Liver Transplantation

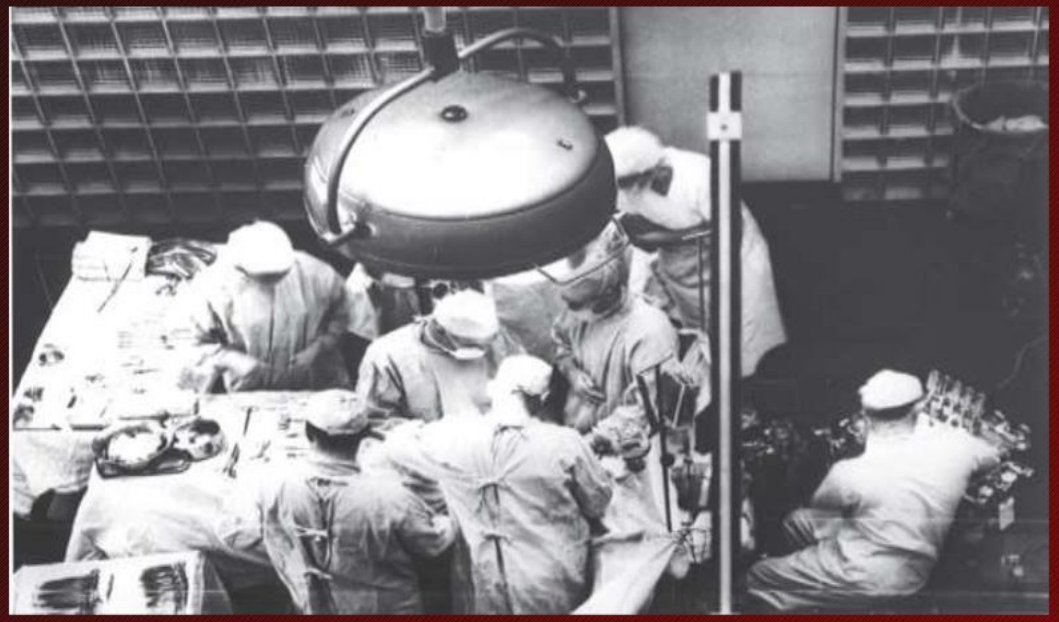
Introduction

- Liver transplantation has been very successful in treating end-stage liver disease, and offers the opportunity for a long healthy life.
- Organ scarcity is the main limitation to the full exploitation of transplantation- Split-liver and living-donor transplantation have contributed to reversing a situation
- During early periods the 1st year survival is used to be less than 25% which is improved to near 90% with the present surgical expertise and the available immunosupressive drugs and better understanding of different disease processes.
- Combined organ transplantations is recent improvement and still future improvements are awaiting.

Alexis Carrel (late 19th century) developed a method for joining blood vessels – …….. Surgical and the biological”

Peter Medawar- Defined rejection process

Joseph Murray- First successful renal transplant between identical twins in 1954



HISTORY

Initial liver transplant techniques were developed in in the 50's & '60's with the pivotal baseline work of Dr Thomas Starzl in Chicago and Boston

1st human liver transplant 1963- University of Colorado
1970s - immunosuppressive regimen based on steroids, azathioprine and horse ALG (anti-lymphocyte globulin)

1976 – discovery of immunosupressive activity of cyclosporine A by – Borel and colleagues

Thomas E. Starzl

1980s
1980 – Starzl moved the transplant program to Pittsburgh
1981- introduction of cyclosporine A into clinical practice by R.Calne
1983 – Cyclosporine approved for use by FDA
1983 – National Institutes of Health Consensus Conference
• LT accepted as definitive therapy for end-stage liver disease (ESLD)
1986 – OKT3 (muromonab-CD3) advanced treatment of rejection
1987 – University of Wisconsin solution (UW) improved organ quality

- Allograft: From one individual to another
- Xenograft: Between different species
- Orthotopic graft: Graft placed in its normal anatomical site
- Heterotopic graft: Graft placed in a site different from that where the organ is normally located

Liver Transplantation

Dr. Thomas Starzl- 1963 - Biliary atresia, coagulopathy

Cyclosporin → Major advancement

Increase demand & less donor - Based on need rather than on time on the list

Advances that serve to increase the donor pool-

- Split liver transplantation
- Live donor liver transplantation
- Use of donors after cardiac death

Patient evaluation

- Extensive evaluation done
- Pulmonary, cardiac, renal, psychological assessement.
- Issue regarding candidacy for transplantation:
  - Whether a given patient would benefit from liver replacement
  - Whether the patient can withstand the challenge of a liver transplantation surgery

Indication

- Any patient with compromise of life from
    - Chronic liver insufficiency
    - Chronic liver disease with acute decompensation
    - Acute liver failure
    - Enzyme deficiencies
    - Primary liver tumors

Common sign & symptom:

- Coagulopathy
- Thrombocytopenia
- Muscle wasting
- Gynecomastia
- Ascites
- Varices
- Encephalopathy
- Renal insufficiency

MOST COMMON INDICATIONS FOR LIVER TRANSPLANTATION IN THE USA

- ALCOHOLIC CIRRHOSIS(ALD) 32%
- OTHER - NASH 35%
- CIRRHOSIS AFTER HCV INFECTION 12%
- CHOLESTATIC DISEASES 8-11%
- HCC 11.3%
- HEPATITIS B 6%
- ALF 1.3%

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1) Fulminant Hepatic Failure

- Acute onset of liver failure with the absence of previous liver disease.

-Encephalopathy within 8 weeks of jaundice.

- Acetaminophen overdose

King's college criteria

Acetaminophen induced ALF

- Ph- <7.3 or
- INR- >6.5 and
- S. creat- >3.4mg/dl

• Nonacetaminophen induced ALF

- INR> 6.5 or

Any three of the following

- Age- <10 or >40
- Duration of jaundice before encephalopathy >7 days
- INR- >3.5
- S.Bilirubin - >17mg/dl

Contraindications

- Systemic infections: Uncontrolled bacterial and fungal infections are absolute contraindication.
- Failure of another organ
- Portopulmonary hypertension : Persistent pulmonary artery pressures >50 mm Hg in the presence of pulmonary vascular resistance.

Contraindication contd…..

- Lack of commitment
- Portal vein thrombosis
  - Metastatic HCC – Absolute contraindication

Milan's criteria: - Single nodule <5 cm

- <3 nodules, largest measuring <3 cm
- No extrahepatic involvement
- No vascular invasion

UCSF criteria: Single nodule < 6.5cm
3 lesions total diameter <8cm

CONTRAINDICATIONS

ABSOLUTE

- Uncontrolled extrahepatobiliary infection
- Active sepsis
- Uncorrectable life limiting congenital anomalies
- Active alcohol abuse
- Advanced cardiopulmonary disease
- Extrahepatobiliary malignancy
- Liver metastasis
- Cholangiocarcinoma
- AIDS
- Life threatening systemic diseases

RELATIVE

- Age> 70
- Prior extensive hepatobiliary surgery
- Portal vein thrombosis
- Renal failure (not related to liver)
- Previous extrahepatic malignancy
- Severe obesity
- Severe malnutrition
- Medical noncompliance
- HIV with CD_4 <100/µL
- Intrahepatic sepsis

Model for End-Stage Liver Disease (MELD)

- The MELD score assigns points that reflect the severity of liver disease
- A patient's priority on the waiting list is based on the medical status as determined by MELD score
- The score is based on a formula that considers bilirubin, INR,Creatinine

MELD = 3.78 x $\log_e$ serum bilirubin (mg/dL) +

11.20 x $\log_e$ INR +

9.57 x $\log_e$ serum creatinine (mg/dL) +

6.43 (constant for liver disease etiology)

NOTES:

If the patient has been dialyzed twice within the last 7 days, then the value for serum creatinine used should be 4.0

Any value less than one is given a value of 1 (i.e. if bilirubin is 0.8, a value of 1.0 is used) to prevent the occurrence of scores below 0 (the natural logarithm of 1 is 0, and any value below 1 would yield a negative result)

$$\text{MELD score} = 9.57 \times \log_e \text{Creatinine (mg/dL)} + 3.78 \times \log_e \text{Bilirubin (mg/dL)} + \log_e \text{INR} + 6.43 \text{ (disease constant)}$$

- Score : 6 in healthy person to 40 in severe ESLD
- Score < 15 should not undergo liver transplantation
- Preference – Sickest patient as per MELD score.

Liver Transplant – Unequal Access

- MELD (Model for End-Stage Liver Disease) scoring system – 2002
  - Sickest patients should get transplanted first
  - Model predicts risk of death from ESLD for adults
    Bilirubin, Coagulation (INR), Creatinine
- MELD = 3.78[Ln **bili (mg/dL)] + 11.2[Ln INR] + 9.57[Ln creat (mg/dL)] + 6.43**

- MELD predicted 3 month mortality
  - 40 or more — 71.3% mortality
  - 30–39 — 52.6% mortality
  - 20–29 — 19.6% mortality
  - 10–19 — 6.0% mortality
  - <9 — 1.9% mortality

- Significant decrease in the rate of death of potential recipients on the waiting list because it allows livers to be directed to the sickest patients.

- The scoring used in pediatric patients is referred to as the pediatric end-stage liver disease (PELD) score.

- Pediatric donors are distributed to pediatric patients preferentially.

Exceptions of MELD score

- HCC, Hepatopulmonary syndrome, metabolic disease, amyloidosis

- Status 1 : To p priority
  - Acute fulminant hepatic failure
  - Primary non function of transplanted graft

- Organs may be obtained from:

  - Living donors (mostly Kidney)
  - Deceased donors (DD)
    - Brainstem-dead heart beating donors (donation after brain death or DBD donors)
    - Donation after circulatory death (DCD) donors

Evaluation of the deceased donor

- Transmissible infectious agents HIV Creutzfeldt–Jakob disease Hepatitis B &C

- Malignancy- Malignancy within the past five years is an absolute contraindication

- Liver donors - Should not have hepatic disease,
  - Impaired liver function tests are common in deceased donors and do not necessarily preclude donation.

Organ recovery from deceased donors

- ❑ Aim - Preserve the functional integrity of the organs
  - Careful monitoring and management of fluid balance.
  - Inotropic support ,Tri-iodothyronine, Argipressin

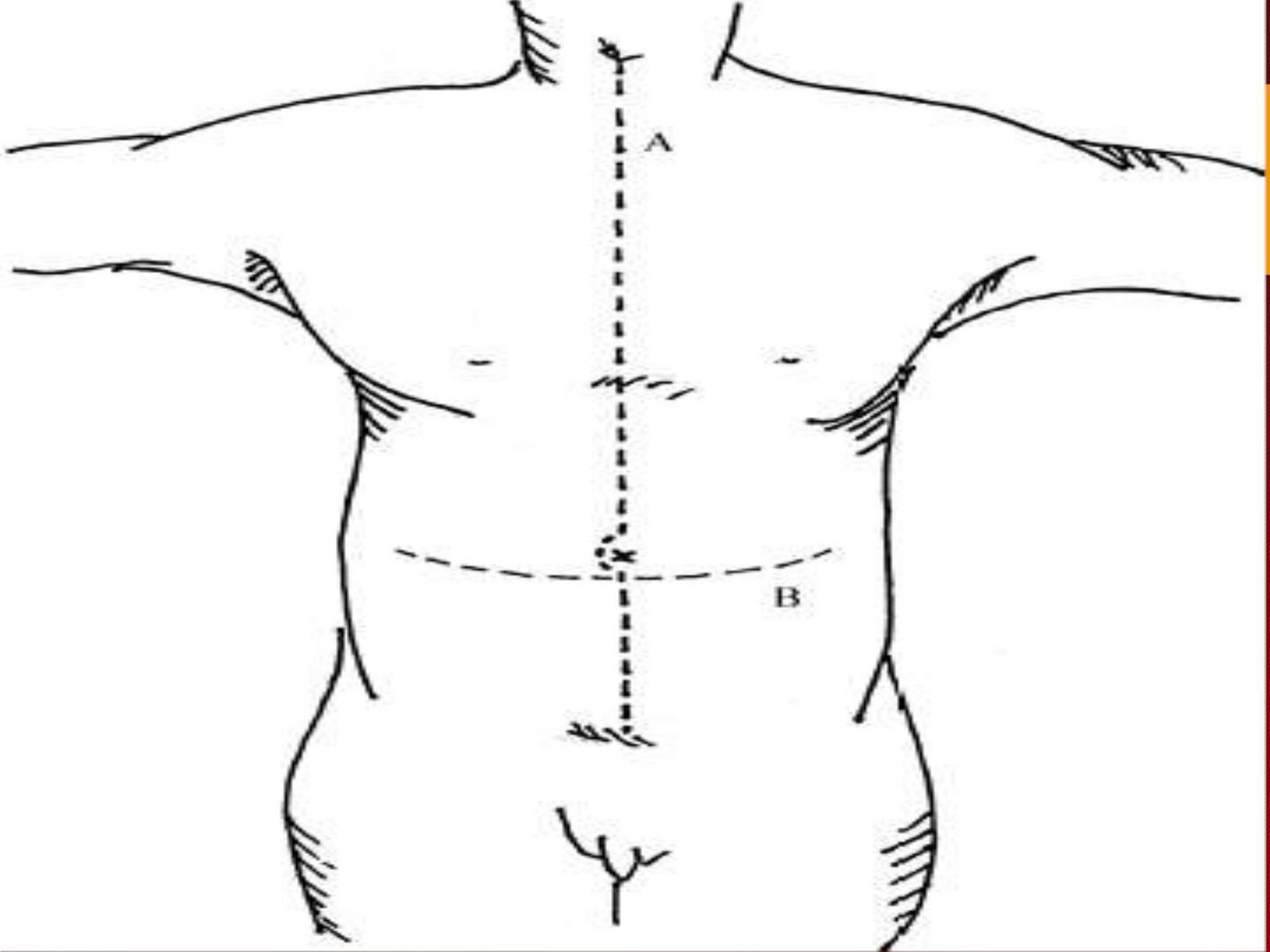
- ❑ Warm ischaemia - Time between the diagnosis of death (cardiorespiratory arrest) and cold perfusion of the organ (up to 45 minutes is acceptable)

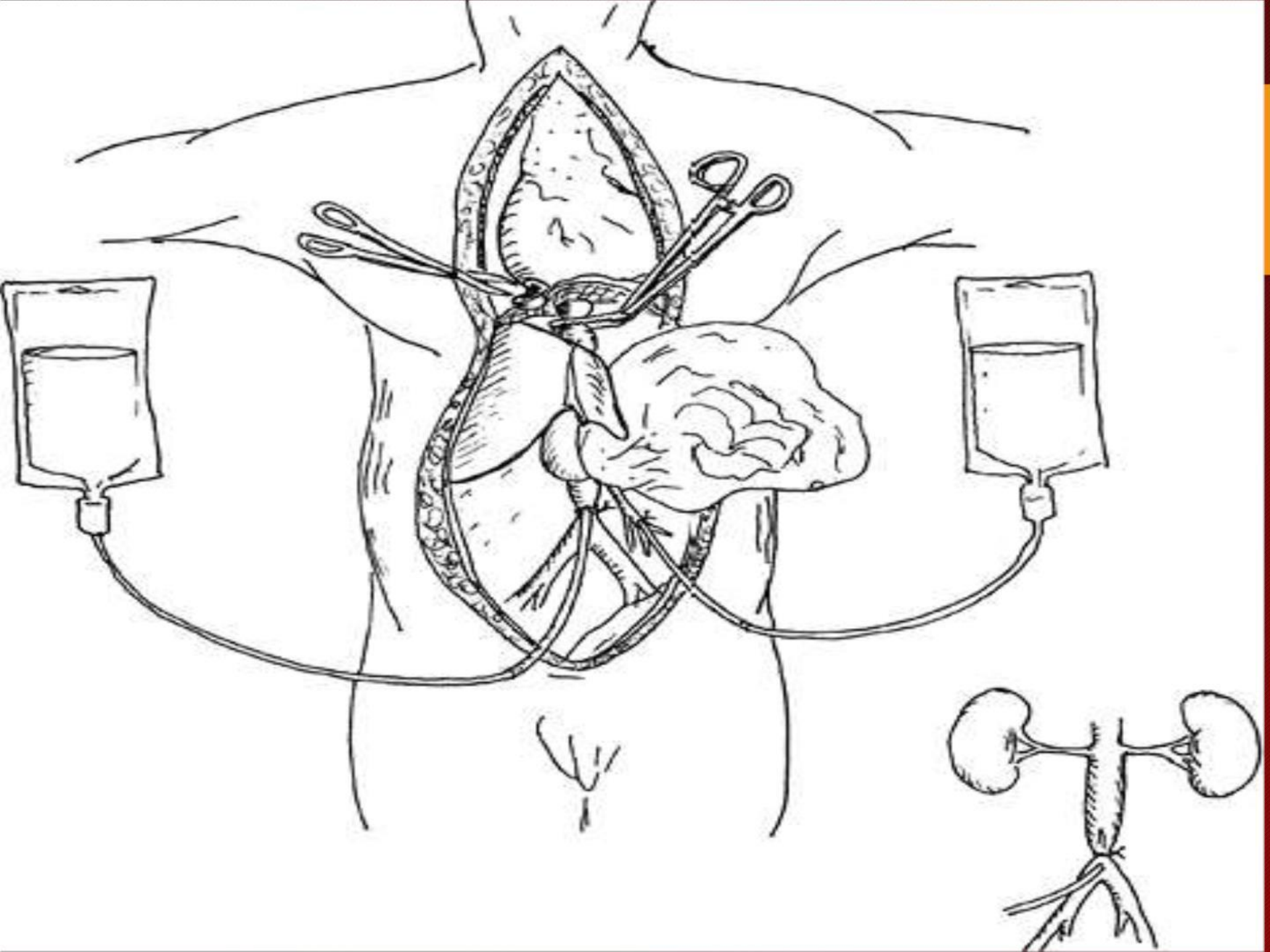
- ❑ Storage time- Liver - <12hrs(Optimal) , 18hrs(Max. time)

Procedure:

- A midline abdominal incision and median sternotomy is used to obtain access.
  - After dissection of the organs to be recovered, they are perfused *in situ*
- *P*erfusion - Chilled organ preservation solution via an aortic and portal cannula.

