

Deep Vein Thrombosis And Pulmonary Embolism

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SUMMARY:

Deep Vein Thrombosis (DVT) and its sequelae — Pulmonary Embolism (PE), are very important disorders which ought to be prevented actively by recognising a high risk category of patients, which should receive prophylactic treatment. There are many diagnostic inadequacies with these disorders and such serious limitations often encourage empirical therapies especially if the patients are asymptomatic. Major general surgery, prolonged immobility, hip arthroplasties etc. are associated with a high incidence of DVTs, as observed by the screening^{1 2 5} I-Fibrinogen uptake test and by the more specific investigations such as Venography, Pulmonary Angiography and the Lung scan. Various protocols of treatment are now popular with varied claims of success.

INCIDENCE OF DVT AND PE:

The true incidence of both DVT and PE is rising and this is in keeping with the increasing life-expectancy. More elderly patients are now being seen with prevailing CCF, Carcinoma and Diabetes, who present for major surgery. Crush injury in road accidents is commoner now than before and this provides cases of pelvic vein thromboses and fat and clot embolisations.

The incidence is also increased in those patients who remain immobile for a long period such as patients suffering from CVA, M.I, DIC, Fractured hips etc.

Surgery in the obese and in the elderly high risk patient, is notoriously associated with DVT and PE. DVT is commoner in patients who have previously suffered from an episode of DVT which may have resolved fully. Spontaneous DVT is associated with users of Oestrogen but it should be clearly understood that only a tiny minority of women on the "Pill" suffer from DVT.

However, although the true incidence of DVT and PE is rising, the true incidence of the diagnosis of DVT and PE is not rising. That is to say that the diagnostic pick up rate is not

keeping pace with the increasing presentation. The explanation is rather amazing! A substantial number of autopsies show presence of PE subsequent to DVT as the prime cause of death, while in-life history as available, does not show significant symptomatology. This means that many patients with DVT remain asymptomatic until a fatal PE occurs.

The other side of the coin is that in many patients (30-35%) in the hospital, in whom there is a positive clinical diagnosis made of DVT, venography does not show any clots! Therefore these patients in spite of their clinical presentations cannot be classed as suffering from DVT, scientifically. Such statistics are very confusing and discouraging inasmuch as it would appear that a majority of DVT sufferers cannot be adequately diagnosed, but a substantial number of PEs in established DVT patients can be prevented! The trick of the trade therefore, is to identify early, those patients who have manifest DVTs or who are likely to develop DVTs in order to prevent its progression to a PE.

The incidence of DVT in hospitalised patients is reported to be between 15 — 75% in various specialties and this constitutes a huge

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number. Such increased pick-up rate is related to a greater use of the 125 I-Fibrinogen Scan in high risk patients (1).

PATHOGENESIS OF DVT:

The three basic characteristics which determine the formation of a clot in the veins are:

1. Hypercoagulability.

Red cell clumping (as in polycythemia rubra vera, sickle cell disease, paroxysmal nocturnal haemoglobinuria), thrombocytosis (as in myeloproliferative disorders (2), alcohol withdrawal syndrome (3), post-splenectomy syndrome (4), hyperosmolar state (dehydration, hyperglycaemia, severe hyperlipidaemia) can all provoke spontaneous coagulation. It has recently been identified that contrary to expectation, the lupus anticoagulant present in SLE can produce thrombosis and not haemorrhage (5)! The clotting factors can be intrinsically triggered by defective platelets or by platelet-activators such as septicaemia and drugs. The fact that antiplatelet agents actively prevent such clots, confirms that platelets and other cells do have a positive role in the causation of thromboembolism (6). Platelets radiolabelled with indium can be seen within the initial plug which constitutes the DVT and the PE (7). In the recent past, the roles of Protein C and antithrombin III have been recognised. If the activity of either of these substances is reduced, there is hypercoagulability produced (4). Thus it can be categorically said that hypercoagulability has a positive role in the production of DVT and PE. Certain malignancies are associated with thrombosis (8). Possible causes may be thrombocytosis (9), impaired fibrinolysis (10) and Coagulation-activation causing DIC in mucin secreting adenocarcinoma, promyelocytic leukaemia etc.

2. Stasis.

Stasis is the single most important determinant of DVTs and this can be easily seen in the predilection of clots for the low pressure venous system of the legs. However it is clear that stasis alone cannot cause DVTs without there being some provocation of the clotting process (11). Factors which reduce stasis (gra-

duated stockings, pneumatic exercises, calf muscle stimulation reduce stasis and reduce the incidence of DVT and PE in the hospitalised patient (1). Stasis, when associated with vascular endothelial damage, even though very minor, can result in severe DVT and consequent PE (12).

3. Endothelial damage.

In the past it had been recognised that arterial but not venous thrombi were associated with endothelial damage caused by plaque separation (13, 14) and bacterial injuries (15). It is now clear that venous wall damage is an equally important factor in producing a DVT (15, 12).

The majority of DVTs occur in deep calf veins (16, 17). Gradual extension occurs into the Popliteal, Femoral and the Iliac Veins in 33% of the patients suffering from lower calf DVTs (18). Using scans and Venography, Kakkar (15) has shown that those DVTs embolise more often where extension has already taken place into the upper thigh veins. The DVTs either resolve fully (majority of patients) without local or systemic ill effects, or produce complications (minority). The complications may be those of the PE or those of the local disorders of the leg. Such local disorders produce lipodermatosclerosis (19) characterised by erythema, pigmentation, induration and tenderness of the inner aspect of the calf, and caused by defective calf pumping, or ulceration of the superficial tissue. The combination of these symptoms produces the "post-phlebotic syndrome" caused basically by the effects of damaged venous valves, gross distortion of the venous drainage system and reduced interstitial fluid clearance (19). Lipodermatosclerosis results in deposition of fibrin around capillaries near the skin surface, which makes the capillaries less permeable. Fibrinolytic activity is therefore reduced in the areas affected. This is confirmed by using stanazolol, an attenuated androgen with fibrinolytic properties, which improves the condition in vivo and in vitro (2, 20).

