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القسم او الفرع : علوم الحياة

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اسم المادة باللغة الإنكليزية : histopathology

اسم المحاضرة الأولى باللغة العربية: اضطرابات الدورة الدموية

اسم المحاضرة الأولى باللغة الإنكليزية : HEMODYNAMIC DISORDERS

II. Introduction

The health and well-being of cells & tissues depend not only on an intact circulation to deliver nutrients but also on normal fluid hemostasis. This chapter reviews the major disturbances involving the hemodynamic system.

III. Edema

Definition: Edema is increased fluid in the interstitial tissue spaces or it is a fluid accumulation in the body cavities in excessive amount.

Depending on the site, fluid accumulation in body cavities can be variously designated as:

a) Hydrothorax – fluid accumulation in pleural cavity in a pathologic amount.

b) Hydropericardium – pathologic amount of fluid accumulated in the pericardial cavity.

c) Hydroperitoncum (ascites) – fluid accumulation in peritoneal cavity.

d) Ancsarca – is a severe & generalized edema of the body with profound subcutaneous swelling.

Mechanism of edema formation:

Approximately 60% of the lean body weight is water, two-thirds of which is intracellular with the remainder in the extracellular compartment.

The capillary endothelium acts as a semipermeable membrane and highly permeable to water & to almost all solutes in plasma with an exception of proteins. Proteins in plasma and interstial fluid are especially important in controlling plasma & interstitial fluid volume.

Normally, any outflow of fluid into the interstitium from the arteriolar end of the microcirculation is nearly balanced by inflow at the venular end. Therefore, normally, there is very little fluid in the interstitium.

Edema formation is determined by the following factors:

1) Hydrostatic pressure

2) Oncotic pressure

3) Vascular permeability

4) Lymphatic channels

5) Sodium and water retention

We will discuss each of the above sequentially.

First) Hydrostatic and oncotic pressures:

The passage of fluid across the wall of small blood vessels is determined by the balance between hydrostatic & oncotic pressures.

There are four primary forces that determine fluid movement across the capillary membrane. Each of them can be listed under the above two basic categories, the hydrostatic pressure & the oncotic pressure. These four primary forces are known as Starling forces & they are:

a. The capillary hydrostatic pressure (Pc)

This pressure tends to force fluid outward from the intravascular space through the capillary membrane to the interstitium.

b. The interstial fluid hydrostatic pressure (Pif)

This pressure tends to force fluid from the interstitial space to the intravascular space.

c. The plasma colloid osmotic (oncotic) pressure (Πp)

This pressure tends to cause osmosis of fluid inward through the capillary membrane from the interstitium. The plasma oncotic pressure is caused by the presence of plasma proteins.

d. The interstial fluid colloid osmotic (oncotic) pressure (Πif)

This pressure tends to cause osmosis of fluid outward through the capillary membrane to the interstitium.

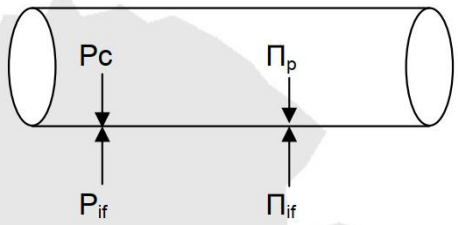

Fig. 5.1 The forces that determine the movement of fluid across the capillary wall.

In addition, some fluid is normally derained by the lymphatic channels.Usually, excess fluid will accumulate in the interstitium (i.e. edema is formed) when the capillary hydrostatic pressure is increased or when the plama oncotic pressure is decreased or when the lymphatic drainage is blocked.

Hence, basically, one can divide pathologic edema into two broad categories:

A. Edema due to decreased plasma oncotic pressure. The plasma oncotic pressure is decreased when the plasma proteins are decreased in various diseases such as:

1. Protein loosing glomerulopathies like nephroticsyndrome with leaky glomerulus.
2. Liver cirrhosis which leads to decreased protein synthesis by the damaged liver.
3. Malnutrition
4. Protein loosing enteropathy.

B. Edema resulting from increased capillary hydrostatic pressure as in the following diseases:

1. Deep venous thrombosis resulting in impaired venous return.
2. Pulmonary oedema
3. Cerebral oedema
4. Congestive heart failure.

