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LATEST FRONTIERS of Hemodynamics, Imaging and Treatment of OBSTRUCTIVE VENOUS DISEASE

With the collaboration of
Massimiliano Veroux • Sonia Ronchey

EDIZIONI MINERVA MEDICA

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Preface

This new book, "Latest Frontiers of Hemodynamics, Imaging and Treatment of Obstructive Venous Disease", is a welcome addition to the literature espousing the importance of the role of the venous system in human physiology and the treatment of venous abnormalities. The many authors of this text are leaders in the field and provide a prescient outlook to both current and future technology. The International Society for Neurovascular Disease (ISNVD) recognizes the importance of the coupled vascular and cerebro-spinal fluid (CSF) system in the brain and looks to new advances in these areas. This book offers the insight necessary to help promote future developments in this area.

The last century focused predominantly on the importance of the arterial system and of the detection of obstruction and prevention of the delivery of oxygen to the tissue. However, the venous system plays multiple roles: 1) the delivery of the deoxygenated blood back to the heart; 2) an interface with the CSF *via* arachnoid granulations, and 3) the role of carrying out macromolecules delivered by the CSF that are transported through the venous endothelium. Imaging, and in particular magnetic resonance imaging (MRI), offers the potential to quantify the levels of oxygen in veins, and uses the sensitivity of the MRI signal to the presence of oxygenation and its changes to measure brain function. MRI can also monitor blood flow at a very high resolution as a function of the cardiac cycle, and map out the entire venous system down to the resolutions of 50 microns using high fields. Lastly, MRI can also be used to map CSF flow and diffusion over time. All of these features help to promote a fundamental understanding of the role of the venous system.

This book is composed of two main parts. The first part contains the study and treatment of large veins. Vein anatomy and function are presented as introductory concepts in Chapters 1 to 4. These first four chapters provide the reader with the background required to appreciate the flow and hemodynamics associated with the major veins in the body. Different diseases and treatments are then covered in Chapters 5 to 22. The second part focuses on venous outflow and its dysfunction in several diseases, such as multiple sclerosis and Meniere's disease (Chapters 23 to 28). This same group of chapters also discusses the new condition of chronic cerebrospinal venous insufficiency and brings the field up to date with new findings from ongoing studies. These fundamental advances are presented in terms of modern imaging methods including MRI, ultrasound, computed tomography, plethysmography, and catheter venography.

In summary, over and above the current modern treatments of venous disease discussed in this book, the ability to quantify venous structure and function in a way that can impact treatment is the main focus of this book, which has been designed to provide the reader with a well-rounded and exciting outlook for the future of venous disease understanding and treatment.

E. Mark Haacke, Ph.D.

Foreword

The Editors have written a thorough current review of diagnosis and management of the challenges associated with and focusing on the large veins of the body. The chapters cover a wide variety of subjects and the accompanying references offer the opportunity for further review and study. The accompanying graphic illustrations add additional information and clarification to the written material. The chapter titles allow rapid access to specific areas of interest in the venous system. The contributors are established physicians and surgeons with extensive experience in managing problems in the venous system including clinical research. This is a most timely contribution with increasing world-wide appreciation of the importance of the venous system in maintaining good health.

William Harvey, an Englishman who studied in Italy at Padua University with Fabricius where he earned his Doctor of Medicine in 1602 taught us about circulation in the seventeenth century emphasizing the important role of the venous system. His classic book Motu Cordis was published in 1628. Yet, and particularly in the twentieth century, with the many exciting discoveries in treating problems associated with the arterial system, the venous system was ignored in great part as noted in the United States. This has changed in the past twenty-five years with multiple new efforts through the American Phebological Society and the American Venous Forum increasing and complimenting similar well-established activities in similar societies throughout the whole world.

The Vietnam Vascular Registry established in 1966 at Walter Reed General Hospital in Washington, D.C., USA provided an early emphasis on the repair of large veins, particularly in the lower extremities, rather than the traditionally accepted ligation. The statistics to support the absence of increased thrombophlebitis and of pulmonary embolism with long-term patency assured have resulted in an increased acceptance of this approach.

A study published in 2017 Journal of Vascular Surgery: Venous and Lymphatic Disorders from Johns Hopkins Hospital in Baltimore, Maryland draws attention to the "perceived weakness in venous education in vascular surgery trainees" in the United States. This book will contribute immensely to educate the next generation of physicians and surgeons in the evaluation and treatment of venous disorders.

