HEMODYNAMIC DISORDERS, THROMBOEMBOLISM AND SHOCK
HYPEREMIA AND CONGESTION

• HYPEREMIA – ACTIVE PROCESS RESULTING FROM ARTERIOLAR DILATION AND INCREASED BLOOD FLOW

• CONGESTION – PASSIVE PROCESS RESULTING FROM IMPAIRED OUTFLOW OF VENOUS BLOOD FROM TISSUE
  • IF LONG STANDING, THE ELEVATED PRESSURES CAN LEAD TO EDEMA AND CAPILLARY RUPTURE PRODUCING FOCAL HEMORRHAGES

• CUT SURFACES OF HYPEREMIC OR CONGESTED TISSUES FEEL WET AND TYPICALLY OOZE BLOOD
EDEMA

• AN ACCUMULATION OF EXTRAVASCULAR FLUID IN TISSUES OR BODY CAVITIES (EFFUSIONS)

• NONINFLAMMATORY CAUSES OF EDEMA INCLUDE:
  
  • INCREASED HYDROSTATIC PRESSURE
    • MAINLY CAUSED BY DISORDERS THAT IMPAIR VENOUS RETURN
  
  • REDUCED PLASMA OSMOTIC PRESSURE
    • REDUCTION OF PLASMA ALBUMIN CONCENTRATIONS LEADS TO DECREASED COLLOID OSMOTIC PRESSURE OF THE BLOOD AND LOSS OF FLUID FROM THE CIRCULATION
  
  • LYMPHATIC OBSTRUCTION
    • COMPROMISES RESORPTION OF FLUID FROM INTERSTITIAL SPACES
  
  • SODIUM AND WATER RETENTION
    • INCREASES HYDROSTATIC PRESSURE DUE TO EXPANSION OF THE INTRAVASCULAR VOLUME
    • OFTEN DUE TO ACTIVATION OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM IN THE KIDNEYS
HEMORRHAGE

• THE EXTRAVASATION OF BLOOD FROM VESSELS, MOST OFTEN DUE TO DAMAGE OR DEFECTIVE CLOT FORMATION

• PETECHIAE – MINUTE (1-2 MM) HEMORRHAGES INTO SKIN, MUCOUS MEMBRANES OR SEROSAL SURFACES OFTEN DUE TO THROMBOCYTOPENIA, DEFECTIVE PLATELET FUNCTION AND LOSS OF VASCULAR WALL SUPPORT

• PURPURA – SLIGHTLY LARGER (3-5 MM) HEMORRHAGES OFTEN DUE TO THE SAME DISORDERS THAT CAUSE PETECHIAE, TRAUMA, VASCULITIS AND INCREASED VASCULAR FRAGILITY

• ECCHYMOSES – LARGER (1-2 CM) SUBCUTANEOUS HEMATOMAS

• CHRONIC EXTERNAL BLOOD LOSS FREQUENTLY CULMINATES IN IRON DEFICIENCY ANEMIA
HEMOSTASIS

• PROCESS INVOLVING PLATELETS, CLOTTING FACTORS AND ENDOTHELium THAT OCCURS AT THE SITE OF VASCULAR INJURY CULMINATING IN THE FORMATION OF A BLOOD CLOT