Clinical classification of edema:

One can also clinically classify edema into localized & generalized types

A) Localized	B) Generalized
1) Deep venous thrombosis	1) Nephrotic syndron
2) Pulmonary edema	2) Liver cirrhosis
3) Brain edema	3) Malnutrition
4) Lymphatic edema	4) Heart failure
	5) Renal failure

Next, we will elaborate on some of the above examples.

1. 1.Localized edema

a. Edema of the brain:

- May be localized at the site of lesion e.g neoplasm, trauma.

- May be generalized in encephalitis, hypertensive crisis, & trauma

- Narrowed sulci & distended gyri.

- ↑ Edema → compression of medulla towards formen magnum → compression of vital centers lead to →- Hernation of the brain

↓ Patient die**s**

b. Pulmonary edema

- Usually occurs in left ventricular failure.

- May occur in adult respiratory distress syndrome (ARDS).

- lung ↑ 2.3x its weight.

2. Generalized edema (anasarca) occurs due to

a. Reduction of albumin due to excessive loss or reduced synthesis as is caused by:

1) Protein loosing glomerulopathies like nephrotic syndrome

2) Liver cirrhosis

3) Malnutrition

4) Protein-losing enteropathy

b. Increased volume of blood secondary to sodium retention caused by congestive heart failure:

Second) Vascular permeability:

Increased vascular permeability usually occurs due to acute inflammation. In inflammation, chemical mediators are produced. Some of these mediators (See the chapter on inflammation) cause increased vascular permeability which leads to loss of fluid & high molecular weight albumin and globulin into the interstitium. Such edema (i.e. that caused by increased vascular permeability) is called inflammatory edema. Inflammatory edema differs from non-inflammatory edema by the following features

a) Inflammatory edema (exudate)

⇒ Due to inflammation-induced increased permeability and leakage of plasma proteins.

⇒ Forms an exudate [protein rich]

⇒ Specific gravity > 1.012

b) Non-inflammatory oedema (transudate)

⇒ A type of edema occurring in hemodynamic derangement (i.e. increased plasma hydrostatic pressure & decreased plasma oncotic pressure. See above)

⇒ Formed transudate [protein poor]

⇒ Specific gravity < 1.012

Third) Lymphatic channels:

Also important is the lymphatic system which returns to the circulation the small amount of proteinaceous fluid that does leak from the blood into the interstial spaces. Therefore, obstruction of lymphatic channels due to various causes leads to the accumulation of the proteinaceous fluid normally drained by the lymphatic channels. Such kind of edema is called lymphatic edema.

Lymphatic edema occurs in the following conditions:

1) Parasitic infection. E.g filariasis which causes massive lymphatic and inguinal fibrosis

2) Lymphatic obstruction secondary to neoplastic infiltration. E.g. breast cancer

3) post surgical or post irradiation, i.e surgical resection of lymphatic channels or scarring after irradiation

Fourth) Sodium and water retention:

Sodium & subsequently water retention occurs in various clinical conditions such as congestive heart failure (See Fig.5.2, above) & renal failure. In these conditions, the retained sodium & water result in increased capillary hydrostatic pressure which leads to the edema seen in these diseases.

Morphology of edema Microscopy

- Manifests only as subtle cell swelling. Clearing & separation of extracellular matrix.

IV. Hyperemia and Congestion

Definition: Both of them can be defined as a local increase in volume of blood in a particular tissue.

Hyperemia:

- is an active process resulting from an increased inflow of blood into a tissue because of arteriolar vasodilation.
- commonly occurs in exercising skeletal muscle or acute inflammation.
- Affected tissue becomes red as there is engorgement with oxygenated blood.

Congestion:

- is a passive process resulting from impaired outflow of blood from a tissue.
- occurs systemically as in cardiac failure or locally as in isolated venous obstruction.
- Affected tissue appears blue-red due to accumulation of deoxygenated blood.
- In long-standing congestion (also called chronic passive congestion states), poorly oxygenated blood causes hypoxia → results in parenchyma cell degeneration or cell death.

a) Pulmonary congestion

Cut surface: hemorrhagic & wet.

