Physical Principles of Vascular Developing and Remodeling

Preprint · December 2021

DOI: 10.13140/RG.2.2.20693.76003

1 author:

Xinggang Wang
Renji Hospital Affiliated to Shanghai Jiaotong University School of Medicine
51 PUBLICATIONS **776** CITATIONS

SEE PROFILE

Physical Principles of Vascular Developing and Remodeling

Xinggang Wang, PhD

Department of Cardiology, Renji Hospital Affiliated to Shanghai Jiaotong University School of Medicine, Shanghai, China

Email: xinggangwang11@fudan.edu.cn

My previous papers demonstrated perivascular adipose tissue (vascular " Kuiper Belt ") and intimal atherosclerotic plaque are both the result of vascular remodeling[1-15]. The perivascular adipocytes are essentially the same as the foam cells in atherosclerotic intima[7,8]. Vascular " Kuiper Belt " is the product of early fetal vascular remodeling, which is similar to the "Kuiper Belt" of solar system. They were born in the stage of system generation and are widely distributed near the edge of the system. Therefore, I name the perivascular adipose tissue as the vascular "Kuiper Belt" (Perivascular adipose tissue = Vascular "Kuiper Belt")[7,8]. This paper involves many physical and mathematical principles, such as hydrodynamics[4,5], mechanical wave, calculus, Newtonian mechanics, etc. I would discuss it from the following 3 aspects.

1. **With the theory of vascular simple harmonic motion (SHM) and vascular media dysfunction, they could interpret the developing and remodeling of early blood vessels, and expounds the formation mechanism of vascular three-layer structure, external elastic membrane, internal elastic membrane, and vascular "Kuiper Belt", etc. Higher hydrostatic pressure can enhance the remodeling**

of fibrous connective tissue, while lower hydrostatic pressure can "desertification" the existing fibrous connective tissue.

2. With the theory of vascular simple harmonic motion (SHM) and vascular media dysfunction, the mechanism of atherosclerosis is completer and more reasonable.
3. To explore promising etiological treatment of vascular diseases, such as atherosclerotic diseases, from the mechanism of vascular changes.

