VENOUS THROMBOEMBOLISM

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ABSTRACT

Venous thromboembolism (VTE) is the condition in which blood clots form within the venous circulatory system, and consist of DVT (deep vein thrombosis) and PEs (Pulmonary emboli).

It is a common condition, with an estimated life-time risk of 8% and an annual incidence of 0.84-1 per 1000 population[1], [2] and represents a significant economic burden: within Australia the annual estimated cost in 2018 being $1.72 billion AUD[3].

The condition is considered aeromedically significant for both aircrew and passengers; diagnosis and treatment may have implications on an aviators medical certificate and the general public are often concerned about developing “economy class syndrome”.

This paper reviews the pathophysiology of VTE, the relationship between VTE and its treatment in the aviation environment. It also reviews some of the international aeromedical regulatory guidelines and provides a suggested approach to certification in case of VTE.

PATHOPHYSIOLOGY

Venus thromboembolism typically results form a combination of factors known as Virchows triad; venous stasis, endothelial injury and hypercoagulability. These predisposing factors lead to development of thrombus from activation of the clotting cascade[4].

Risk factors include:

- Older age
- Obesity
- Previous history/Family history of VTE
- Antiphospholipid syndrome/Thrombophilia
- Active cancer
- Recent immobilisation/travel/surgery
- Pregnancy/post-partum
- Oestrogen therapy (hormone replacement therapy and oral contraceptive pill)

The clinical presentation of VTE is dependent on the location of the thrombosis and may be non-specific, generally the signs and symptoms include:

Deep vein thrombosis – peripheral oedema, unilateral limb pain and erythema.

Pulmonary embolism – chest pain, dyspnoea, haemoptysis, tachycardia and syncope.

Long-term morbidity includes pulmonary hypertension and post-thrombotic syndrome. Post-thrombotic syndrome is common and is estimated to occur in 1 in 3 patients following a DVT[5].

TREATMENT

Treatment of VTE is usually with anticoagulation therapy. The choice and duration of treatment is dependent on location and the presence of risk factors (whether it was provoked or unprovoked). Recommended treatment duration is from between 3-6 months however, therapy may continue life-long if there is a risk of recurrence.

A provoked VTE occurs in the presence of either a transient risk factors such as pregnancy, post-partum, surgery immobility or oestrogen therapy (menopause therapy or oral contraceptive pill) or a persistent risk factor, such as are an inherited thrombophilia or palliative malignancy.

A provoked VTE caused by a transient risk factor is usually considered favourable and will usually require a shorter duration of treatment.

Another important factor when considering treatment duration is the location of the VTE.

A distal DVT is one located below the knee, and confined to the calf veins and will result in a shorter duration of treatment, or often not require any treatment.

Pharmaceutical

- DOAC/NOACs

Direct oral anticoagulants/Novel oral anticoagulants are non-vitamin K antagonists are considered first-line for treatment due to their safety profile and work by blocking factors within the clotting casacade.

Within Australia rivaroxaban, apixaban and dabigatran are the most common NOACs used.

- *Warfarin*

Warfarin blocks hepatic synthesis of enzymes used in the reactivation of Vitamin K thereby inhibiting vitamin K dependent clotting factors (II, VII, IX, and X).

Warfarin has a narrow therapeutic index and therefore monitoring is essential.

- Low Molecular weight heparin (LMWH)

LMWH also works by inhibiting various clotting factors. It is given subcutaneously and therefore more commonly used either during initial treatment of VTE or when NOACs or warfarin are contraindicated.

- Other types of treatment

Other treatments include the inferior vena cava filter, thrombolysis and thrombectomy but are uncommon, typically reserved for severe risk factors or contra-indications to treatment. Within aviation, the underlying reason for using these treatments may be incompatible with continued certification. In addition, there is a risk of thrombosis with the use of filters which could also be considered incompatible with ongoing certification[6].

EFFECTS OF AVIATION ENVIRONMENT ON THE CONDITION AND TREATMENT

Multiple aspects within the aviation environment are thought to contribute to the development of venous thromboembolism.

Looking specifically at Virchows triad and the associated aviation factors.