1. Acute pulmonary congestion:

ƒ Alveolar capillaries engorged with blood

ƒ Septal edema

2. Chronic pulmonary congestion:

- Thickened & fibrotic septa

- Alveolar spaces contain hemosiderin-laden macrophages resulting in an appearance termed brown indurations.

- Can result in pulmonary hypertension.

b) Hepatic congestion

1) Acute hepatic congestion:

- Central vein & sinusoids are distended

- There may be even central hepatocyte degeneration.

- Peripheral hepatocytes better oxygenated & develop only fatty changes.

2) Chronic passive congestion of liver:

- Central lobules grossly depressed because of loss of cells & appear red brown (nutmeg liver).

- Hemosiderin laden macrophages

- In longstanding hepatic congestion, commonly associated with cardiac failure, there is a grossly evident hepatic fibrosis called cardiac cirrhosis.

V. Hemorrhage

Definition:

Hemorrhage is extravasation of blood outside the blood vessel.

Causes:

• Physical trauma – Stabbing

- Stick injury

- Gunshot

- Motor vehicle accident

• Inadequacies in blood clotting which can be due to:

A. Too few or poorly functioning platelets (i.e. qualitative & quantitative defect of platelets)

B. Missing or low amount of clotting factors

E.g. Low levels of prothrombin, fibrinogen & other precursors.

Inadequate vitamin K leads to clotting factor deficiency because this vitamin is important in the synthesis of the clotting factors by the liver.

Terminology:

1) Hemorrhage enclosed within a tissue or a cavity is knownas hematoma.

2) Minute 1-2 mm hemorrhages occurring in the skin, mucosal membrane, or serosal surface are called petechiae.

3) Slightly > 3mm hemorrhage occurring in the skin is referred to as purpura.

4) Larger than 1-2cm subcutaneous hematoma is called eccymosis (bruises). It is typical after trauma.

Effects of haemorrhage: depend on the rate and amount of blood loss:

• If > 20% the total blood volume is rapidly lost from the body, it may lead to hypovolumic shock & death.

• Chronic loss of blood leads to anaemia.

VI. Hemostasis and Blood Coagulation

Hemostasis:

Definition: Hemostasis is the maintainence of the clot-free state of blood & the prevention of blood loss via the formation of hemostatic plug.

Hemostasis depends on three general components:

a) Vascular wall

b) Platelets

c) Coagulation pathways

Whenever a vessel is ruptured or severed, hemostasis is achieved by several mechanisms:

A. Vascular spasm

B. Formation of platelet plug

C. Formation blood clot as a result of blood coagulation

D. Eventual growth of fibrous tissue in to the blood clot to close the hole in the vessel permanently.

Remark: The student is advised to revise his physiology lecture note on the above topics.

VII. Thrombosis:

Under this topic, we will discuss the definition, pathogenesis, morphology, fates, & clinical significance of thrombi, in this order.

Definition: Thrombosis is defined as the formation of a solid or semisolid mass from the constituents of the blood within the vascular system during life.

Pathogenesis:

1- There are three factors that predispose to thrombus formation. These factors are called Virchow's triad:

A: Endothelial injury

B: Stasis or turbulence of blood flow C: Blood hypercoagulability

A: Endothelial injury

2- It is the most important factor in thrombus formation and by itself can lead to thrombosis.

3- Endothelial injury is particularly important in thrombus formation in the heart & arterial circulation.

4- Some Examples:

• Endocardial injury during myocardial infarction & eosinophilic endocarditis in which eosiophils release from their granules crystals called Charcot – Leyden damaging the endocardial endothelium.

• Injury over ulcerated plaque in severely atherosclerotic arteries.

• In hemodynamic stress like severe hypertension & turbulence of flow over scarred valves directly damaging the endothelium.

• Bacterial endtoxin & hyperchloestrolemia, radiation & cigarette smoking may be sources of endothelial injury.

5- Irrespective of endothelial damage, the final event is exposure of the highly thrombogenic subendothelial extracellular matrix, mainly collagen & tissue factors up on which platelets undergo adherence & contact activation.