NATURAL HISTORY OF DVT AND PE:

A majority of the DVTs remain unrecognised and it must be assumed that these undergo

spontaneous lysis. 80% of the DVTs resolve and recent studies involving scans and venography support the contention that only in about 20% of those cases headward extension takes place and in this subgroup approximately 50% of the patients develop detectable PEs. About 50 - 70% of the PEs are spontaneously lysed with symptom-resolution and around 30% of the PE sufferers in fact, die of the complication. When the DVT is fixed to the venous wall, it does not often calcify. It usually gets broken off and is fibrinolysed with progressive restoration of the lumen. When it does become organised and calcified, the lesion is permanently fixed and does not embolise itself, although it still attracts platelet plugs which in turn embolise headwards.

If PE "total" and occludes the pulmonary artery, a segmental infarction follows, with subsequent collapse of the bronchopulmonary segment of the lung. The infarction and retraction of pleura produce the clinical features which simulate MI. A majority of the PEs are subtotal and may only produce relative ischaemia. The segmental destruction is therefore gradual and an interstitial lung disease may result over a period of time leading to pulmonary hypertension. This, however, is rather rare.

If the majority of the patients suffering from DVT and PE spontaneously improve then it becomes very difficult to project any one particular method of treatment as the method of choice. Certainly the morbidity of the disease may not be much improved with any one particular type of treatment but statistics suggests that the mortality related to PE can certainly be brought down with early and appropriate treatment of the DVT and of the early-onset PE.

RISK FACTORS:

Unlike the risk factors associated with thromboses in the arteries, the risk factors associated with DVT and PE are more well defined. These include obesity, immobility, prolonged surgical operations and an increasing age. All of these factors probably relate to stasis, however some degree of intrinsic activation

of the coagulation cascade must be occurring to promote the degree of DVT which becomes symptomatic or which leads on to pulmonary embolism. This has been well documented by the reduction in the incidence of DVT with simultaneous injection of subcutaneous Heparin prophylactically, in high risk subjects undergoing major surgery (15, 21).

Heparin enhances the activity of Anti-thrombin III (AT-III), which inhibits the number of activated clotting factors including Thrombin, factors Xa and IXa. Postoperative value of Heparin, particularly relates to blockage of factor Xa (11). Hip surgery is associated with a much higher incidence of DVT and this is improved with adjunct use of subcutaneous Heparin. Here the major disorder may be the damage to the femoral vein rather than stasis (21).

An important factor of interest is smoking. There is no doubt that smoking is a positive hazard and a significant factor in the causation of arterial athero-thrombotic disease. It is surprising to see that not only is smoking unrelated to venous thrombosis but that it may have a protective effect against post-operative venous thrombosis (22, 23). However such impressions should be evaluated against another important consideration and that is the choice of the patients in the quoted studies. In the groups studied (22, 23), the patients were younger age and to absence of obesity, may have conferred protection. Unless such studies are compared on a life-time cumulative chart, such impressions cannot be generalised and therefore cigarette abuse should not be encouraged.

In the recent past it has also been shown that the inhibition of coagulation activation as produced by AT-III and Protein C, have a positive protective role against the development of DVT. AT-III, synthesised in the liver, is the most important physiological inhibitor of thrombin and activated factor X (24). In addition, it also actively inhibits, though to a lesser extent, Factors IXa, XIa and XIIa (24). Cases have been reported where there is a constitutional (genetic) reduction of the plasma pool of the AT-III, associated with recurrent

thrombotic venous disease (25). Reduced AT-III is also seen in liver diseases, DIC and in women taking contraceptive pills (26). There is evidence that patients who undergo major hip surgery with less than 80% of AT-III have a higher risk of developing postoperative DVTs (15, 21).

There is a similar recognition of the inhibitory effects of the clotting factors seen with Protein C, which is a vitamin K dependent factor. Protein C, when activated, reduces and inhibits, factors V and VIII. The effects of Protein C are augmented by cofactor S. Both Protein C and cofactor S are reduced with oral anticoagulant therapy. Protein C is also reduced in those conditions (4) which produce widespread DIC and generalised thrombotic disorders related to a greater consumption of clotting factors (Septic abortion, prolonged labour).

INVESTIGATIONS OF DVT AND PE:

It must be re-emphasised that inert thrombi are present in about 50% of the high risk patients, who remain asymptomatic and who do not present with any physical signs. Even in those patients in whom a clinical diagnosis of DVT is suspected about 30% do not show any clots on any of the available investigations. Therefore, to a large extent, the diagnosis of DVT at least, must remain clinical and the initial treatment, empirical. In classical presentations of PE, the reliability of Ventilation/Perfusion scan is so good that in most patients the diagnosis can be confirmed. This is just the opposite of DVT.

