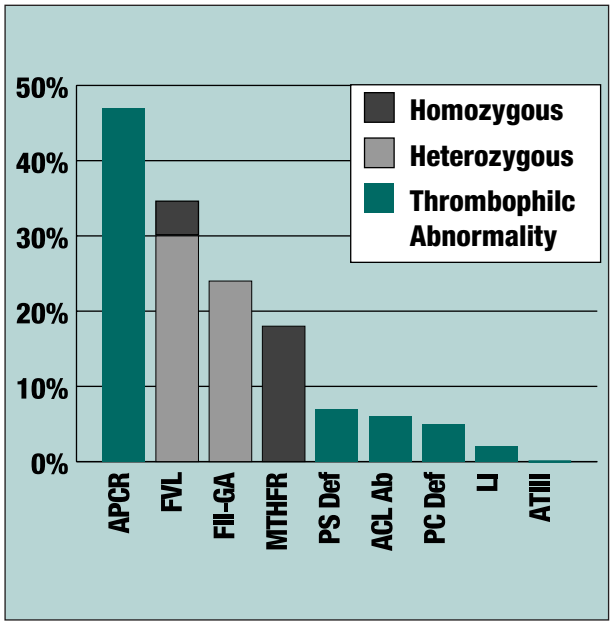

Figure 4: *Distribution of thrombophilic abnormalities in patients with TVTE.*

APCR: Activated Protein C Resistance; FVL: Factor V Leiden; F II-GA: Factor II mutation; MTHFR: Methylene Tetrahydrofolate Reductase gene mutation; PS Def: Protein S deficiency; ACL Ab: Anti-cardiolipin antibodies; PC Def: Protein C Deficiency; LI: Lupus Inhibitor; AT-III: Antithrombin deficiency. Adapted from reference 88 with permission.

Table 5: *Procoagulant abnormalities in different populations and relative risks*

Procoagulant Factor	PREVALENCE			
	TVTE Patients[74]	General population	VTE patients	RR
APCR	47%	3-7%	20-60%	See FVL
FVL	34%	3-7%	20-60%	
- Heterozygous	30%	3-7%		5-10x
- Homozygous	4%	0.02-0.15%		50-100x
FII-GA	24%	1-4%	5-7%	2.8x
MTHFR C677T	44%	50%	See below	
- Heterozygous*	26%	40%	-	-
- Homozygous	18%	10%	5-10%	<2x
Protein S Deficiency	7%	<1%	1%	
Protein C Deficiency	5%	<0.2%	1-2%	7-10x
Antiphospholipid Ab	8%	1-5%	15-20%	
- ACL Antibodies	6%	Unknown	Unknown	Unknown
- Lupus anticoagulant	2%	1-2%	5-15%	9x
Antithrombin- III	0%	<0.1%	1%	
-High Risks Type	0%	0.01%		20-50x
-Type II HBS	0%	0.05-0.1%		5-10x

*Not considered a risk factor; TVTE: Travellers Venous Thromboembolism; VTE: Venous Thromboembolism; RR: Relative Risk; APCR: Activated Protein C Resistance; FVL: Factor V Leiden; MTHFR C677T: Methylene Tetrahydrofolate Reductase gene C→T mutation; F II-GA: Factor II (prothrombin gene) G→A mutation. Ab: antibodies; ACL: Anticardiolipin, HBS: Heparin Binding Site. Adapted from reference 74 with permission.

assayed.[202] The levels of PS are affected by many other exogenous factors such as age, OCP, and pregnancy which make the interpretation of the laboratory results difficult. This is why the population prevalence of PS deficiency is not very well known and it may be 1% or even much lower.[1] Protein C and S levels may also be falsely low in the presence of factor V Leiden.[202]

Methylene Tetrahydrofolate Reductase (MTHFR) Polymorphism and Hyperhomocysteinemia

