**Special Contribution**

## Changing Concept on Vascular Malformation: No Longer Enigma

Byung-Boong (BB) Lee, MD, Ph.D, FACS

### INTRODUCTION

**Old Concept**

There have been numerous documentations on vascular malformations in the medical literatures for centuries, describing only general/natural appearance of this inborn error. But the vast majority were simple reports of anecdotal experiences with limited information on the basis of poor investigational methods then; its complicated nature has never been properly explained and often described as a name-based ‘syndrome’ (e.g. Klippel-Trenaunay Syndrome) to make it look more enigmatic.

Following the turn of the last century, however, a good many clinicians challenged to such unique condition of the vascular defects seriously in the middle of much confusion to define its nature. But they were only able to catch a glimpse of thousands faces of this birth defect involving various locations of the vascular system in various conditions, extents, and severities. And it was not possible till lately to draw whole picture with a bird’s-eye view due to the limited resource and technology.

Its extreme variety of clinical appearance and unpredictable behavior in general with a stigma of recurrence gave such notorious reputation to entire group of vascular malformations as an enigma in modern medicine.

This once condemned and abandoned disease is now newly defined as congenital vascular malformation (CVM) and this new terminology began to clear much confusion on this unique vascular disorder as a universal language replacing many nosologies.

**New Concept with New Terminology & New Classification**

Through the last half of the century, advanced new technology assisted more accurate investigation for better understanding on this complex nature of CVMs and many newly developed diagnostic and therapeutic modalities corrected previous misunderstanding on the CVMs.

However, wrong concept on the CVMs for many decades was partly responsible by many confusing terminologies (e.g. angiodysplasia, cavernous hemangioma, cystic hygroma/lymphangioma) and especially by many name-based eponyms: Klippel-Trenaunay Syndrome (KTS), Parkes-Weber Syndrome (PWS), etc.

These name-based eponyms gave a tremendous contribution to understand the CVMs in its haydays and it still gives much help to communicate with lay persons in particular. Their role in the past was fully justified with limited information on various CVMs then and their diagnosis was solely made based on the clinical evaluation. But with current technology to define all the detailed status of individual vascular malformation, its old role became rather obsolete and only remains to become a source of confusion among clinicians.

For example, the vascular malformation component of KTS is now properly defined as hemolymphatic malformation (HLM) based on new classification, which is consisted of venous malformation (VM), lymphatic malformation (LM), and capillary malformation (CM). And those of PWS are VM, LM, CM and AV malformation (AVM).

‘Cystic/cavernous hemangioma’, once popular name for the CVMs, is also correctly defined as VM to clear unnecessary confusion with true ‘hemangioma’. Genuine hemangioma represents only ‘infantile/neonatal’ heman-
gioma, which is not a vascular malformation but a vascular tumor.\textsuperscript{9,10}

The difference between cystic/cavernous hemangioma and true (infantile/neonatal) hemangioma is so crucial for their clinical management that its importance cannot be overemphasized.

True hemangioma is a vascular tumor belonging to the vascular anomaly together with vascular malformation but hemangioma generally appears in early neonatal period as a rapidly growing tumor. But, the hemangioma has a distinctive pattern of self-limited growth with initial proliferate phase followed by slow regression in involution phase, and it is generally resolved spontaneously with minimum morbidity before reaching to the age of 7 to 9 years.\textsuperscript{11}

On the contrary, the vascular malformation is generally distinctive on birth as an inborn error and steadily grows commensurably in proportion to the general/systemic growth; it never disappears nor regress. Therefore, the management is naturally quite different from each other.

Such confusion was successfully cleared by improved terminology and modern technology and finally a new classification became feasible for the contemporary diagnosis and treatment through the last two decades.

On the basis of the consensus meeting in Hamburg in 1988, a new classification, also known as European/Hamburg classification, was formulated to meet the mandate condition for the contemporary concept.\textsuperscript{8,12–14} This Hamburg classification gave a solid ground to adopt new information on the etiology and anatomo-patho-physiology of the CVMs, replacing old name-based eponyms effectively (Table 1).

The original Hamburg classification was further modified to accommodate entire group of CVMs; it grouped various CVMs based on its predominant component: VM, LM, AM (arterial malformation), AVM, and their combined form named as HLM, in addition to CM.

Each malformation (type) was further subgrouped to the “extratruncular” and “truncular” subtypes based on its embryologic stage when the developmental arrest occurred, which is so crucial to the clinicians to formulate right treatment strategy.