INVESTIGATIONS FOR DVT:

1. Venography.

Into the dorsal vein of the big toe, via a butterfly needle, dye (Urografin 75%) is injected and its ascent seen on the screen. Cinephlebography is very reliable and initial screening must be done to judge the time taken for the dye to reach the suspect area before documenting views on the cut-films. As in Varicose-Vein Venography, the Long Saphenous Venous occlusion via a tourniquet, diverts the major part of the dye into the deep system of veins. Care must be taken to prevent dislodgement

of the clot headwards by an injection using undue pressure. The presence of the DVT is shown by a filling defect. If the obstruction is complete, the ascent of the dye is totally blocked and it is then diverted via "collateral channels". Partial blocks show up as partial but consistent filling-defects. Often, due to the destructive effects of the solid clot, the valves are damaged and blood leads into side channels through these incompetent valves. This can be best studied with the patient standing upright on the X-ray table during cinephlebography. Another method of such assessment, although not very popular now, is the Descending Venography performed via a downward puncture of the Femoral Vein.

If the Deep Vein (Tibial, Popliteal, Femoral) appears to be totally blocked, there may or may not be side-channel collateral veins visible. However there may be a false positive "block" present. In this, in an unguarded and poorly prepared patient, during the injection of the dye, a violent contraction of the calf muscles may totally block a patent Vein by mechanical extrinsic compression. It is for this reason that dynamic cinephlebography is considered superior to cut-film views (15). Partial occlusions show up as incomplete filling defects (translucent) with a rim of contrast medium surrounding the filling defects.

The dangers of venography include intimal damage leading to fresh thromboses or dislodgement of the existing thrombus with embolisation. These dangers can be minimised by flushing the veins with heparinised saline after each dye injection and subsequently for a few minutes (15).

Venography is the most reliable investigation for DVT (15) and most of the true DVTs are positively diagnosed by this method but because of its invasiveness, costs, risks of radiation etc. it is not practical to use it as a screening test in a given population of patients. It shows the site, shape and size of the clot very accurately and therefore the test should be reserved for confirmation rather than for screening. Because of its simplicity, reproducibility and accuracy, it is used as a standard parameter against which other investigations such as scans, doppler flow

study, plethysmography etc. are compared. Venography is easily available in most hospitals now, in Pakistan.

2. Doppler Ultrasound.

The doppler ultrasonic flow velocity detector consists of a small hand held crystal probe which creates and directs ultrasound percutaneously into the deep tissue. The beam goes through to the veins and is reflected back by the RBCs. These reflected beams are picked up by a receiving crystal incorporated in the same probe but working in a different frequency. If there are more RBCs in the area (as in occlusion or in turbulence from partial occlusion), more of the transmitted sound will be reflected back. The reflected sound is amplified and can be heard and recorded on paper. The magnitude of the sound is proportional to the velocity of the blood flow. This velocity of the blood flow in major veins such as the femoral and the Popliteal, can be temporarily increased by mechanical calf compression. The increased or "Augmented" ('A') Sound can be easily heard and recorded. In presence of a distal clot, the manoeuvre will fail to produce the 'A' sound.

Doppler ultrasound can also locate reflux of the blood via leaky or incompetent valves. It is fairly accurate but cannot diagnose smaller clots. It is totally non-invasive and is fairly reliable for major clots of the Popliteal, Femoral and the Iliac Veins.

It can be falsely positive when a superficial crossing vein is present over a clot, or when large collaterals are present in the vicinity. It can be falsely negative when the clots are small. Doppler tests are now available in Pakistan.

Its main value lies in its ability to locate major clots and in the serial follow-ups, in showing a progressive reduction of the clot. As an adjunct to the Venography, it is an extremely useful non-invasive tool. Venography diagnoses and locates the clot and the sequential recordings of the doppler ultrasound show the response of the anticoagulants in reducing the size of the clot.

3. Radioactive Iodine-fibrinogen Uptake Test:

The principle of the test is that all fresh thrombi preferentially take up Fibrinogen into their receptor sites. Fibrinogen is conveyed to the site of the thrombus tagged with Iodine. The Iodine isotope selected is one possessing a relatively short half life. However any administered Iodine will first be taken up by an active Thyroid for conversion and storage and since unnecessary exposure of the Thyroid to energy-emitting Isotope is potentially hazardous, to spare the Thyroid of such a noxious damage, the Thyroid receptors of iodine are first saturated. The patient is given oral or Intravenous (depending on the urgency) Sodium Iodide. This will be trapped, converted, bound and stored in the Thyroid, thus saturating it.

¹²⁵I-Fibrinogen complex is then injected I/V into a peripheral arm vein. The dose of the Isotope Iodine (¹²⁵I) is 100 Ci. Since the Thyroid is fully saturated, the complex will go to the Heart, the Kidneys and to the site of the fresh thrombi. A good admixture takes place in 4 hours and at this time the thrombus is enriched with ¹²⁵I-Fibrinogen complex and begins emitting radiation. Therefore 4 hours after the Isotope injection, a reading of the praecordial area is first taken. Irrespective of the numeric energy reading of the isotope at the site of the heart, the value is expressed as 100% of the Isotope. Against this parameter of 100% uptake of the heart, percentage values at different sites of the legs are calculated. Wherever the percentage is very high, that is the site of the thrombus. Pre-marked sites (traditionally seven sites in the leg and seven in the thigh) are then measured for radioactivity by an Isotope detector/counter and the values expressed as percentages of the cardiac reading. The criteria of diagnosis are:

(a) If the radioactivity is 20% or more than the contralateral site after 24 hours.

(b) The radioactivity persists beyond 24 hours.

(c) If the radioactivity is higher than the adjacent site and remains so for more than 4 hours within the first 24 hours. This is a weak

criterion.

This test is sufficiently sensitive and easy to perform to be regarded as a screening test in the high risk patients. It is fairly accurate in DVTs of legs and thighs. In the groin and in the Pelvis, because the Isotope-filled bladder masks the Pelvic venous thrombi readings, it is inaccurate. Similarly in hip surgery, where the incidence of the postoperative DVT is high, the Fibrinogen is accumulated in the operated sites and gives an artificially higher reading. Overlapping large veins may similarly mask a small clot in the leg.