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Part one

The large veins

1 From anatomy to function of large vein

B.B. Lee, J. Laredo

MACROSCOPIC TO MICROSCOPIC ASPECTS OF VENOUS ANATOMY

Veins are defined as a transportation conduit to carry back the blood toward the heart from tissue, starting from the venules in peripheral tissues and organs to converge to create various sizes of small and then larger veins. The ultimate "large" veins to deliver the blood to the right atrium of the heart is the vena cava, superior and inferior, the largest veins in the human body. These two large veins deliver the blood to the right atrium of the heart from above and below; the superior vena cava (SVC) from the upper extremities and head and neck, the inferior vena cava (IVC) from the lower extremities and abdomen/torso to the heart.[1-4]

However, the microvasculature, so called "venule", which is composed of blood vessels that are smaller than 100 microns only visible through the microscope, is separately grouped as part of the tissue it is connected to, in view of a regulatory function controlling vascular permeability and myogenic responses that can adapt blood flow.[5-7] Only those veins of the macrovasculature, visible with the naked eye, are considered as independent anatomical entities of venous system.[8, 9] Although they both belong to the basic functional unit of the cardiovascular system, they are different structurally and functionally from each other in their architecture and cellular components.

Indeed, small venules are the tubes of endothelium (up to 40-50 μm diameter) surrounded by pericytes, contractile cells, to control blood flows through the microvasculature while large venules (50-100 μm diameter) are surrounded further by one or two layers of smooth muscle cells, and a thin layer of connective tissue beyond the pericytes and the smooth muscle cells.

Hence, the venular endothelium is able to keep a unique anatomical structure of labile junctions/gaps between the cells to "open" under the influence of serotonin, histamine, bradykinin and other agents through inflammatory reactions resulting in increased permeability and subsequent local swelling.

On the contrary, the veins belonging to macrovasculature in general are structurally different from venules; they stay 'collapsible' since they do not encounter high systolic pressure like arteries but low pressure based on "vis-a-tergo" (*i.e.* pushing force acting from behind), the residual arterial pressure transmitted through the capillaries for the venous return.

Such collapsible nature of the conduit is physiologically as well as hemodynamically more ideal for complex venous flow patterns in intermittent nature, varying from high velocity to no flow, and also for the role as "capacitance vessels" containing most (60-70%) of the blood volume as the 'reservoir' of the venous system in addition to its primary function as transport system.[5, 10-12]

The venous volume/flow will be controlled by the delicate balance among transmural pressure, active tone of the muscular media layer and passive compliance of the adventitial layer. Large diameter veins with a high passive compliance and variable venous tone are capable to store blood and also mobilize quite easily by increasing the tone of the venous wall with a low variation of transmural pressure whenever needed.[5, 10]

To meet such natural mandate as illustrated above, they have made of much thinner smooth muscle cell layers in tunica media, the middle layer among three layers of vein wall – tunica interna, media, and externa – in comparison to those of arteries while tunica adventitia/externa, the outer layer of vein wall is made of thick connective tissue. Indeed, veins in small and medium sizes contain only a few layers of smooth muscle cells to compose a thin media although these groups of veins have a much thicker adventitia composed of collagen and some longitudinal smooth muscle fibers occasionally.

Veins of larger diameter have thinner walls than arteries but the tunica adventitia makes up the bigger part of the venous wall so that large veins are considerably thicker in the tunica adventitia than the tunica media in general. Extreme example is IVC which presents with much reduced or absent tunica media and an adventitia with large bundles of longitudinally disposed smooth muscle.

Veins are, therefore, less muscular than arteries in general, sufficient to carry blood back from the tissue to the heart, in contrast to arteries but a new additional structure of one way "valves" evolved in most veins to prevent reflux/backflow throughout systemic venous system in various extents depending upon the location. Valves are usually bicuspid with the leaflets centrally directed of venous blood flow.[13, 14]

Venous valves are present in nearly all of the veins of the lower extremities; in general, the further away from the central circulation, the more frequent a venous valve is present in the venous system. Venous valves are often absent in the iliac veins and inferior vena cava while venous valves are found in the deep and superficial veins and most perforating veins.[5, 10]

However, to meet the special functional needs in certain organs with unique anatomical conditions there are variations in the structure of blood vessels. Pulmonary arteries, for example, have thin walls with a significant reduction in both muscular and elastic elements, while the veins have a well-developed media of smooth muscle cells. Umbilical vessels are another example, to show the vein with a thick muscular wall with two to three muscle layers while the arteries with two layers of smooth muscle cells without a prominent internal elastica or adventitia.