Fetal early vascular developing, remodeling and desertification

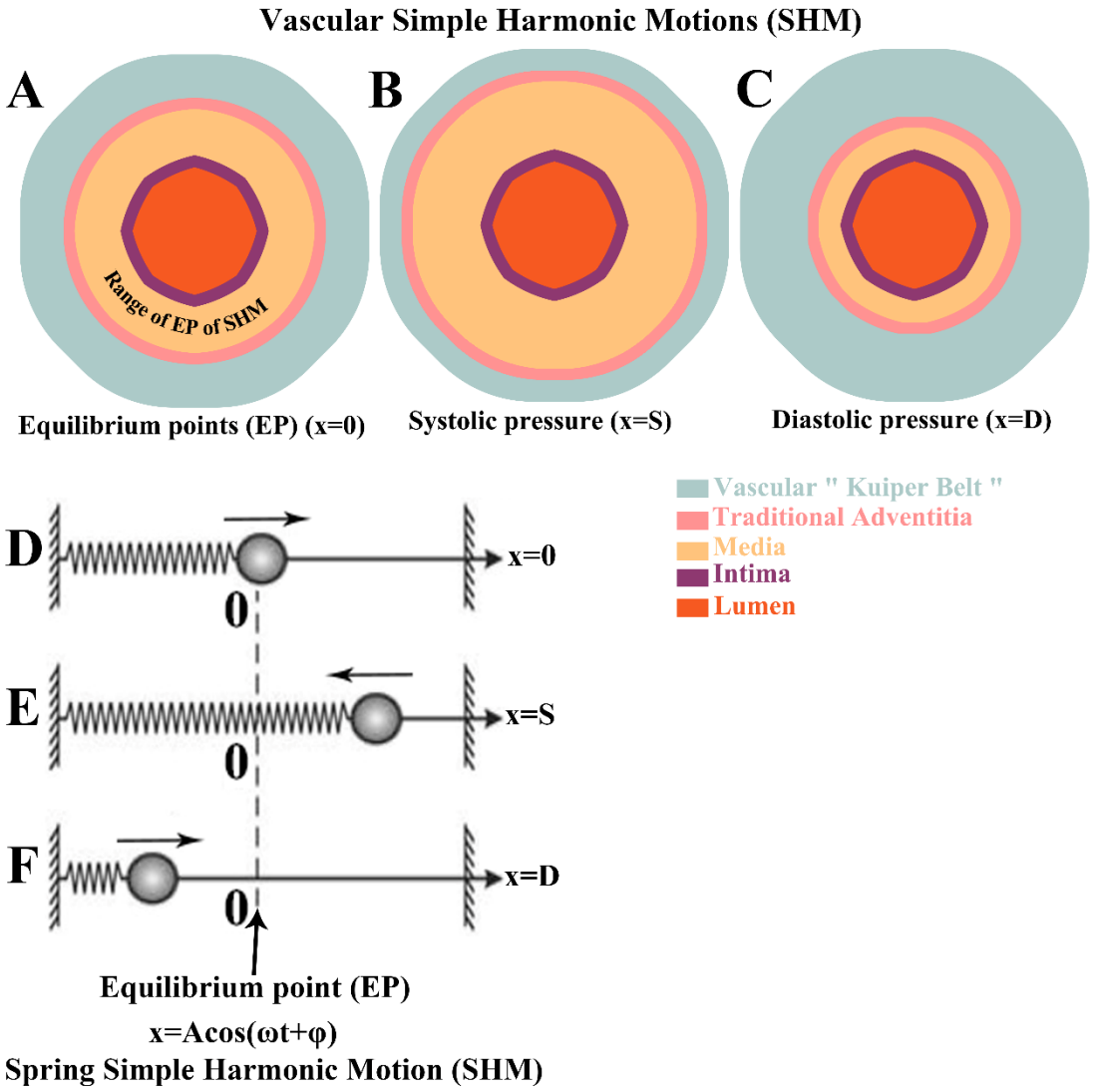

Figure 1. Vascular simple harmonic motions (SHM)

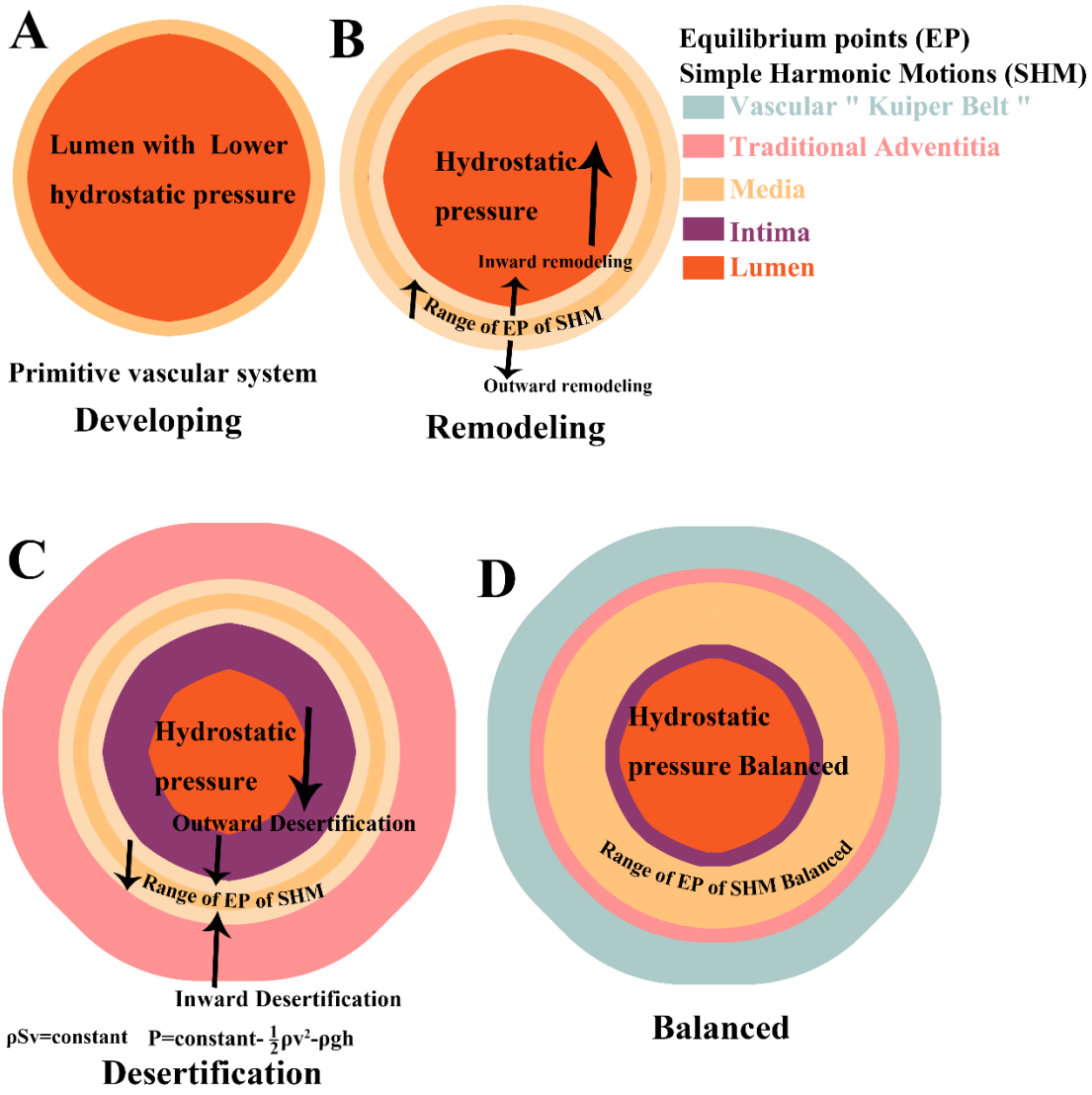

Figure 2. Fetal early vascular developing, remodeling and desertification

Early embryonic angiogenesis may directly or indirectly come from mesenchymal stem cells, which can differentiate into various cells, such as smooth muscle cells, endothelial cells, fibroblasts, myofibroblasts, etc. Therefore, mesenchymal stem cells should play a decisive role in the formation of early blood vessels. At the beginning of the primitive cardiovascular system, just like capillaries and venules[16], the vascular system is composed of single or several layers of cells. At this time, the blood vessels are very thin, which are not divided into intima, adventitia or media (Figure.2A). With the developing of fetus, the hydrostatic pressure in the