The test is semi-invasive but is relatively safe. It is popular and compares well with Venography with a positive correlation of 80%.

In large screening studies, most researchers have found that the Isotope test picks up more cases than Venography. Kakkar suggests that this is due to a higher pick-up rate of muscular veins with DVTs which are not efficiently outlined by conventional Venography (15).

4. Impedence Plethysmography:

This is a relatively inert and non-invasive technique based on the principle that in the leg, electric current is conducted more easily in presence of a good quantity of blood, since blood is a better conductor than the extravascular soft tissue. Thus if blood is trapped in the calf, as is the case in venous thromboses or following entrapment by a pneumatic cuff application in the lower thigh, then the increased blood quantity trapped in the calf will conduct current faster. In other words, presence of blood reduces the resistance to the flow of electrical current. The test is performed bilaterally using electrodes, an impedence plethysmograph, ECG strip paper, and a thigh sphygmomanometer cuff.

The patient lies supine breathing comfortably (overbreathing alters venous return and produces a false reading). A 15 cm wide cuff is applied to the mid thigh and is kept deflated. Four electrodes are applied to the calf and are strapped in position. A known current is then passed from one electrode to the other and the electrical

resistance, (resisting the passage of the current between the electrodes) is recorded by an impedence plethysmograph. At this point, the thigh cuff is inflated to 45 cm H₂O to occlude the venous return and the cuff pressure is maintained for two minutes. Electrical resistance readings are taken and recorded on the paper. The cuff is then suddenly deflated and further reading is taken of the electrical resistance. During the inflation of the cuff, with the increased volume of blood trapped in the leg, the resistance reduces and this fact is recorded on the strip paper. This test is as yet not available in Pakistan.

In presence of the DVT-occlusion, there is a greater pooling of blood in the calf and the resistance remains lower than normal. The test is performed bilaterally and several times, to remove errors. The method is insensitive to calf vein thromboses and usually only the popliteal vein occlusions produce acceptable results. The only danger with the test is the propagation by milking of the clot and therefore this test is not altogether non-invasive. Not enough data is available to categorise the risk of iatrogenic embolism but this is certainly not high.

5. Radionuclide Venography:

Macro-aggregated human albumin particles are tagged with an isotope (technitium ^{99m}). The mixture is then injected into the dorsum of the foot. Images are taken by a gamma camera of the energy radiation of the Isotope, from the calf, the thigh, the groin, the pelvis and the lower abdomen. A cobalt disc is positioned on the symphysis pubis to mark the midline. Wherever more dye is trapped, increased radioactivity will be detected and accordingly, the clot, wherever it may be, will take up more of the tagged albumin and the increased activity will be recorded by the gamma camera. Sequential radionucleograms of the Tibial, Popliteal, Femoral, Iliac Veins and of the Inferior Vena Cava are taken and compared with the opposite side. Because, often, DVT occurs bilaterally, the test should be performed bilaterally. (15, 35). The test is possible in our Isotope Centres but special preparation is required.

The test is minimally invasive (in respect of the radiation hazards) but is fairly reliable for large vein clots. It is expensive and superior to plethysmography but is inferior in reliability to venography and to ^{125}I -Fibrinogen uptake test.

6. Blood Coagulation Assays:

Serial measurement of FDPs (which are increased in presence of a thrombinrelated enzymatic degradation of the fibrinogen), serial dilution tests utilising protamine sulphate dilution of fibrin monomer complexes, can show an active state of haemostatic imbalance. In established and static thrombotic conditions (the majority), such tests are not useful but in conditions where early DVT is being suspected, as screening tests these show some promise in future research. Evaluation of FDP is now easily possible in various parts of Pakistan but the concept of coagulation tests in following up DVT and PE has not yet evolved beyond a diagnostic screen or as a measure of anticoagulant activity during therapy.

INVESTIGATIONS FOR PE:

An important aspect in the overall management is to appreciate the value of early diagnosis and prompt treatment. Delay in treatment adds more emboli to the previously impacted site and to adjacent areas and the size of the pulmonary infarct increases. Large emboli usually cause death if untreated but these are preceded by multiple showers of emboli which can both be treated but even more important—prevented.

1. Chest X-ray.

This may show linear shadows in PE. The result of the impairment of lung perfusion is to cause a reduction in the vascular lung markings (patchy oligoemia) in the affected zones. Pear shaped hilar shadows representing a cut-off of pulmonary arteries due to the PE may be seen especially in the right hilum. Infarct shadows may be seen on good chest X-rays.

The main value lies in correlating the X-ray findings with the findings of the lung scan and

the pulmonary angiograms. Many diseases are represented reliably on the Chest X-ray such as tuberculosis, pneumonia etc. and if the chest X-ray is not taken as well then a lung scan which shows a perfusion disorder may be misinterpreted as PE.

2. ECG:

Although the sudden development of a S_1, Q_3, T_3 pattern is pathognomonic of PE, ECG changes are generally non specific. A serial study is therefore desirable and an ECG prior to the development of symptoms and signs, if available, is extremely useful for comparison. A rightward shift of the Axis is also very common and so is the RSR^1 pattern on V_1 and V_2 . (29). Only about 10-20% of the patients subsequently shown to be suffering from PE, in fact do have classical ECG changes. A very important role of the ECG is to assess the state of the myocardium. Many patients with MI are thought of as suffering from PE. Many patients suspected of PE, may have MI. The classical signs on the ECG and the substantive enzyme results differentiate MI from PE.