The “extratruncular” lesions are embryologic tissue

<table>
<thead>
<tr>
<th>Table 1A</th>
<th>Hamburg classification* -type</th>
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<tr>
<td>Predominantly arterial defects</td>
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<td>Predominantly venous defects</td>
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<td>Predominantly AV (arteriovenous) shunting defects</td>
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<td>Predominantly lymphatic defects</td>
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<td>Combined vascular defects</td>
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*Based on the consensus on CVM through the international workshop in Hamburg, Germany, 1988.

*Capillary malformation was not included

<table>
<thead>
<tr>
<th>Table 1B</th>
<th>Hamburg classification -subtype</th>
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<tbody>
<tr>
<td>I. Extratruncular forms</td>
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<tr>
<td>Diffuse, infiltrating</td>
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<td>Limited, localized</td>
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<td>II. Truncular forms</td>
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<tr>
<td>Aplasia or obstruction</td>
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<tr>
<td>Hypoplasia; Aplasia; Hyperplasia</td>
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<tr>
<td>Stenosis; Membrane; Congenital spur</td>
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<tr>
<td>Dilatation</td>
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<tr>
<td>Localized (aneurysm)</td>
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<td>Diffuse (ectasia)</td>
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- Developmental arrest at the different stages of embryonal life: earlier stage - extratruncular form; latter stage - truncular form.
- Both forms may exist together; may be combined with other various malformations (e.g. capillary, arterial, AV shunting, venous, hemolympathic and/or lymphatic); and/or may exist with hemangioma.
remnants from the ‘earlier’ stage of embryogenesis so that they still possess mesenchymal cell characteristics to grow when stimulated externally (e.g. trauma, surgery, and hormone) or internally (e.g. menarch, pregnancy). This embryologic characteristic has never been understood properly till lately and poor treatment strategy without appropriate consideration on such critical factor only provoked dormant/silent lesion to grow rapidly.

Therefore, all the extratruncular lesions regardless of its type carry this risk of recurrence in addition to the hemodynamic impact to the affected vascular system.

The extratruncular lesions also give a pressure effect to the surrounding tissues/organs/ systems as well since they grow in diffusely infiltrating condition by its nature.

On the contrary, the “truncular” lesions are vascular defects developed along the ‘latter’ stage of embryogenesis so that they have lost this critical mesenchymal cell characteristic, presenting only hemodynamic impact to the involved circulation system. The truncular lesions are generally in the aplastic, hypoplastic or hyperplastic condition of normally developing truncal vessel (e.g. rudimentary femoral vein, absence of iliac vein); they also present various defective vessel conditions (e.g. vein web, aneurysm, ectasia). And occasionally embryonic/fetal vessels remain without further involution (e.g. lateral/marginal embryonic vein) to give complicated hemodynamic impact to the deep vein system.

**Diagnosis In General**

New concept on the CVM mandated a precise diagnosis to provide accurate information on its histo-pathologic, hemodynamic, and embryologic characteristics; this new information in turn allowed a new prospect to its management with a new view.

Now we know there are many different vascular malformations with different clinical significances and we no longer consider them as an enigma since we have enough knowledge to verify many different aspects of each CVM lesion either existing alone or as combined with other CVMs.

Many newly developed tests, mostly non-invasive, can now provide precise diagnosis of each CVM to confirm the clinical impression.

The diagnosis per se is now feasible only with these non- to less-invasive tests in the majority of CVMs: Duplex ultrasonography, Magnetic resonance image (MRI) study, Whole body blood pool scintigraphy (WBBPS), Transarterial lung perfusion scintigraphy (TLPS), Air plethysmography, MR arteriography (MRA) and/or MR venography (MRV), Radioisotope (RI) lymphoscintigraphy, Ultrasound lymphangiography, MR lymphangiography, etc. (Table 2).

All the detailed information on each test was fully documented through previous publications.

And the invasive tests (e.g. arteriography, phlebography) in general could be saved till needed as a road map for the treatment except the differential diagnosis with hemangioma or AVM.

Precise defining of the type (e.g. VM, LM, HLM, AVM) and nature (e.g. truncular or extratruncular lesion) of each CVM involved should follow detailed assessment of its extent, severity, and its secondary impact to the related systems/organs, which is also now feasible with non- to less-invasive tests alone in its majority. All the related information on the primary CVM lesion and its secondary effect is therefore, mandated to move to the next crucial step for the decision on whether the lesion should be treated or not, and if so, when and how.
MANAGEMENT

Principle

Not all the CVMs are equal in terms of clinical management point of view.