FUNCTIONAL ASPECTS OF VENOUS ANATOMY

Primary function of venous system is to deliver deoxygenated blood from the tissue to the right atrium of the heart for systemic circulation. For the return of blood to the heart, the action of the (calf) muscle pump and the thoracic pump action of breathing during respiration is essential in addition to the residual arterial pressure transmitted through the capillaries for the venous return, so called "vis-a-tergo" (*i.e.* pushing force acting from behind).[5, 10]

However, not all veins take deoxygenated blood back to the heart; there is an exception, the pulmonary and umbilical veins, both of which carry oxygenated blood to the heart. The venous blood delivered to the right atrium is further transferred to the right ventricle so that it is pumped through the pulmonary arteries to the lungs to get the necessary re-oxygenation through pulmonary circulation.

In pulmonary circulation, oxygenated blood returns from the lungs to the left atrium through the pulmonary veins and then into the left ventricle, completing the cycle of blood circulation. Indeed, the systemic circulation is by far the larger of the two, which transports oxygen from the heart to the tis-

sues of the body, but proper pulmonary circulation, that is, deoxygenated blood from the heart to the lungs by the pulmonary arteries and return blood from the lungs to the heart by pulmonary veins remains essential for complete cycle of systemic circulation.

In addition, the hepatic-portal veins circulation carry the blood between capillary beds from the capillary beds in the digestive tract to the capillary beds in the liver, where it is taken up by the hepatic veins before it is taken back to the heart.

Blood flow through the venous system is under neuromuscular control and is affected by gravity and muscular contractions. Competent venous valves warrant for this normal venous function. Normal valve function can provide a water-tight closure against a retrograde pressure gradient opposite to the direction of the leaflets. This function ensures unidirectional flow for physiologic drainage of venous compartments emptying the venous blood/flow from superficial to deep venous system of lower extremity, regardless of posture or changes in intra-abdominal or intrathoracic pressures. The valve leaflets remain passively open when the pressure gradient is antegrade in the same direction as the leaflets.[15-18]

Normal valve closure also produces dynamic fracturing of the gravitational hydrostatic pressure and is essential for proper function of the peripheral muscle pumps. Muscular activity such as walking can reduce the hydrostatic pressure from 90 mmHg to 30 mmHg only by competent venous valves that fractionate the pressure column during lower extremity muscular contraction (systole) and relaxation (diastole).[5, 10, 15-18]

EMBRYOLOGICAL ASPECTS OF VENOUS ANATOMY

Throughout the last century, advanced diagnostic technology led by Duplex ultrasonography, magnetic resonance imaging, and computerized tomography has provided enormous amount of new information on the venous system including its neglected relationship with the lymphatic system. Now, a new concept on the venous system is established as one of dual drainage system together with the lymphatic system [19] with a new prospect. And it further warrants a new interpretation of the venous system with fresh insights based on hemodynamic aspect [10] as well as embryological aspect.[20]

Indeed, proper understanding of the anatomy of the vena cava as ultimate 'large veins' warrants correct embryological interpretation of their complex structure from functional point of view. Because, a defective development of this 'large' vein would accompany with much profound clinical impacts (*e.g.* suprahepatic inferior vena cava occlusive disease,[1, 2] known as primary Budd-Chiari syndrome).

Four pairs of the cardinal veins should go through complicated evolutional/maturation process to interconnect among a total of eight different segments to form one new vena cava system in right side of the body cavity in the later stage of embryogenesis. Some parts of the cardinal veins would disappear through this due process of natural involution, while some would become incorporated into newly formed inferior vena cava (IVC)-bilateral iliac vein system as well as superior vena cava (SVC)-innominate-jugular vein system combined with azygos-hemiazygos system.

Naturally, such complex process to form the large veins (*e.g.* inferior and superior vena cava) would accompany with substantial risk of developmental defects.[1-4, 20, 21] Hence, a precise understanding of this unique embryological aspect of 'large' vein, that is, vena cava is warranted.