MTHFR catalyses the reduction of methylene tetrahydrofolate to methyl tetrahydrofolate with folate as a co-factor. Methyl tetrahydrofolate is important in re-methylation pathway of homocysteine which also requires dietary folate and vitamin B12. Homozygosity for MTHFR mutation is found in about 10% of the normal population in Australia[203] but its prevalence ranges from a low of 0 to 1.4% in African Americans up to 15% in Europe, Middle East and Japan.[204, 205] Heterozygosity found in up to 40% of the population does not seem to have an impact on plasma homocysteine levels even when the folate levels are low.[206-208] Homozygosity, however, has been associated with almost doubling of the plasma homocysteine levels.[209, 210] Several reports have found a positive association between the homozygous mutant genotype and different forms of cardiovascular disease, including coronary artery disease, cerebrovascular disease, and VTE.[209-217] Other studies have not seen this association.[208, 218, 219] Differences in these studies may be due to the influence of dietary intake of folate on the phenotypic expression of MTHFR gene.[207] In the study by the authors, 44% (18% homozygous, and 26% heterozygous) demonstrated a mutation in MTHFR gene. Heterozygosity was not considered a risk factor for VTE (Table 5).[74]

A number of large studies have identified hyperhomocysteinemia as an important risk factor for initial and recurrent VTE particularly when the fasting levels exceed 20 µmol/L.[220-225] It can lead to a two to three fold increase risk of VTE. Plasma total homocysteine status

Table 6: *Patient characteristics and risk factors*

	Parsi (n=64)[88]	Kesteven (n=26)[68]	Arfvidsson (n=25)[116]	Ferrari (n=39)[20]	Partsch (n=39)[87]	Rege (n=20)[65]	Mercer (n=33)[24]	Eklof (n=44)[33]	Milne (n=25)[42]
Number of Patients with VTE	64	26	25	39	39	20	33	44	25
Number of VTE events	70								
Frequency in acute VTE	3.3%	4.1%		24.5%	7.2%			17.3%	
Patient Characteristics									
Mean Age (years)	49	61		65.3	63.1			63	
Median Age (years)	48					40	48		51
Age Range (years)	22-83	42-84	36-79			22-66	19-80	32-86	19-84
M:F	32:32	12:14	11:14		24:15	5:15	27:6	24:20	
Mean Weight (kg)	79.6								
Mean BMI	26.3								
Mean Height (cm)	172								
Multiplicity of Risk Factors									
At least one risk factor	98%	87.5%	92%	25%		75%	74%	84%	
Average number of risk factors	4		3						
Range	0-10								
Risk Factors									
Thrombophilia	72%					30%			
OCP/HRT	62%	35%	40%			35%	3%	16%	12.5%
Obesity	58%		76%						
Previous VTE	37%	20%	28%			20%	18%	34%	33%
Family History of VTE	29%					20%			21%
Surgery/trauma	12%		28%			10%	3%	20%	4%
Infection	8%					5%			
Malignancy	4%	5%	28%			5%	18%	25%*	4%
Pregnancy	0%					0%			
Prior Immobilisation	0%					0%			
Puerperium	0%					5%			

*Not considered a risk factor; TVTE: Travellers Venous Thromboembolism; VTE: Venous Thromboembolism; RR: Relative Risk; APCR: Activated Protein C Resistance; FVL: Factor V Leiden; MTHFR C677T: Methylene Tetrahydrofolate Reductase gene C→T mutation; F II-GA: Factor II (prothrombin gene) G→A mutation. Ab: antibodies; ACL: Anticardiolipin, HBS: Heparin Binding Site. Adapted from reference 74 with permission.

is determined by clusters of homocysteine modulating factors and more than half of the individuals defined as carriers of hyperhomocysteinemia are not homozygous for the C677T mutation.[226] Acquired hyperhomocysteinemia may be due to chronic conditions such as chronic renal failure, low vitamin intake as found in B12, B6 and folate deficiency or induced by a number of drugs such as methotrexate and cyclosporine. Heterozygous carriership of cystathione B-synthase (CBS) which in homozygous form causes classic homocystinuria with extremely high levels of homocysteine (fasting levels >100µmol/L) is an infrequent cause of hyperhomocysteinemia.[223, 227] For screening purposes, sensitivity for detecting elevated levels of serum homocysteine may be increased by measuring both the fasting and post-methionine loading levels.[207]

OTHER PATIENT RELATED RISK FACTORS

Most individuals with thrombophilia will not experience overt thrombosis unless other risk factors are present.[228] In the author's study, 98% experienced additional personal risk factors in addition to those presumed to be associated with travel (Tables 6 and 7).[88] In-depth review of all general risk factors of VTE is beyond the scope of this paper and only a few relevant ones are discussed here.

