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The title of the article

A New Perspective: The Association Between Chronic Venous Insufficiency and Cardiovascular Disease

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Abstract

Chronic venous insufficiency (CVI) has traditionally been treated as a local issue. The 2021 Gutenberg Health Study demonstrated that higher CEAP classification serves as a strong predictor of cardiovascular disease (CVD) development over 10 years in individuals without pre-existing heart disease. Moreover, CVI has been identified as a significant predictor of overall mortality. Many studies have also highlighted shared risk factors between CVI and CVD. Our research revealed that 35% of asymptomatic CVI patients had a coronary artery calcium score (CACS) of ≥100, suggesting that CVI is an independent risk factor for coronary artery disease and a marker for asymptomatic ischemic heart disease. Additionally, CVI contributes to systemic edema, extending its impact beyond the legs. Thus, CVI is no longer merely a local issue; it represents a systemic cardiovascular condition. Education, screening, and management of atherosclerosis risk factors are crucial. This requires the collaboration of all healthcare professionals involved in leg care.

Keywords

Chronic venous insufficiency, cardiovascular disease, shared risk factors, coronary artery calcium score (CACS), systemic edema

1. Prevalence of Chronic Venous Insufficiency

Chronic venous insufficiency (CVI) and chronic venous disorders (CVD) are conditions caused by venous hypertension in the lower limbs, encompassing primary varicose veins, post-thrombotic syndrome, and functional venous insufficiency.[1] Historically, the Basel Study has been frequently referenced for understanding venous disorders. In the current CEAP classification, CVI corresponds to C4, C5, and C6 stages, indicating severe disease.[2]

The definition of CVI has varied across studies, leading to inconsistencies in reviews. However, the CEAP classification was standardized internationally in 1993, with the latest revision released in 2020.[3] According to the 2022 edition of *European Journal of Vascular and Endovascular Surgery*,

the prevalence rates by CEAP classification were: C0S: 9%, C1: 26%, C2: 19%, C3: 8%, C4: 4%, C5: 1%, and C6: 0.4%, totaling 67.4%.

The Gutenberg Health Study analyzed data from 12,423 individuals, reporting a prevalence of varicose veins at 13% and CVI at 41%.[4] Among individuals aged 70 years and older, CVI prevalence exceeded 60%, highlighting its significance as a major public health concern.

In Japan, while the Japanese Society of Phlebology conducts surveys, they are limited to treated conditions, leaving a lack of comprehensive epidemiological data on CVI prevalence in the general population.

2. Association Between Chronic Venous Insufficiency and Cardiovascular Disease

Reports on the relationship between varicose veins and peripheral arterial disease (PAD) have emerged since around 1981. Patients with varicose veins have been found to have a higher risk of intermittent claudication.[5] Mäkivaara LA et al. conducted a 5-year follow-up study of 6,874 individuals and reported that patients with varicose veins had an odds ratio of 2.0 for developing new PAD.[6]

The 1988 Framingham Study analyzed 3,822 individuals and found that women with varicose veins were more likely to exhibit obesity, inactivity, hypertension, and sedentary behavior (e.g., standing or sitting for over 8 hours).[7] These women also had a significantly higher prevalence of atherosclerotic cardiovascular diseases compared to those without varicose veins. Weight control and exercise were recommended to reduce the risks of both varicose veins and atherosclerotic cardiovascular diseases.

Furthermore, women with chronic venous disorders (CVDs) were reported to have significantly higher rates of coronary artery disease, diabetes, obesity, dyslipidemia (elevated triglycerides, low HDL levels), and C-reactive protein (CRP), highlighting a strong association between chronic venous disorders and cardiac risk factors.[8]

In terms of the relationship between varicose veins and heart failure, patients with varicose veins have been shown to have a higher risk of heart failure even after adjusting for gender, age, obesity, PAD, and hypertension.[9] Tamura et al. reported elevated BNP levels in patients with varicose veins preoperatively, which significantly decreased postoperatively. This suggests that varicose veins impose a certain degree of cardiac load, which may be alleviated after treatment.[10]

The 2021 Gutenberg Health Study, which analyzed 12,423 individuals, conducted an epidemiological investigation including CEAP classification. The study demonstrated that CVI shares common risk factors with cardiovascular diseases and that higher CEAP classifications are strong predictors of cardiovascular disease over a 10-year period in individuals without prior heart disease.[4] The follow-up period was 6.4 ± 1.6 years, during which CVI was identified as a significant predictor of all-cause mortality, with a hazard ratio of 1.46.