CARDINAL VEINS: EMBRYOLOGICAL VEINS

The development of the axial/truncal venous system is preceded by the complex capillary/reticular plexuses in early embryonic stage;

the primitive circulation system develops from the mesoderm as early as 15 to 16 days of gestation to form heart and blood vessels, starting as isolated masses and cords of mesenchymal cells.[1-4, 20] An extensive network of blood vessels has formed from the clusters of angiogenetic cells/mesenchyme throughout the embryonic body by the beginning of the fourth week, to establish a communication with extra-embryonic vessels to create a "primitive vascular system": vitelline-umbilical-cardinal vein system (Figures 1.1, 1.2).[1-4]

The primitive vascular complex in structure of capillary and reticular plexuses is soon replaced by the newly developed four paired cardinal veins in the early embryonic stage as an axial, truncal venous system: anterior cardinal, posterior cardinal, supracardinal and subcardinal veins. These cardinal veins subsequently go through complicated evolutional process to form two ultimate large veins: SVC and IVC.

Paired anterior and posterior cardinal veins merge to become the 'common cardinal veins,' draining centrally into the sinus venosus (sinus horns) and also receiving the paired 'vitelline' vessels from the yolk sac to develop into the hepatic portal system and also the paired 'umbilical' veins from the chorion and body stalk to form the ductus venosus (Figure 1.1).

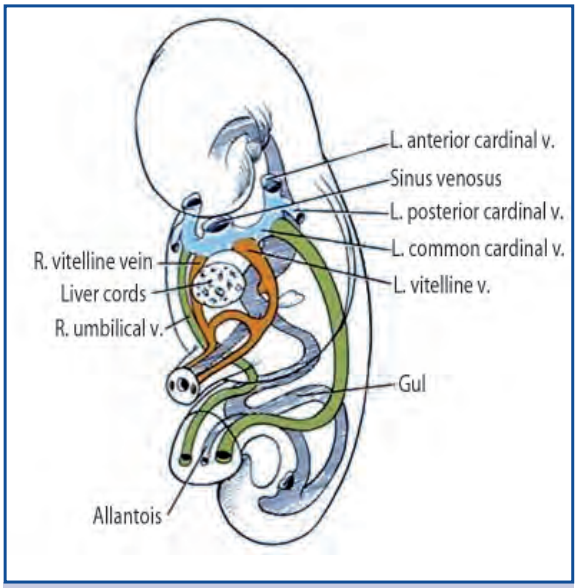

FIGURE 1.1. Embryonic veins at the 5th week: anterior/posterior/common cardinal veins and vitelline/umbilical veins developmental process. The embryo demonstrates the development of paired sets of the 'vitelline' and 'umbilical' veins in its 5th week, which initially drain the yolk sac and allantois but later drain the intestines and the placenta, respectively and also paired sets of anterior and posterior cardinal veins join to form the "common cardinal veins", draining centrally into the sinus venosus. The common cardinal veins also receive "vitelline" and "umbilical" veins, as depicted (adapted from: Lee BB [20]).

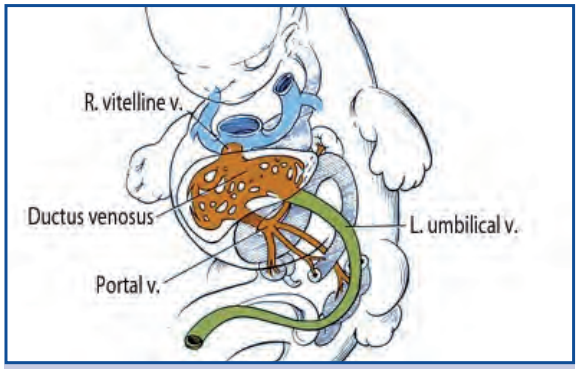

FIGURE 1.2. Embryonic veins at the 7th week: vitelline/umbilical veins developmental process. Till the 7th week of embryonal development, the entire right umbilical vein and proximal left umbilical vein regress; the distal left umbilical vein subsequently anastomoses with the hepatic sinuses to form ductus venosus. Ductus venosus allows venous blood from the umbilical vein and the portal vein directly to the inferior vena cava (IVC); distal/upper most segment of the right vitelline vein remains as the most proximal segment of IVC reaching to the heart tube via paired sinus venosus while all other parts of the vitelline veins regress/involute completely (adapted from: Lee BB [20]).