Age - The risk of VTE increases sharply with age, from roughly 1 per 10,000 people per year before the age of 40 to 1 in 100 per year for those over age of 75 years.[2, 3] The median age in the author's study was 48 years and age range was 22 to 83.[88] Consistently, previous studies of TVTE have shown a wide range demonstrating the involvement of younger age groups (Table 6).

Weight and Height - 58% of patients in the author's study were considered overweight with a BMI greater than 25.[74, 88] Obesity has a clear association with the development of postoperative VTE[229] and in women is significantly and independently associated with PE.[230] Spontaneous DVTs have been described in the legs of tall men, each of whom was taller than 6 ft (182.9 cm).[231] It has been postulated that in tall people the greater vein length may increase the difficulty of venous return to the vena cava thus predisposing to stasis.[231] The average height in the author's study was 172 cm.[88]

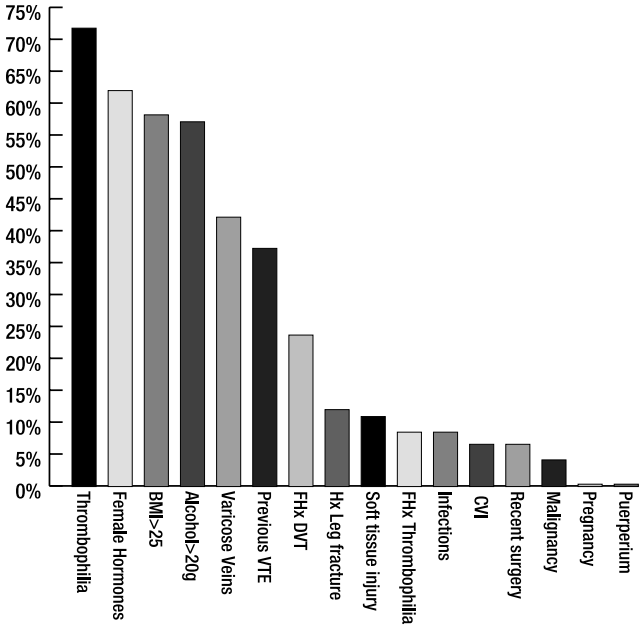

Figure 5: *Potential risk factors identified in patients with TVTE.*

BMI: Body Mass Index, VTE: Venous Thromboembolism, DVT: Deep Venous Thrombosis, FHx: Family History, Hx: history; CVI: Chronic Venous Insufficiency. Alcohol>20g refer to consumption of alcoholic drinks during the trip. Adapted from reference [88] with permission.

Table 7: *Acquired patient related risk factors*

Acquired Patient Related Risk Factors	TVTE[88]	Prevalence (%)	Population Attributable Risk	Relative Risk
OCP * [233]	73%	6-33%	50-66%	4-6x
-and thrombophilia	81%			
Oral HRT † [246]	53%	25-40%	40-50%	4x
- and thrombophilia	87.5%			
Surgery/trauma[1]	12%	4%	16%	6x
Malignancy[262]	4%	2 – 3%	10-15%	7x
Pregnancy[1,263,264]	0%	5%	10%	4-5x
Immobilisation ‡ [1]	0%	2%	15%	11x
Puerperium[1]	0%	1%	12%	14x

*Pre-menopausal women, † Post-menopausal women, ‡ Immobilisation prior to the trip. TVTE: Travellers Venous Thromboembolism. Adapted from reference 88 with permission.

Female Hormonal Supplements -73% of pre-menopausal females in the authors study were taking the OCP.[88] Oral contraceptives are taken by approximately 65 million women worldwide corresponding to 6% of all women of reproductive age.[232] This prevalence varies from country to country. For instance, in the Netherlands more than one third of women aged 15-49 use oral contraceptives which accounts for one-half to two-thirds of all thrombotic events in women in this age group.[1] OCP alone increases the risk of VTE by a factor of 4 in healthy women.[233] The oestrogen component is the most thrombogenic component of the OCP demonstrating a dose-dependant effect.[234-240] The increased risk of VTE is apparent within 4 months after starting the OCP, is unaffected by duration of current use, and lasts for 3 months after stopping the OCP.[233] The risk conferred is not limited to the oestrogen content as it also depends on the type of progestagen. Third generation progestagens (desogestrel and gestodene) confer a two-fold increased risk of VTE when compared to second-generation progestagens (levonorgestrel).[241-245]