  Uncontrolled donor – via femoral cutdown
- Removal - Heart and lungs - Liver and pancreas - kidneys


A
B



- After removal from the donor, the organs may undergo a further flush with chilled preservation solution

- Organ is placed in double/ triple sterile bags and stored at 4°C by immersion in ice while they are transported to the recipient centre and await implantation.
- Preservative Solution : University of Wisconsin (UW) solution and Euro-Collins solution
  - impermeants to cell swelling, buffers to counter acidosis and electrolytes

LIVE DONOR LIVER TRANSPLANTATION

- Alternative, developed to meet the demand
- Otte and colleagues - Pared down adult-sized livers for use in pediatric patients
  - Observed that the liver can regenerate after major liver resection for cancer
- High risk of death to donor - Pulmonary emboli
- Current estimates are that the risk of death from liver donation is 1 in 500 to 1000

Ideal weight of the graft - >0.8% of the recipient's body weight to prevent injury from hyperperfusion

Right lobe graft (60-80% liver mass)

- Most commonly used
- More physiologic strains on the donor
- Emergent donor transplantation
- Better for recipient

Left lobe graft (30% to 40% liver mass)

- Less physiologic strains on the donor
- No report of emergent donor transplantation
- Injury to the graft from hyperperfusion and endothelial damage due to:
  - high portal flow generated by the enlarged spleen
  - other vascular manifestations of portal hypertension

Donor's post operative complication

- 30% to 40% suffer one or more postoperative complications
- Most include pulmonary emboli
- Portal vein thrombosis
- Bile duct injury
- Liver insufficiency secondary to a resection that is too extensive

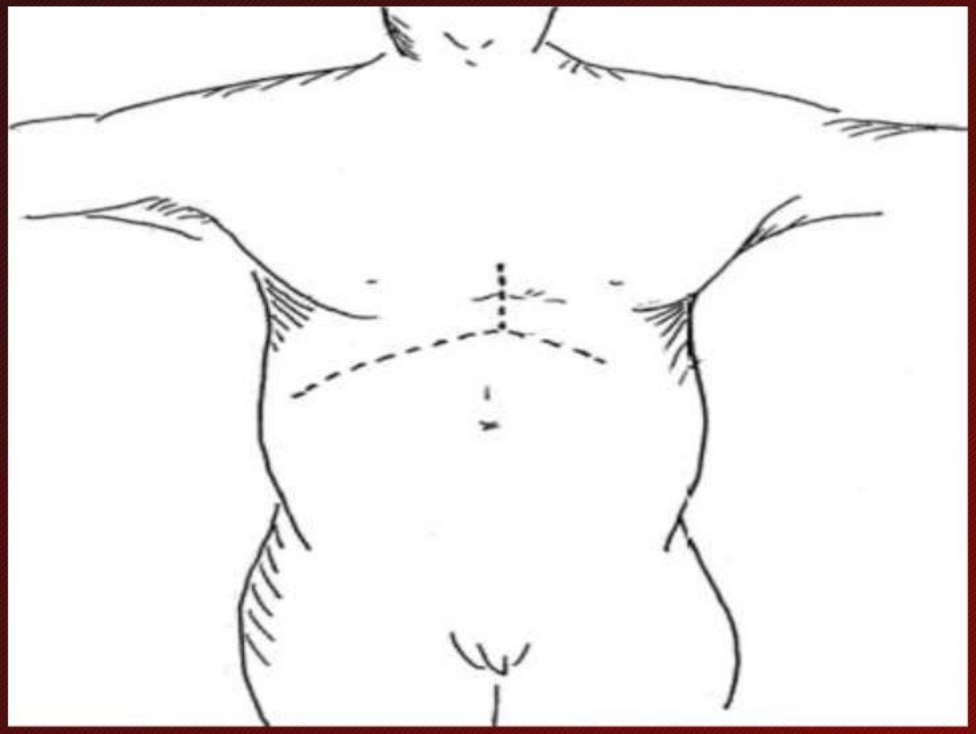
Recipient outcomes from live liver donors

- ❑ Superior to those receiving deceased donor transplants
  - Recipient is in relatively good health
  - Free of preservation insult
  - Avoidance of the negative effects of brain death on organ viability
  - Immunologic advantage of a live donor graft

- ❑ Complications in the recipient related to the bile duct anastomosis is twice as high

Implantation of cadaver whole allograft

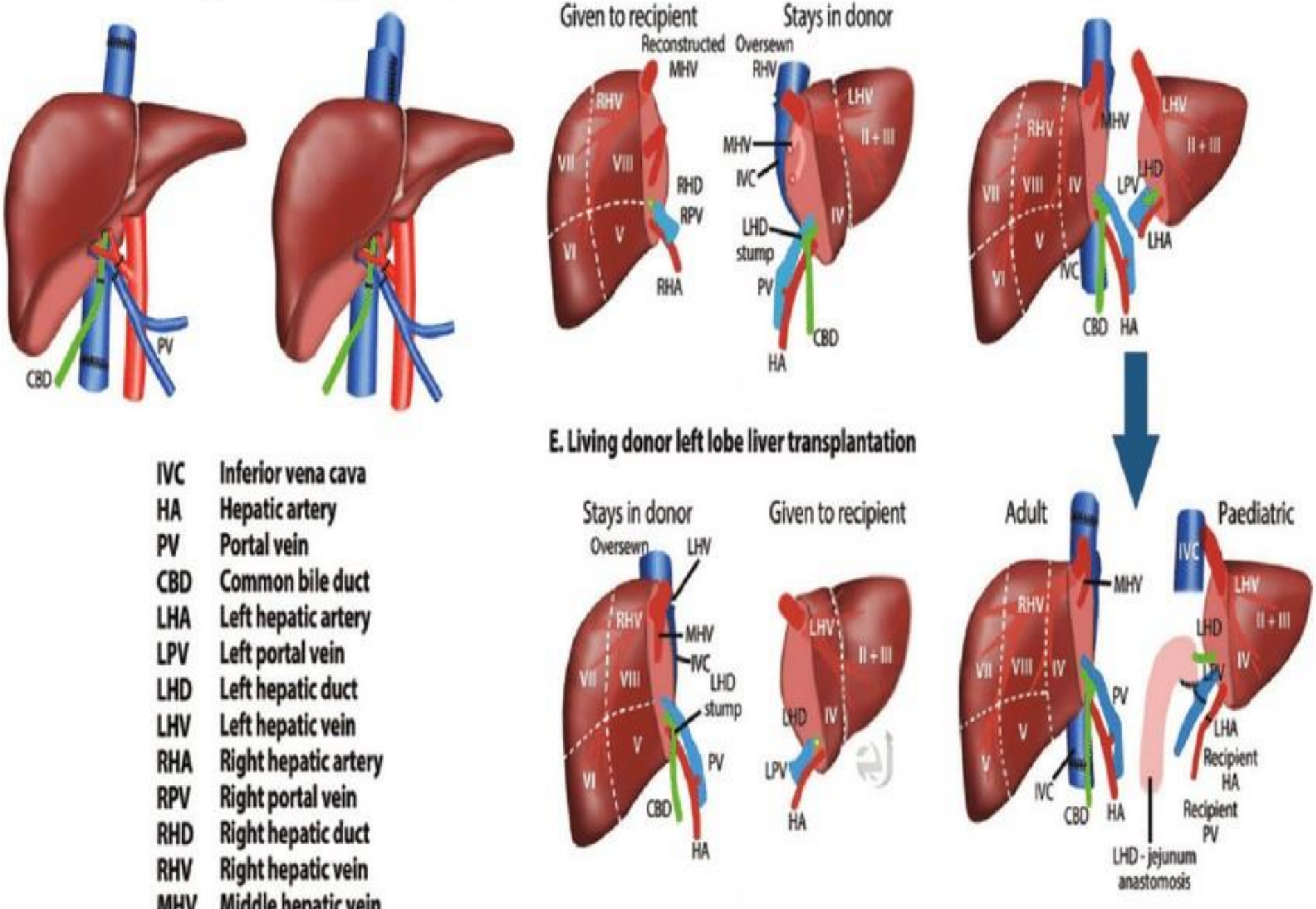
- Unlike the kidney transplant, the liver is placed orthotopically in its native position within the abdomen



- The procedure involves removal of the host liver and replacement with a whole or partial graft

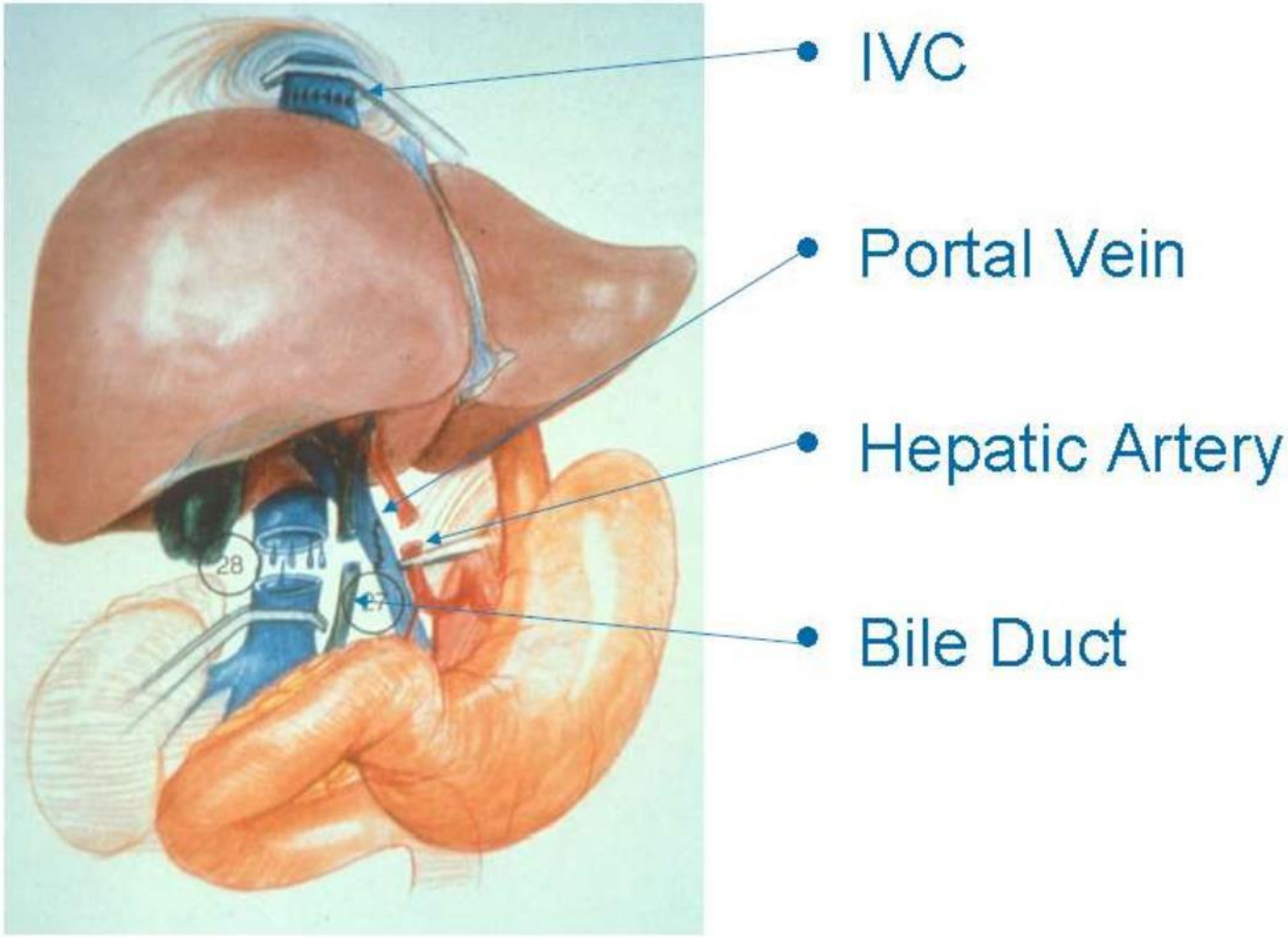
- Removal of the host liver is challenging because of the portal HTN and coagulopathy

- The anhepatic phase - Period during which the new liver is sewn in and the patient is without a liver.



IVC	Inferior vena cava
HA	Hepatic artery
PV	Portal vein
CBD	Common bile duct
LHA	Left hepatic artery
LPV	Left portal vein
LHD	Left hepatic duct
LHV	Left hepatic vein
RHA	Right hepatic artery
RPV	Right portal vein
RHD	Right hepatic duct
RHV	Right hepatic vein
MHV	Middle hepatic vein

Liver Transplant **4 main connections**



Procedure- (Classic approach)

a) Suprahepatic vena cava anastomosis

b) Infrahepatic vena cava anastomosis

c) Portal vein anastomosis

d) Arterial anastomosis

e) Biliary anastomosis

is of hepatic arteries of the donor and recipient is performed by direct conn

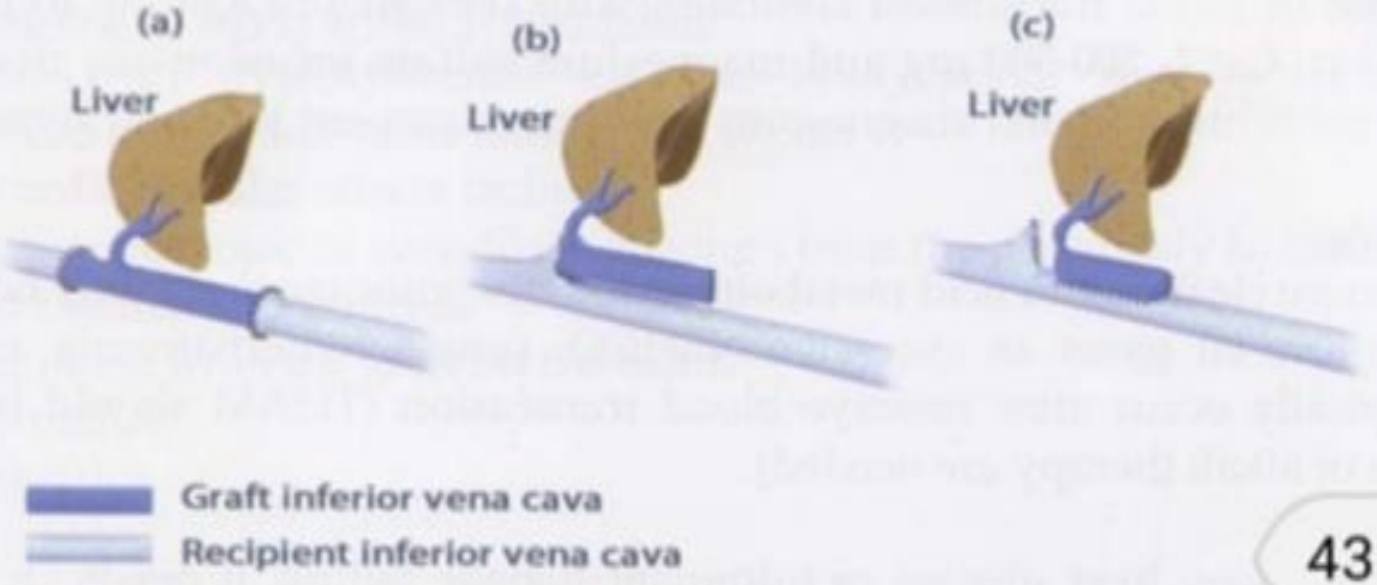


Figure 22-7: IVC connections

Piggyback technique - An alternative to the conventional implantation technique

- Native retrohepatic cava is preserved

Advantage:

- Shorten the anhepatic phase
- Improve cardiovascular stability

The anhepatic phase ends with reperfusion of the graft

- Inflow from the portal vein
- Outflow through the vena cava

Venovenous bypass – Shunt tubing is placed in the host portal vein and infrahepatic cava and returned to the central venous circulation to maintain vascular stability during the anhepatic phase.

Centers that do not use the bypass technique rely more on anesthesia support of the blood pressure through volume administration and pressers.