The paired umbilical veins return blood from the placenta to capillary networks in the liver at 4 weeks. During the fifth week of development, the right umbilical vein regresses/involutes together with the proximal portion of the left umbilical veins, leaving only the *distal part of the left* umbilical vein to return/carry blood from the placenta to the embryo as a single vein.

At 8 weeks when left umbilical vein loses its original connection with left sinus horn, the distal left umbilical vein anastomoses with the hepatic sinuses and to the newly formed ductus venosus (direct venous shunt of oxygenated blood from placenta to heart), which allows venous blood from the umbilical vein and the portal vein to bypass the liver and flow directly to the IVC and finally to reach the heart via the paired sinus venosus. Ductus venosus is a single oblique channel among intrahepatic anastomoses, draining directly into nascent IVC as crucial shunt to right atrium from umbilical system (Figure 1.2).

When regression of left vitelline vein is completed, its drainage is shunted to right vitelline vein through new intrahepatic anastomoses. And superior portion of right vitelline vein (portion between liver and heart) becomes the terminal portion of IVC.

Such complicated vascular changes on vitelline vein and umbilical vein system involving ductus venosus development and eventual regression through the obliterating process will add more risk of developmental anomalies. Since superior portion of right vitelline vein (portion between liver and heart) becomes terminal portion of inferior vena cava, IVC and hepatic veins has high risk during the fusion process of umbilical vein and vitelline vein besides the risk of overextension into hepatic vein-IVC system.[3]

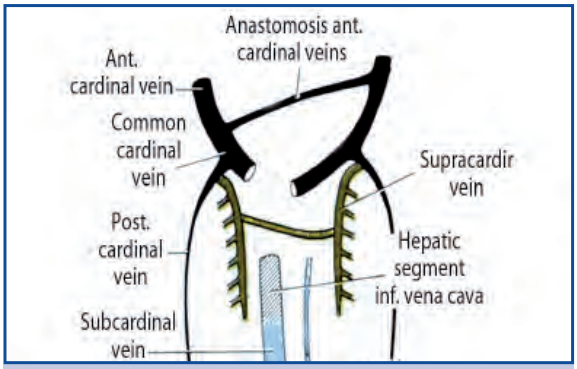

FIGURE 1.3. A, B) Precardinal/anterior cardinal vein-involved developmental process. Paired anterior cardinal veins form common cardinal veins with paired posterior cardinal veins, draining centrally into the sinus venosus (sinus horns) as depicted. Paired anterior cardinals soon form an anastomosis between them; the connection grows from the left to the right anterior cardinal vein to form the left brachiocephalic (innominate) vein. The left anterior cardinal vein distal (cranial) to the anastomosis becomes the "left internal jugular vein" while left anterior cardinal vein proximal to the brachiocephalic anastomosis regresses to become the base of the "coronary sinus" of the heart as displayed. Right anterior cardinal vein proximal to the right brachiocephalic vein forms SVC with common cardinal, and terminal/proximal segment of posterior cardinal vein (adapted from: Lee BB [20]).

SUPERIOR VENA CAVA (SVC): EVOLUTION OF ANTERIOR CARDINAL VEINS

Initially, "bilateral anterior cardinal veins", also known as the precardinal veins, drains the body portion cephalad to the developing heart (head, neck, upper torso and upper limbs), while "bilateral posterior cardinal veins", also known as the postcardinal veins, drains the caudal portion of the body (torso and lower limb).[20-23] But, soon, major evolutional process is evolved along the anterior cardinal veins; paired anterior cardinal veins form an anastomosis first through newly formed left brachiocephalic (innominate) vein to let the blood drain from the 'left anterior cardinal vein' into the "right anterior cardinal vein".

The distal (cephalad) portion of the left anterior cardinal vein to the brachiocephalic anastomosis becomes the 'left internal jugular vein' and subsequently joins the 'left subclavian vein' from the developing upper limb. Accordingly, the distal (cephalad) portion of bilateral anterior cardinal veins become the bilateral internal jugular veins and the blood from the left internal jugular vein passes through the left brachiocephalic veins draining directly into the SVC [24, 25] (Figure 1.3).