• GENERAL SEQUENCE OF EVENTS LEADING TO HEMOSTASIS:
  • ARTERIOLAR VASOCONSTRICTION – REDUCES BLOOD FLOW TO THE INJURED AREA; MEDIATED BY REFLEX NEUROGENIC MECHANISMS AND FACTORS SUCH AS ENDOTHELIN
  • PRIMARY HEMOSTASIS – THE FORMATION OF THE PLATELET PLUG
    • EXPOSED SUBENDOTHELIAL VON WILLEBRAND FACTOR (VWF) AND COLLAGEN PROMOTE PLATELET ADHERENCE AND AGGREGATION VIA SHAPE CHANGE AND RELEASE OF SECRETORY GRANULES
  • SECONDARY HEMOSTASIS – DEPOSITION OF FIBRIN
    • EXPOSED TISSUE FACTOR BINDS AND ACTIVATES FACTOR VII TRIGGERING A CASCADE THAT RESULTS IN THE GENERATION OF THROMBIN
    • THROMBIN CLEAVES CIRCULATING FIBRINOGEN INTO FIBRIN CREATING A FIBRIN NETWORK WHICH FURTHER ACTIVATES PLATELETS
  • CLOT STABILIZATION AND RESORPTION
    • THESE AGGREGATES UNDERGO CONTRACTION TO FORM A SOLID PLUG
    • COUNTERREGULATORY MECHANISMS (TISSUE PLASMINOGEN ACTIVATOR, T-PA) THEN TAKE OVER WHICH LIMIT FURTHER CLOTTING AND EVENTUALLY LEAD TO CLOT RESORPTION AND REPAIR
HEMOSTASIS
B. PLATELET ACTIVATION AND AGGREGATION

1. Platelet adhesion
2. Shape change
3. Granule release (ADP, TXA$_2$)
4. Recruitment
5. Aggregation (hemostatic plug)

Endothelium  Basement  Subendothelium
C. ACTIVATION OF CLOTTING FACTORS AND FORMATION OF FIBRIN

1. Tissue factor

2. Phospholipid complex expression

3. Thrombin activation

4. Fibrin polymerization

Tissue factor
HEMOSTASIS

D. CLOT RESORPTION

Expression of:
- t-PA (fibrinolysis)
- thrombomodulin (blocks coagulation cascade)

Trapped neutrophil
Trapped red blood cells
Polymerized fibrin
HEMOSTASIS - PLATELETS

• FORM THE PRIMARY PLUG AND PROVIDE A **SURFACE** THAT BINDS AND CONCENTRATES ACTIVATED COAGULATION FACTORS

• FOLLOWING CONTACT WITH VWF AND COLLAGEN, PLATELETS UNDERGO A SEQUENCE OF REACTIONS:
  
  • PLATELET ADHESION – DUE TO INTERACTIONS BETWEEN VWF AND GLYCOPROTEIN IIB
    • DEFICIENCY OF VWF: VON WILLEBRAND DISEASE
    • DEFICIENCY OF GLYCOPROTEIN IIB: BERNARD-SOULIER DISEASE
  
  • PLATELETS RAPIDLY CHANGE SHAPE – BECOME SPIKY INCREASING THEIR SURFACE AREA
    • PLATELETS ALSO ALTER GLYCOPROTEIN IIB/IIIA INCREASING THEIR AFFINITY FOR FIBRINOGEN
    • DEFICIENCY OF GLYCOPROTEIN IIB/IIIA: GLANZMANN THROMbasthenia
    • NEGATIVELY CHARGED PHOSPHOLIPIDS TRANSLOCATE TO THE SURFACE (SERVE AS NUCLEATION SITES FOR THE ASSEMBLY OF COAGULATION FACTOR COMPLEXES)
  
  • SECRETION OF GRANULE CONTENTS – ACTIVATED PLATELETS PRODUCE THE PROSTAGLANDIN THROMBOXANE A2, A POTENT INDUCER OF PLATELET AGGREGATION
  
  • PLATELET AGGREGATION – GLYCOPROTEIN IIB/IIIA BINDS TO FIBRINOGEN FORMING BRIDGES BETWEEN PLATELETS LEADING TO THEIR AGGREGATION
    • ACTIVATION OF THROMBIN STABILIZES THE PLATELET PLUG PROMOTING PLATELET CONTRACTION
    • THROMBIN CONVERTS FIBRINOGEN TO FIBRIN CEMENTING THE PLATELETS IN PLACE
HEMOSTASIS - PLATELETS

Deficiency: Glanzmann thrombasthenia

Deficiency: Bernard-Soulier syndrome

Gpllb-IIIa complex

Platelet

Fibrinogen

ADP induces conformational change

Endothelium

Subendothelium

vW factor

Deficiency: von Willebrand disease
HEMOSTASIS – COAGULATION CASCADE

• A SERIES OF AMPLIFYING ENZYMATIC REACTIONS THAT LEAD TO THE DEPOSITION OF AN INSOLUBLE FIBRIN CLOT

• STEPWISE SERIES OF REACTIONS INVOLVING ENZYMES (ACTIVATED COAGULATION FACTORS), SUBSTRATES (INACTIVE PROENZYME FORM OF COAGULATION FACTORS) AND COFACTORS (REACTION ACCELERATORS)