3. Enzyme Tests:

Elevation of LDH and bilirubin with a normal SGOT raises suspicion of PE and in the pre-scan era, this was a standard test performed.

4. Lung Function Tests:

Because the predominant effect is vascular interruption with no ventilatory disturbance at least in the early phase of the disorder, the FEV, and the Vital Capacity both remain within normal limits. The Gas Transfer Factor (TLCO) is reduced in keeping with the diffusion defect produced as a result of impending pulmonary infarction (29). In the Single breath Carbon Monoxide Transfer Test, the subject inhales from Residual Volume to TLC (total lung capacity), a small known concentration of CO and a known concentration of Helium (He). The breath is held by the patient for 10 seconds and is then fully exhaled. The CO will have diffused completely because of its high diffusion capacity and the helium will have become

diluted. Using curves, such a transfer is expressed per litre of alveolar volume. (30). Although the static lung function tests are available in Pakistan, the gas transfer tests are as yet not available but are shortly expected to be introduced.

5. Blood Gases:

Transfemoral blood gas measurement is likely to show reduced $P_a \text{CO}_2$ and reduced $P_a \text{O}_2$ in an un-oxygenated patient. With oxygenation these values may become normal. Such measurements are common place in most hospitals now in Pakistan.

6. Lung Scanning:

The Isotope Perfusion lung scan is the single most valuable diagnostic test available for the diagnosis of PE. There are 300 million pulmonary arterioles present with a diameter ranging from 15-30 μ . There are 280 billion pulmonary capillaries with a diameter 5-7 μ . (29). Microsphere or macroaggregate particles (pyrogen free human albumin) which have the same density as the RBCs and the range of size from 15-70 μ , are gagged with $^{99}\text{Tc}^m$. These microspheres or macroaggregates are trapped in those blood logged zones of the lung where an embolism has occurred. From the regional perfusion defects, gamma ray emission takes place from the technitium and the gamma camera records their emission. The test is performed with a single injection of 1.4mCi of $^{99}\text{Tc}^m$ which contains about 150,000 of these microparticles.

It is essential to obtain accurate anatomical information about pulmonary perfusion and therefore multiple views of the lung are assessed. A minimum of Anterior, Posterior, Right lateral and Left lateral views are essential (15). In addition, right and left posterior oblique views are also recommended to complete the topographical study (29). The reliability of the lung scan is so good that if the scan is normal and no perfusion defect is seen then it can be said that there is no PE present. If however, there is a perfusion defect present then it is likely to be due to a PE but there are many other lung conditions (pneumonia, TB, COAD and Carci-

noma etc.) which can also cause a regional perfusion defect. Therefore the evaluation of a positive scan should be made in the light of a chest X-ray. An important development is the availability of the Ventilation Scan.

The Ventilation Scan is performed by inhaling quietly, a mixture of air and Krypton-81m (half life = 13 seconds). Because of the short half life, the amount of radioactive gas in any part of the lung at any one time relates to the regional ventilation of that part. Before the availability of Krypton-81m, Xenon-133 was in use (half life = 5.27 days).

In actual practice, the patient is injected with the microparticles tagged with technitium and a perfusion scan is taken. In the the same position, the patient is asked to breathe an air/Krypton mixture from a mask and another view of the same patient-position is taken which will now show the ventilation scan of the same region. The position of the patient is then altered and the procedure is repeated. Because the emission characteristic is different for the two radionuclides ($^{81}\text{Kr}^m = 191 \text{ Kev}$, $^{99}\text{Tc}^m = 140 \text{ Kev}$), using an "energy window" on the gamma camera, the images of each can be separately recorded in the same patient-position. This gives a unique comparative views of the area in question in respect of perfusion defect and ventilation defect. The availability of Ventilation Scan makes the diagnosis possible in those conditions where the perfusion defect is present but additional disorders appear on the Chest X-ray. Where the Ventilation Scan is not available, the information gathered on the basis of a Perfusion Scan will yield three groups of patients:—

(a) *The lung scan is normal.*

If the scan is adequate then the diagnosis of PE can be excluded.

(b) *A high probability lung scan.*

Here the scan shows a segmental or lobar perfusion defect but the chest X-rays do not show a corresponding (ventilation-related) abnormality. The diagnosis of PE in such cases is correct to the extent of 85% (15).

(c) A low probability lung scan.

Here the lung scan does show a non-segmental perfusion defect, but the corresponding chest X-rays also show lung abnormalities (pneumonia, TB, COAD, Carcinoma etc.). In this situation the reliability of the perfusion scan is no more than 10-20% (15).

The V/P scan combination is therefore essential for the diagnosis of PE in the Low probability scan-positive patients.

PE exhibits two features which produce a characteristic disturbance of regional perfusion and ventilation. The first feature is that emboli frequently plug segmental pulmonary arteries producing multiple segmental perfusion defects. Secondly, these perfusion defects are not associated with corresponding ventilation defects because of "collateral ventilation".

Perfusion Scan is easily available in Pakistan. Because Xenon is expensive and Krypton needs to be continuously made from cyclotron rubidium-81, which is itself a very complicated and expensive procedure, Ventilation Scan is sadly not available in Pakistan. The use of the Perfusion Scan is therefore basically to exclude PE rather than to confirm it.

PULMONARY ANGIOGRAPHY:

This is the definitive investigation for PE and is very accurate in localising the extent of the occlusion. A peripheral venous catheter is guided into the pulmonary trunk and 75% Urografin injected by hand injection. The test will outline the two divisions of the trunk, lobar, segmental and the first two subdivisions of the segmental arteries. A filling defect will be visible at the site of the clot and in total obstructions, a total cut off of the dye will be seen.