Meanwhile, the proximal (caudal) portion of left anterior cardinal vein to the anastomosis regresses to form the great cardiac vein with the terminal segment of the left posterior cardinal vein. The oblique vein of the left atrium (vein of Marshall) on the back of left atrium and the "coronary sinus" of the heart comprise the great cardiac vein. On the right side, the proximal part of right anterior cardinal vein forms the SVC with the right common cardinal vein in conjunction with right horn of the Sinus Venosus (Figure 1.3).

SVC is therefore made up of three different segments:

1. right anterior cardinal vein proximal to the brachiocephalic anastomosis;
2. right common cardinal vein;
3. right horn of the Sinus Venosus.

Hence, the anterior cardinal veins remain largely intact through such complicated evolution to become the veins of the heart and SVC and its tributaries together with common cardinal and terminal/proximal posterior cardinal veins. Indeed, these veins are further involved in the formation of the arch of azygos vein together with the proximal segment of the right posterior cardinal vein. The

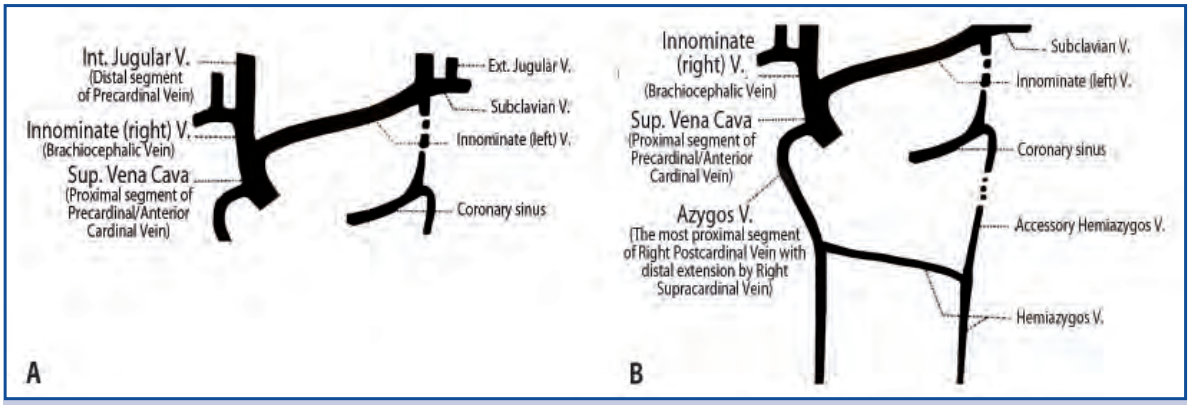

FIGURE 1.4. A,B) Three sets/pairs of cardinal veins: precardinal, postcardinal, and supracardinal, are evolved to azygos vein system. Azygos venous system is initially derived from the paired supracardinal vein; proximal segment of right supracardinal vein forms the arch of azygos vein together with the cranial part of the right posterior cardinal vein while (cranial part of) left supracardinal vein becomes the hemiazygos and also accessory azygos veins. The hemiazygos vein on the left side drains into the azygos vein located in the right side before it is drained into SVC; 'accessory' hemiazygos vein along the course of the involuted left common cardinal vein, drains into the hemiazygos vein before it crosses over the midline to the azygos vein (adapted from: Lee BB [20]).