blood vessels gradually increases, and these thin primitive blood vessels must gradually thicken to bear higher hydrostatic pressure. In the formation of primitive vascular system, vascular remodeling is very strong for the participation of mesenchymal stem cells. The outer side of the vessel began to grow outward and the inner side of the vessel began to grow inward to form fibrous granulation tissue remodeling from both sides following the gradual increase of hydrostatic pressure (Figure.2B). With the developing of the fetus, the fetal heart starts to pump blood periodically, so the early blood vessels begin to adapt to periodic pressure remodeling. Because the heart pumps blood periodically and the blood vessels are elastic (similar to the simple harmonic motion (SHM) of spring) (Figure 1), we can regard vasodilation and vasocontraction as the superposition of many simple harmonic motions (SHM). Among these simple harmonic motions (SHM) (Equation of simple harmonic motion (SHM) : $x=A\cos(\omega t+\varphi)$), the extreme values at two time points are special: One is the systolic pressure corresponding to the maximum degree of vasodilation (Like the maximum distance the spring is stretched) (Figure 1B, Figure 1E), the other is the diastolic pressure corresponding to the maximum degree of vasoconstriction (Like the maximum compression of the spring) (Figure 1C, Figure 1F), and other simple harmonic motions (SHM) lies between the two extremes (Figure 1A). Therefore, the degree of vasodilation and vasoconstriction of the same location is determined by these two extreme values, so we focus on the two extremes of systolic pressure and diastolic pressure. According to the principle of simple harmonic motion (SHM) in physics, the simple harmonic motion (SHM) moves outward and inward around the equilibrium point (Figure 1D, Figure 1E, Figure 1F).

These equilibrium points (EP) are determined by the intravascular hydrostatic pressure and natural characteristics of the blood vessel. Systolic pressure determines the outermost edge (external elastic membrane) of the vascular equilibrium points, while diastolic pressure determines the innermost edge (internal elastic membrane) of the vascular equilibrium points. Other vascular equilibrium points (EP) of simple harmonic motions (SHM) are between the external elastic membrane and the internal elastic membrane (Range of EP of SHM) (Figure 1A). Fetal systolic pressure and diastolic pressure basically determine the thickness of fetal vascular media in an individual. Of course, fetal vascular media would be different for vascular bending / bifurcation or different locations, which change the vascular hydrostatic pressure[4]. In addition, if the blood vessels are located in the myocardial bridging / parenchymal tissues, these surrounding parenchymal tissues would bear part of the hydrostatic pressure[5,10]. The media of coronary artery in myocardial bridging or the vascular media in parenchymal tissues would be relatively thin[5]. Therefore, the thickness of the vascular media in the same fetus is also different. Due to the outward diffusion of pressure (energy) outside the outermost equilibrium point determined by the systolic pressure, the adventitia would remodel outward from the outermost equilibrium point (external elastic membrane). The farther away from the lumen, the earlier the tissue formed, while the tissue near the external elastic membrane formed later in fetal vascular adventitia developing (Figure 2B). According to the natural characteristics of simple harmonic motion (SHM), the innermost equilibrium point determined by the diastolic pressure is opposite to the outermost equilibrium point. The intima would remodel inward from

the innermost equilibrium point (internal elastic membrane). The closer to the vascular lumen, the earlier the tissue formed, while the tissue near the internal elastic membrane formed later in fetal vascular intimal developing (Figure 2B).

In contrast to **higher hydrostatic pressure strengthening fibrous connective tissue remodeling**[1,4-12,17](Figure.2A, 2B, 3B, 3C, 4A,), the **lower hydrostatic pressure would "desertification" the existing fibrous connective tissue and form adipocytes / foam cells** (Figure. 2C, 2D，3D，3E，4B，4C，5A，5B). Due to the dynamic changes of intravascular hydrostatic pressure or vascular structure during fetal developing, the range of equilibrium points (EP) of vascular simple harmonic motions (SHM) is constantly changing, resulting in the continuous change of the position of each layer of blood vessels. With the thickening of the vascular wall and the narrowing of the lumen, with the Continuity equation (ρSv=constant, ρ= blood density, S= sectional area, v= blood velocity) and the Bernoulli equation ($P+\frac{1}{2}\rho v^2+\rho gh$=constant, P: hydrostatic pressure, ρ: fluid density, v: blood velocity, g: gravitational acceleration, h: height), the hydrostatic pressure on the vascular wall becomes lower[4,5], so the range of equilibrium points (EP) of simple harmonic motions (SHM) would gradually be reduced, resulting in the gradual reduction of hydrostatic pressure in the adventitia / intima and the gradual "desertification" of the existing fibrous connective tissue in the adventitia / intima, which leads to perivascular adipose tissue (vascular "Kuiper Belt") / intimal atherosclerotic plaque(Figure 2C, 2D). Vascular "Kuiper Belt" / intimal foam cells are evidences of the range of equilibrium points (EP) of vascular simple harmonic motions

(SHM) moves gradually[7,8]. The cells involved in this process include mesenchymal stem cells, pericytes, myofibroblasts, fibroblasts, endothelial cells, macrophages, etc[15].