Veno-venous bypass – largely abandoned

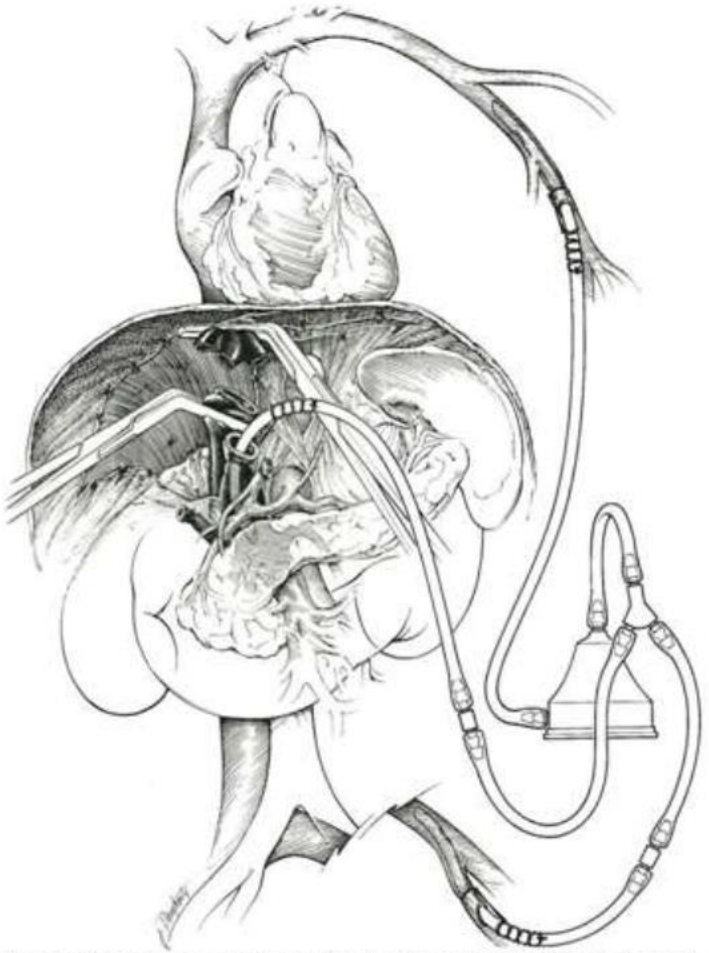
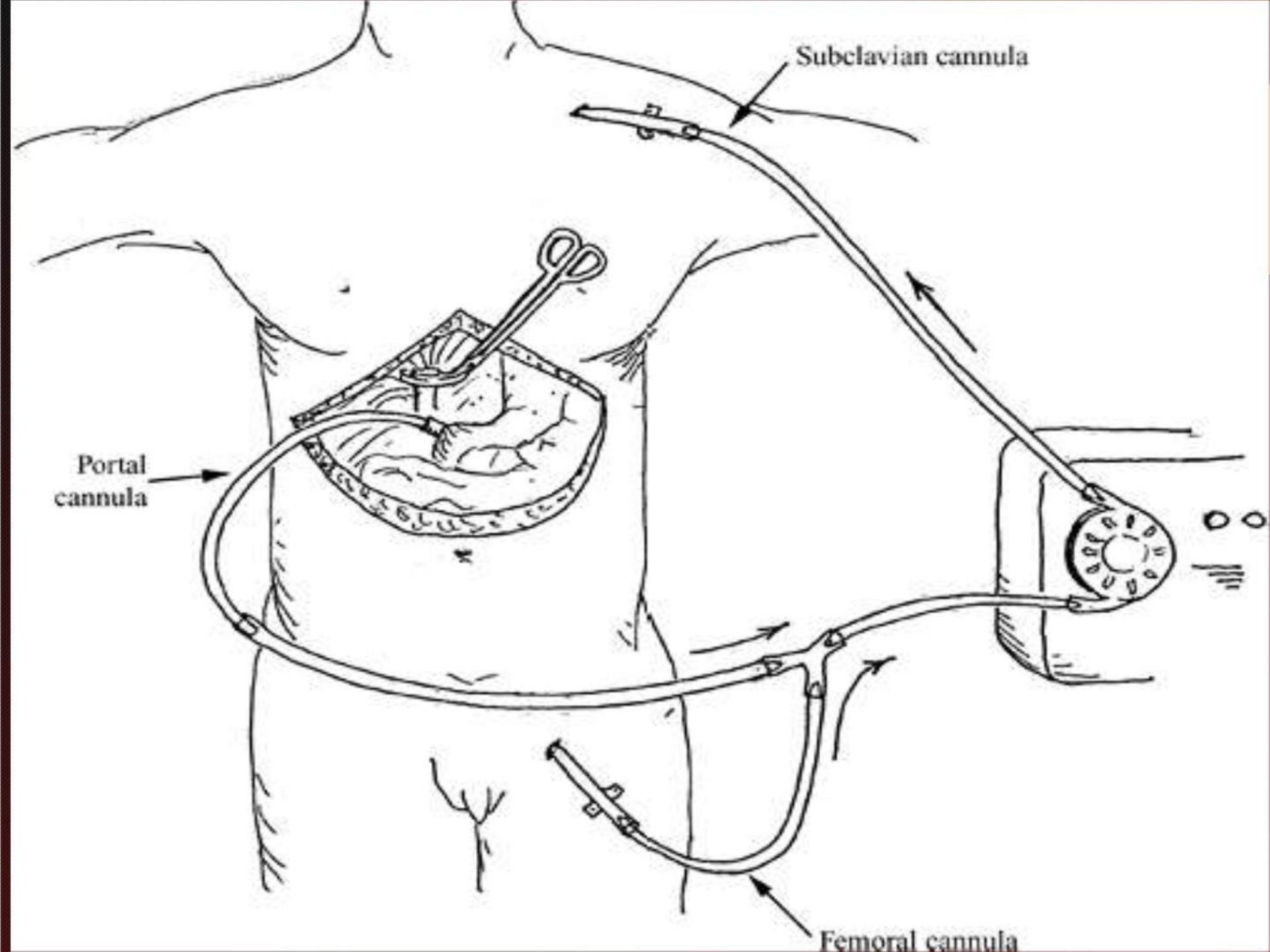
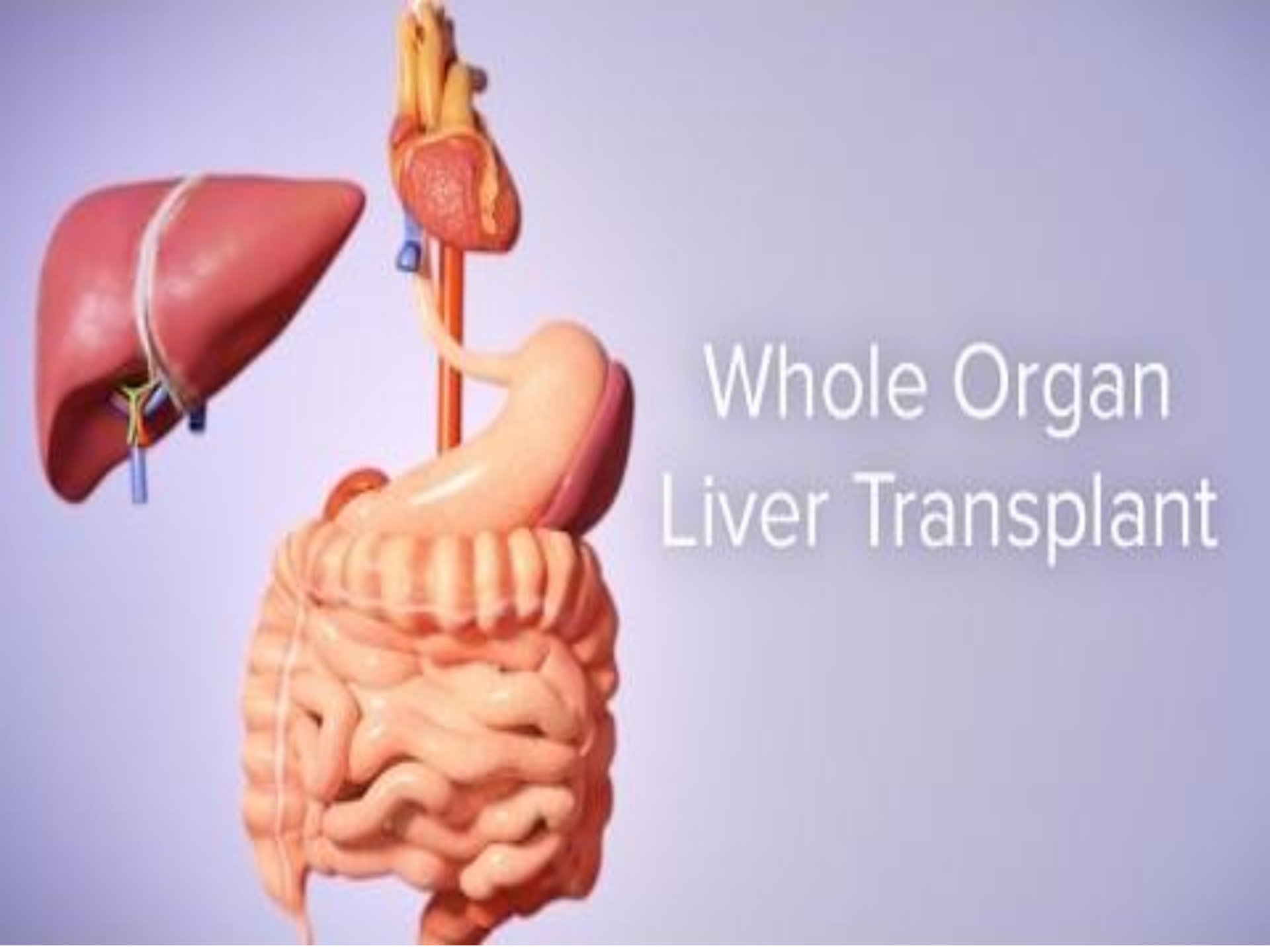


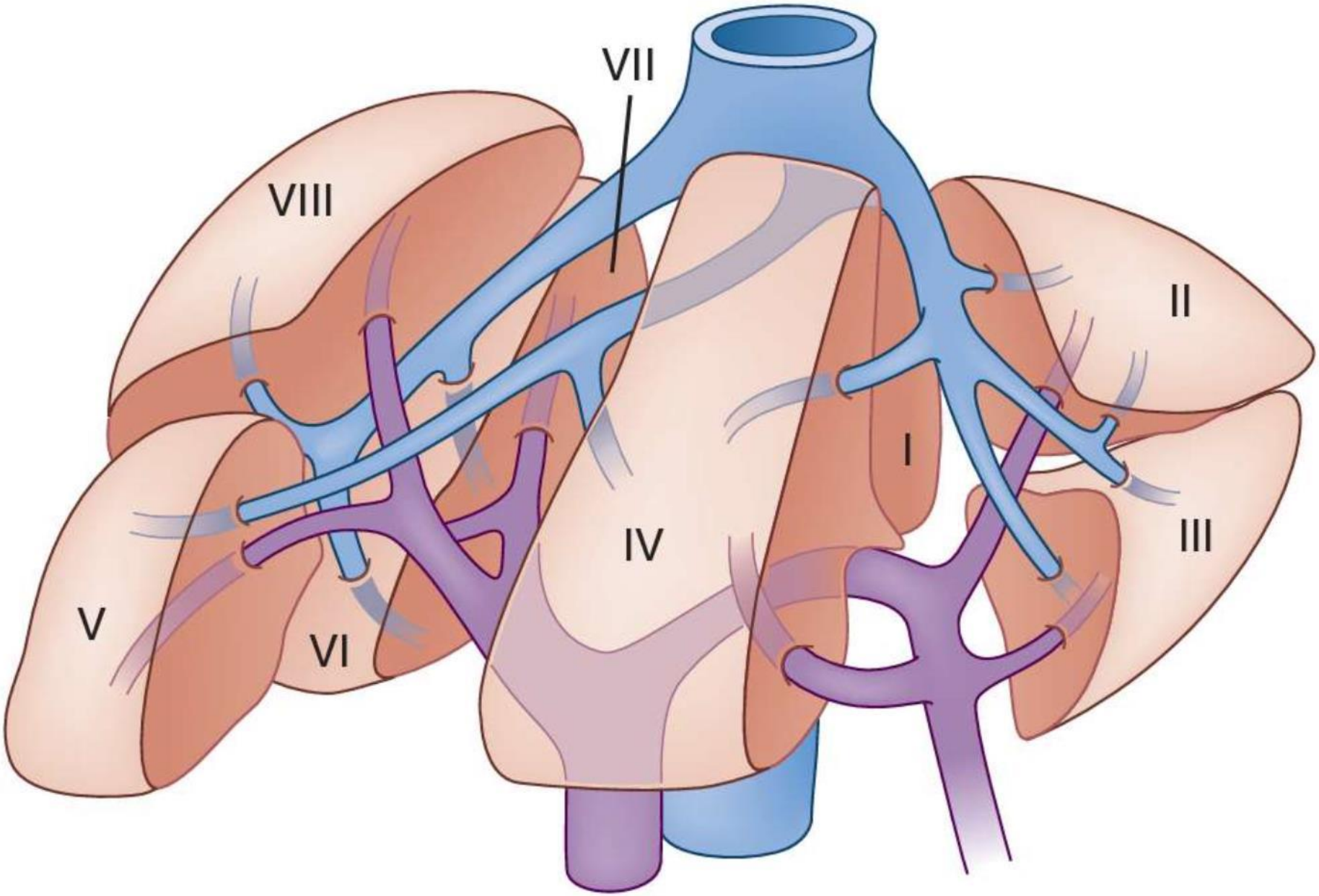
Figure 3–2. With the liver removed, the important anhepatic-anatomic relationships are schematically shown. Redundant venae cavae remain after the diseased liver has been removed. Both of these structures are debrided to accommodate the graft vena cava. The upper vena cava is usually transected through one or more hepatic vein confluences, depending on the graft vena cava size. With the patient on venovenous bypass, the retroperitoneal bleeding is controlled prior to implanting the liver.


Subclavian cannula
Portal cannula
Femoral cannula


Whole Organ
Liver Transplant

Reduced-size liver transplantation

- first described by Bismuth *et al*
- consists in the procurement of the whole liver from an adult cadaver donor, which is reduced in its size on the back-table- the left lobe (Couinaud liver segments 1 to 4), including the vena cava, was transplanted in a child.
- The graft is transplanted retaining the recipient's vena cava, anastomosing the graft left hepatic vein to the recipient's vena cava.
- shows outcomes in line, if not superior, to whole-liver transplantation, and has become an essential part of the technical expertise of pediatric transplant centers
- main limitation is that it withdraws organs from the larger adult recipient pool.
- For this reason, after the development of living-related and split-liver transplantation, reduced-size live transplantation is used increasingly less, and should not be considered an option anymore.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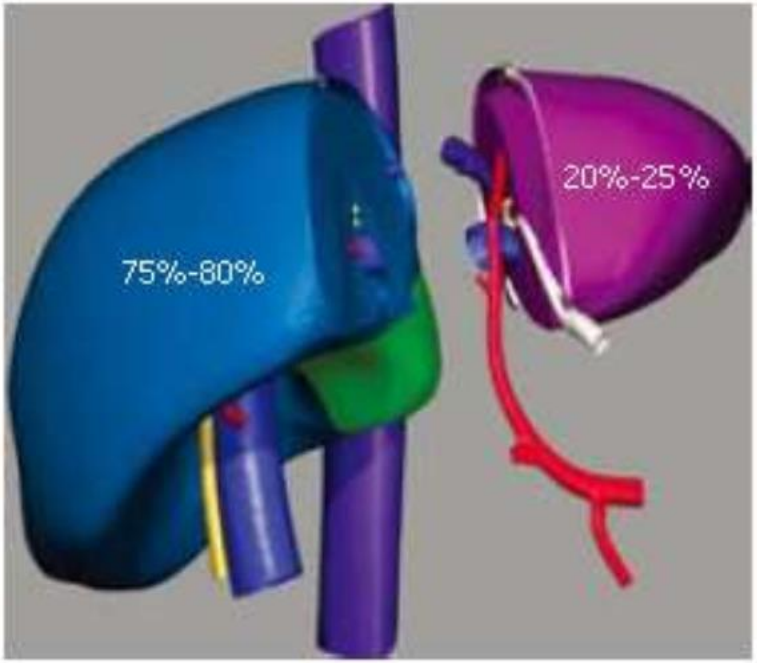


Spit liver allows for the procurement of two separate grafts of different sizes

A section of the liver is made along the falciform ligament and
divides the left lateral segment from the extended right liver. The left graft, composed of segments 2 and 3, and representing 20%-25% of the total liver volume, includes the left hepatic vein, the left branch of the portal vein, and the left branch of the hepatic artery, along with the common hepatic artery and the celiac tripod. The right graft composed of segments 1 and 4-8, and representing 75%-80% of the total liver volume, includes the vena cava, the right branch of the hepatic artery, and the portal vein.

Split Liver Transplant

- Child (receive segments 2 & 3 /segments 2, 3,& 4
- Adult (receive segments1, 4, 5, 6, 7& 8 or 1, 5, 6, 7 &8
- Right lobe graft - includes the donor vena cava and right hepatic artery
- Pediatric graft - Based on the celiac trunk providing the left hepatic artery, left portal vein, and left hepatic vein

Live Donor Operation

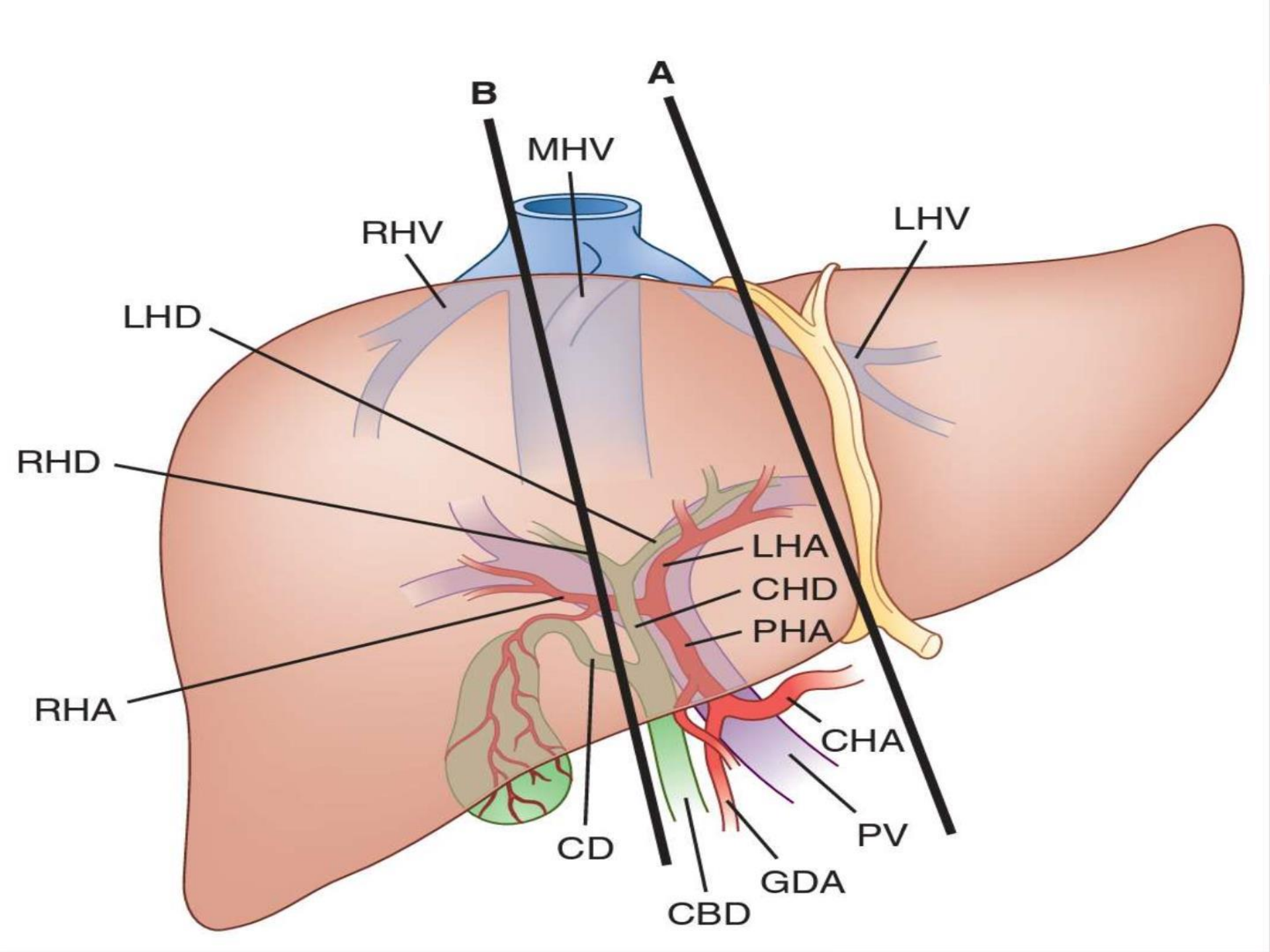
❖ ***Segment 2-3 Hepatectomy***

- Segments 2 and 3 is most appropriate for infants and small children (up to 5 years of age)
- Midline incision - round ligament divided, retracted, and mobilized
- Left hepatic artery & vein and left portal vein mobilized.
- Resection line - Right edge of the left hepatic vein to the bile duct plate

-Parenchymal dissection done and the segment 2-3 is lifted superiorly and dissected free from segment 1

- Results in an isolated segment 2-3 with left hepatic artery, left portal vein, and left hepatic vein, along with the segment 2-3 duct.

- The segment 2-3 is flushed through the left portal vein and left hepatic artery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A
MHV
RHV
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LHD
RHD
LHA
CHD
PHA
RHA
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PV
CD
GDA
CBD

❖ *Right Lobe Dissection for Live Donor Liver Transplantation*

- Most commonly used for adult to adult live donor liver transplantation.
- Incision : A bilateral subcostal or midline
- Cholecystectomy is performed
- The right hepatic artery and right portal vein are isolated and temporarily occluded which is used to plan the plane of resection

- This line typically runs at the left edge of the gallbladder fossa to the medial aspect of the right hepatic vein

- Once the parenchymal dissection is complete and the right duct divided, vascular clamps are placed on the right hepatic artery, right portal vein and right hepatic vein for resection of the right lobe

❖*Left Lobe Dissection for Live Donor Liver Transplantation*

- Based on segments 2, 3, 4, and 5
- Inflow from the left hepatic artery and left portal vein and outflow from the middle and left hepatic veins
- The operation includes the parenchymal dissection along Cantlie's line, the same line as for the right hepatic lobectomy.
- The parenchymal dissection is done in the same manner as for right hepatic lobectomy

❖ Implantation of Partial Liver Graft

- The piggyback technique is the basis for implantation of a graft from a live donor

- Venous anastomosis : Between the graft hepatic vein and a wide cavotomy, using one of the recipient hepatic vein orifices

- Depending on whether the donor graft is the right/left lobe, either the right/left hepatic artery branches from the recipient may be used for inflow

- Similarly, inflow may be from the right or left portal vein branch

- Biliary drainage :
    - Duct to duct anastomosis
    - Roux-en-Y anastomosis to the donor duct (depending on the duct sizes)

- Care must be taken to avoid tension on this anastomosis.