All the CVMs can neither be treated nor should be treated equally since they behave differently with different natural course/progress and prognosis.26

For example, AVM in general is a potentially life, if not limb threatening condition but VM is not. Therefore, the treatment principles for these two CVMs are basically different; the AVM has to be treated aggressively regardless of its extent/severity27,28 unless the price to pay for the control is prohibitively high and sometimes an amputation is the safest and most effective way to control the lesion as a life-saving measurement.

But, the VM, which is the majority of CVMs, is not a life-threatening condition in general, except a few unique conditions related to their critical location to interfere/threaten the vital function -seeing, breathing, eating, hearing- or to the proximity to the active joints with the risk of injury/trauma (e.g. hemarthrosis).29

Therefore, the strategy for the VM management should be different from those for the AVM, and not all the VM lesions should require treatments immediately and the traditional conservative approach is still recommended for the vast majority of VM lesions.30,31

A typical VM lesion without abnormal bone growth involvement can be monitored until the age of two or more years when the child is matured enough to tolerate various diagnosis and treatment procedures.

But earlier intervention is required even for the VM when the VM lesion produces the vascular bone syndrome resulting in discrepancy of long bone growth, or when the lesion is located at a life or limb threatening anatomic area as mentioned above.32,33

The LM lesion, which is also one of two most common CVMs with VM, is also different from other CVMs since its majority belongs to the ‘truncular’ lesion often known as ‘primary’ lymphedema affecting only lymph-transporting system. But its extratruncular lesion also known as ‘cystic/cavernous lymphangioma’ behaves like other CVM’s extratruncular lesion.

But this extratruncular LM is clinically much benign comparing other CVM’s extratruncular lesion and generally required a treatment only when it becomes symptomatic or develops complications (e.g. leakage, sepsis).34,35

However, when these three different CVMs: AVM, VM, and LM should coexist as a combined form of CVMs: hemolymphatic malformation (HLM), its clinical management becomes much complicated due to their interwound hemodynamics. Additional precaution is mandated when the treatment is required to one of the coexisting CVMs since it often affects to other remaining CVM component negatively to worsen the condition.

Multidisciplinary Approach

Through many decades the surgeons took the initiative to challenge to this relatively rare vascular condition only with the surgical means alone. The outcome of a surgical excision based on limited knowledge and experiences was often disastrous; since surgeons aimed at the ‘cure’ as an ultimate and ideal solution, it often led to a surgical excess accompanying with prohibitively high morbidity and complication.

To make the condition worse, they all recurred by their unique embryologic characteristics following incompete excision giving a bad reputation of recurrence to every vascular malformation surgeons attacked and subsequently resulted in a wrong prejudice to the CVMs altogether.

Surgeons, once led this challenge, were burned with frustration to this intolerable outcome and blamed unfairly on the CVM itself for bad results rather than their own cavalier approach by mistake.3,36 But it soon became clear that most of these self-inflicted wounds were due to their wrong approach especially to ‘surgically inaccessible’ lesions.

Now, based on much improved assessment of its extent and severity including its relationship with surrounding tissues/systems, the decision for the treatment as well as the selection of the treatment modality can be made quite accurately.

Hence, a new concept based on new classification and new diagnostic and therapeutic modalities allowed a ‘multidisciplinary team approach’ combining traditional open surgical therapy with the endovascular therapy as a new treatment modality.37

The traditional surgical treatment38–47 is now fully integrated with various endovascular therapies48–57 utilizing modern interventional technology.

Endovascular therapy with varous combinations of emboloscleragents is now the treatment of choice to the ‘surgically inaccessible’ lesions, and open surgical therapy can also be delivered to the ‘surgically accessible’ lesions more effectively with much reduced risk of complication and morbidity by perioperative embolosclerothera-
py as an adjunct supplemental therapy. Especially preoperative embolotherapy gave a new guideline for precise dissection with minimum intraoperative bleeding and complication/morbidity.

Endovascular treatment with the sclerotherapy is therefore, excellent as an 'independent therapy' to non to poor surgical candidate in particular with diffuse infiltrating type of extratruncular lesion. It is the treatment of choice for extensive lesions beyond deep fascia with involvement of muscle, tendon and bone.