B: Turbulence or Stasis (Alterations in normal blood flow)

Under physiologic conditions normal blood flow is laminar, that is, the cellular elements flow centrally in the vessel lumen separated from endothelium by slowing moving clear zone of plasma. Stasis & turbulence therefore:

a. Disrupt the laminar flow and bring platelets in to contact with the endothelium

b. Prevent dilution of activated clotting factors by freshly flowing blood

c. Retard or make a time lag in the inflow of clotting factor inhibitors and permit the build up of thrombi.

d. Turbulence causes reduction in endothelial PGI2 and tissue-type plasminogen activator (t-PA) which has fibrinolytic activity causing endothelial cell activation.

• Stasis is a major factor in the development of venous thrombi while turbulence contributes to arterial & cardiac thrombosis by causing direct endothelial injury or by forming countercurrents & local pockets of stasis.

Examples:

a) Ulcerated atherosclerotic plaque, which forms a sort of irregularity on endothelial surface, not only exposes subendothelial extracellular matrix but are also sources of local turbulence.

b) Aneurysms are favoured sites of stasis

c) Myocardial infarction not only has endothelial injury but also has a region of noncontractile myocardium, creating an area of stasis resulting in mural thrombus formation.

d) Mitral valve stenosis after chronic rheumatic fever may result in left atrial dilation, usually associated with arterial fibrillation. A dilated left atrium is a site of stasis & a prime location of thrombus development.

e) Hypervisicosity syndrome, i.e an increase in hematocrit in excessive amount due to various reasons such as polycythemia causes stasis in small vessels.

C: Hypercoagulablity

Definition: Hypercoagulability is any alteration of the coagulation pathway that predisposes to thrombosis. Hypercoagulability is a less common cause of thrombosis & it can be divided into:

1. Primary (Genetic)

ƒ Mutations in factor V[Lieden factor]

ƒ Anti thrombin III deficiency

ƒ Protein C or S deficiency

2. Secondary (Acquired) which, in turn, can be categorized into:

A: High-risk for hypercoagulablity

‰ prolonged bed rest or immobilization

‰ Myocardial infarction

‰ Tissue damage (surgery, fracture, burns)

‰ cancers (Cancers release procoagulant tissue products to cause thrombosis)

‰ Prosthetic cardiac valves

‰ Disseminated intra vascular coagulation.

B: Low risk factor for hypercoagulablity

ƒ A trial fibrillation

ƒ Cardiomyopathy

ƒ Nephrotic syndrome

ƒ Smoking

ƒ Oral contraceptives

ƒ Hyperestrogenic state eg. Pregnancy.

Morphology of Thrombi

• Thrombi may develop anywhere in the cardiovascular system.

• According to their location, thrombi can be divided into venous & arterial thrombi. (Cardiac thrombi can be considered as arterial thrombi because of certain similarities between the two).

The differences between arterial & venous thrombi are:

Arterial thrombi	Venous thrombi
a) Arise at the site of endothelial injury	a) Arise at area of stasis
b) Grow in a retrograde fasion, against site of attachment.flow towards the heart	b) Grow in the direction of blood flow from its
c) Has firm attachment	c) Has loose attachment, hence, propagating tail may undergo fragmentation.
d) They usually occlude the blood flow	d) Almost invariably occlusive

The most common site of arterial thrombi in descending order are:

o Coronary arteries

o Cerebral arteries

o Temporal arteries

• Damaged valves can be infected by bacteria or fungi (infective endocarditis) which leads to the development of small infected thrombi on the valves. These small infected thrombi (vegetations) can further damage the valve.

Fates of a thrombus

A thrombus can have one of the following fates:

A: Propagation:

The thrombus may accumulate more platelets and fibrin & propagate to cause vessel obstruction.

B: Embolization:

The thrombus may dislodge and travel to other sites in the vasculature. Such a traveling thrombus is called an embolus. An embolus may obstruct a vessel. The obstruction leads to the death of the tissue supplied by the blood vessel. Death of a tissue due to a decreased blood supply or drainage is called infarction. Therefore, an embolus can eventually lead to an infarction of an organ. E.g cerebral infarction can be caused by a thromboembolus. We will discuss embolism & infarction shortly (See p.).

C: Dissolution:

The thrombus may be removed by fibrinolytic activity.