The investigation is very invasive and can dislodge the clot forward or can precipitate further thrombi on the existing embolus. It does not assess infarction well since the dye will not go beyond the occlusion in 100% blocks. Total blocks are more diagnostic but in incomplete blocks, a partial filling defect, asymmetry of flow and 'pruning' of the peripheral pulmonary

vessels is seen and these features are much less diagnostic.

Pulmonary angiography is justified where lung scans are not available and also when diagnosis is not easy (concomitant lung diseases).

CLINICAL FEATURES OF DVT:

On a number of occasions, the earliest feature of DVT is the clinical development of a PE and then the attention is directed towards the DVT in the lower limbs. To repeat again, a large number of patients who suffer from DVT remain asymptomatic and the diagnosis comes to light on venography. Some patients with established DVTs on venography remain totally asymptomatic and without localising physical signs.

Basically DVT of the peripheral lower limbs can occur in any one of the two common forms. A superficial thrombophlebitis or deep phlebothrombosis.

The superficial thrombophlebitis presents with a local pain and tenderness overlying the cord like thickened vein. Occasionally it is related to local infection and then the features of cellulitis mask the true venous inflammation. This type of inflammation rarely leads to embolisation.

The true deep phlebothrombosis of the deeper veins usually produces local congestive pain due to venous stasis and increased hydrostatic interstitial pressure. A bursting type of pain is described in total blocks of the main limb veins, becoming worse on dependency, especially on prolonged standing. This is usually relieved, to a large extent, on recumbency and on limb elevation. The local pain can range from a dull ache to a severe bursting type of pain and is usually localised to the segment involved. In major thrombosis of the iliofemoral veins, the entire lower limb is painful.

Local oedema is present and the girth measurements performed serially will show dynamic changes relating to posture. More than 1 cm of distension is generally regarded as abnormal. Tenderness at the site of occlusion and the surrounding area (which is aseptically

inflamed), is present.

Homan's sign (pain in the calf on dorsiflexion of the big toe) is positive. Local discoloration is present in advanced cases with regional cyanosis due to stasis of reduced blood overlying the DVT. Collateral superficial veins are engorged and the affected segment is warmer than normal. In very severe cases, the progressive DVT can produce massive local oedema producing a compartment syndrome type of arterial compression leading to "venous" gangrene.

In chronic DVTs the adjacent valves are either destroyed by the thrombus or due to high pressure drainage from the collateral veins and this leads to the production of a distended, high pressure, incompetence-related varicosities, oedema, brownish pigmentation, eczema and ulceration. (Postphlebotic syndrome).

Occasionally lymphangitis accompanies the venous disorder and the combined lesion produces a mixture of venous and lymphatic oedema.

CLINICAL FEATURES OF PE :

Acute minor embolisms :

1. Asymptomatic. When the embolism is peripheral into the lung and is small in size.

2. The main symptoms relate to the development of distal pulmonary infarction which produces pleuritic and bronchopulmonary symptoms. Because the lung possesses a dual blood supply (bronchial and pulmonary), generally infarction is not followed by necrosis as is seen in arterial gangrenes of the periphery. Rarely if a perfusion disorder is present beforehand and PE develops subsequently, the lung can necrose but this is very rare. Since the lesion is minor, no significant haemodynamic features develop.

3. Pleuritic pains and haemoptysis are produced late.

4. Local exudation leads to the development of a pleural rub, crepitation and a linear radiological shadow which develops within 24

hours and resolves fully with resolution of the embolism.

Acute massive pulmonary embolism :

More than 50% of the lumen of the major pulmonary artery is obstructed suddenly and as such, there is not much initial peripheral lung or pleuritic involvement present. (Less than 33% of the patients develop pleuritic pain or haemoptysis). If with a major PE, pleuritic pain and haemoptysis are present then these usually indicate that minor emboli were causing minor Pulmonary infarctions preceding the major PE. Considerable haemodynamic instability occurs and this is reflected by an acute right ventricular failure, acute ventilation/perfusion (V/Q) defects and acute reduction of cardiac output.

The right ventricular failure is produced due to congestive overload of the right ventricle and the right ventricular end-diastolic pressure (RVEDP) rises considerably, and with this, the CVP also rises. RV ejection delay and reduced stroke volume are present. Raised CVP, gallop rhythm and a central chest pain (in 33% of the patients) are present. This presentation should be distinguished from an MI where LVF occurs with pulmoanry hypertension and the patient seeks a reclining posture to overcome orthopnoea. In PE, RVF occurs with normal pulmonary BP and the patient prefers to lie supine.

The acute V/Q defects result in the development of a sudden dyspnoea. The respiratory rate is increased and hyperventilation develops rapidly with resultant hypocapnoea. Since a large part of the lung is infarcted and the available oxygen is desaturated, there is hypoxia present, despite hyperventilation. A combination of low pO₂ (around 50mm Hg) and low pCO₂ (around 35mm Hg) is virtually diagnostic of PE in presence of dyspnoea. Cyanosis occurs in 66% of the patients and is a result of arterial desaturation which could occur due to shunting via a patent foramen ovale or due to perfusion of the lung in the presence of atelectasis. The peripheral pulmonary arteries beyond the embolism are said to undergo spasm under the effect of local serotonin but this remains unproven.

Acute reduction of the cardiac output occurs because following acute massive PE the RVF leads to reduced left heart filling. The reduced left heart filling pressure leads to a low left ventricular output and consequently "collapse" which is the commonest symptom of a massive PE.