COMPLICATIONS OF LIVER TRANSPLANTATION

- Primary nonfunction- Transplanted liver does not work. It is rare (<2%) and is fatal without retransplantation
- Hepatic artery thrombosis (2% to 4%)
- Portal venous thrombosis- May present with gastrointestinal bleeding or coagulopathy
- Bleeding, inadequate production of clotting factors (poor initial function)
- Complication due to immunosuppressive therapy

EARLY POSTOPERATIVE PERIOD

- consists of managing problems related to technical complications and to the prevention, diagnosis, and treatment of acute rejection and infection episodes.
- usually present with a combination of cholestasis, rising hepatocellular enzyme levels, and variable fever, lethargy and anorexia

Vascular complications

Hepatic artery thrombosis

- hepatic artery anastomosis carries the highest risk of thrombosis (5%-18%) and leads to massive graft necrosis in cases of early onset
- 3-4 times >adults and occurs most often within the first 30 d after transplantation and in small babies transplanted with whole livers.
- If identified early, reconstruction can be attempted to avoid allograft necrosis
- When allograft failure develops, urgent retransplantation is the only option

- Late thromboses can manifest with biliary complications (stenosis or dehiscence of the biliary anastomosis, intrahepatic bilomas) or sepsis.
- Clinical manifestations include cholestasis or graft failure caused by diminution in hepatic blood flow.
- diagnosis relies on Doppler ultrasound- Treatment modalities include revision of the anastomosis or balloon angioplasty.

- Common causes of graft dysfunction

<1 mo Post-LT	1–12 mo Post-LT	>1 y Post-LT
Early graft dysfunction	Rejection (acute or chronic)	Rejection (acute or chronic)
Vascular complications (ie, HAT, vascular impairment)	Recurrence of primary disease (ie, HCC, HCV)	Recurrence of primary disease (ie, HCC, HCV, alcoholism)
Biliary complications (ie, bile leak, strictures)	Vascular complications	Development of de novo liver disease (ie, NAFLD)
Infection (ie, sepsis)	Infection (ie, CMV)	—

GRAFT REJECTION

- Allografts provoke a powerful immune response that results in rapid graft rejection unless immunosuppressive therapy is given

- Allografts trigger a graft rejection through,
  - ABO blood group antigens
  Human leukocyte antigens (HLA)

ABO blood group antigens

The ABO blood group antigens are expressed not only by red blood cells, but by most other cell types as well

Permissible transplants are:

- group O donor to group O, A, B or AB recipient
- group A donor to group A or AB recipient
- group B donor to group B or AB recipient
- group AB donor to group AB recipient

There is no need to take account of rhesus antigen compatibility in organ transplantation.

IMMUNOSUPPRESSION AFTER LIVER TRANSPLANTATION

Hurdles –

- ❑ Nonspecific to the alloimmune response- recipients need
  number of agents to control the normal immune response adequately
- ❑ Global immune target
- ❑ Targets any cells undergoing maturation or division
- ❑ Cost

Phase of immunosuppression

- Induction immunosuppression

  - Intense immunosuppression
  - Heightened state of inflammation
  - Time of initial antigen exposure
  - Involves complete deletion/aggressive diminution of the T cell response

- Maintenance immunosuppressants
  - Remainder of the patient's life

- Rescue agents.

- Privileged organ(Liver) - Need for immunosuppression decreases over time (unlike kidney and heart)

- Immunosuppression combination:
  - Calcineurin inhibitor(tacrolimus or cyclosporine)
  - Steroids (methylprednisolone)
  - Antiproliferative agent (mycophenolate mofetil)
  - Sirolimus rapamycin inhibitor – Immunosuppressive + antineoplastic

Corticosteroids	Widespread anti-inflammatory effects
Azathioprine	Prevents lymphocyte proliferation
Mycophenolic acid Preperations	Prevents lymphocyte proliferation
Calcineurin inhibitors (ciclosporin/tacrolimus)	Blocks IL-2 gene transcription
mTOR inhibitors	Blocks IL-2 receptor signal transduction
ALG	Depletion and blockade of lymphocytes
Anti-CD25 mAb	Targets activated T cells
Anti-CD52 mAb	Depletion of lymphocytes
Anti-CD20	Depletion of B lymphocytes

Side effects of non-specific immunosuppression

- Infection
  - Viruses (Risk -greatest during first six months)
    - Reactivation of latent virus or from primary infection
    - Cytomegalovirus is a major problem
    - Herpes simplex virus (HSV)
    - Chemoprophylaxis - Antiviral

➢ Bacterial infection (Risk -highest during the first month)

- Wound, respiratory tract and urinary tract
- Perioperative broad-spectrum antibiotic cover

- Tuberculosis - Concern in previously infected patient & from the Indian subcontinent
  - Chemoprophylaxis for 6–12months

- Fungal infection
  - Usually occurs in the first three months
  - Pneumocystis jiroveci
  - Candida/Aspergillus
  - Chemoprophylaxis is highly effective and usually continued for up to six months

INFECTIONS

- Infectious complications now represent the most common source of morbidity and mortality after transplantation.

- Bacterial infections occur in the immediate posttransplantation period and are most often caused by Gram-negative enteric organisms, enterococci, or staphylococci.

- Fungal infection most often occurs in high-risk patients requiring multiple operative procedures, re-transplantation, hemodialysis or continuous hemofiltration, pre-transplant chemotherapy, and multiple antibiotic courses - prophylaxis with liposomal amphotericin B.

Viral

Early and severe viral infections –

- Herpes family
  - EBV, CMV and
  - Herpes simplex Herpes virus 6 and 7

Risk of CMV and EBV infections –

- pre-operative serological status of recipient and donor
- D+ / R- greatest risk of primary infection

CMV infection

-fever, leukopenia, rash
-hepatitis
-pneumonitis
-GIT involvement
    -CMV colitis frequently serum PCR negative needs tissue diagnosis

EBV infection

-mononucleosis-like syndrome
-hepatitis resembling rejection
-post transplant lymphoproliferative disease

Monitor CMV and EBV PCR
    all children receive IVI Gancyclovir
    conversion to oral Valgancyclovir

- ❑ Malignancy

- Posttransplant lymphoproliferative disease (PTLD)

- Skin cancer

- Kaposi’s sarcoma

EVALUATION

- Abnormal LFT - Do not differentiate the specific problem that may be present in the liver;
  - Vascular occlusion
  - Bile duct stricture
  - Preservation injury
  - Recurrent hepatitis
  - Rejection

- Ultrasonography - Evaluate hepatic artery, portal vein flow and bile duct caliber

- Percutaneous liver biopsy(If USG is normal)
  - Acute rejection
  - Preservation injury.

Outcome

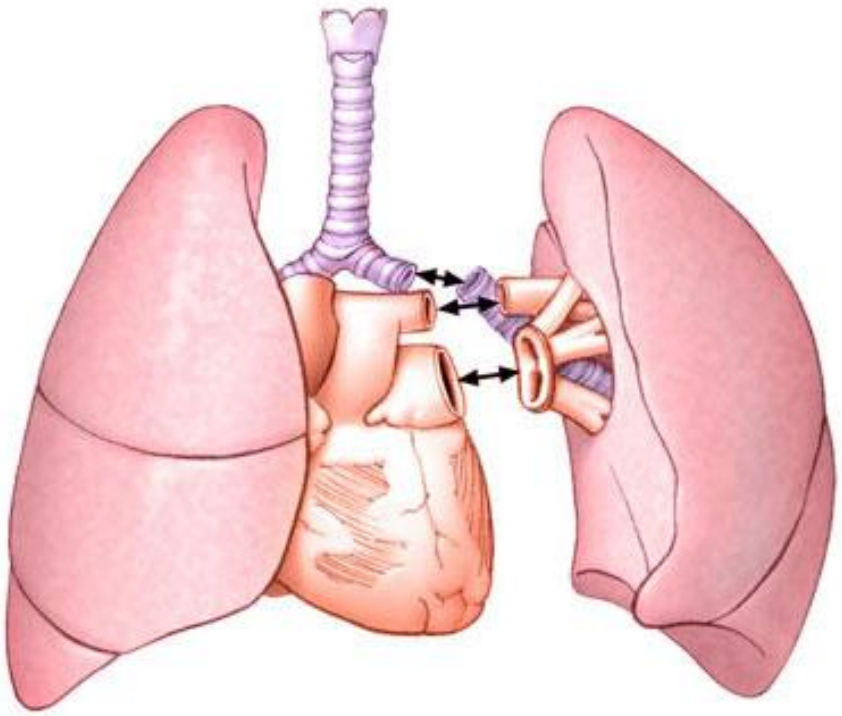
- 1-year survival rates - 88%
- 5-year patient and 75%,

(Results depend on the specific disease for which the transplantation is performed)

- Early signs that a newly implanted liver is functioning:
  - - Acid clearance
    clotting parameters
  - Bile production

Thank you

LUNG TRANSPLANTATION



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Introduction

- Lung transplantation involves removal of one or both diseased lungs from a patient and the replacement of the lungs with healthy organs from a donor
- May refer to single, double, or even heart-lung transplantation
- Accepted modality of treatment for end stage lung disease that is unresponsive to medical therapy

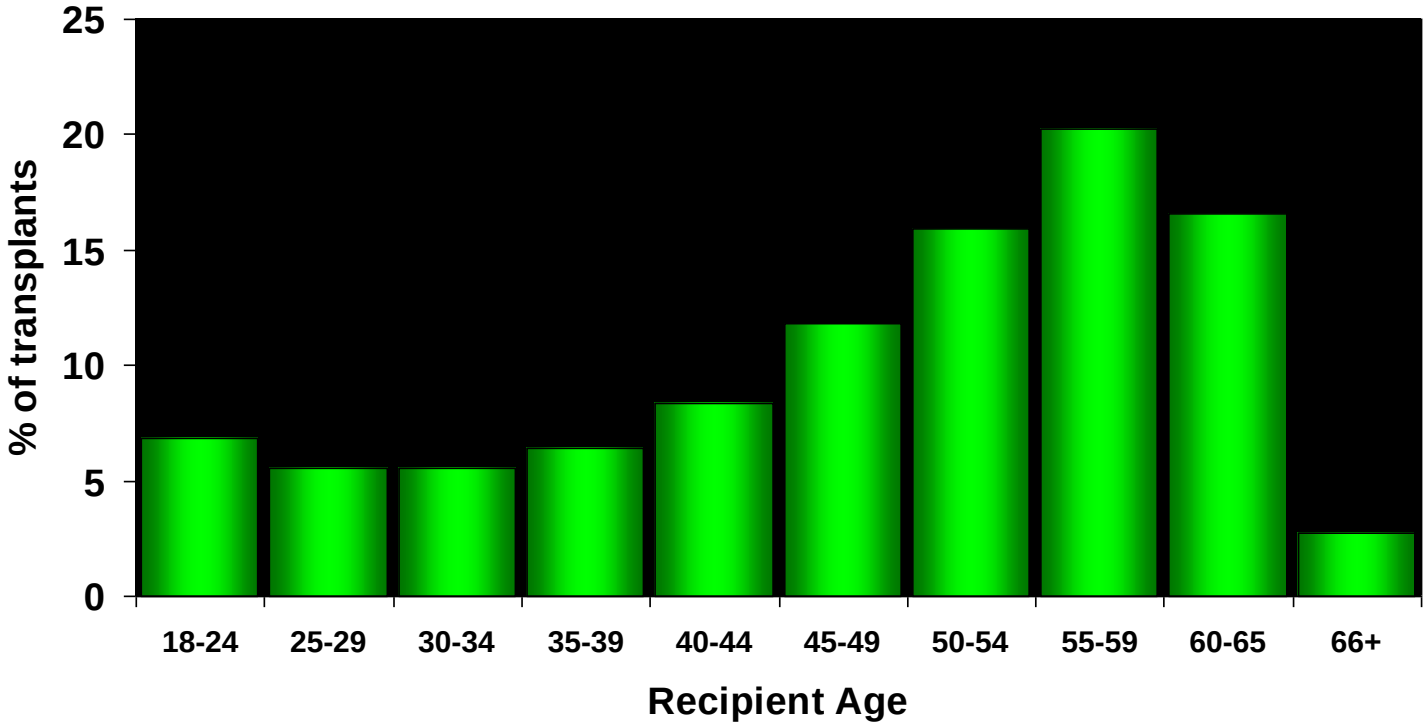
Purpose

- To replace a lung that no longer functions with a healthy lung.
- To perform a lung transplantation, there should be potential for rehabilitated breathing function.
- Other medical treatments should be attempted before transplantation.

History of procedure

- First human lung transplantation was done in 1963. Recipient of the lung transplant survived only 18 days.
- 1983- Dr. Joel Cooper- first successful single lung transplant
- 1985- Cooper / Patterson- double lung transplant

AGE DISTRIBUTION OF LUNG TRANSPLANT RECIPIENTS



J Heart Lung Transplant 2008;27: 937-983

Indications for lung transplantation

- **Obstructive lung disease**:
  - A. Chronic obstructive pulmonary disease
- **Restrictive lung diseases**:
  - A. Idiopathic pulmonary fibrosis (IPF)
  - B. Interstitial lung disease

Indications for lung transplantation

- **Septic lung disease**:
  - A. Cystic fibrosis (CF)
  - B. Bilateral bronchiectasis
- **Pulmonary vascular disease**:
  - A. Primary pulmonary hypertension (PPH)
  - B. Eisenmenger's syndrome

- **Prognostic criteria-**
  1)age
  2)sex
  3)FEV1
  4)weight for age
  5)Pancreatic insufficiency

Primary Pulmonary Hypertension

- Symptomatic progressive disease despite optimal medical treatment for 3 months
- Cardiac index < 2 lit/min/m2
- Right atrial pessure>15 mm Hg
- PAP mean > 55 mm Hg

Eisenmengers syndrome

- Better prognosis than patients with PPH with similar PAP levels
- Epoprostenol therapy improved survival & reduced need for transplantation
- Heart -lung transplantation is preferred

Sarcoidosis

- Most patients benign course
- In 10-20% permanent sequel
- Which stage ?
- FVC < 50% & FEV1 < 40%

Contra-indication (Absolute)

- Malignancy in the last 2 years
- Non-curable chronic extra pulmonary infection including chronic active hepatitis B , C , and HIV
- Untreatable advanced dysfunction of another major organ system
- Current cigarette smoking

- Poor nutritional status
- Poor rehabilitation potential
- Significant psychosocial problems
- Substance abuse
- History of medical noncompliance
- Active Tuberculosis

Relative Contraindications :

- **Age** : advanced age is associated with higher mortality rates
- Age cut-off

  55 years for -**H**eart-lung transplantation,

  60 years for- **B**ilateral lung transplantation,

  65 years for -**S**ingle-lung transplantation.

- **Ventilator dependence**
- A prolonged wait while the patient is on a mechanical ventilator may lead to various complications such as infections, cardiovascular de-conditioning.
- **Psychosocial issues**

- **Decreased Body weight**
- **Obesity (BMI >30)**
- **Extra pulmonary organ dysfunction**

Donor-related issues:

- Younger than 65 years for lung transplantation and younger than 45 years for heart-lung transplantation
- Absence of severe chest trauma or infection
- Absence of prolonged cardiac arrest
- Minimal pulmonary secretions
- Negative screens for HIV, hepatitis C,

- Blood type (ABO) compatibility
- Close match of lung size between donor and recipient
- PaO_2 > 300 mm Hg on 100% fraction of inspired oxygen
- Clear chest radiograph
- No history of malignant neoplasms

Surgical techniques

- Heart–lung transplantation
- Single lung transplantation
- Double lung transplantation

Heart–lung transplantation

- Reserved for patients with combined parenchymal and cardiac disease
- Is it useful for cor pulmonale?
- After excision of the heart and lungs of the donor en bloc, the trachea is anastomosed in the recipient just above the carina
- The integrity of the anastomosis is maintained as a result of extensive collateral arterial blood supply to the lower trachea from the coronary arteries.

Advantages

- immediate restoration of normal cardiac output (an important factor in patients with severe pulmonary hypertension)

Disadvantage

- Requires cardiopulmonary bypass
- Significantly higher risk of perioperative bleeding
- Heart can also be involved in chronic rejection
- The use of both lungs and heart limits the number of potential recipients who can benefit from the donation
- The results are poorer

Single lung transplant (SLT)

- Most common indication (~ 60%) → COPD

- Other indications :
  - Pulmonary fibrosis and
  - Primary or secondary pulmonary hypertension.

Single lung transplant (SLT)

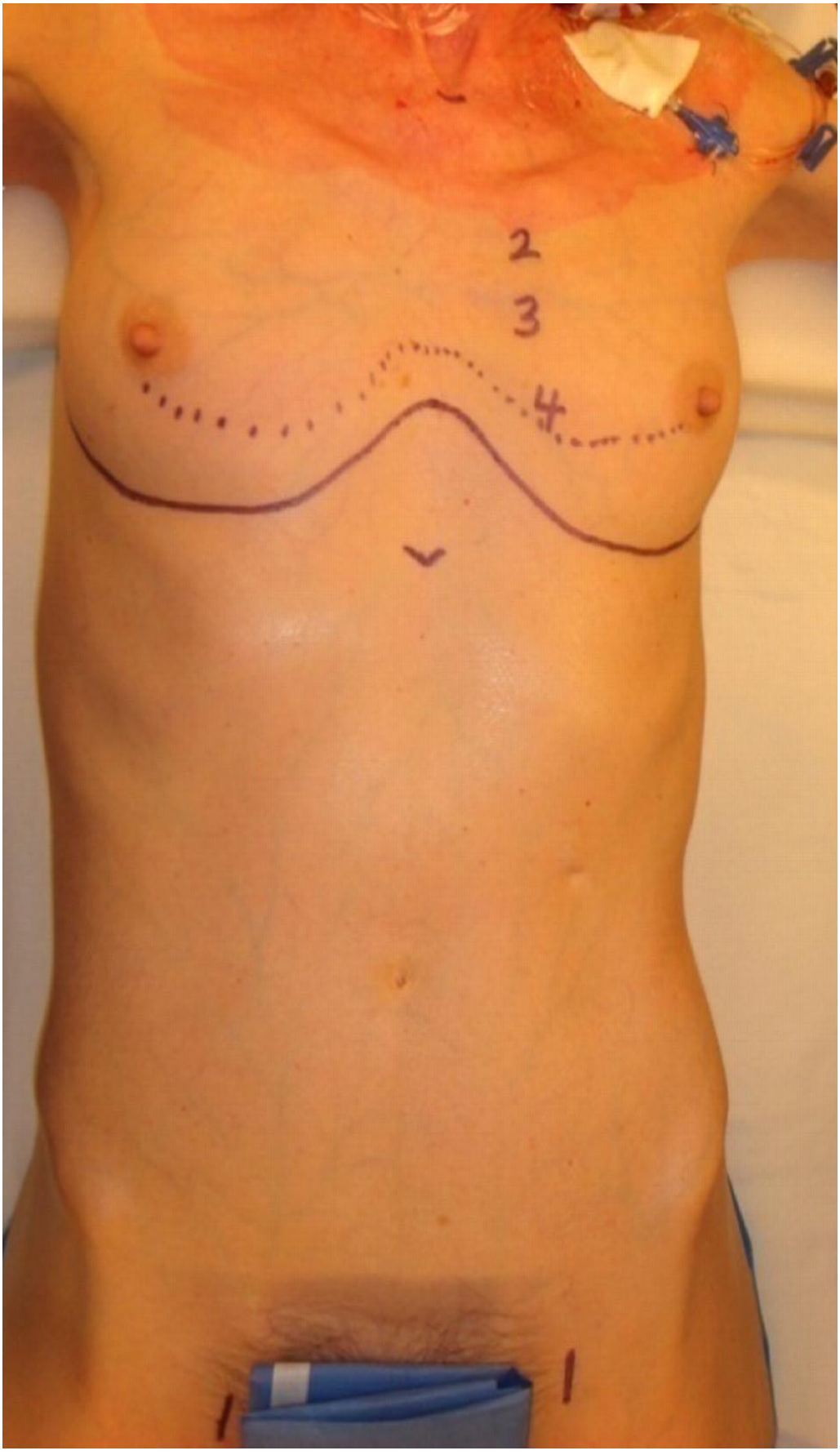
- For SLT, the native lung with the poorest pulmonary function according to the preoperative quantitative perfusion scan is excised.
- Exclude bronchiectasis
- The lung is exposed via a posterolateral thoracotomy through the fifth intercostal space.