With the principles of physics, human anatomy and cell biology, this theory perfectly explains the developing or remodeling of fetal blood vessels, the formation of vascular three-layer structure, external elastic membrane, internal elastic membrane, thickness of vascular media, vascular "Kuiper Belt"[7] and neonatal atherosclerosis(Figure 1, Figure 2).

Pathological vascular remodeling

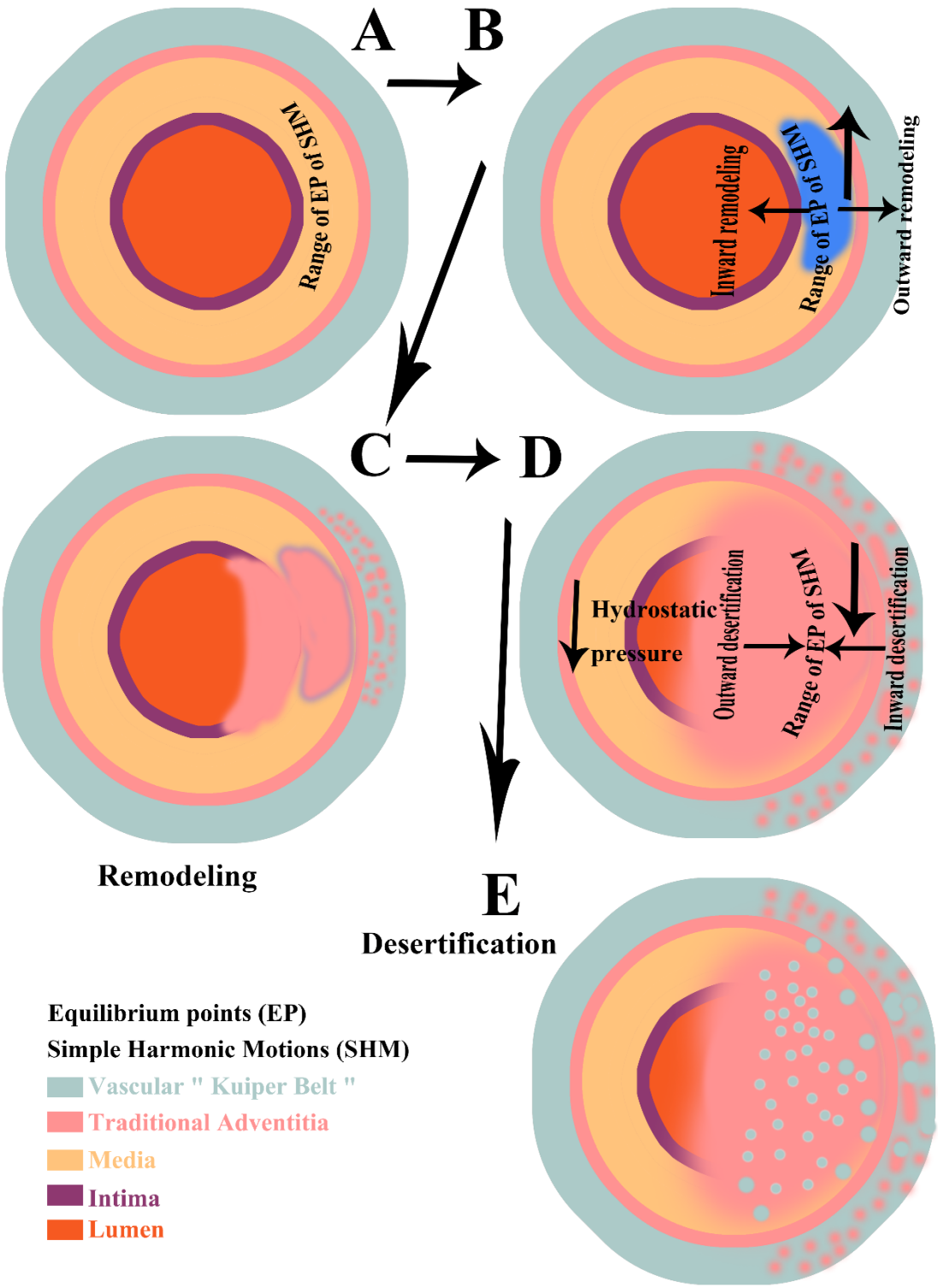

Figure 3. Pathological vascular remodeling

Pathological vascular remodeling has both differences and similarities with fetal early vascular developing and remodeling (Figure 2, Figure 3). Different from fetal early vascular remodeling, with the growth and developing of the body, mesenchymal

stem cells are basically lost and the three-layer vascular structure is basically stable. My previous papers have described in detail the difference among the three layers of blood vessels[5,12]. Due to the very weak regeneration of smooth muscle cells in the media[18], vascular media dysfunction would form when loss / dysfunction of smooth muscle cells occurs in the media. In my previous papers, I have described in detail the remodeling of vascular media, intima or adventitia when media dysfunction occurs, resulting in vascular changes such as atherosclerosis, stiffening or aneurysm, etc[5,7,12].