Venous Stasis

- Immobility – long periods of immobility in any form of travel can increase risk of VTE.

Flight duration is recognised to be a risk factor in PE/DVT with flights greater than 4 hours having an absolute risk of a symptomatic event if 1 in 4600 flights[7]. In addition, Lapostolle et al found that the incidence of pulmonary emboli increased with distance travelled (0.01 case per million <5000km compared to 4.8 cases per million > 10 000km)[8], [9].

Although the general public often call VTE in travel "economy class syndrome", the class of travel has been found not to be a factor in the development of thrombosis[10], [11].

- Fluid retention with lower leg oedema[12]

Hypercoagulability

- Dehydration - reduced fluid intake and reduced cabin humidity resulting in haemoconcentration thereby increasing blood viscosity and reduced flow[13].
- Increased erythropoietin – Gunga et al noted that erythropoietin levels were increased in-flight[14]

Endothelial Injury

- Hypoxia due to hypobaric conditions can cause endothelial injury and activate the coagulation pathway[15]

Interestingly, although long-haul travel is associated with increased risk of DVT in the general population, this has not been found in the pilot population. A study published in 2014 found that the incidence of VTE was not increased amongst the pilot population; this was postulated to be due to the "healthy worker effect" amongst aviators[16].

EFFECT OF THE CLINICAL CONDITION ON FUNCTIONAL CAPABILITY

- Overt incapacitation from sudden death or syncope

Untreated pulmonary embolism has a significant risk of mortality, estimated to be 26 to 30%[17], with 10% of acute PEs dying within 2 hours[18].

- Subtle incapacitation due to distraction from symptoms such as dyspnoea, chest pain, haemoptysis, leg pain, dizziness.

Although it can be assumed that not all DVTs will be incapacitating, it is important to acknowledge that all PEs will have the risk of incapacitation and therefore the risk of developing a PE needs to be considered. Unfortunately it is difficult to estimate this risk. A meta-analysis by Wu et al found that the incidence of

PE in patients with a symptomatic calf DVT ranged from 0 to 6.2% however, other studies have found that a silent PE in up to 50% of patients with a DVT[19], [18], [20],[21].

Furthermore, the risk of recurrence of VTE must also be considered. It is now recognised that the risk of recurrence is higher than previously assumed with strong risk factors including an unprovoked VTE, PE, persistent risk factor such as active cancer, anti-phospholipid syndrome, anti-thrombin, protein C or S deficiency. Other thrombophilia disorders such as Factor V Leiden are no longer thought to have an effect on recurrence[5].

Recurrence of VTE as per Thrombosis and Haemostasis Society of Australia and NZ Guidelines[5]

For a provoked distal VTE, unprovoked, the recurrence at 1 year post ceasing anticoagulation and at 5 years is 5% and 15% respectively. For a proximal DVT or PE this increases to 10% and 30% respectively. For a second episode of unprovoked VTE the risk increases to 15% at 1 year and 45% at 5 years.

For a provoked VTE due to surgery or cancer, in comparison, the risk is 1% at 1 year and 3% at 5 years which fits within aeromedical risk guidelines such as the 1% rule.

EFFECT OF TREATMENT OF CLINICAL CONDITION ON FUNCTIONAL CAPABILITY

- Incapacitation due to side-effects of medication such as major haemorrhage

The main concern with treatment is the risk of haemorrhage.

The International Society of Thrombosis and Haemostasis classify bleeding risk as major bleeding, clinically relevant non-major bleeding and minor bleeding[22], [23].

Major bleeding defined as:

- *Fatal bleeding and/or;*
- *Symptomatic bleeding in a critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome and/or;*
- *Bleeding causing a fall in haemoglobin level of 2g/dL or more, or leading to transfusion of two or more units of while blood or red cells.*

Within clinical studies, it is the major bleeding which would be considered aeromedically significant.

It is generally well accepted that risk of bleeding in otherwise healthy individuals on lower dose NOACs is lower that previously thought.