Single lung transplantation(SLT)

- Advantages
  - potentially two lung recipients and one cardiac recipient can be treated with organs from one donor.
  - No cardiopulmonary bypass is needed and so patients up to the age of 65 years are being considered for this form of transplantation.

Double lung transplantation(DLT)

- Performed as two sequential lung transplants, one side followed by the other.
- Operation of choice for cystic fibrosis and bronchiectasis, and is also now advocated for patients with primary pulmonary hypertension
.
- No need for cardiopulmonary bypass and the risk of bleeding is less than in HLT.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3
4
1
1

Intraoperative details

- Bilateral sequential SLT is associated with a lower incidence of bronchial complications than the en-bloc DLT procedure and is technically less difficult to perform than en-bloc DLT.

- The exposure for bilateral sequential lung transplantation is via bilateral anterolateral thoracotomies through the fourth or fifth intercostal space, connected by a transverse sternotomy, i.e., the "clam-shell" incision.

Living lobar transplant

- Involves bilateral implantation of the lower lobes from 2 blood group–compatible living donors.
- Donation of a lobe decreases the donor's lung volume by an average of approximately 15% and is not associated with long-term functional limitation
- The need for close matching between the donor and recipient is not necessary

Complications

- Causes of respiratory failure

Early

- ischemia reperfusion injury
- infection
- technical problems
- acute rejection

>3months

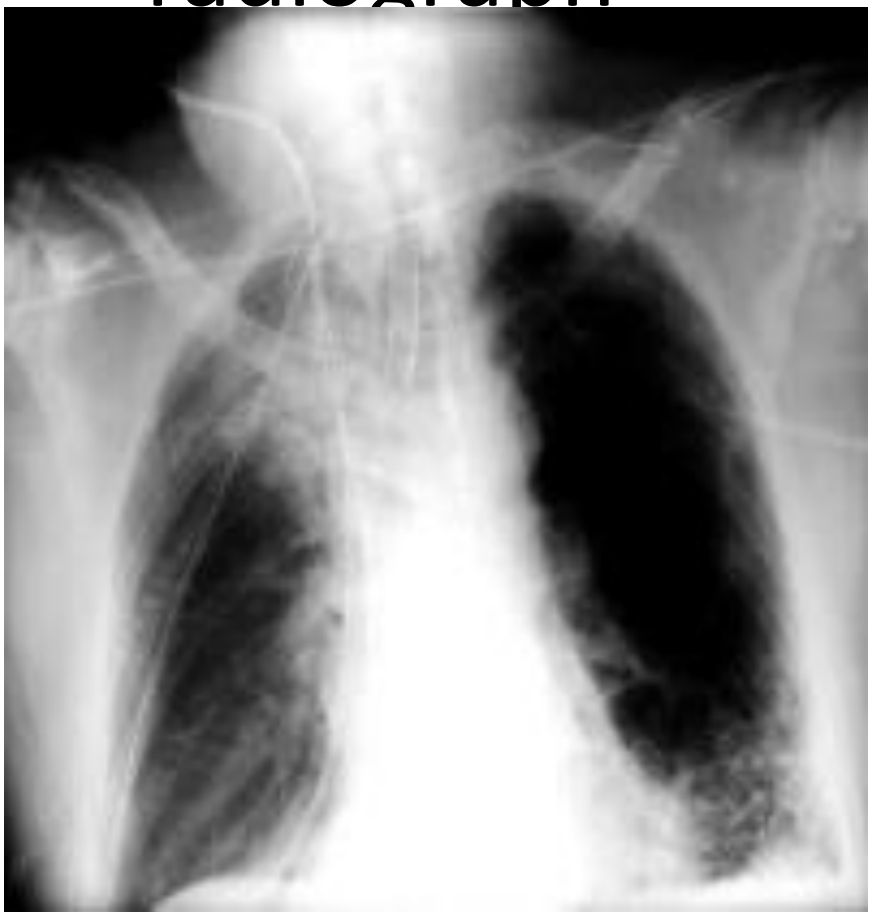
- Infections
- BOS

Curr.opin.Crit.care 2006 Feb;12, 19-24

Ischemia reperfusion injury

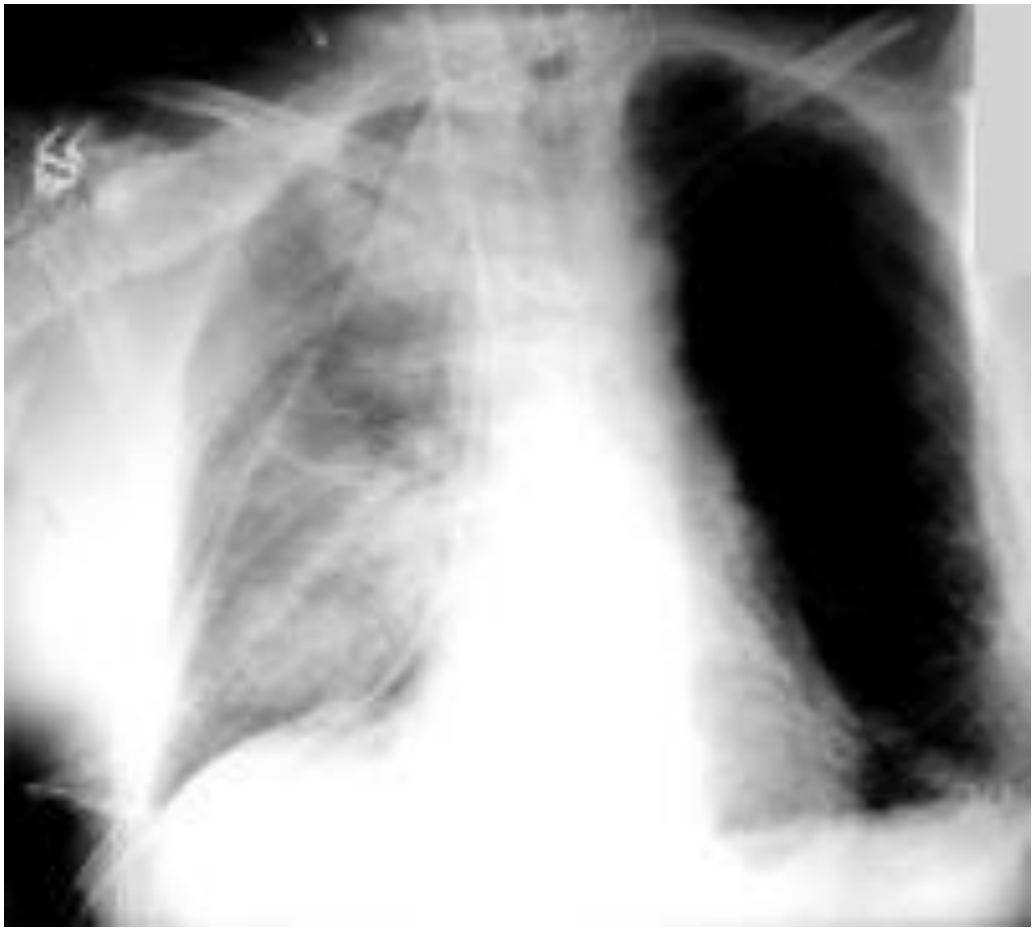
- Most frequent cause of early mortality
- presents as ALI / ARDS
- noncardiogenic pulmonary edema related to effect of free oxygen radicals and cytokines

Post lung transplantation chest radiograph



Chest radiograph performed 24 hours following right unilateral lung transplantation - within normal limits.

Ischemia reperfusion injury



Seventy-two hours following lung transplantation

Infections

- **Bacterial**
  - A) pseudomonas
  - B) nocardia
  - C) legionella , mycobacteria (rare)
- Routine antibiotic prophylaxis reduced the incidence
- Sputum cultures & antibiotic sensitivity done every 3 months

Viral infections

CMV predominates

- within 30-100 days after transplant
- occurs as reactivation or primary infection (donor)
- routine prophylaxis replaced by close monitoring
- Treatment-gancyclovir 5mg/kg for 2-3 weeks

- HSV&VZV can cause pnuemonia
- Acyclovir prophylaxis effective in patients not on gancyclovir
- EBV related post-transplant lymphoproliferative disease
- Recently Rituximab (anti CD20 Ab) found effective

Fungal infections

- Aspergillus most common
  1) ulcerative tracheitis
  2) bronchitis
  3) pneumonitis
  4) disseminated disease
  5) ABPA
- I.V. or aerolised amphotericin-B used for prophylaxis

Complications

- Causes of respiratory failure

Early

- ischemia reperfusion injury
- infection
- technical problems
- acute rejection

>3months

- Infections
- BOS

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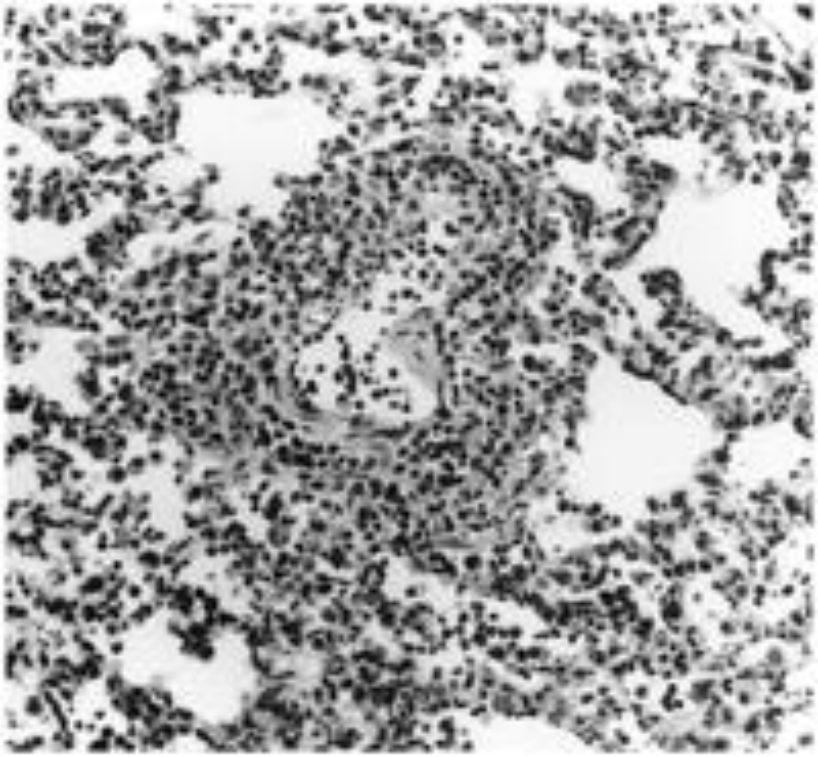
Rejection

- Acute rejection-
- < 7 days onset
- low grade fever, dyspnoea
- CXR- 1) Clear
  2) illdefined infiltrates
  3) pleural effusion
- reduced FEV1

Acute rejection

- **TBLB -** gold standard in diagnosis
- Treatment- bolus I.V. steroids + increase in maintenance immunosuppression
- role of surveillance bronchoscopy to detect rejection early is controversial

Acute lung rejection



- **Characterized by perivascular mononuclear cell infiltrates with extension into the adjacent alveolar septa**

Chronic rejection

- **Bronchiolitis Oblitrans Syndrome (BOA) :**

- Predominantly a small airway disease
- occurs in 50% patients surviving for 5 years
- onset > 6months
- major cause of mortality
- CXR- can be normal, late cases- bronchiectesis
- HRCT- mottled appearance with peripheral lucency

➢ **TBLB- gold standard**

- Role of induced sputum & BAL-

1) Induced sputum – RANTES levels and eosinophils correlate with BOS development

2) BAL- IL8 & neutrophil levels have negative correlation

Immunosuppressive therapy

- Majority receive a triple-drug maintenance regimen
  - calcineurin inhibitor (either cyclosporine or tacrolimus),
  - cell-cycle inhibitor (either mycophenolate mofetil or azathioprine)
  - steroids.

Immunosuppression

- The first-line treatment of an episode of acute rejection is high-dose intravenous steroid pulses.
- For recurrent acute rejection, the strategy is to switch from cyclosporine to tacrolimus.

Post-op. Management

Antimicrobial therapy

- Bacterial prophylaxis
- HSV prophylaxis → Acyclovir
- PCP → Cotrimoxazole
- Candida → Nystatin
- CMV -- Ganciclovir

Prognosis

- Mortality rate is higher for patients with primary pulmonary hypertension, idiopathic pulmonary fibrosis, or sarcoidosis and lower for those with COPD or α1-antitrypsin deficiency.

- Mortality risk factors include cytomegalovirus mismatching, human leukocyte antigen mismatching, diabetes, and prior need for mechanical ventilation or inotropic support.

- Exercise capacity has been the most interesting functional outcome observes in lung transplant recipient .
- Typically transplant recipient can walk 100 to 120m/min within 6 months of transplantation.


Thank You!

Heart transplantation

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- DEFINITION
- Cardiac transplantation is a therapeutic procedure whereby the heart of a suitable donor is implanted into a recipient

- Carrel and Guthrie first reported successful heterotopic cardiac transplantation in dogs in 1905
- 1933 Mann and colleagues at Mayo Clinic reported successful transplantation of the heart into the neck of dogs.
- Medawar was the first to develop concepts of immunology applicable to transplantation.
- Lower and Shumway first reported successful experimental orthotopic cardiac transplantation in 1960.
- Orman Shumway is widely regarded as the father of heart transplantation although the world's first adult human heart transplant was performed by a South African cardiac surgeon,**Christiaan Barnard**, utilizing the techniques developed and perfected by Shumway and Richard Lower.

- In 1964, Hardy and colleagues performed the first heart transplant into a human, using a chimpanzee heart.
- The first human-to-human heart transplant (allograft) was performed in Cape Town South Africa, by Christiaan Barnard on December 3, 1967.

The recipient was Louis Washkansky, a 53-year-old ex-boxer with end-stage ischemic cardiomyopathy

- Barnard performed the third human heart transplant on Philip Blaiberg, a 46-year-old dental surgeon with refractory heart failure, severe coronary artery disease, and a large left ventricular aneurysm.
- He became the first long-term survivor, living for 18 months. Norman Shumway performed the fourth heart transplant 4 days later, and this patient died 2 weeks later.

- By the early 1970s, cardiac transplantation had largely disappeared from clinical practice.
- The report of Caves and colleagues describing a method of transvenous endomyocardial biopsy was an important clinical advance because it allowed monitoring cardiac allograft rejection on a serial basis

DENTON COOLEY AND CARDIAC TRANSPLANTATION

Figure 6.18. Denton Arthur Cooley.

- Denton Arthur Cooley (born August 22, 1920) is an American heart surgeon famous for performing the first implantation of a total artificial heart.
- Cooley had by far the largest experience.
- DeBakey, Cooley, and Shumway, had treated two dozen patients; of them thirteen were alive in 1970s.

Indications for heart transplantation

The ACC/AHA guidelines include the following indications for cardiac transplantation:

1.Refractory cardiogenic shock requiring intra-aortic balloon pump counterpulsation or left ventricular assist device (LVAD);

2.Cardiogenic shock requiring continuous intravenous inotropic therapy (i.e., dobutamine, milrinone, etc.);

3.Peak VO2 (VO2max) less than 10 mL/kg per min;

4.NYHA class of III or IV despite maximized medical and resynchronization therapy;

5.Recurrent life-threatening left ventricular arrhythmias despite an implantable cardiac defibrillator, antiarrhythmic therapy, or catheter-based ablation;

6.End-stage congenital HF with no evidence of pulmonary

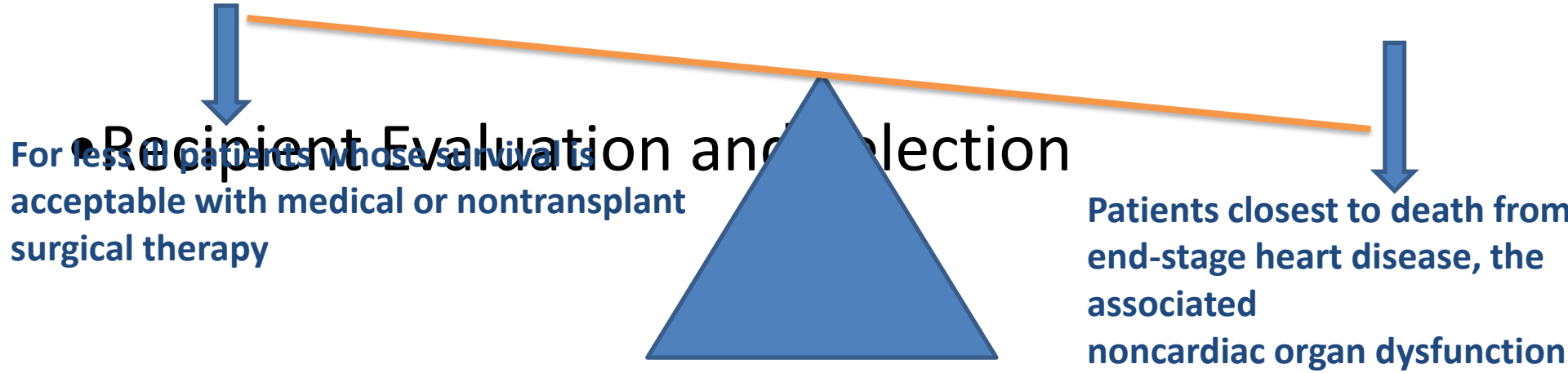
ESC: Features that must be met before consideration for heart transplant which are more specific and include, functional, structural and symptoms parameters:

1. Severe symptoms, with dyspnea at rest or with minimal exertion (NYHA class III or IV);
2. Episodes of fluid retention (pulmonary or systemic congestion, peripheral edema) or of reduced cardiac output at rest (peripheral hypoperfusion);
3. Objective evidence of severe cardiac dysfunction (at least one of the following):

- Left ventricular ejection fraction less than 30%,
- Pseudonormal or restrictive mitral inflow pattern on Doppler echocardiography,
- High left and/or right ventricular filling pressure
- Severely impaired functional capacity demonstrated by one of the following: inability to exercise, 6-minute walk test distance less than 300 m (or less in women or patients who are age 75 and older), or peak oxygen intake less than 12 to 14 mL/kg/min;

4. One or more hospitalizations for HF in the past 6 months.

•Recipient Evaluation and Selection



For less ill patients whose survival is acceptable with medical or nontransplant surgical therapy

Patients closest to death from end-stage heart disease, the associated noncardiac organ dysfunction

If patients were selected primarily on the basis of highest expected posttransplant survival and quality of life at 1, 5, and 10 years, transplantation would be recommended

Decision making is important why?