But various surgical treatments remain essential for the proper management of the VM. The operation to correct hemodynamic derangement often requires various reconstructive (e.g. venous bypass, venous aneurysmorrhaphy) and/or ablative (excisional) surgery (e.g. removal of marginal vein, excision of the VM lesions).

Various orthopedic as well as many plastic and reconstructive surgeries are actively utilized to correct/improve the consequence of secondary impact by the VM (e.g. Achilles tendon lengthening).

But, the treatment, either surgical or endovascular, should be committed only with appropriate indication to avoid unnecessary complication and morbidity$^{50}$ (Table 3); the decision should be made on the basis of the consensus by the multidisciplinary team.

A 'controlled,' aggressive approach must be coupled with a realistic assessment of the long-term results of the treatment regimen.

A realistic assessment of the associated risks and benefits is mandated when formulating any potential treatment plan. This is especially true for life-threatening and limb-threatening situations (e.g. hemorrhage).

For example, severe VM lesions producing a nonfunctional limb with significant growth discrepancy should be treated with early amputation as a practical solution and allow early rehabilitation with a proper prosthesis.

Without having all these detailed information, precocious decision on the treatment only invites increased risk of complication and morbidity.

For example, the Achilles tendon lengthening before the completion of the therapy to the lesions affecting calf muscles brings more difficulty than the benefit later like burning the bridge before you safely cross.$^{18,19}$

When the treatment is committed, however, the destruction of the lesion ‘nidus’ itself is warranted to prevent a recurrence. The occlusion/embolization of feeding arteries alone should be condemned since it only stimulates the nidus of the lesion possessing the mesenchymal cell characteristics; the nidus will respond as an embryonic tissue remnant with more aggressive neovascular recruitment and subsequent regrowth exceeding the pre-treatment condition becomes inevitable. Therefore, the complete destruction of the nidus is essential to control the CVM lesions effectively.

**Clinical Experiences**$^*$$^{30,31}$

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<thead>
<tr>
<th>Table 3</th>
<th>Treatment-indication (general)</th>
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<tr>
<td>Hemorrhage</td>
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<td>High output heart failure (AV shunting malformation)</td>
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<tr>
<td>Secondary ischemic complications (AV shunting malformation)</td>
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<tr>
<td>Secondary complications of chronic venous hypertension (venous malformation)</td>
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<tr>
<td>Lesions located at life threatening region (e.g. proximity to the airway), or located at the region threatening vital functions (e.g. seeing, eating, hearing, or breathing)</td>
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<tr>
<td>Disabling pain</td>
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<tr>
<td>Functional impairment</td>
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<tr>
<td>Cosmetically severe deformity</td>
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<tr>
<td>Vascular-bone syndrome</td>
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<tr>
<td>Lesions located at the region with potentially high risk of complication (e.g. hemarthrosis, deep vein thrombosis and/or pulmonary embolism)</td>
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<tr>
<td>Lymph leak with/without infection</td>
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<tr>
<td>Recurrent sepsis, local and/or general</td>
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Among total 1,203 CVM patients, 453 were identified as predominantly VM (37.7%) (male-202, female-251, mean age of 19.5 years).

Among a total of 453 VM patients, 186 patients were
indicated for the various treatments: sclerotherapy alone- 137, surgical therapy alone- 20, and combined surgical and endovascular therapy- 29.

Sclerotherapy mostly with ethanol (434/512) to 166 (152 with ET lesions) patients: 512 sessions.

Embolotherapy with NBCA (N-butyl cyanoacrylate) as preoperative adjunct therapy for subsequent surgical excision: 42 sessions to 22 extratruncular form independently or in conjunction with ethanol sclerotherapy.

Immediate success rate of ethanol sclerotherapy following each session was 98.8% (504 sessions among 512 sessions on 186 patients) and its failure rate was 1.6% (8/512 sessions).

Late results following completion of multisession therapy (average 3.8 sessions per patient) have shown excellent results with no evidence of recurrence (follow-up period - average 42.2 months).

All 49 patients with surgical therapy including 22 patients, who underwent preoperative embolo/sclerotherapy with various combinations of NBCA and ethanol, achieved 100% success rate with minimum morbidity, and no recurrence (41.2 months follow-up).

AVM27, 28


Among a total of 1,203 patients with various CVMs, 145 patients (12.1%) were confirmed as AVM, mostly (91/145) of diffuse infiltrating extratruncular form with macro-AV shunting nidus.