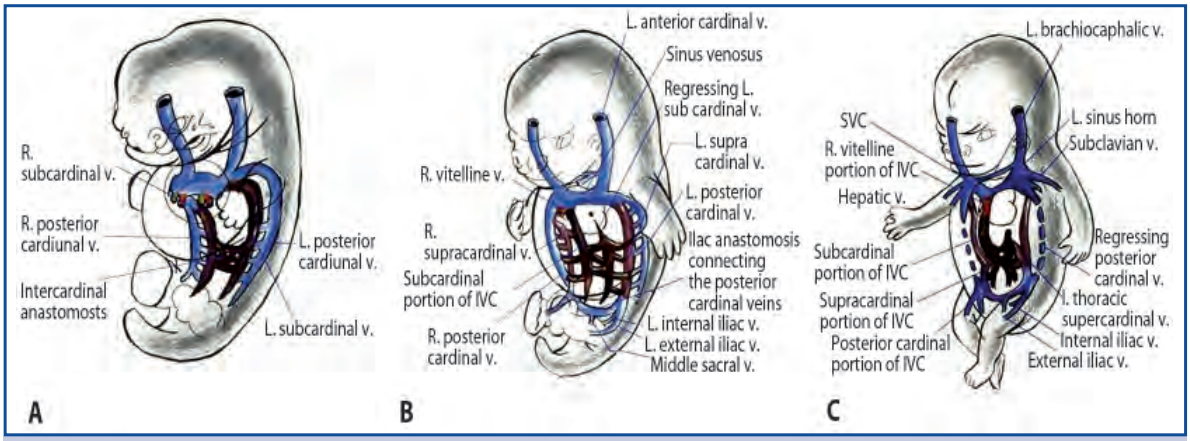

FIGURE 1.5. A-C) Developmental process of inferior vena cava involved by posterior cardinal, supracardinal and subcardinal veins. Three pairs of the posterior-/sub-/supra-cardinal veins go through much more extensive evolution as well as involution process to form the IVC as well as hepatic veins together with bilateral vitelline and umbilical veins. The role of posterior veins, the first pair of embryological vein for the caudal body venous drainage, is soon taken over by subsequently developing pairs of subcardinal and supracardinal veins, to finish the formation of the IVC as shown (adapted from: Lee BB [20]).

termination of the left posterior cardinal vein transforms into great cardiac vein draining into left atrium as illustrated as above.

Azygos venous system is initially derived from the paired supracardinal venous system, one of three cardinal veins that drain caudal portion of the body, together with the posterior cardinal veins.[26, 27] Another word, the right supracardinal vein forms "azygos vein" together with the cephalad part of the right posterior cardinal vein finally to the arch of azygos vein. And the left supracardinal vein becomes the hemiazygos vein and also accessory azygos vein.

The hemiazygos vein located on the left drains into the azygos vein on the right side before it drains into SVC. The "accessory" hemiazygos vein along the course of the involuted left common cardinal vein, drains into the hemiazygos vein before it crosses the midline to flow into the azygos vein (Figures 1.4, 1.5).

INFERIOR VENA CAVA (IVC): EVOLUTION OF POSTERIOR, SUPRA AND SUB-CARDINAL VEINS

The posterior cardinal (postcardinal) veins are the first pair of embryonic veins among three cardinal veins to drain caudal body, but

its leading role is soon taken over by subsequently developed two additional pairs of subcardinal and supracardinal veins. The shift of systemic venous return to right side to line up with right atrium initiates the radical remodeling of these three pairs of cardinal venous systems through the final vascular trunk maturation stage of embryogenesis.[20, 28-30]

These three pairs of posterior cardinal, subcardinal, and supracardinal veins go through extensive evolution as well as involution to form the IVC to drain the trunk and lower extremities.[18, 19]

This complicated process for the completion of vena cava development involves an intricate series of new development, regression, and anastomosis to compose multi-segments of vena cava from different origins for the final replacement of three cardinal veins altogether.[20, 28-30] Eventually, the IVC is formed through the following embryonic structures:

1. suprahepatic segment of the IVC: it is the most proximal segment of the IVC developed from the persistent proximal portion of the right vitelline vein which is the precursor of the common hepatic vein;
2. new hepatic segment: it develops from an anastomosis between the segments of right vitelline vein and the right subcardinal vein distal to the developing liver to connect this proximal-most (suprahepatic) segment to the distally located right subcardinal vein while allowing the drainage of the hepatic veins/liver;
3. renal/mesenteric segment: it is represented by a preserved segment of the right subcardinal vein;
4. new junctional segment of the IVC: it is formed through the anastomosis between the right subcardinal vein and the more distally located right supracardinal vein;
5. infrarenal segment: it is represented by the preserved segment of the right supracardinal vein;
6. last caudal segment of the IVC: it is formed as a new segment to connect the right supracardinal and most distal part of the bilateral posterior cardinal veins.

The IVC is therefore, an embryologically compound vessel as the outcome of a complicated fusion process among multiple segments of different embryonic veins: vitelline, supracardinal, subcardinal, and posterior cardinal, and their anastomosis among them and also between own sub- and supra-cardinals. Naturally there exists a high risk of developmental anomalies occurring during this complicated IVC formation process.[31, 32]

Depending upon the location as well as the extent of anatomical variation caused by anomalous development of vena cava, its clinical impact to the target organs/tissues will vary heavily by the collaterals developed as compensatory route of venous drainage.[33-35]

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