There are many intermediary conditions ranging from minor chronic PE to acute massive PE and similarly the symptoms and signs range over this spectrum.

Clinical syndromes of PE

Syndrome	Symptom	Sign	Pa Systolic pr
Acute minor PE	Pleurisy	Pleural rub	Normal
	Haemoptysis	crepitations	
	None	None	
Acute major PE	Collapse sudden dyspnoea chest pain	RVF Major V/Q defect	41mmHg (+/- 1.2)

adapted from Scient Found of Resp Med: Heineman, London, GAH Miller, 1981.

TREATMENT OF DVT AND PE:

The most satisfactory approach is one of actively preventing this disorder in the high risk patients and various protocols of treatment exist for this purpose.

The routine treatment includes prevention of further DVTs and prevention of PE if this has not developed already. Elevation of the foot end of the bed, applying of elasticated bandages from toes to groin, regular exercises and use of some form of anticoagulation is necessary. The protocol for the use of anticoagulation varies widely in different Centres. Basically there are two groups of drugs in use, one which prevents deposition of further thrombus (anti-thrombotics or anticoagulants) and those which remove existing fibrin and fibrin-related metabolites, (namely the Fibrinolytic drugs).

Oral anticoagulants:

These reduce the hepatic synthesis of

various clotting factors which are dependent on Vitamin K (II, VII, IX, X, Protein C). The indirectly acting anticoagulant, the indanedione derivative (Dindevan) and the 4-hydroxycoumarin group of drugs (Warfarin) can be used. Of the two, the more popular is the coumarin group of drugs. Warfarin (Wisconsin Alumni Research Foundation) is a long acting drug which requires 48-72 hours to act after the initial dose and is therefore unsuitable on its own for use in an emergency or for rapid induction of anticoagulation. A twice daily dosage is necessary to maintain an adequate blood level. The regulation of the drug-dosage is based on the estimation of prothrombin time which should be maintained at around 1.5 to twice that of control. This level of anticoagulation prevents the growth of the thrombus and reduces further deposition of thrombi or emboli at the site of an existing clot (32, 33). There are many drugs which interfere with the action of Warfarin either by competitively blocking receptor sites or by degrading Warfarin.

Drugs which increase prothrombin time during Warfarin therapy:

- Allopurinol
- Anabolic steroids
- Chloramphenicol
- Cimetidine
- Clofibrate
- Indomethacin/phenylbutazone
- Metronidazole
- Oral hypoglycaemics
- Salicylates
- Cotrimoxazole
- Phenothiazines

Drugs which reduce prothrombin time during Warfarin therapy include:

- Barbiturates
- Griseofulvin
- Oral contraceptives
- Rifampicin

Some conditions which prevent breakdown of Warfarin may enhance or prolong the effects of Warfarin, such as hepatic damage caused by alcoholism.

Any condition which alters the transport of Vitamin K, will adversely affect Warfarin transport and hence usage as well eg., change in the intestinal flora due to antibiotic abuse or decreased lipid pool.

If overactivity develops (haemorrhage), stoppage of Warfarin should be assisted with I/V Vitamin K and sometimes transfusion of whole blood supplying fresh clotting factors. In the initial therapy with Warfarin it should be remembered that some 3-4 weeks following initiation of therapy, an antibody to Warfarin develops which reduces the effects of Warfarin necessitating a greater maintenance dosage for continued anticoagulation. This has been termed the PIVKA effect (Protein induced by Vitamin K antagonist). With continued usage, this PIVKA effect diminishes but during its peak, an increase in the maintenance dosage should be made. In the author's view, the duration of treatment with Warfarin should not be less than three months. Warfarin has a proven role in the reduction of clot size with passage of time and this leads to eventual recanalisation of the vessel.

Rarely, in cases where Protein C is deficient, initial Warfarin therapy provokes a skin necrotic response due to microthrombosis of skin vessels (27).

Defibrinating agents:

Ancrod is an agent which degrades free plasma fibrinogen into small sized "microclots". These microspheres are rapidly fragmented by the dynamic high flow circulation and are eliminated by the RES cells from the body. The available Fibrinogen pool is therefore reduced but in order to do so the infusion of ancrod must be constantly topped up to keep pace with the constant manufacture of the fibrinogen.

The treatment is usually started in the form of an infusion but the initial therapy is administered slowly. The earliest microclots of fibrinogen can occlude smaller vessels and therefore the infusion starts slowly and as the available Fibrinogen pool is gradually reduced the rate of infusion of the ancrod is gradually increased. The initial therapy generally recommended is

1 unit/kg body weight dissolved in 250 mls of N/Saline given over 6 hours. The maintenance dose varies from 40-60 units every 6 hours. The infusion is easy to control and side effects are minimal. The drug is usually avoided within the first 48 hours of major abdominal surgery. It is very expensive.

Fibrinolytic agents:

The most popular agent is streptokinase. This is made commercially from Lancefield Group C beta (β) haemolytic streptococci and is a powerful antigenic protein which quickly produces human antibodies. In previously and repeatedly infected man, the level of circulating antibodies against streptococci may bind the antigen (streptokinase) quickly, inhibiting its effects or may produce an antigen-antibody reaction quickly. Its mode of action is the activation of plasminogen to plasmin which rapidly lyses clots by a specific proteolytic effect on both fibrin as well as on fibrinogen (15, 31). In a patient with a significant number of circulating antibodies a state of immunoparalysis should first be achieved by a large inducting dose of streptokinase to overcome the available antibodies before the streptokinase can exert a useful action on the plasminogen. The initial dose, therefore, must be fairly high in such situations (15). 500,000 units of streptokinase administered via a peripheral vein over 30 minutes, usually overpowers these antibodies and thereafter a maintenance dose of 600,000 units per hour must be given. The streptokinase can only act on "unused" or free plasminogen and therefore the cause of activation of intrinsic coagulation cascade should be concurrently controlled. The best results are obtained when the thrombi are fresh (less than 7 days). Intracoronary streptokinase therapy is gaining popularity in patients presenting with acute MI within 6 hours of onset.