In the authors study, 53% of post-menopausal female patients were taking the oral Hormone Replacement Therapy (HRT).[88] Several studies have demonstrated an association between oral HRT and a 2 to 4-fold increased risk of VTE with oestrogen only as well as with the combined oestrogen-progestagen replacement therapy.[246-250] The relative risk of 2 to 4 is very similar to that of OCP even though it applies to a much older group of women. The baseline incidence of thrombosis is much higher in post-menopausal women. As a result, HRT leads to a much higher number of women developing thrombosis than does the OCP.[1]

In the study by the authors, altogether 20 of 32 female patients (62%) were on some form of oral female hormonal supplement.[74, 88] This is a much higher rate compared to previous studies of TVTE which have reported a range of 3.5 to 35% (Table 6). The difference could partially reflect the local trends in different countries.

MULTIPLICITY AND INTERACTION OF RISK FACTORS

VTE is a multigenetic phenomenon.[251] The penetrance of clinical manifestations is lower in individuals with a single defect than those with two or more defects. The thrombotic risk is higher in patients with combined defects than in those with either of the two gene defects.[252] For instance, FVL has been shown to be an additional genetic risk factor in patients with FII-GA as well as deficiencies of PC, PS or antithrombin.[184, 253-257] In the study by the authors, 72% of patients had a thrombophilic abnormality: 49% had one, 21% had two, and one patient (2%) had 4 thrombophilic abnormalities.[88] Apart from thrombophilic abnormalities, many other established risk factors for VTE have been identified amongst the TVTE patient population (Tables 6 and 7, Figure 5). In the authors' study, on average, there were 4 risk factors per thrombotic event. In one patient with PE, 10 individual risk factors were identified.[88] It has been demonstrated that the same number of risk factors may cause VTE in one individual and not in another, and that the same risk factors do not cause VTE in children but may do so in older people.[6] We have previously demonstrated that the same number of risk factors may cause various forms of thrombosis (STP vs. DVT vs. PE) in different individuals and that increased number of risk factors does not necessarily cause more severe forms of thrombosis.[88] As multi-causal models cannot predict the formation of thrombosis on the basis of the number of risk factors, a time dependant model incorporating interaction of genetic and acquired risk factors has been proposed by Rosendaal.[6] According to this model thrombosis potential is age dependant and the interaction of risk factors can be additive or synergistic. Synergism occurs when VTE risk factors interact to produce an effect that exceeds the sum of their individual effects. An example of synergism is the interaction of the OCP with a number of thrombophilic abnormalities especially FVL. The use of OCP in women with a heterozygous mutation of FVL renders a relative risk of 35 and with a homozygous mutation renders a relative risk of 200 (Table 8).[258-260] In the authors' study, 81% of all pre-menopausal female patients who were taking the OCP had thrombophilic abnormalities.[88]

Acquired VTE risk factors are known to be the precipitating factors for the disease.[252] Consistently, De Stefano has shown that 49% of thromboembolic events in patients with thrombophilia are preceded by a triggering event.[261] Acquired travel related conditions may therefore interact in an additive or even synergistic fashion with the pre-existing personal risk factors precipitating the thrombotic event. This may explain why TVTE may occur in predisposed individuals after relatively short trips.

Table 8: *Estimated risk of VTE in women with thrombophilia*

	OCP	FVL	
		Heterozygous	Homozygous
One risk factor only	4x	7x	50x
OCP	-	35x	>200x

OCP: Oral contraceptive pill; FVL: Factor V Leiden mutation (modified from references 164, 258, 259, 265)

PREVENTION AND RECOMMENDATIONS

The presence of multiple genetic and patient-related risk factors in passengers who suffer from TVTE has been previously demonstrated.[88] Some potential travellers will have multiple personal factors which may be compounded by the presence of travel related risk factors. Assessment of passengers' individual risks is therefore essential in planning the appropriate prophylaxis. Optimal VTE prophylaxis should aim at reducing symptomatic as well as

asymptomatic DVTs which may equally lead to fatal PE or post-phlebitic syndrome. Preventive measures and specific recommendations may then be offered appropriate to the risk category prior to the trip. We propose 4 categories of No Risk, Low Risk, Moderate Risk, and High Risk (Table 9). VTE prophylaxis includes mechanical and pharmacological intervention.