• COMPONENTS ARE ASSEMBLED ON A NEGATIVELY CHARGED PHOSPHOLIPID SURFACE PROVIDED BY ACTIVATED PLATELETS

• BASED ON ASSAYS PERFORMED IN CLINICAL LABORATORIES, THE COAGULATION CASCADE IS DIVIDED INTO EXTRINSIC AND INTRINSIC PATHWAYS:
  • PROTHROMBIN TIME (PT): ASSESSES FUNCTION OF THE EXTRINSIC PATHWAY - FACTORS VII, X, V, II (PROTHROMBIN) AND FIBRINOGEN
    • INITIATED BY THE ADDITION OF TISSUE FACTOR
  • PARTIAL THROMBOPLASTIN TIME (PTT): ASSESSES FUNCTION OF THE INTRINSIC PATHWAY – FACTORS XII, XI, IX, VIII, X, V, II AND FIBRINOGEN
    • INITIATED BY THE ADDITION OF NEGATIVELY CHARGED PARTICLES (KAOLIN, GROUND GLASS)

• IN VIVO, THE FACTOR VIIA/TISSUE FACTOR COMPLEX IS THE MOST IMPORTANT ACTIVATOR OF THE COAGULATION CASCADE
HEMOSTASIS – COAGULATION CASCADE

• THROMBIN IS THE MOST IMPORTANT COAGULATION FACTOR DUE TO:
  • CONVERSION OF FIBRINOGEN INTO CROSSLINKED FIBRIN
  • AMPLIFIES THE COAGULATION PROCESS BY ACTIVATING FACTOR XI AND TWO COFACTORS (FACTOR V AND VIII)
  • STABILIZES THE SECONDARY HEMOSTATIC PLUG BY ACTIVATING FACTOR XIII
  • POTENT INDUCER OF PLATELET ACTIVATION
  • ON ENCOUNTERING NORMAL ENDOTHELIUM THROMBIN CHANGES TO AN ANTICOAGULANT

• FACTORS THAT LIMIT COAGULATION
  • PLASMIN – BREAKS DOWN FIBRIN AND INTERFERES WITH ITS POLYMERIZATION
    • GENERATED BY ENZYMATIC CATABOLISM OF PLASMINOGEN BY EITHER FACTOR XII OR TISSUE PLASMINOGEN ACTIVATOR (T-PA)
      • T-PA IS SYNTHESIZED BY ENDOTHELIUM AND IS MOST ACTIVE WHEN BOUND TO FIBRIN
  • THE REQUIREMENT FOR NEGATIVELY CHARGED PHOSPHOLIPIDS
  • SIMPLE DILUTION
COAGULATION CASCADE

CLOTTING IN THE LABORATORY

Intrinsic pathway
Negatively charged surface (e.g., glass beads)