1.Supply of organs is inadequate

2.Allocation of a donor heart to a patient with a relatively better prognosis would deprive a more seriously ill patient with a short life expectancy (but preserved noncardiac organ function) the opportunity for transplantation at a time when his or her benefit would still be maximal, and

3.Cardiac transplantation is not curative, is associated with its own chronic morbidity and survival limitation, and should therefore not be offered to patients with intermediate- or long-term survival approaching that of transplantation.

Current Recipient Status Criteria of the United Network for Organ Sharing (UNOS)*

Status IA

A. Patients who require mechanical circulatory assistance with one or more of the following devices:
   1. Total artificial heart
   2. Left and/or right ventricular assist device implanted for 30 days or less
   3. Intra-aortic balloon pump
   4. Extracorporeal membrane oxygenator (ECMO)

B. Mechanical circulatory support for more than 30 days with significant device-related complications

C. Mechanical ventilation

D. Continuous infusion of high-dose inotrope(s) in addition to continuous hemodynamic monitoring of left ventricular filling pressures

E. Life expectancy without transplant less than 7 days

Status IB

A. A patient who has at least one of the following devices or therapies in place:
   1. Left and/or right ventricular assist device implanted for more than 30 days
   2. Continuous infusion of intravenous inotropes

Status II

All other waiting patients who do not meet status Ia or Ib criteria

Absolute contraindications

1.Systemic illness with a life expectancy 2 y despite HT, including Active or recent solid organ or blood malignancy within 5 y (eg. leukemia, low-grade neoplasms of prostate with persistently elevated prostate-specific antigen)

2.AIDS with frequent opportunistic infections

3.Systemic lupus erythematosus, sarcoid, or amyloidosis that has multisystem involvement and is still active

4.Irreversible renal or hepatic dysfunction in patients considered for only HT

5.Significant obstructive pulmonary disease (FEV1 1 L/min)

6.Fixed pulmonary hypertension

- Pulmonary artery systolic pressure 60 mm Hg
- Mean transpulmonary gradient 15 mm Hg

Donor selection

- Brain death is a hostile environment for the donor heart that undoubtedly contributes to the occurrence of primary graft failure (PGF) after HT.

Matching Donors & Recipients

- **Matching is based upon:**

  ABO blood group

  Body size compatibility (± 20% body weight)

  Antibody screen (PRA)

  No HLA *prospective* matching done unless high levels of pre-formed antibodies on screening (PRA > 10-20%)

- **Allocation is determined by:**

  Recipient's priority on waiting list

    Status code (1A, 1B, 2)

    Time accrued *within* a status

  Geographic location from donor

Matching Donor and Recipient

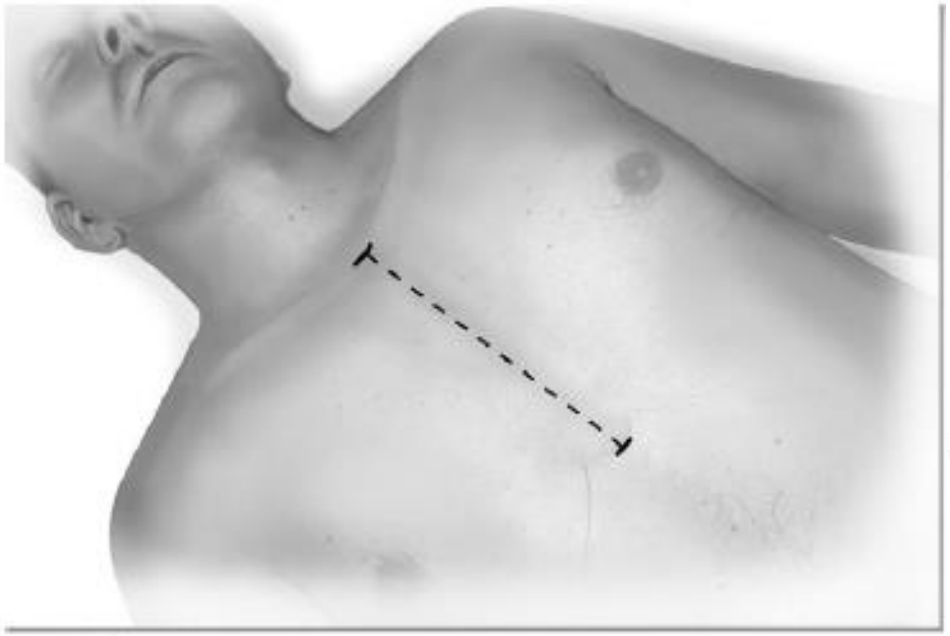
- Because ischemic time during cardiac transplantation is crucial, donor recipient matching is based primarily not on HLA typing but on the severity of illness, ABO blood type (match or compatible), response to PRA, donor weight to recipient ratio (must be 75% to 125%), geographic location relative to donor, and length of time at current status.
- In the renal transplant population, prospective lymphocyte cross-matching is routinely performed; however, prospective donor recipient cross-matching is often not feasible for thoracic transplantation

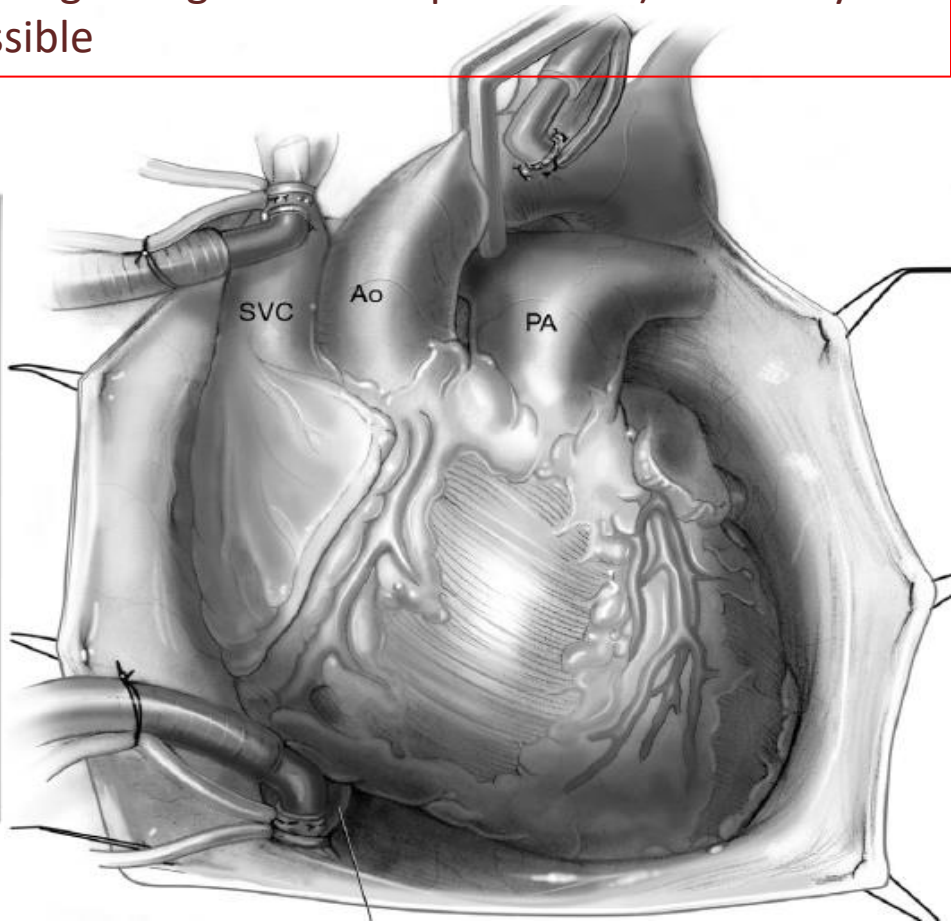
Donor-Recipient Size Matching

- Oversizing of a donor heart can occur
- (1) in pediatric HT when the size of the donor heart for a smaller recipient is misjudged;
- (2) when the native heart disease does not result in cardiomegaly and a larger donor heart is implanted; or
- (3) after multiple previous operations resulting in rigidity of the mediastinum despite maneuvers such as opening the left side of the pericardium to allow the donor heart to protrude into the left pleural space.
- These situations may be associated with inability to close the chest without hemodynamically important cardiac compression.
- Severe undersizing is also an important issue, since a small donor heart may be unable to support the circulation of a much larger recipient. Making the determination of the adequacy of the size of a donor for a specific recipient and judgment is required.

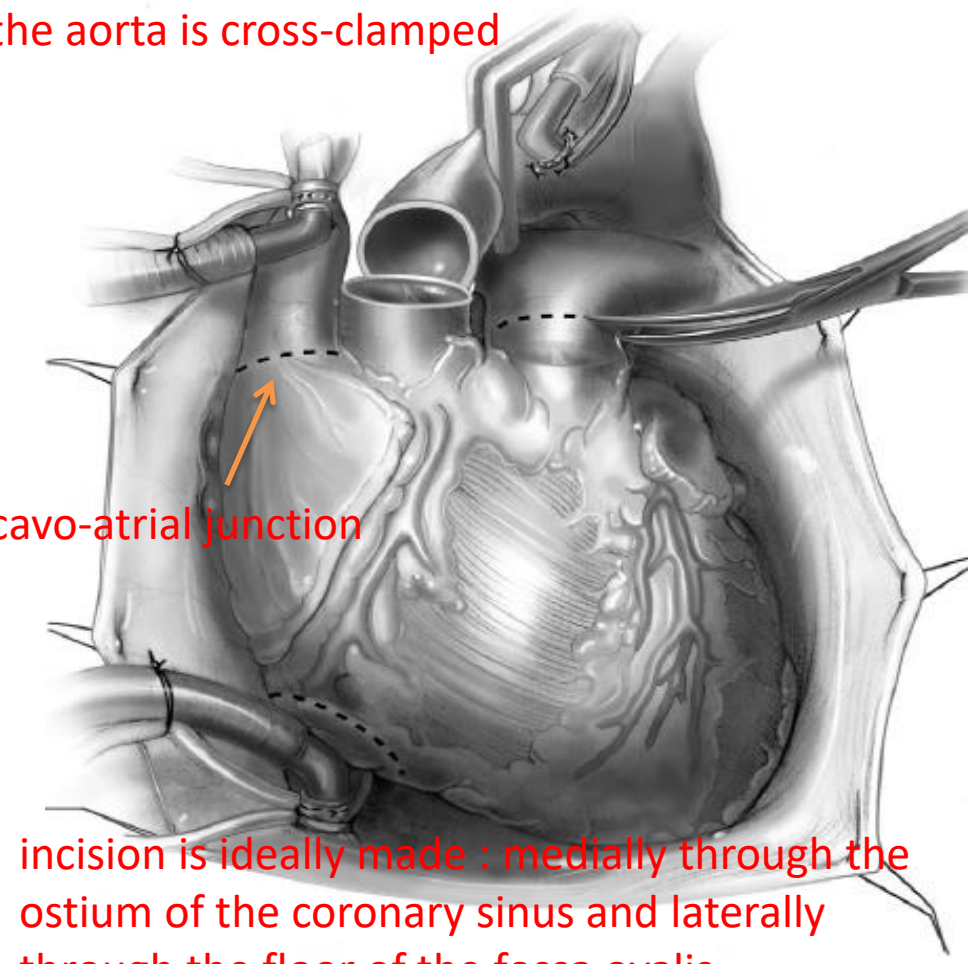
- Determination of donor/recipient size match is complicated by the poor relationship between echocardiographic adult heart size and body weight.
- As a general rule, the donor weight should be within 30% of the recipient weight for adults.
- However, in non-urgent recipients survival was not adversely affected by undersizing of donor hearts up to a donor to recipient body weight ratio of 0.8.
- In contrast, survival was inferior in UNOS status 1 recipients, if they received an undersized heart presumably due to a smaller cardiac reserve.

Standard median sternotomy is Performed	The vena cavae are also cannulated (preferably with right-angled metal tip cannulas) as distally as possible





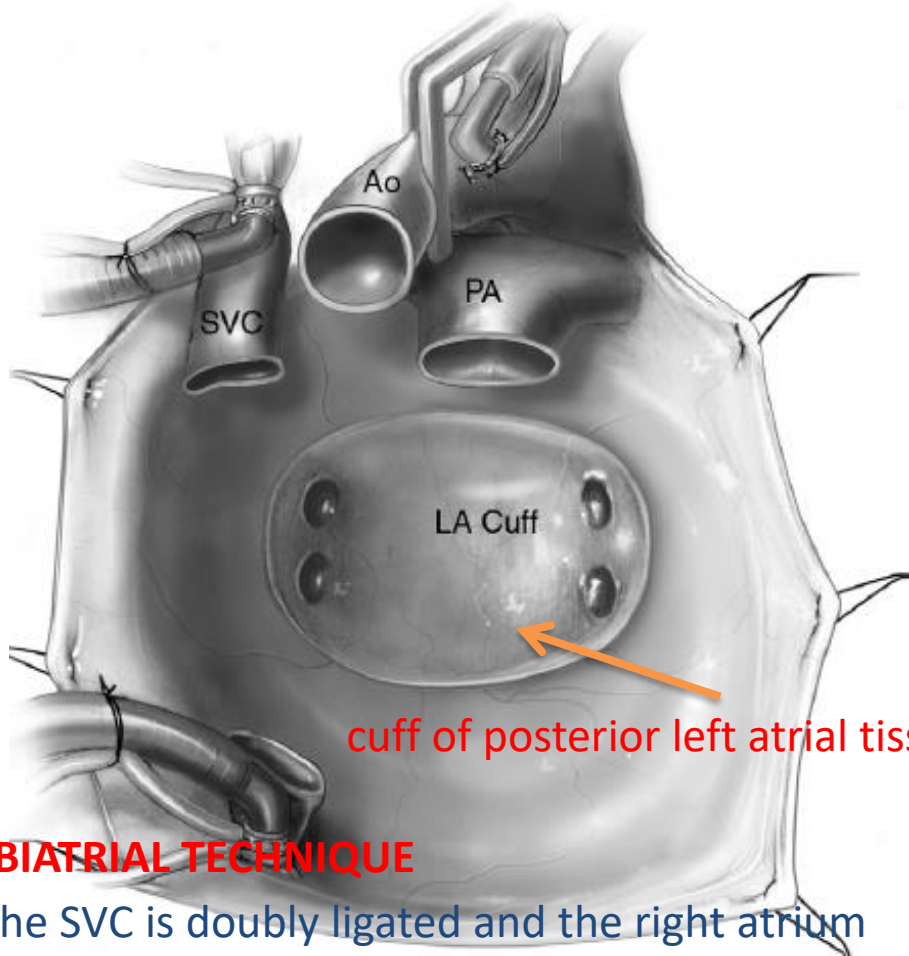
Recipient cardiectomy



the aorta is cross-clamped

cavo-atrial junction

incision is ideally made : medially through the ostium of the coronary sinus and laterally through the floor of the fossa ovalis



cuff of posterior left atrial tis

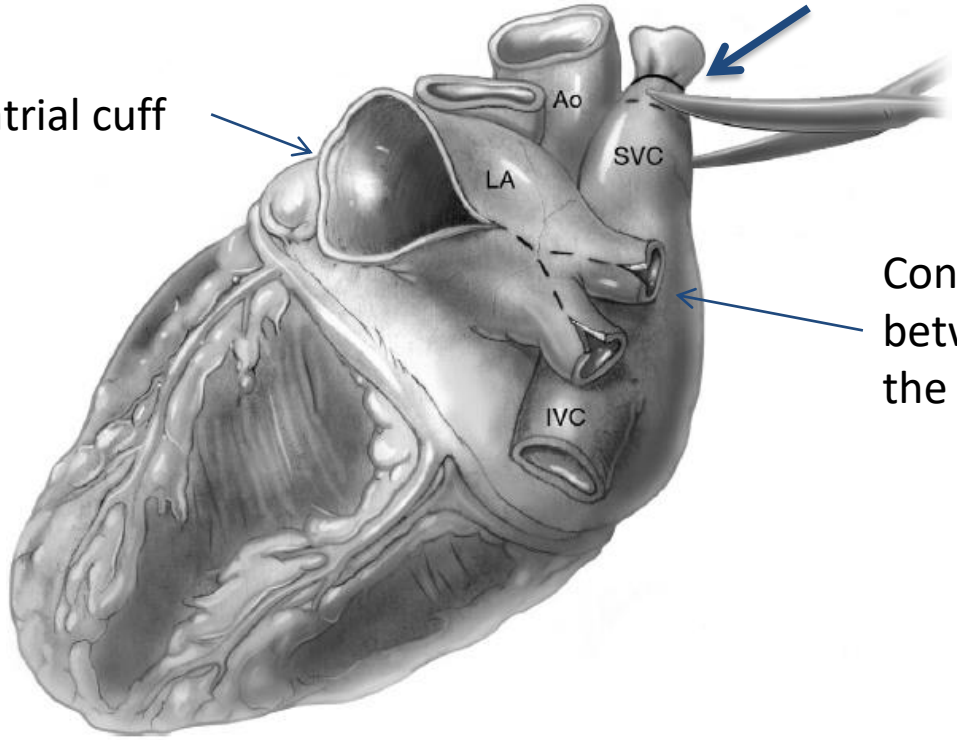
BIATRIAL TECHNIQUE

The SVC is doubly ligated and the right atrium is opened from the lateral IVC toward the right atrial appendage, to avoid the sinus node