Mechanical Prophylaxis

Graduated Compression Stockings (GCS) - GCS act via an increase of the venous blood flow velocity. In a meta-analysis study, 9.3% of post-operative patients who wore GCS experienced DVT, as compared to 24.5% in the placebo group (P<0.001).[266] In another meta-analysis, the corresponding figures were 11.1% and 27%.[267] In 1987, Marshall and Dormandy investigated the effects of a 14-hour flight from Frankfurt to Kyoto and found an increase of 60 ml in lower limb volume when no preventive measures are taken.[268] In 1998, Lowe et al investigated the efficacy of 25-32 mmHg GCS for preventing venous oedema during a 14.4 h night flight.[82] In this study, the volume of the non-stockinged leg increased significantly on both outward-bound and return flights by an average of 122 ml and 63 ml while the volume of the stockinged leg hardly altered. Benigni et al demonstrated a 3.7% rise in leg volume without GCS as against a 4.1% decrease with GCS following a 4 hour long flight.[81] Subsequently, Sadoun et al demonstrated a reduction in leg volume from 727 cm^3 to 697 cm^3 (p<0.001) after the application of GCS in a 4 hour-long journey.[269]

In a recent randomised trial,[79] volunteers over 50 years of age with no previous history of VTE were allocated to wearing or not wearing below-knee class I GCS during long haul flights from Heathrow airport returning within 6 weeks. Venous duplex ultrasounds and d-dimers were performed within 48 hours of participants returning to London. In this study, none of the patients wearing the GCS developed DVT compared with 12/116 passengers (10%) who did not wear the GCS. Thus, in this study GCS produced a 100% DVT risk reduction. However, 4/116 passengers (3%) wearing knee-high GCS developed STP in their varicose veins at the level of the knee. None of the passengers who were not wearing GCS developed STP.

It seems generally accepted that GCS should be used to prevent oedema and symptoms on long distance trips. However, further studies are needed to establish the role of GCS in prevention of TVTE and to establish the best and most appropriate class of graduated compression

Mobility and exercise - Passengers are generally advised by healthcare workers to exercise and move about during long distance plane trips to prevent thrombosis.[47, 270] If travelling by car, they are advised to stop occasionally and walk around for a few minutes. Airlines, by contrast, ask the passengers to remain seated with the safety belt firmly fastened for most of the flight. The Airlines reasoning is based on the inherent dangers of flying and possibility of turbulence which may lead to fatal accidents. Is there any evidence that exercise is beneficial? In 1952 Wright and Osborn showed that venous velocity was doubled after vigorous dorsivolar flexion of the foot.[271] Sochart et al have shown that all passive or active movements (ankle dorsiflexion and plantar flexion, subtalar inversion and eversion, and a combination) resulted in an increase in mean and peak blood velocities in common femoral vein over the established resting levels. Active combined movements produced the highest velocities with an increase of 38% in mean and of 58% in peak flow velocities, significantly greater than those produced by passive movements.[272] These studies and those focussing on lower leg oedema re-enforce the importance of active movements in promotion of venous return.

Pharmacological Prophylaxis

This includes low molecular weight heparins (LMWH), anti-platelet agents and low dose warfarin. LMWH probably form the mainstay of VTE prophylaxis and have gradually replaced un-fractionated heparins (UFH) for various clinical indications. When compared with UFH, they demonstrate a higher bioavailability coupled with longer half-lives. This results in a more predictable anti-thrombotic response that allows administration of subcutaneous LMWH without dose adjustment and laboratory monitoring. LMWH have been shown to be effective for the prevention of VTE in high-risk patients, such as those undergoing major hip or knee surgery or patients with major trauma or acute spinal cord injury.[273] We recommend LMWH for travellers who are known to be at high risk before, during and after the trip continuing for 48 hours after resuming normal activities.[73]

The protective effect of antiplatelet agents is thought to be much less than that of anticoagulant drugs.[274] These agents generally do not require routine laboratory monitoring except for ticlopidine which may cause pancytopenia. A meta-analysis performed by Antiplatelet Trialists' Collaboration[275] found aspirin to significantly reduce DVT and PE but due to the poor quality of many studies included in this analysis many authorities remain sceptical.[274] According to the latest consensus guidelines, the use of aspirin to prevent VTE is controversial and therefore not recommended by the authors.[276]

OTHER RECOMMENDATIONS

The term "Economy Class Syndrome" - This term suggests that TVTE is limited to Economy Class passengers. We know from the previous studies that this is certainly not the case.[20, 88] This term is therefore misleading as it excludes other classes of air travellers, cabin and flight crew and other long-distance travellers. 'Traveller's Venous Thromboembolism' or 'Travel-associated Venous Thromboembolism' may be more appropriate.