Extrinsic pathway
Tissue factor

CLOTTING IN VIVO

Vascular damage
Exposure of tissue factor

Prothrombin
Thrombin
Fibrinogen
Fibrin clot

Fibrinogen

Prothrombin

Thrombin

Fibrin clot

TF
HEMOSTASIS - ENDOTHELIUM

• INVOLVED IN ANTICOAGULANT AND PROCOAGULANT ACTIVITIES

• ANTITHROMBOTIC PROPERTIES:
  - PLATELET INHIBITORY EFFECTS – SHIELD PLATELETS FROM VON WILLEBRAND FACTOR AND COLLAGEN AND RELEASE PROSTACYCLIN (PGI2), NITRIC OXIDE AND ADENOSINE DIPHOSPHATASE
  - ANTICOAGULANT EFFECTS – SHIELDS COAGULATION FACTORS FROM TISSUE FACTOR AND RELEASE THROMBOMODULIN, ENDOTHELIAL PROTEIN C RECEPTOR, HEPARIN-LIKE MOLECULES AND TISSUE FACTOR PATHWAY INHIBITOR
    • THROMBOMODULIN AND ENDOTHELIAL PROTEIN C RECEPTOR BIND THROMBIN AND PROTEIN C RESPECTIVELY IN A COMPLEX ON THE ENDOTHELIAL SURFACE – THIS CAUSES THROMBIN TO LOSE ITS ABILITY TO ACTIVATE THE COAGULATION CASCADE AND PLATELETS AND INSTEAD ACTIVATES PROTEIN C
      • PROTEIN C – A VITAMIN K DEPENDENT PROTEASE THAT, WHEN BOUND TO THE COFACTOR PROTEIN S, INHIBITS COAGULATION FACTORS V AND VIII
    • HEPARIN-LIKE MOLECULES BIND AND ACTIVATE ANTITHROMBIN III WHICH INHIBITS THROMBIN AND FACTORS IX, X, XI AND XII
    • TISSUE FACTOR PATHWAY INHIBITOR – ALSO REQUIRED PROTEIN S AS A COFACTOR AND INHIBITS TISSUE FACTOR/FACTOR VII COMPLEXES
  - FIBRINOLYTIC EFFECTS – SYNTHESIZE T-PA
THROMBOSIS

• THE PRIMARY ABNORMALITIES THAT LEAD TO INTRAVASCULAR THROMBOSIS ARE ENDOTHelial INJURY, STASIS OR TURBULENT BLOOD FLOW AND HYPERCOAGULABILITY (VIRCHOW TRIAD)

• ENDOTHELIAL INJURY:
  • SEVERE ENDOTHELIAL INJURY EXPOSES VWF AND TISSUE FACTOR
  • ENDOTHELIAL CELLS ACTIVATED BY CYTOKINES/INFLAMMATORY FACTORS DOWNREGULATE THE EXPRESSION OF THROMBOMODULIN, PROTEIN C AND TISSUE FACTOR PROTEIN INHIBITOR

• ABNORMAL BLOOD FLOW:
  • TURBULENCE CONTRIBUTES TO THROMBOSIS BY CAUSING ENDOTHELIAL INJURY OR DYSFUNCTION AS WELL AS BY FORMING COUNTERCURRENTS AND LOCAL POCKETS OF STASIS

• HYPERCOAGULABILITY:
  • AN ABNORMALLY HIGH TENDENCY OF THE BLOOD TO CLOT, TYPICALLY CAUSED BY ALTERATIONS IN COAGULATION FACTORS

• MORPHOLOGICALLY, THROMBI ARE ATTACHED TO THE UNDERLYING VASCULAR SURFACE AND APPEAR LAYERED (LINES OF ZAHN)
HYPERCOAGULABILITY

• PRIMARY (INHERITED) HYPERCOAGULABILITY:
  • FACTOR V MUTATION (LEIDEN MUTATION) – ALTERS AN AMINO ACID RESIDUE IN FACTOR V AND RENDERS IT RESISTANT TO PROTEOLYSIS BY PROTEIN C; AN IMPORTANT CAUSE OF RECURRENT DVT
  • A SINGLE NUCLEOTIDE SUBSTITUTION IN THE PROTHROMBIN GENE RESULTS IN INCREASED PROTHROMBIN TRANSCRIPTION
  • ELEVATED LEVELS OF HOMOCYSTEINE CONTRIBUTE TO ARTERIAL AND VENOUS THROMBOSIS AS WELL AS ATHEROSCLEROSIS