Donor heart

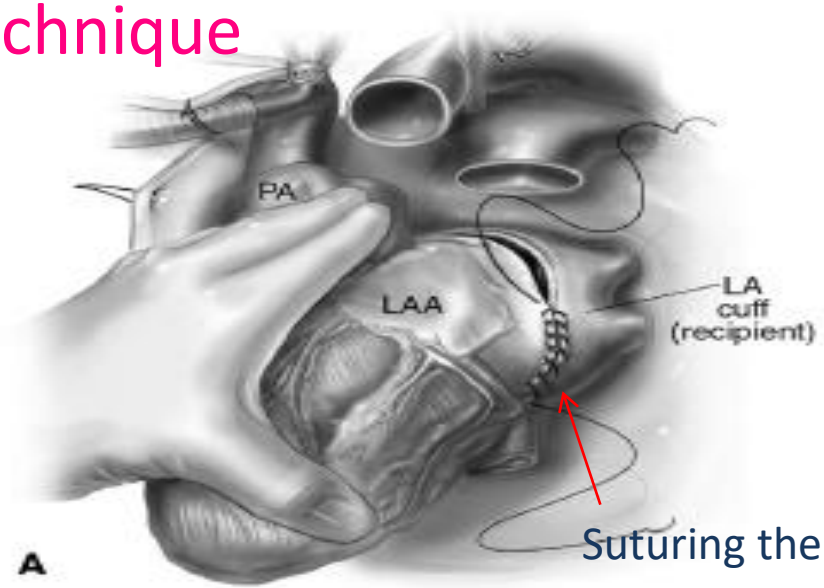
The superior vena caval cuff is trimmed at the level of the azygous vein opening and more if adequate recipient cuff is present

The left atrial cuff

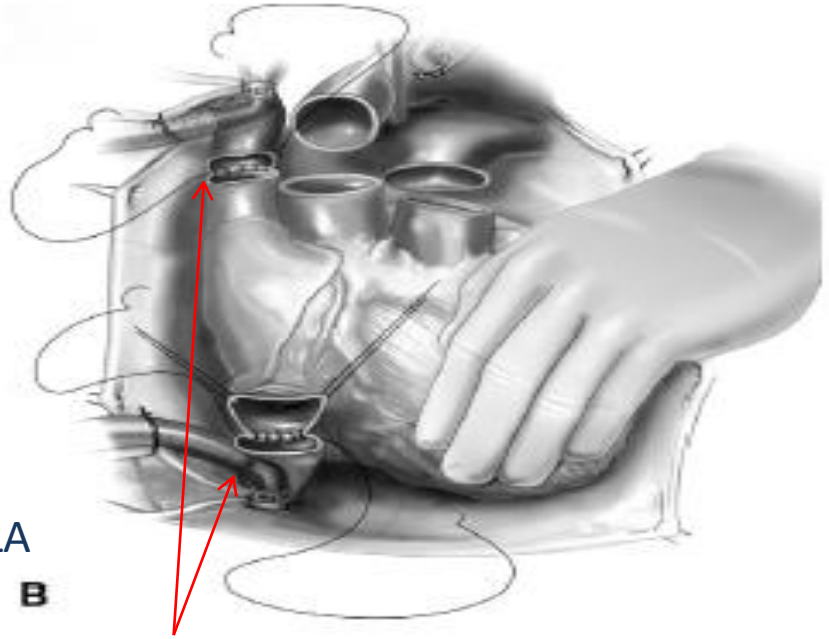


Connecting incisions between each of the 4 pulmonary veins

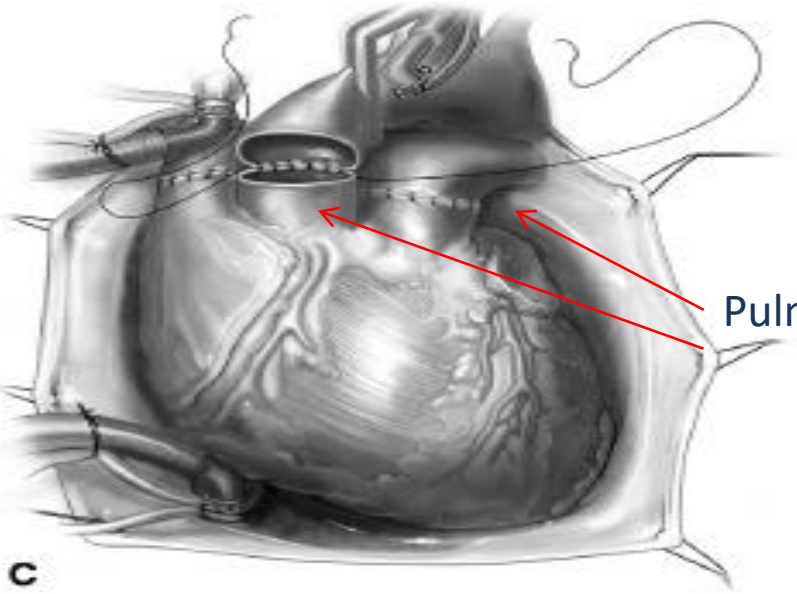
Orthotopic heart transplantation: bicaval anastomosis technique



Suturing the LA

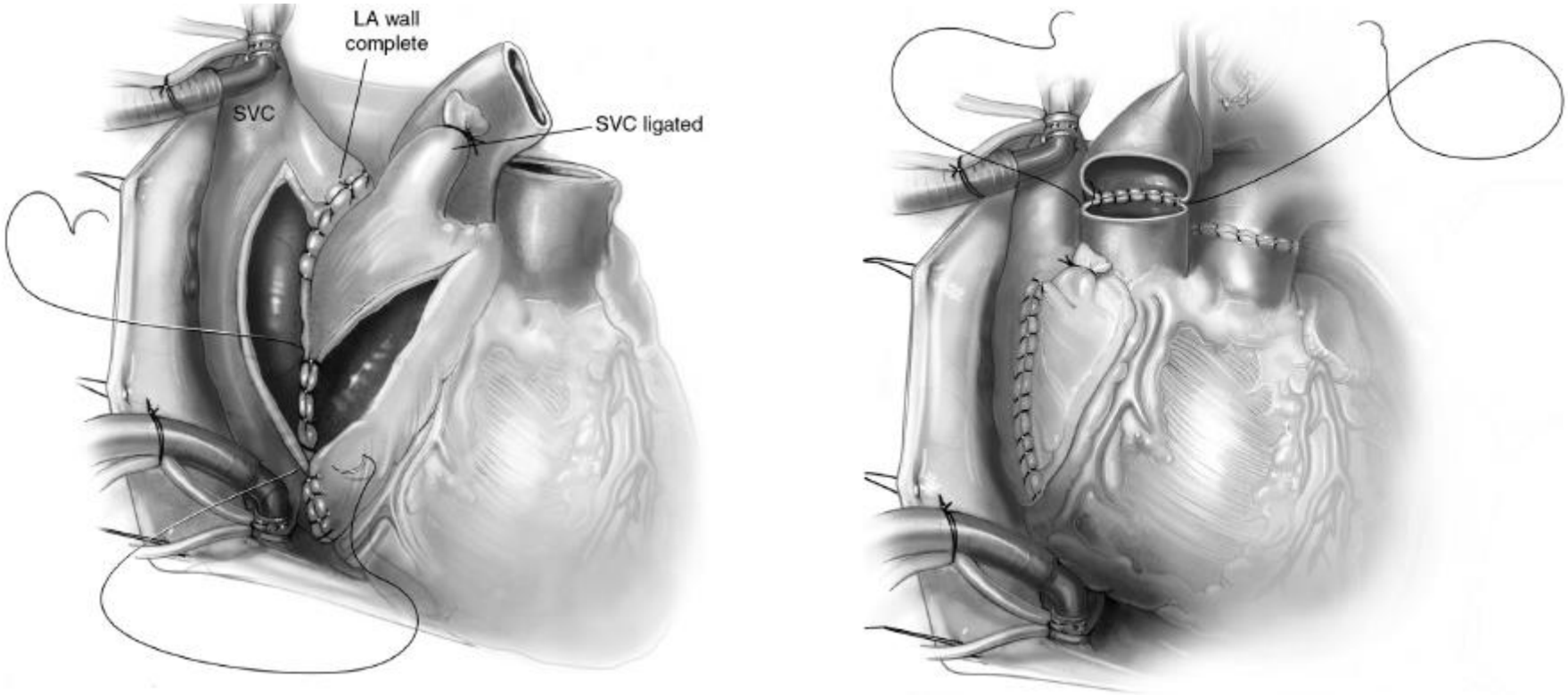


Superior and inferior vena caval anastomosis

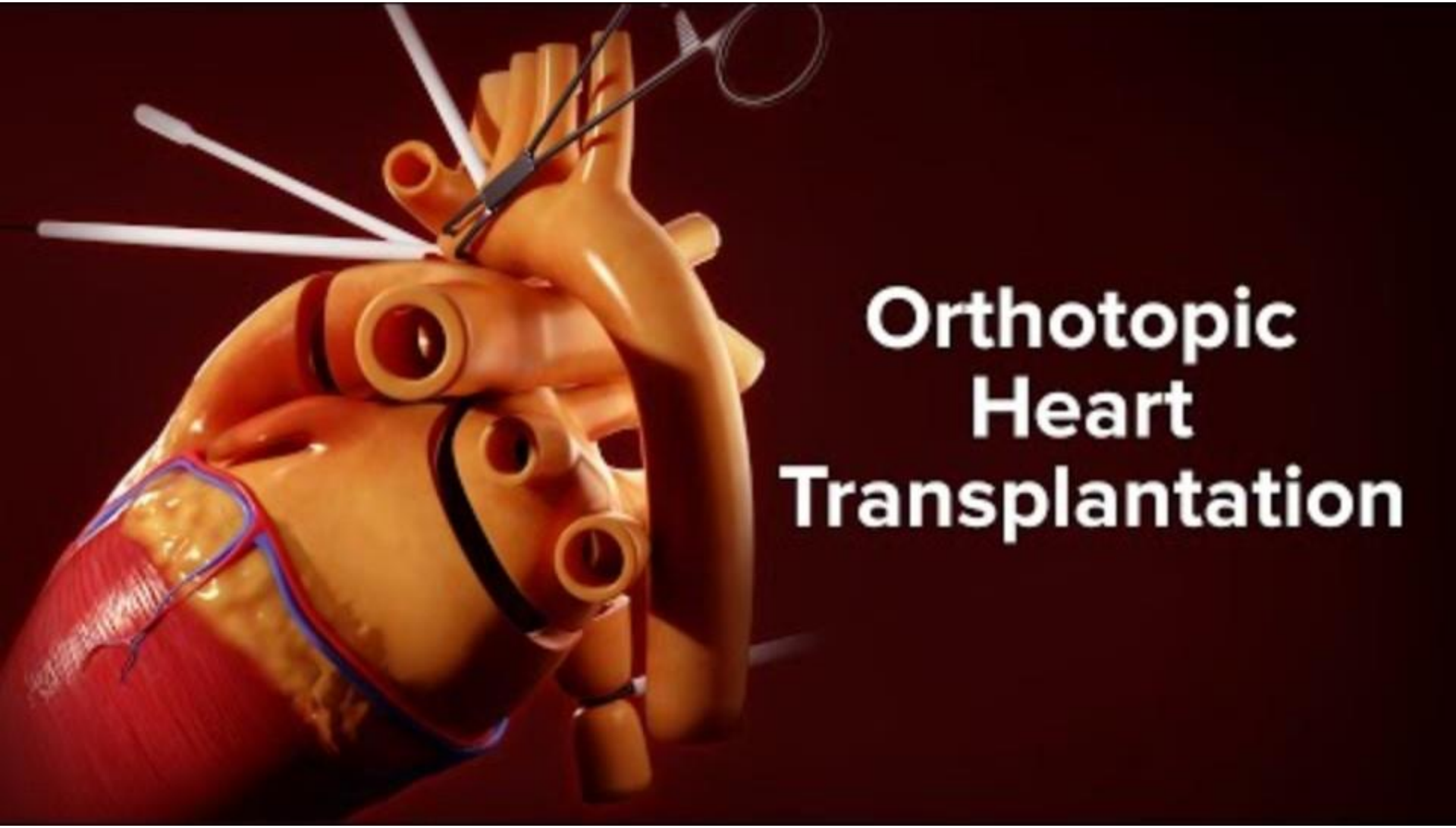


Pulmonary artery and aortic anastomosis.

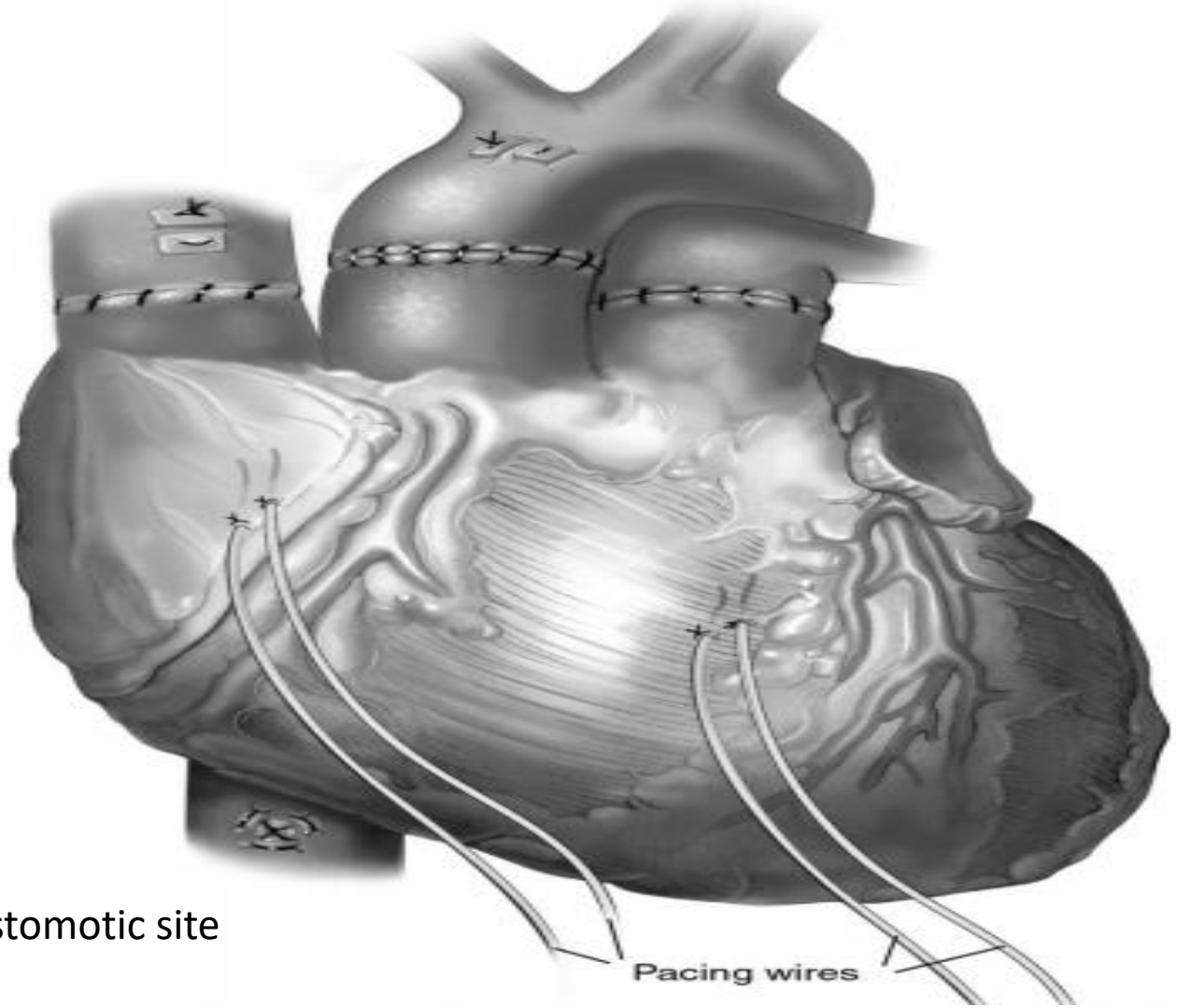
Orthotopic heart transplantation: biatrial anastomosis technique



The right atrial anastomosis is initiated at the superior end of the atrial incision. A long 3-0 Prolene suture is used and the suture ends are carried both inferiorly and superiorly to first complete the septal anastomosis, and then they are joined at the lateral wall of the septum.


Orthotopic
Heart
Transplantation

Completed orthotopic heart transplantation



Reperfusion
Look for LA anastomotic site bleed
RA RV site
Inotropic support
Vasodilators

Post transplant physiology

- Cardiac denervation is an inevitable consequence : a denervated donor heart.
- The atrial remnant of the recipient remains innervated, but no impulses will cross the suture line.
- As a result, the donor atrium is responsible for heart rate generation.
- The transplanted heart has a higher intrinsic rate and reduced rate variability.
- Resting heart rates range from 90 to 110 beats per minute.
- Normal responses to changes in position, e.g. orthostatic changes, are lost as are the variations in response to stimuli such as the Valsalva manoeuvre, carotid sinus massage.

Primary Graft Failure and Right Ventricular Dysfunction.

- Primary graft failure after HT is the presence of severe mechanical dysfunction without obvious anatomic (surgical) or immunologic causes such as hyperacute rejection.
- Primary graft failure has been variably defined in the literature as heart allograft dysfunction requiring 2 or more inotropes, or the need for mechanical circulatory support, either with an IABP or a VAD within 24 hours of HT.
- The true prevalence, therefore, depends upon the criteria used for diagnosis, but estimates range from approximately 1.4% to 30.7%.82, 83, 96-100
- It is important to recognize that PGF can result in RV, LV, or biventricular failure.

Immunosuppression

- Three situations require specific combinations of immunosuppressive therapies:
- (1) *initial* high-dose immunosuppression to facilitate graft acceptance, minimize the chance of early rejection, and potentially favour induction of tolerance;
- (2) *maintenance* therapy for chronic acceptance of the allograft; and
- (3) *augmented* immunosuppression to reverse episodes of acute rejection.