***Table 9**: Risk Groups and recommended prophylaxis*

RISK CATEGORY	RECOMMENDATIONS
No Risk No known risk factors	• Exercise foot and calf muscles whilst seated for 2 minutes every half an hour. • Walk down the aisle occasionally. • Avoid excessive alcohol and caffeine-containing drinks before and during the trip. • Adequate fluid intake for 24 hours before and during the trip (at least 1 litre per 5 hours of trip).
Low Risk Age over 40 BMI more than 25 Recent minor surgery Varicose veins Lower limb oedema OCP, HRT Pregnancy	As above plus the following: • Do not take sleeping tablets. • Take only short periods of sleep. • Wear graduated compression stockings/socks.
Moderate Risk Age over 60 Previous history of DVT, PE (more than 12 months before) Recent lower limb injury History of cardiac failure Puerperium (within 6 weeks) Family history ofVTE Family history of thrombophilia	As above plus the following • Take professional medical advice about the risks involved. • Consider LMWH or low dose warfarin
High Risk DVT or PE within the past 12 months Residual proximal deep vein abnormality Documented thrombophilia Recent major surgery (3/12) Recent stroke, myocardial infarction (3/12) Recent hospitalisation (3/12) Lower limb paralysis Lower limb cast Current treatment for malignancy	As above plus the following • Duplex scanning of lower limb deep veins. • Consider stopping the female hormonal supplements. • LMWH in adequate doses before and during the flight OR • Warfarin in adequate doses.

BMI: Body Mass Index; OCP: Oral Contraceptive Pill; HRT: Hormone Replacement Therapy; DVT: Deep Vein Thrombosis; PE: Pulmonary Embolism; LMWH: Low Molecular Weight Heparin

Role and Responsibility of Transport Industry - The airline industry has never acknowledged a possible association between air travel and VTE and up until the recent publicity made no attempt to inform the passengers of the potential risks. The principal sources of initial advice to passengers have been consultations with medical professionals and sporadic articles in the print media. In 1997, a study of in-fight magazines of airlines flying out of Australia found that more than 25% of these magazines gave no health advice at all and when available it occupied 0.02 to 1.3% (mean 0.25%) of the total magazine. Only 3 magazines (27%) gave advice regarding in-flight exercise and only 1 (9%) gave specific advice regarding hydration.[277] When available, this information was buried deep in the magazine and it was open to question how many passengers read

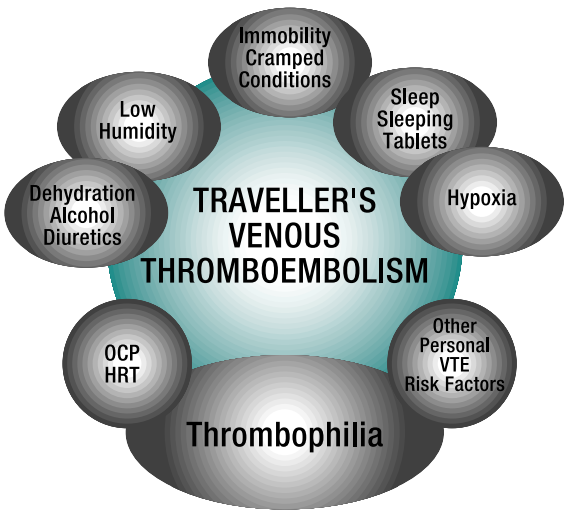

Figure 6: *Multiplicity of TVTE risk factors*

these articles. Facing several lawsuits, Qantas began offering specific advice about avoiding thrombosis in the December 2000 issue of its in-flight magazine.[278] The amount of information was increased in the January 2001 issue which included a number of diagrams demonstrating an in-flight workout.[279] This has been recently complemented by a 'DVT In-flight Video'. Some other airlines have recently announced their plans to print stickers or pamphlets to accompany tickets.[280] British Airways has announced its plans to issue passengers with leaflets warning of VTE risk as well as some prevention tips. The leaflet will be distributed along with posters to doctor's surgeries in Britain.[281]

Airlines should consider providing this information in the form of a "Health Card" in the same style as the currently used "Safety Cards" which are available from the seat pockets. The provision of a "Health Card" will make the information more accessible and will demonstrate the emphasis on importance of health and preventative measures.