The AMPLIFY-EXT study looked at apixaban, compared to placebo and found that the risk of recurrence of symptomatic VTE occurred in 1.7% of both higher (5mg bd) and lower (2.5mg bd) of apixaban compared to 8.8% recurrence in placebo. The rate of major bleeding in the placebo group was 0.5% with 0.1% in the 5-mg apixaban group and 0.2% in the 2.5mg apixaban group[24].

The EINSTEIN CHOICE study in 2017 compared rivaroxaban to aspirin in VTE found that recurrence was reduced in the rivaroxaban groups compared to those receiving aspirin, without a significant increase in bleeding[25]. Major bleeding occurred in 0.5% of the 20mg od rivaroxaban group, 0.4% in 10mg od and 0.3% in the aspirin group. Recurrence rates were 1.5% in 20mg rivaroxaban group, 1.2% in the 10mg group and 4.4% in the aspirin group.

	Recurrence	Major bleed
Rivaroxaban 10mg od	1.2%	0.4%
Rivaroxaban 20mg od	1.5%	0.5%
Aspirin 100mg od	4.4%	0.4%
Apixaban 2.5mg bd	1.7%	0.2%
Apixaban 5mg bd	1.7%	0.1%
Placebo	8.8%	0.5%

Furthermore, a large meta-analysis by Wang et al in 2018 found that Vitamin K antagonists were associated with low rates of recurrence of VTE (0.15-0.23) however, higher risks of major bleeding (4.14-4.42)[26]. This is in keeping with a study by van Es et al who found similar efficacy in preventing VTE recurrence between NOACs and Vitamin K antagonists however risk of bleeding in NOACs was significantly less with a relative risk of 0.61[27].

REGULATORY ADVICE - NOACs

Internationally, ICAO Annex 1 Chapter 6 states[28]:

"An applicant for any class of Medical Assessment shall be required to be free from:

d) any effect or side-effect of any prescribed or non-prescribed therapeutic, diagnostic or preventative medication taken;"

"6.3.2.8 There shall be no significant functional nor structural abnormality of the circulatory system."

"6.3.2.17 Applicants with diseases of the blood and/or the lymphatic system shall be assessed as unfit unless adequately investigated and their condition found unlikely to interfere with the safe exercise of their licence and rating privileges."

Australia[29]

If an applicant is stable, on an oral anti-coagulant, then the clinical practice guidelines for CASA state that Class 1 and Class 3 applicants will be restricted to either multi-crew or proximity restrictions. However, applicants may be individually assessed regarding these restrictions.

New Zealand CAA[30]

The NZ CAA advise that an applicant who is currently treated with anticoagulants would be considered safety relevant.

Specifically for NOACs, if the applicant is free of side-effects, they may be issued a certificate however, those with a Class 1 would have the following restriction "not valid for single pilot air operations carrying passengers"

UKCAA[31]

The UK CAA look at NOACs on a case by case basis but generally advise that dabigatran, rivaroxaban and apixaban are acceptable and that pilots should be stabilised for a period of 3 months with no side-effects.

RECOMMENDATIONS

When considering the aeromedical significance of VTE, it is important to consider the underlying reason for the episode and the treatment.

The current evidence shows that the risk of major bleeding on NOACs are low with studies revealing a <1% risk; this can be considered acceptable within aviation.

In addition, the risk of recurrence of VTE may be higher than 1% however, as discussed above, not all VTEs will be incapacitating.

For example, a patient with a PE will have a recurrence risk of 30% at 5 years = 6%pa, which would be unacceptable for many regulators.

If, however this applicant is treated with a long term low dose NOAC (e.g. apixaban 2.5mg bd) then the risk of recurrence would be 1.7% but incapacitation risk can be considered to be 50% of this i.e 0.85%.

In addition, the risk of major bleed would be 0.2%pa.

It would be reasonable to conclude that this applicant can be considered safe to fly without any restrictions, based on the combination of the recurrence and treatment risks.

Medicine is ever changing, and it is important as aeromedical examiners and regulators, to continue to review medical literature in order to apply up to date reasoned, evidence based aeromedical decision making.

VTE is one such condition where over time, studies with respect to novel treatments have provided more reassuring risk profiles that may allow more favourable certification outcomes.

The views expressed in this paper are those of the author and do not reflect CASA policy

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