The theory of vascular media dysfunction can explain the occurrence characteristics, prone sites and non-prone sites of human atherosclerosis, and solved the questions that the traditional hypotheses of atherosclerosis cannot explain[5,12]. Unfortunately, the vascular media dysfunction theory fails to explain the formation of foam cells / vascular "Kuiper Belt"[7] (the vascular "desertification" of existing fibrous connective tissue)(Figure 3D, 3E). This issue can be perfectly explained by combining the principle of vascular simple harmonic motion (SHM) with the vascular media dysfunction theory[4-6,12]: Vascular media dysfunction (absolute or relative)[10] increase the range of equilibrium points (EP) of vascular simple harmonic motions (SHM) (The spring gets looser (absolute) or bigger force on the spring (relative) can obviously increase the amplitude of simple harmonic motion (SHM)): The outermost point of the equilibrium points (EP) moves outward and the innermost point of the equilibrium points (EP) moves inward (Figure 3B). At this time, the hydrostatic pressure borne by vascular adventitia / intima increases significantly, resulting in the remodeling of granulation tissue dominated by myofibroblasts in adventitia / media / intima. Immune

cells, such as macrophages[15], also involved in fibrous connective tissue remodeling (Figure 3B). However, the adventitia is mainly the vascular "desertification" "Kuiper belt" and lacks sufficient supply of nutrients[5]. Although fibrous connective tissue remodeling could still be formed in the sites with vasa vasorum, which is similar to the "Oasis" in the "Desert"[5], its remodeling is insufficient in the vascular "desertification" "Kuiper Belt" (Figure 3C). Unlike adventitia "desertification" "Kuiper belt", the intima has enough nutrients to form a large number of granulation tissue remodeling avoiding to form aneurysm or rupture of the artery with higher hydrostatic pressure, and thus the atherosclerotic plaque (fibrous plaque) is formed[5,12](Figure 3C). The intimal excessive remodeling of the fibrous connective tissue makes the lumen smaller[5,7,8]. With the Continuity equation (ρSv=constant) and the Bernoulli equation ($P+\frac{1}{2}\rho v^2+\rho gh$=constant), the hydrostatic pressure on the vascular wall becomes lower[4,5], so the range of equilibrium points (EP) of simple harmonic motions (SHM) would gradually be reduced (Figure 3D), resulting in the gradual reduction of hydrostatic pressure in the adventitia / media / intima and the gradual “desertification” of the existing fibrous connective tissue in the adventitia / media / intima, which leads to adipocytes / intimal foam cells(Figure 3E). This is a vicious cycle, which leads to the continuous intimal thickening. Fibrous connective tissue "desertification", degeneration, necrosis or calcification results in the formation of various composite plaques. Combining the theory of the vascular media dysfunction[4-6,12] with the vascular simple harmonic motion (SHM), it can perfectly explain human atherogenesis (Figure 3).