Airlines can help prevent VTE by providing advice and by encouraging travellers to discuss prophylactic measures with appropriate physicians especially if risk factors are present. It is crucial that airlines provide this information prior to the trip. This allows the travellers enough time to arrange a medical consultation which may be followed by further investigations and provision of prophylactic measures. The airlines should advise the passengers on appropriate foot and leg exercises, discourage the use of narcotics and tranquilisers and encourage the use of GCS. The airlines should also encourage appropriate fluid intake while discouraging dehydrating beverages and diuretics unless medically indicated. Similar procedures should be followed by authorities in charge of other forms of public transport such as national train and coach companies.

Apart from information in the in-flight magazines, there are a number of other methods through which airlines could provide travel health advice. These include information pamphlets in airports, pamphlets to accompany airline tickets, in-flight video and audio presentations, and information on the airlines websites. Airlines can also encourage travel agencies to include this information in promotional brochures. A study by Reid et al demonstrated that about one third of travel agent promotional brochures carried no travel health advice and those that did only contained general information.[282]

In the authors study, three events involved flight attendants and one involved a pilot.[88] There have been other reports of flight attendants suffering from TVTE.[283] Following a near fatal PE in a flight attendant, Qantas issued 'specific and additional' warnings to its 6000 cabin staff.[283] It is clearly crucial to identify members of cabin or flight crew who have additional risk factors such as those with thrombophilic abnormalities or females on the OCP and provide them with appropriate advice and prophylactic measures.

Currently, a number of Airlines are introducing a super-economy class with more spacious seating. British Air Transport Association has estimated that adding a couple of inches to existing seat pitch would put fare prices up by about 10%.[121] According to the British Airways, 15-20% of economy class passengers might pay a small premium for increased seat pitch.[121] The airlines should consider increasing the seat pitch and the seat width in standard economy class as well as providing the option for pre-booking seats with extra leg-room located at the emergency exit doors and front of cabin. This is especially relevant to tall passengers and those above the average size who may be at a higher risk of TVTE.

We have demonstrated a large variability in the seat pitch definition and dimensions amongst various airlines.[88] Australian Civil Aviation Safety Authority (CASA) and ICAO should develop an unambiguous set of definitions for seat dimensions taking into account the seat-space reductions from reclination of the seat in front.

Finally, the airline industry should cooperate with the medical profession and support prospective studies on different groups of passengers as well as basic physiological research. Future prospective studies will further establish the importance of travel and the importance of travel related conditions in the pathogenesis of VTE.

CONCLUSION

VTE is a multi-factorial phenomenon with both genetic and acquired risk factors contributing to the pathogenesis of the disease. The genetic factors provide lifelong increased risk of thrombosis. The acquired risk factors may cause decreased flow as found in prolonged immobilisation or hypercoagulability as found in pregnancy, oral contraception, and malignancies. The acquired risk factors often appear to be the precipitating factors for the disease.[252]

The phenomenon of VTE following long distance travel has been known for many decades. The authors have previously demonstrated the importance of patient related risk factors and in particular the presence of thrombophilic abnormalities found in 72% of patients.[88] These risk factors may interact to produce an effect that exceeds the sum of their individual effects (synergism).[6] The combined effect of all risk factors involved and the interplay between the genes and the travel environment may create a hypercoagulable state at a specific time (Figure 6). The severity of the final outcome depends on the delicate balance between pro-coagulant and anti-coagulant factors.

Clearly, there is a need to identify those in the high-risk category to provide appropriate advice and prophylactic measures. With the increasing number of travellers to Australia and its remote location to the rest of the world requiring long distance air travel, the safety and health of the passengers will grow in importance in years to come.

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