• SECONDARY (ACQUIRED) HYPERCOAGULABILITY:
  • HEPARIN INDUCED THROMBOCYTOPENIA (HIT) SYNDROME
    • OCCURS IN UP TO 5% OF PATIENTS TREATED WITH UNFRACTIONATED HEPARIN
    • MARKED BY THE DEVELOPMENT OF AUTOANTIBODIES THAT BIND TO PLATELET FACTOR-4 IN A HEPARIN DEPENDENT FASHION RESULTING IN PLATELET ACTIVATION, AGGREGATION AND CONSUMPTION AS WELL AS ENDOTHELIAL INJURY
    • BOTH VENOUS AND ARTERIAL THROMBoses CAN OCCUR AND CAN CAUSE SEVERE MORBIDITY
  • ANTI-PHOSPHOLIPID ANTIBODY SYNDROME (LUPUS ANTI-COAGULANT SYNDROME):
    • ANTIBODY THAT BINDS TO PHOSPHOLIPIDS AND PROTEINS ASSOCIATED WITH THE CELL MEMBRANE
    • IN VIVO, THE ANTIBodies ARE THOUGHT TO INTERACT WITH PLATELET MEMBRANE PHOSPHOLIPIDS INCREASING ADHESION AND AGGREGATION OF PLATELETS (THROMBOSIS)
    • IN VITRO, THE ANTIBODIES INTERFERE WITH PHOSPHOLIPIDS USED TO INDUCE COAGULATION (PROLONGED PTT)
    • ANTIBODIES CAN CAUSE A FALSE-POSITIVE SEROLOGIC TEST FOR SYPHILIS
EMBOLISM

• A detached intravascular solid, liquid or gaseous mass carried by the blood from its point of origin to a distant site where it often causes tissue dysfunction or infarction

• Pulmonary thromboembolism:
  • Most common; originate from deep venous thromboses in the legs
  • Most (60-80%) are small and clinically silent, however, large emboli that can block the right and left pulmonary arteries (saddle embolus) occur and cause sudden death
  • If atrial or ventricular defects are present, the embolus can enter the systemic circulation (paradoxical embolism)
  • Multiple emboli over time can lead to pulmonary hypertension and right ventricular failure (Cor pulmonale)

• Systemic thromboembolism:
  • Most arise from intracardiac mural thrombi (80%)
  • These can travel virtually anywhere often resulting in ischemia and infarction
EMBOLISM

• FAT EMBOLISM:
  • DUE TO SOFT TISSUE CRUSH INJURIES OR RUPTURE OF BONE MARROW VASCULAR SINUSOIDS (LONG BONE FRACTURES)
  • FAT AND BONE MARROW EMBOLIZE IN THE MICROCIRCULATION BUT PATIENT'S RARELY SHOW ANY SIGNIFICANT CLINICAL FINDINGS
  • A MINORITY OF PATIENTS DEVELOP A SYMPTOMATIC FAT EMBOLISM SYNDROME – PULMONARY INSUFFICIENCY, NEUROLOGIC SYMPTOMS, ANEMIA, THROMBOCYTOPENIA AND DIFFUSE PETECHIAL RASH

• AMNIOTIC FLUID EMBOLISM:
  • AN UNCOMMON COMPLICATION OF LABOR IN THE IMMEDIATE POSTPARTUM PERIOD
  • CHARACTERIZED BY SEVERE DYSPNEA, CYANOSIS, SHOCK, SEIZURES AND COMA INITIALLY FOLLOWED BY PULMONARY EDEMA AND DISSEMINATED INTRAVASCULAR COAGULATION (DIC)
  • THE CAUSE IS ENTRY OF AMNIOTIC FLUID AND CONTENTS INTO THE MATERNAL CIRCULATION VIA TEARS IN THE PLACENTAL MEMBRANES AND/OR UTERINE VEIN RUPTURE
  • HISTOLOGIC ANALYSIS SHOWS SQUAMOUS CELLS, LANUGO HAIR AND MUCIN IN THE MATERAL PULMONARY MICROCIRCULATION

• AIR EMBOLISM:
  • GAS BUBBLES IN THE CIRCULATION CAN COALESCE AND OBSTRUCT VASCULAR FLOW CAUSING ISCHEMIC INJURY
  • DECOMPRESSION SICKNESS – CAUSED BY SUDDEN CHANGES IN ATMOSPHERIC PRESSURE
EMBOLISM
DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