Remodeling mechanism of graft vessel

1. Remodeling of venous graft into arterial system

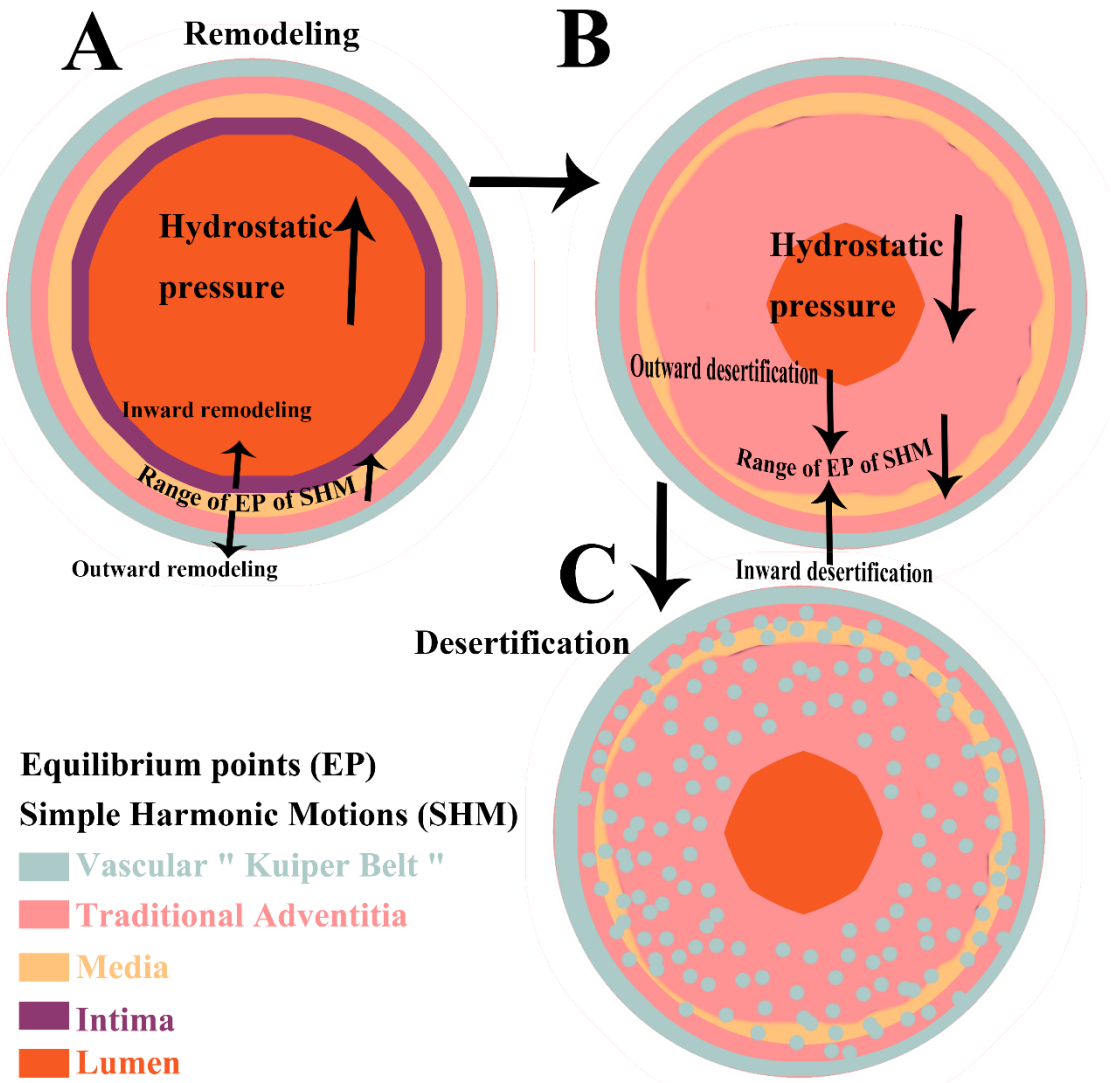

Figure 4. Remodeling of venous graft into arterial system

The remodeling of venous graft into arterial system is similar to that of early fetal blood vessels (Figure 2, Figure 4). Because the media of venous graft is very thin, when transplanted into the arterial system, the hydrostatic pressure increases significantly, the media dysfunction is serious, and the range of equilibrium points (EP) of vascular simple harmonic motions (SHM) would increase significantly as mentioned earlier (Figure 4A). At this time, both the adventitia and intima of venous graft bear higher

hydrostatic pressure (Figure 4A). Therefore, vessels need to be remodeling and thickening to bear higher hydrostatic pressure. Unfortunately, the remodeling ability of adventitia fibrous connective tissue is poor for the poor microcirculation of adventitia. At this time, higher hydrostatic pressure would exacerbate the remodeling of intimal fibrous connective tissue to compensate for the media dysfunction, so it would form obvious thickening / atherosclerotic plaque of the intima (Figure 4B). With the aggravation of lumen stenosis, as mentioned earlier, according to hydrodynamics, the hydrostatic pressure borne by blood vessels decreases, which would “desertification” the formed fibrous connective tissue and form various composite atherosclerotic plaques (Figure 4C). If the remodeling of fibrous connective tissue is insufficient, hemangioma would form on the venous graft.