The only practical test to control the effects of streptokinase appears to be the Thrombin-time and this can be easily performed in most laboratories.

Side effects relate mainly to antigenicity and include bleeding, pyrexia, nausea, headaches, cramps, hypotension, flushing and anaphylaxis.

If the patient subsequent to one therapy produces massive antibodies then further therapy is contraindicated. The role of prophylactic hydrocortisone is controversial (15).

Urokinase, an extract of foetal kidneys or maternal urine, is a good alternative to streptokinase and works through identical mechanism but does not suffer from the problems of anaphylaxis. It is however very expensive and is therefore not easily available in General Hospitals.

Heparin:

This is a sulphate containing mucopolysaccharide, a highly negatively charged acidic substance, which is also made intrinsically by most cells and other haemostatic cells. Its anticoagulant action depends upon its ability to bind and to activate antithrombin III (AT-III). This inhibits several activated clotting factors such as IXa, Xa, XIa, XIIa and thrombin. It is a fast activating substance and is used both for a rapid induction of anticoagulation (I/V) as well as for the purpose of prophylaxis (Subcutaneous route).

Numerous trials of Heparin (27 trials in 5 years upto February, 1988) have shown a significant and beneficial result in postoperative prophylaxis of DVT (34, 36, 37, 38, 39).

Using the ^{125}I -fibrinogen scan and venography in appropriate cases, it has been shown (15) that in the surgical patients, DVTs occur in the calf veins and that 20% of these extend headwards to the Popliteal, Femoral and to the Iliac Veins. The extension-thrombus usually metastasises as the PE. With heparin prophylaxis, such cranial extension of the DVT is significantly inhibited, thus reducing the incidence of the PE (34, 39, 37, 38). Use of Heparin also reduces the fatality of PE (34) with a convincing significance ($P < 0.005$).

Studies on heparin fraction of different molecular weights have shown a molecular size relationship of the anticoagulant activity. The inhibition of factor Xa in the plasma system increases with a decreasing molecular weight. However APTT decreases with decreasing molecular weight. There has thus evolved a

concept that the low molecular weight heparin possesses antithrombotic properties without causing bleeding (40). The low molecular weight heparin, in addition, spares the platelets from destruction and thus its plateleticidal effect is much reduced (41) in a single daily dose of heparin, making the management easier. Numerous independent trials have been carried out to see the prophylactic efficacy of low molecular weight single dose heparin in different categories of surgical patients. Many trials have shown that miniheparin prophylaxis reduces both the incidence of calf venous thromboses in the smaller veins and also in the major pulmonary vessels (42, 43). Kakkar's trial (44) showed a 7.5% incidence of DVTs in the untreated group in general surgical patients which was reduced to 2.5% with such a therapy. This was significant. Similarly Turpie (45) reported a reduction from 42% in the unprotected hip arthroplasty patients to 12% in the prophylactically treated patients. A multicentre trial is at present underway to critically assess this aspect of DVT prophylaxis.

Heparin and dihydroergotamine combination:

Ergot compounds increase vascular tone and constrict vessels and a subcutaneous injection of dihydroergotamine (0.5 mg) increases calf muscle blood flow for upto 5 hours (46). Combination of this compound with a low molecular weight heparin reduces the incidence of DVT by 50% (47) as detected on ^{125}I -Fibrinogen scan and on venography. The combined use produces a much better prophylaxis. The isolated use of miniheparin has been disappointing in hip arthroplasties (48, 49). The isolated use of dihydroergotamine has similarly been not very promising. A combined use (2500 units of low molecular weight heparin and 0.5 mg dihydroergotamine) has produced much better results and is not associated with haemorrhages (15).

Heparin and antiembolic stockings:

Graduated compression full length antiembolic stockings (TED, Kendall or Eschmann), when used in combination with a low molecular weight heparin appears to reduce the incidence of DVT from 12% to 2% (50). This was significant statistically ($p < 0.05$) in the trial mentio-

ned (50). The stockings should be applied in the proper manner and should be in constant use, assisted by mobilisation. The elasticity of the stockings usually lasts for a week and unless changed periodically, it should be discarded after that time.

Heparin in a low dose should not be less than 2500 units and this should be administered subcutaneously to delay absorption and should be administered 2 hours pre-operatively and should then continue in a 12 hourly regime for upto 7 days.

PREVENTION OF PE IN ESTABLISHED DVT PATIENTS:

Here, there is urgency, for rapid dissolution of existing clots. Fresh thrombi can be treated with systemic or local streptokinase. Delayed thrombi are best treated with aggressive doses of heparin. Heparin infusion delivering a daily dose of 30000 — 40000 units via a pump is adequate but it has been shown that properly timed subcutaneous doses also achieve the same desired elevation of APTT (1.5 - twice control) (1). In this respect the subcutaneous doses can be administered regularly and in safety. Protamine Sulphate should be readily available to reverse any untoward bleeding. Heparin therapy should be continued for at least seven days. On day 5, oral Warfarin can be started in a dose which will raise the prothrombin time to 2 - 2½ times of control). On day 8, heparin can be stopped. Warfarin should generally be given for about three months.

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