- A complication of a wide variety of disorders and is caused by systemic activation of coagulation resulting in the formation of thrombi throughout the microcirculation
  - Platelets and coagulation factors are consumed and fibrinolysis is activated
  - Thus, DIC can give rise to either tissue hypoxia/microinfarcts and/or to a bleeding disorder related to activation of fibrinolysis and depletion of elements required for hemostasis (consumptive coagulopathy)
    - In addition, microthrombi traumatize red blood cells causing hemolysis (microangiopathic hemolytic anemia)
- DIC usually is triggered by either:
  - The release of tissue factor or thromboplastic substances into the circulation
  - Widespread endothelial cell damage
- Clinically, DIC can take one of two forms:
  - Acute DIC – more aggressive and life threatening, typically dominated by bleeding
  - Chronic DIC – more indolent, typically dominated by thrombotic manifestations
IMMUNE THROMBOCYTOPENIC PURPURA (ITP)

• CAUSED BY ANTIBODIES DIRECTED AGAINST PLATELET MEMBRANE GLYCOPROTEINS IIb/IIIa OR Ib/IX COMPLEXES

• INCLUDES TWO CLINICAL SUBTYPES:
  • ACUTE ITP – SELF-LIMITED FORM SEEN MOSTLY IN CHILDREN FOLLOWING VIRAL INFECTIONS
  • CHRONIC ITP – TENDS TO AFFECT WOMEN BETWEEN 20 AND 40 YEARS OF AGE

• BONE MARROW BIOPSY WILL SHOW INCREASED NUMBERS OF MEGAKARYOCYTES

• CLINICAL FINDINGS INCLUDE PETECHIAE, EASY BRUISING, EPISTAXIS, GUM BLEEDING

• TREATMENT USUALLY INVOLVES THE USE OF IMMUNOSUPPRESSIVE AGENTS AND, IN SOME CASES, SPLENECTOMY
VON WILLEBRAND DISEASE

• AUTOSOMAL RECESSIVE MODE OF INHERITANCE
• PRESENTS AS SPONTANEOUS BLEEDING FROM MUCOUS MEMBRANES, EXCESSIVE WOUND BLEEDING AND MENORRHAGIA
• COMMON AND UNDERDIAGNOSED

DIVIDED INTO DIFFERENT SUBTYPES:

• TYPE 1:
  • THE CLASSIC AND MOST COMMON VARIANT
  • THE QUANTITY OF CIRCULATING VON WILLEBRAND FACTOR IS REDUCED
• TYPE IIA:
  • LACK OF SYNTHESIS OF HIGH MOLECULAR WEIGHT MULTIMERS OF VWF
• TYPE IIB:
  • SYNTHESIS OF ABNORMAL “HYPERFUNCTIONAL” HIGH MOLECULAR WEIGHT MULTIMERS OF VWF THAT ARE RAPIDLY REMOVED FROM THE CIRCULATION
  • THESE MULTIMERS CAUSE SPONTANEOUS PLATELET AGGREGATION
• TYPE III:
  • ALMOST COMPLETE ABSENCE OF VWF IN THE BLOOD
HEMOPHILIA

• HEMOPHILIA A:
  • THE MOST COMMON HEREDITARY CAUSE OF SERIOUS BLEEDING
  • X-LINKED RECESSIVE DISORDER CHARACTERIZED BY REDUCED FACTOR VIII ACTIVITY
  • VARYING DEGREES OF FACTOR VIII DEFICIENCY ARE EXPLAINED BY DIFFERENT MUTATIONS
  • PATIENTS HAVE A TENDENCY TOWARD EASY BRUISING AND SPONTANEOUS HEMORRHAGE
  • PATIENTS HAVE A PROLONGED PTT THAT IS CORRECTED BY MIXING A PATIENT’S PLASMA WITH NORMAL PLASMA
  • TREATED WITH FACTOR VIII INFUSIONS

• HEMOPHILIA B:
  • X-LINKED RECESSIVE MODE OF INHERITANCE
  • CAUSED BY MUTATIONS IN COAGULATION FACTOR IX
  • CLINICALLY INDISTINGUISHABLE FROM HEMOPHILIA A BUT IS MUCH LESS COMMON