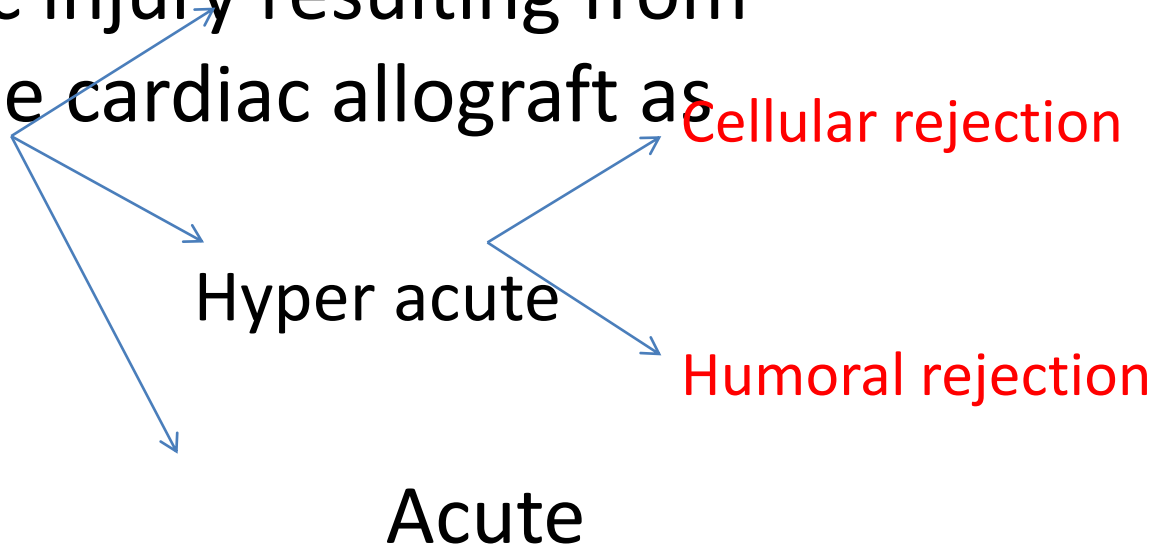
- Maintenance immunosuppression
- Three main group of drugs
- 1. steroids
- 2. calcineurin inhibitors
- 3. antiproliferative drugs

Table 2 Maintenance Regimens Used In Heart Transplantation

Regimens*	Indication or Characteristic
Calcineurin inhibitor and mycophenolate mofetil	Most common regimen used; older transplant patients may still be on a calcineurin inhibitor and azathioprine combination
Calcineurin inhibitor and proliferation signal inhibitor	Regimen often considered in patients with established allograft vasculopathy or malignancy
Mycophenolate mofetil and proliferation signal inhibitor	Calcineurin-free regimen considered in patients with severe renal insufficiency
Tacrolimus monotherapy	Preliminary data suggest the safety of tacrolimus monotherapy in heart transplantation (45)

TICTAC trial

- Rejection
- Rejection involves cell- or antibody-mediated cardiac injury resulting from recognition of the cardiac allograft as non-self.
- Three types



- *Acute* cellular rejection or cell-mediated rejection is a mononuclear inflammatory response, predominantly lymphocytic, directed against the donor heart;
- It is most common from the first week to several years after transplantation, and it occurs in up to 40% of patients during the first year after surgery.

- The key event in both the initiation and the coordination of the rejection response is T cell activation, moderated by interleukin-2, a cytokine.
- Interleukin-2 is produced by CD4+ cells and to a lesser extent by CD8+ cells and exerts both an autocrine and a paracrine response.
- The endomyocardial biopsy remains the gold standard for the diagnosis of acute rejection.

- ***Identifying a Rejection Episode:***
- A major part of care after cardiac transplantation is directed toward identifying rejection.
- Endomyocardial biopsy remains the most important method of identification and, along with echocardiographic evaluation, is generally performed every 7 days for the first 4 to 6 postoperative weeks.
- Biopsy frequency is gradually reduced to every 3 to 4 months.
- Subltle symptoms that include unexplained fever, joint pain, personality change, and any symptom that can result from cardiac failure are an indication for emergency endomyocardial biopsy and immediate institution of therapy if results are positive.

- Mild rejection does not require specific intervention.
- Moderate rejection usually requires some degree of intensification of immunosuppression, which generally includes an oral or intravenous bolus of corticosteroid, and an increase in regular therapies.
- Any rejection with haemodynamic compromise requires haemodynamic support commensurate with the clinical presentation, and aggressive intensification of immunosuppression.

Box 21-20 Therapeutic Strategy for Rejection with Hemodynamic Compromise

- Always consider this a life-threatening event
- Methylprednisolone 1 g IV and daily for 3 days
- Prompt inotropic support (preferably with dopamine, milrinone, or dobutamine, depending on blood pressure and heart rate)[a] to maintain effective cardiac output
- If cardiac output is clinically depressed and/or there is more than mild decrease in ejection fraction (<35%), place Swan-Ganz catheter for hemodynamic monitoring
- Prompt plasmapheresis (patients > 15 kg) and daily for 3 days
- Cytolytic therapy with thymoglobulin or OKT3
- Heparinize
- Continue maintenance immunosuppression[b]
- Schedule photopheresis[c]

- 1 to 8 pulses of intra venous methylprednisolone in doses of 10 – 20 mg/kg each.
- Persistent rejection may need biological immune modulators such as ATG or anti CD3 monoclonal antibodies(OKT3).
- Reccurent refractory episodes may respond to tacrolimus (0.1mg /kg /day).

- Antibody-mediated rejection is a serious complication after heart transplantation and is manifested as “graft dysfunction” or hemodynamic abnormalities in the absence of cellular rejection on biops
- Patients at greatest risk for antibody-mediated rejection are women and patients with a high PRA level or a positive crossmatch.
- It is estimated that significant antibody-mediated rejection occurs in about 7% of patients, but the rate may be as high as 20%.

- *Chronic* rejection, or late graft failure, is an irreversible gradual deterioration of graft function that occurs in many allografts months to years after transplantation
- The current concept suggests that donor heart dysfunction in the chronic stages of maintenance immunosuppression is either related to chronic rejection mediated by antibodies, or a result of progressive graft loss from ischemia.

Complications

Infection

- Infections cause approximately 20% of deaths within the first year after transplantation and continue to be a common contributing factor in morbidity and mortality throughout the recipient's life.

The most common infections in the first month after surgery are nosocomial bacterial and fungal infections related to mechanical ventilation, catheters, and the surgical site

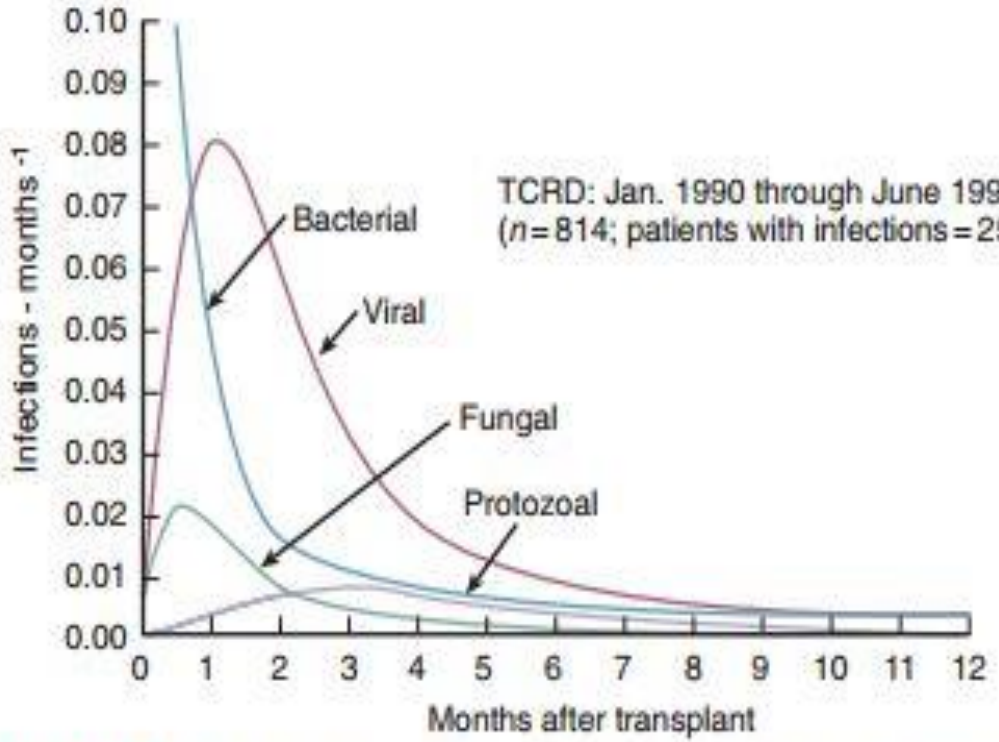


Figure 21-15 Hazard function (instantaneous risk over time) for first infection of each major category of infectious agent. Key: *TCRD*, Transplant Cardiologists Research Database. (From Miller and colleagues.[M12])

- Mortality is highest for fungal infections, followed by protozoal, bacterial, and viral infections.
- Aspergillosis and candidiasis are the most common fungal infections after heart transplantation.
- Viral infections, especially those due to cytomegalovirus, can enhance immunosuppression, potentially resulting in additional opportunistic infections.
- *Pneumocystis jirovecii,* and herpes simplex virus infections and oral candidiasis, to be used during the first 6 to 12 months after transplantation.
- Prophylactic intravenous ganciclovir or oral valganciclovir generally is given for variable periods in cytomegalovirus-seronegative recipients of a transplant from a cytomegalovirus-positive donor.

Table 21-13 Infection Prophylaxis after Heart and Heart-Lung Transplantation (UAB)

Infectious Complication	Prophylaxis (Adult Dosages)
Perioperative wound and line sepsis	Vancomycin 15 mg·kg^{-1} preoperatively, then 10 mg·kg^{-1} every 8 hours × 4 days Ceftazidime 15 mg·kg^{-1} preoperatively, then 1 g every 8 hours × 4 days
Pneumocystis carinii	Trimethoprim/sulfamethoxazole 1 daily (1 year); for patients allergic to sulfonamides, dapsone 50 mg daily (1 year) or pentamidine 300 mg via nebulizer every month (1 year)
Mucocutaneous candidiasis	Topical, nonabsorbable antifungal (nystatin) 500,000 units three times daily (6 months)
Toxoplasmosis: Recipient negative, donor positive	Pyrimethamine 25 mg daily and leucovorin 10 mg daily (6 months); serology is checked at 3 months, 6 months, and 1 year
Cytomegalovirus[a]: Recipient negative, donor positive Recipient positive, donor positive Recipient negative, donor negative	Valganciclovir 900 mg daily PO × 3 months, then acyclovir 200 mg 3 times daily PO × 1 year Other option in addition to above: CytoGam 150 mg·kg^{-1} IV within 72 hours after transplant, then every 2 weeks × 4 doses, then 100 mg·kg^{-1} IV every 4 weeks × 2 doses (round dose to nearest 2500)
After cytolytic therapy	Acyclovir 200 mg PO 3 times daily × 1 year Valganciclovir 900 mg daily PO × 6 weeks
Epstein-Barr virus (EBV): Recipient negative, donor positive	EBV IgM IgG serologies are checked at 6 weeks, 3 months, and every 3 months for the first year and then every 6 months until seroconversion; at seroconversion, patient is treated with IV ganciclovir (6 weeks), then ganciclovir 1 g 3 times daily PO for 6 months, then acyclovir 200 mg PO 3 times daily for 6 months[b]
Herpes simplex 1 and 2	Acyclovir 200 mg PO 3 times daily (6 months)[c]

From Kirklin and colleagues.[814]

[a]Cytomegalovirus antigenemia test obtained monthly for the first 5 months after transplant.

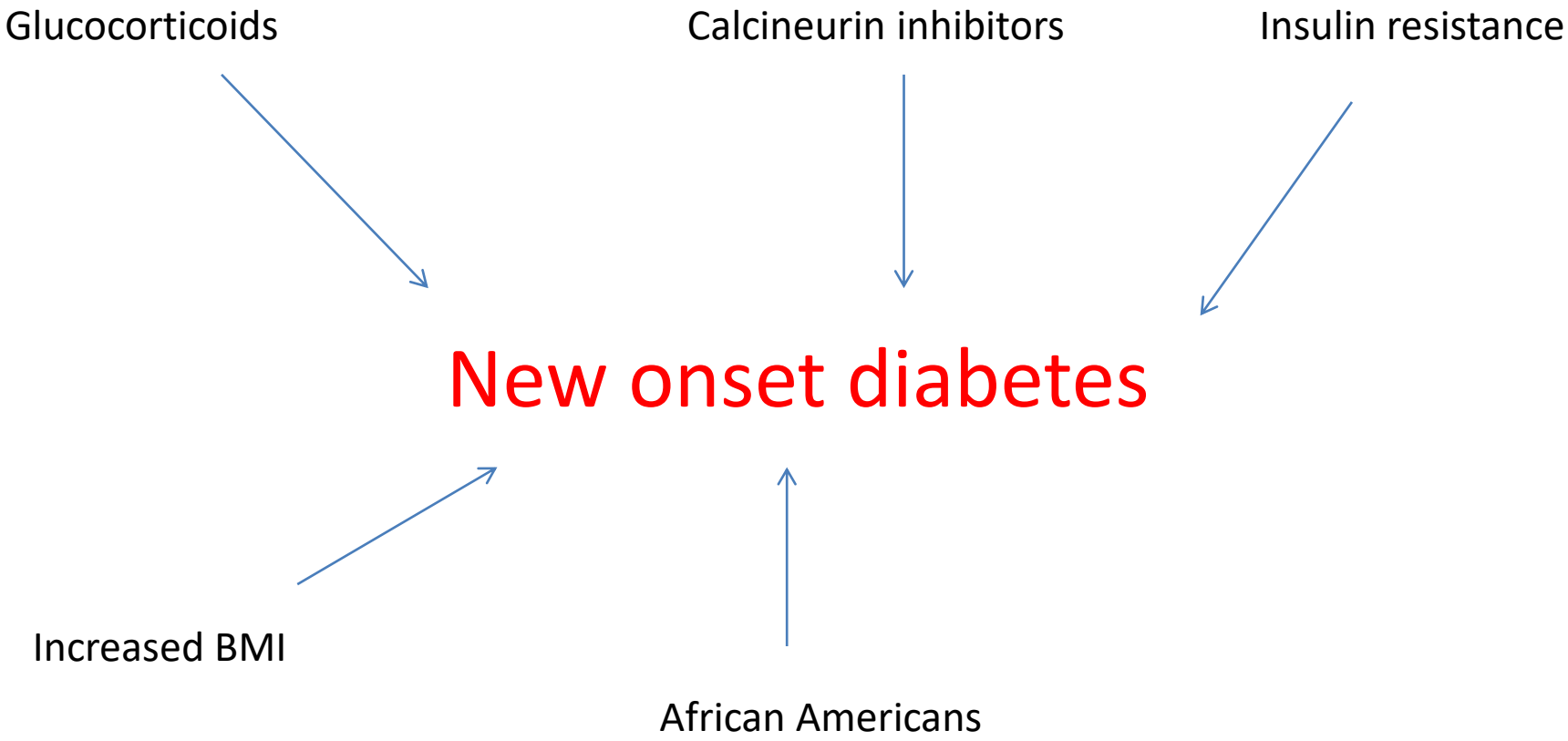
[b]Dose is adjusted according to renal function.

[c]Acyclovir is held during administration of ganciclovir.

Key: *IV*, Intravenous; *PO*, orally.

TABLE 28-5 Post–Heart Transplantation Morbidity for Adult Patients*

OUTCOME	WITHIN 5 YEARS	TOTAL NO. OF PATIENTS WITH KNOWN RESPONSE	WITHIN 10 YEARS	TOTAL NO. OF PATIEN WITH KNOWN RESPON
Hypertension	93.8%	8266	98.5%	1586
Renal dysfunction	32.6%	8859	38.7%	1829
Abnormal creatinine <2.5 mg/dL	21.2%		24.4%	
Creatinine >2.5 mg/dL	8.4%		8.2%	
Chronic dialysis	2.5%		4.9%	
Renal transplantation	0.5%		1.2%	
Hyperlipidemia	87.1%	9237	93.3%	1890
Diabetes	34.8%	8219	36.7%	1601
Cardiac allograft vasculopathy	31.5%	5944	52.7%	896



Patient survival and graft survival, may be adversely affected

Renal Insufficiency

Hypertension

- The excess risk of hypertension is related primarily to the use of
- Calcineurin inhibitors because of both direct effects of the drugs on the kidney and the associated renal insufficiency that also is highly prevalent. The incidence of hypertension may be lower with tacrolimus than with cyclosporine
- Post-transplantation hypertension is difficult to control and often requires a combination of several antihypertensive agents..

Hyperlipidemia

- Typically,
- total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides increase by 3 months after transplantation and then
- generally fall somewhat after the first year.
- Cyclosporine increases serum LDL cholesterol and binds
- to the LDL receptor, decreasing its availability to absorb cholesterol
- from the bloodstream.

- **Malignancy**
- Neoplastic disorders after cardiac transplantation arise from three major causes: preexisting malignancies, transmission of malignancy from donor to recipient, and de novo malignancy arising after transplantation.
- Tumors most likely to recur in heart transplant recipients are carcinoma of the lung, lymphoma, skin cancer, and carcinoma of the bladder
- The incidence of de novo recipient malignancy is approximately 100 times that of the non–age-

- Cardiac allograft vasculopathy: annual incidence rate of 5% to 10%.
- CAV is detectable by angiography in 8% of survivors within the first year, in 32% within the first 5 years, and in 43% within the first 8 years after HTx.
- Severe CAV is positively correlated with persistent inflammation and a higher degree of HLA mismatch.

- In contrast with eccentric lesions seen in atheromatous disease, CAV results from neointimal proliferation of vascular smooth muscle cells, so that it is a generalized process.
- Characterized by concentric narrowing that affects the entire length of the coronary tree, from the epicardial to the intramyocardial segments, leading to rapid tapering, pruning, and obliteration of third-order branch vessels

- The first clinical manifestation of CAV may be myocardial ischemia and infarction, heart failure, ventricular arrhythmia,or sudden death.
- Angina is rare because of denervation of the heart.

- Invasive Detection of CAV
- Intravascular Ultrasound Intravascular ultrasound (IVUS) is the most sensitive tool for the diagnosis of CAV. IVUS allows a reproducible view of both actual lumen diameter and the appearance and thickness of the intima and media
- Rapidly progressive CAV, defined as an increase of 0.5 mm in maximal intimal thickness within the first year after HTx, is associated with a significantly increased risk of all-cause death, myocardial infarction, and the subsequent development of angiographically severe CAV

- **Coronary Angiography**
- Coronary angiography is still the standard for the diagnosis of CAV in most transplant centers, and the angiographic detection of significant epicardial coronary stenoses conveys a poor prognosis.
- CAV is detectable by angiography in 30% to 50% of HTx survivors after 5 years

- **Single-Photon Emission CT**
- Annual myocardial single-photon emission CT (SPECT) has a high negative predictive value and appears to be well suited to screening for significant CAV.
- **Multidetector CT**
- MDCT with adaptive multisegment reconstruction has a sensitivity and specificity of 86% and 99%, respectively

- **Biomarkers and Gene Profiling**
- Elevated C-reactive protein concentrations are associated with progression of CAV,
- Whereas persistently elevated levels of troponin I are associated with a significantly increased risk for subsequent development of CAV.
- The clinical use of brain natriuretic peptide (BNP) levels as a predictor of survival after HTx remains controversial.

- **Therapeutic Options**
- Statins
- Vasodilators
- Endothelial Protection
- Infection and CAV (CMV INFECTION)
- Immunosuppression: mTOR inhibitors

- The use of everolimus from the time of HTx has shown to preserve the coronary artery lumen at 1 year.

- FUTURE PERSPECTIVES
- Need for improved immunosuppression with less rejection, cardiac allograft vasculopathy and side effects
- Need for better non-invasive methods to detect acute and chronic rejection
- Need to focus on improved survival and quality of life
- Challenges in performing long-term adequately powered multi-centered trials

Thank you