2. Remodeling of arterial graft into venous system

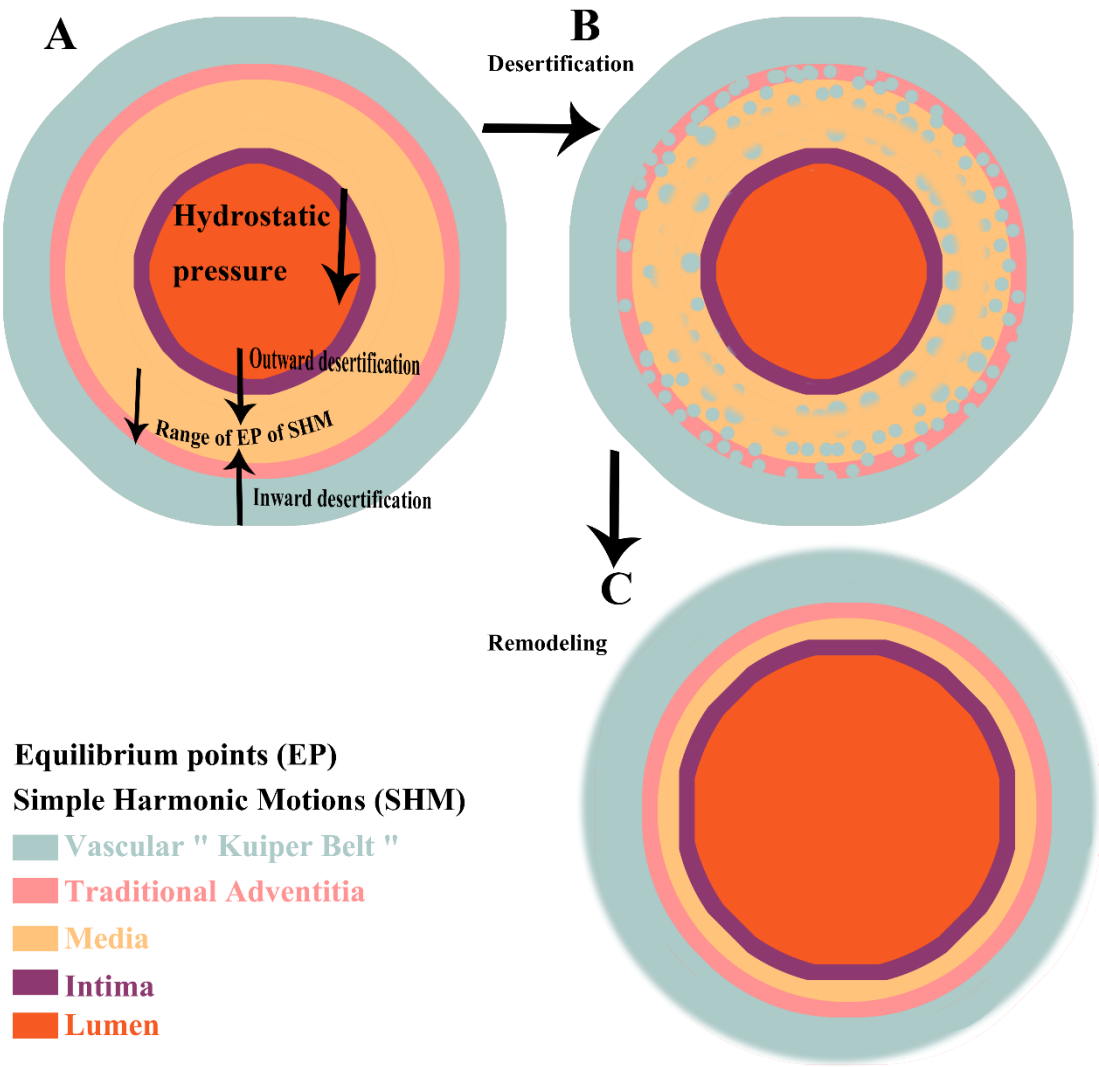

Figure 5. Remodeling of arterial graft into venous system

After arterial graft into the venous system, the range of equilibrium points (EP) of simple harmonic motions (SHM) of arterial graft decreased significantly for the hydrostatic pressure decreased significantly: The outermost point of the equilibrium points (EP) moves inward and the innermost point of the equilibrium points (EP) moves outward. At this time, the hydrostatic pressure borne by vascular adventitia / media / intima decreases significantly (Figure 5A), resulting in the “desertification” of existing fibrous connective tissue in adventitia / media / intima of arterial graft forming adipose tissue / foam cells (Figure 5B). During this process, macrophages

also play as a “scavenger” and would form macrophage derived foam cells / adipocytes[15] . The wall of the arterial graft would gradually become thinner and the lumen of the arterial graft would gradually become larger (Figure 5C).