D: Organization and recanalization

Organization refers to the ingrowth of endothelial cells, smooth muscle cells, and fibroblasts into the fibrin-rich thrombus. Organization is accompanied by the formation of capillary channels across the thrombus, re-establishing lumen continuity to some extent. This is known as recanalization. The recanalization eventually converts the thrombus into a vasscularized mass of tissue which is later on incorporated as a subendothelial swelling of the vessel wall.

Clinical significance of thrombi

• Thrombi are significant clinically because:

- They cause obstruction of arteries and veins &

- They are possible source of emboli.

VIII. Embolism

Definition: -

An embolus is a detached intravascular solid, liquid or gaseous mass that is carried by blood to sites distant from its point of origin. After traveling via the blood, the embolus can obstruct a vessel**.**

Causes of embolism:An embolus can arise from:

o Thrombus (99% of emboli arise from a thrombus. Such an embolus is called thromboembolus)

o Platelets aggregates

o Fragment of material from ulcerating atheromatous plaque

o Fragment of a tumour

o Fat globules

o Bubbles of air

o Amniotic fluid

o Infected foreign material

o Bits of bone marrow

o Others.

Unless otherwise specified, the term embolism should be considered to mean thromboembolism. This is because thromboembolism is the commonest form of embolism. Next, we will discuss it in more detail.

Thromboembolism

Based on its sites of origin & impaction, thromboembolism can be divided into:

a) Pulmonary thromboembolism (PTE)

o PTE is refers to the impaction of an embolus in the pulumonary arteries & their branches. Such an embolus is derived from a thrombus in the systemic veins or the right side of the heart.

b) Systemic thromboembolism

o Systemic emboli arise from the left side of the heart or from thrombi & atheromatous debris in large arteries. And they impact in the systemic arteries**.**

c) Crossed embolism (Paradoxical embolism)

o This occurs in the presence of patent foremen ovale when an embolus is transferred from the right to the left side of the heart, then into the systemic circulation.

Now, we will elaborate the first two.

a) Pulmonary thrombeomblism (PTE)

95% of PTE arise from thromi in the deep leg veins. The thromboembolus will travel long with the venous return & reach the right side of the heart. From there, it will go into the pulmonary trunk & pulmonary arteries. Depending on the size of the embolus and on the state of pulumonary circulation, the pulmonary embolism can have the following effects:

1. If the thrombus is large, it may block the outflow tract of the right ventricle or the bifurcation of the main pulumonary trunk (saddle embolus) or both of its branches,causing sudden death by circulatory arrest. Sudden death, right side heart failure (cor pulmonale), or cardiovascular collapse occurs when 60% or more of the pulumonary circulation is obstructed with emboli.

2. If the embolus is very small (as in 60-80% of the cases), the pulmonary emboli will be clinically silent. Embolic obstruction of medium sized arteries manifests as pulmonary haemorrhage but usually does not cause infarction because of dual blood inflow to the area from the bronchial circulation.

3. If the cardiorespiratory condition of the patient is poor (i.e., if the patient previously had cardiac or pulmonary disease), then obstruction of a medium sized pulmonary artery by a medium-sized embolus can lead to pulmonary infarction.

4. Recurrent thromboembolism can lead to pulmonary hypertension in the long run. A patient who has had one pulmonary embolus is at high risk of having more.

b) Systemic thromboembolism

• Systemic thromboembolism refers to emboli travelling within arterial circulation &impacting in the systemic arteries.

• Most systemic emboli (80%) arise from intracardiac mural thrombi. In turn, two thirds of intracardiac mural thrombi are associated with left ventricular wall infarcts and another quarter with dilated left atria secondary to rheumatic valvular heart disease.

• The remaining (20%) of systemic emboli arise from aortic aneurysm, thrombi on ulcerated athrosclerotic plaques, or fragmentation of valvular vegetation.

• Unlike venous emboli, which tend to lodge primarily in one vascular bed (the lung), arterial emboli can travel to a wide variety of sites**.**

The major sites for arteriolar embolization are the lower extremities (75%) & the brain (10%), with the rest lodging in the intestines, kidney, & spleen. The emboli may obstruct the arterial blood flow to the tissue distal to the site of the obstruction. This obstruction may lead to infarction. The infarctions, in turn, will lead to different clinical features which vary according to the organ involved.