Ninety patients (82-extratruncular; 8-truncular) out of 145 patients were selected for the treatment with various indications, underwent endovascular: embolo/sclerotherapy with various combinations of absolute ethanol, NBCA glue, contour particles (e.g. ivalon) and coils as independent therapy or as adjunct therapy prior to surgical therapy.

Twenty among 21 patients with surgically accessible lesions, completed total 27 multisessions of preoperative endovascular therapy with various combinations of the embolo/scleroagents and subsequent surgical excisions.

All 21 patients including 1 with surgical therapy alone have shown excellent interim results with no evidence of recurrence during the limited follow-up periods of 41.0 months in average following the surgery.

Sixty nine patients with surgically inaccessible lesions underwent total 334 sessions of multisession independent endovascular therapy with various combinations of the agents.

Interim results following the completion of multisession therapy were excellent in majority (48/69) and good to fair among the rest (12/69), with recurrence from poorly controlled lesions (9/69) during the limited follow-up period of 32.2 months in average.

In General29

Among various embolo/scleroagents available, we selected the absolute ethanol as main scleroagent to surgically inaccessible, diffuse infiltrating extratruncular lesions especially for AVM and NBCA glue for surgically excisable lesions as preoperative emboloagent to reduce morbidity during the subsequent surgical therapy.

Ethanol is the most powerful scleroagent with excellent long term results/outcome as we have shown but it accompanies highest risk of complication/morbidity among the agents.

Therefore, serious consideration on its risk involved should be exercised before the commitment. Not only local (e.g. skin/soft tissue necrosis) and/or regional (e.g. nerve palsy, venous thrombosis) complications, but also its systemic complication (e.g. pulmonary spasm) should be anticipated with appropriate preparation.

Pulmonary hypertension induced by the ethanol toxicity when it reaches to the pulmonary bed from the lesion treated is a potentially fatal morbidity and it is warranted to stop further progression to pulmonary spasm (e.g. cardiopulmonary arrest).

The importance of close monitoring of cardio-pulmonary-vascular system, therefore, during the ethanol sclerotherapy cannot be overemphasized; appropriate/immediate handling of the increased pulmonary pressure when the ethanol should reach to the pulmonary bed is absolutely mandatory.

Therefore, indiscriminating use of the ethanol throughout entire CVM group should be discouraged especially for the LM lesion which can be treated much effectively with lymphatic endothelial -specific scleroagent (e.g. OK 432).34, 55

However, once this ethanol is indicated, it should be given in multi-sessions with minimally possible amount for each session to reduce potential risk of acute/chronic morbidity and complication.

And careful assessment of potential risk of collateral damage to the surrounding tissues (nerve, vessel, cartilage, skin and soft tissue) by the ethanol should be repeated on each session. Unless the damage is absolutely needed to accept as the price to control the lesions with the ethanol, every effort should be exercised to avoid, if
not reduce it.

Close communication and consent for the anticipated morbidity/complication by the patient/family is absolutely needed before the procedure is committed with the ethanol in particular.

Recently the foam sclerotherapy has gained momentum over traditional liquid sclerotherapy in the management of VM lesions with excellent interim treatment outcomes. Our experience with 1% polidocanol foam was also excellent although limited to the localized VM lesions with high risk of skin/mucosa necrosis by ethanol sclerotherapy. Although the recurrence is high as expected, it is particularly recommendable for the lesion with proximity to the skin/oral mucosa with/without transdermal extension to avoid the risk of tissue/skin necrosis.

These VM lesions on finger, palm, toe, sole, oral mucosa, lip and tongue have a potential for significant injury by other stronger sclerosing agents and will have significant morbidity even after the successful skin graft (e.g. loss of tactile sensation).

We now extended its use to various CVMs including LM with the plan to repeat the therapy to control the recurred lesion while maintaining minimum complication/morbidity and favorable interim results.

There remains, however, controversy regarding the true risk of paradoxical air embolization through a patent Foramen Ovale with foam sclerotherapy. This issue remains to be cleared.

**CONCLUSION**

Fully integrated traditional open surgical therapy with endovascular therapy can achieve improved treatment results even to once tabooed lesion due to prohibitively high morbidity accompanied.

Multidisciplinary team approach with new treatment strategy can improve long term treatment results with a reduced morbidity and recurrence over the conventional approach.

**REFERENCES**