Etiological treatment of vascular diseases

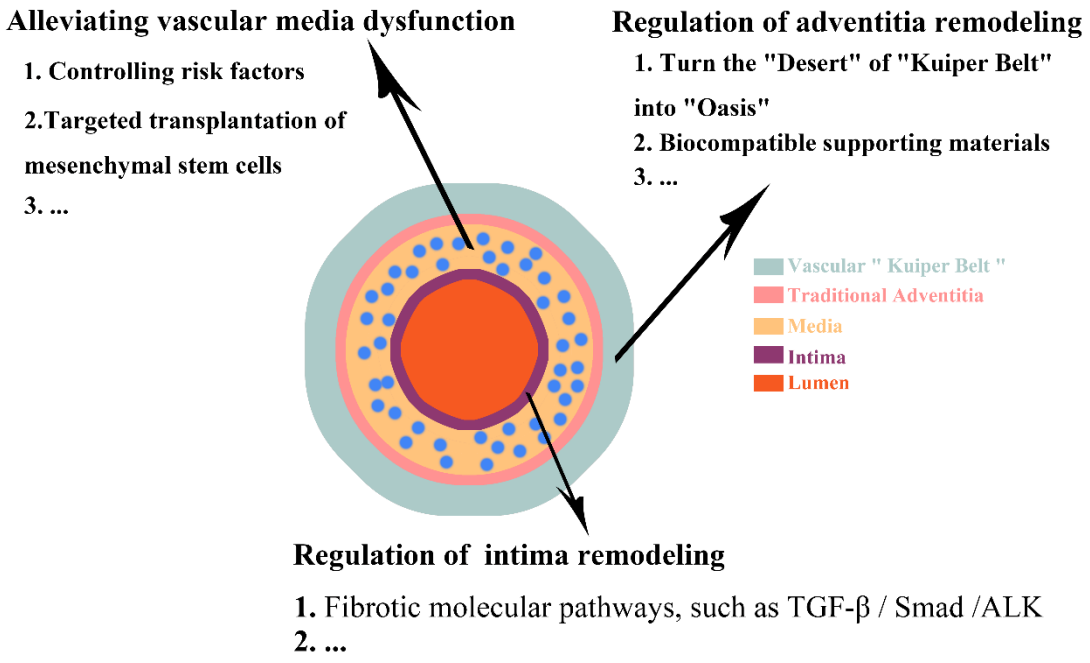

Figure 6. Etiological treatment of vascular diseases

The main mechanism of vascular developing and remodeling has been clarified above. These findings can provide a theoretical basis for the etiological treatment of vascular diseases, such as atherosclerotic diseases, aneurysm, dissection, etc. This paper briefly describes the promising etiological treatment of vascular diseases in the following 3 aspects (Figure 6):

1. Alleviating vascular media dysfunction

1.1 With controlling risk factors, reduce the damage of vascular smooth muscle cells, and alleviate or reverse vascular media dysfunction[5,14].

1.2 After vascular media injury, targeted transplantation of mesenchymal stem cells is one of the possible methods to reverse vascular media dysfunction.

2. Regulation of adventitia fibrous connective tissue remodeling

2.1 Strengthen microcirculation of vasa vasorum, turn the "Desert" of vascular "Kuiper Belt" into "Oasis" inducing the fibrous connective tissue outward remodeling to reduce intimal inward remodeling.

2.2 Biocompatible supporting materials are given to the adventitia of diseased vessels.

3. Regulation of vascular intima fibrous connective tissue remodeling

Treatment of vascular diseases by regulating the fibrotic molecular pathways of myofibroblasts[14].

References

1. Wang X, Ge J. Hypertension Aggravates Atherosclerosis: A Matter of Pressure Remodeling of Myofibroblasts or LDL Accumulation? J Am Coll Cardiol 2021;77(20):2619-2620. DOI: 10.1016/j.jacc.2021.03.305.
2. Wang X, Ge J. Atherosclerotic Plaque Healing. New England Journal of Medicine 2021;384(3):293-293. DOI: 10.1056/NEJMc2033613.
3. Wang X, Ge J. Spontaneous Coronary-Artery Dissection. New England Journal of Medicine 2021;384(11):1077-1077. DOI: 10.1056/NEJMc2100339.
4. Wang X, Ge J. Haemodynamics of atherosclerosis: a matter of higher hydrostatic pressure or lower shear stress? Cardiovasc Res 2021;117(4):e57-e59. DOI: 10.1093/cvr/cvab001.
5. Wang X, Sun A, Ge J. Medial Injury/Dysfunction Induced Granulation Tissue Repair is the Pathogenesis of Atherosclerosis. arXiv:2010.06683. (https://arxiv.org/abs/2010.06683).
6. Wang X, Ge J. Myofibroblast Forms Atherosclerotic Plaques. bioRxiv:2020.07.20.212027. DOI: 10.1101/2020.07.20.212027.
7. Wang X. Perivascular Adipocytes are Components of Adventitia: Vascular “Kuiper belt”. Researchgate:357025934. DOI: 10.13140/RG.2.2.34338.35520.
8. Wang X. Intimal Foam cells and Perivascular Adipocytes are Essentially Similar. Researchgate:356972652. DOI: 10.13140/RG.2.2.29364.17284.
9. Wang X. Muscle Dysfunction and Myofibroblasts Remodeling in Cardiovascular Diseases. Researchgate:355910950. DOI: 10.13140/RG.2.2.29958.09284.
10. Wang X. Types of Vascular Media Dysfunction and Possible Risk Factors.

Researchgate:355486212. DOI: 10.13140/RG.2.2.16052.99202.
11. Wang X. In Situ Venous Atherosclerosis. Researchgate:355339577. DOI: 10.13140/RG.2.2.11589.99040.
12. Wang X. Atherosclerosis. Researchgate:354706286. DOI: 10.13140/RG.2.2.28605.18402/1.
13. Wang X. Steroid Hormones Affect Vascular Diseases through Myofibroblasts. Researchgate:354534894. DOI: 10.13140/RG.2.2.17257.62565.
14. Wang X. Promising Etiological Treatments of Artery Diseases. Researchgate:354507399. DOI: 10.13140/RG.2.2.15802.72641/1.
15. Wang X. Macrophages Transform into Foam Cells by Phagocytosing Tissues Formed by Myofibroblasts. Researchgate:354508855. DOI: 10.13140/RG.2.2.26707.91680/2.
16. Standring S. GRAY'S Anatomy. 41 ed. UK: elsevier, 2016.
17. Tomasek JJ, Gabbiani G, Hinz B, Chaponnier C, Brown RA. Myofibroblasts and mechano-regulation of connective tissue remodelling. Nature Reviews Molecular Cell Biology 2002;3(5):349-363. DOI: 10.1038/nrm809.
18. Holifield B, Helgason T, Jemelka S, et al. Differentiated vascular myocytes: Are they involved in neointimal formation? Journal of Clinical Investigation 1996;97(3):814-825. DOI: 10.1172/jci118481.