Prochaska et al. concluded that CVI increases the risk of mortality independently of age, gender, and other cardiovascular risk factors. The editorial by Hamburg NH in the *European Heart Journal* emphasized the clinical importance of this study:

"Until now, it was commonly believed that leg veins, unlike cardiac arteries, do not contribute to heart attacks. However, Prochaska et al. challenged this conventional view, advocating for a shift in perspective. Varicose veins, traditionally regarded as a localized issue, should be recognized as indicators of systemic disease. Their findings underscore the need for an integrated approach to managing CVI alongside cardiovascular risk factors."

The American Heart Association (AHA) has previously campaigned to encourage individuals to "take off your socks and check your feet," primarily focusing on PAD. Prochaska et al.'s findings suggest the necessity of a broader perspective that includes CVI. Moving forward, treatment paradigms should extend beyond localized management of CVI to include comprehensive risk management for cardiovascular diseases.

Wu NC et al., using data from the Taiwan Insurance Database, also reported that patients with varicose veins had higher risks of cardiovascular events and mortality, further highlighting the need for careful consideration of varicose veins in terms of prognosis and treatment.[12]

3. Shared Risk Factors and Pathophysiology Between Chronic Venous Insufficiency and Cardiovascular Disease

Common risk factors for chronic venous insufficiency (CVI) and cardiovascular diseases include obesity, age, smoking, and diabetes. Shared pathophysiological mechanisms involve endothelial dysfunction, inflammation, and thrombosis.[11] Beebe-Dimmer et al. reviewed risk factors for varicose veins and functional venous insufficiency, identifying common risk factors such as age, family history, prolonged standing, and a history of cellulitis.[13] Varicose veins are associated with female gender and obesity, while functional venous insufficiency shows variability in its associations with female gender, obesity, occupation, and hypertension.

In the 2003 San Diego Study, advanced age was found to strongly influence the risk of both varicose veins (odds ratio [OR] 2.4) and CVI (OR 4.9).[14] Obesity (BMI ≥30) significantly increased the risk of CVI in both men (OR 6.5) and women (OR 3.1).[15] The mechanisms by which obesity affects CVI and atherosclerotic lesions include reduced blood flow velocity, hypercoagulability, increased LDL cholesterol and triglycerides, hypertension, and diabetes, all of which contribute to endothelial dysfunction and inflammation.

Regarding the relationship between varicose veins and diabetes, diabetic patients with varicose veins have been reported to exhibit more complications at the microvascular level compared to non-diabetic individuals. Venous function has also been linked to blood glucose and triglyceride levels.[16] Jarošíková R et al. reported that diabetic patients have an elevated risk of both varicose veins and PAD.[17] While diabetes and varicose veins are fundamentally distinct disease entities, it is increasingly recognized that shared atherosclerotic risks induce similar endothelial dysfunction and inflammatory responses in both arterial and venous systems.[18]

Venous hypertension activates numerous inflammatory cascades. Shear stress and adhesion molecules are affected, leading to leukocyte adhesion to endothelial cells, infiltration, vascular wall damage, and interstitial inflammation.[19] Lattimer CR et al. reported significantly elevated levels of inflammatory cytokines such as IL-6, IL-8, and MCP-1 in blood samples collected from varicose veins.[20] Furthermore, Al-Benna et al. detected high levels of hydrogen peroxide and oxidative stress markers in blood samples from the saphenous veins of angina patients. These findings indicate that oxidative stress influences endothelial dysfunction, with LDL cholesterol identified as a critical determinant of vascular endothelial damage.[21]

Although thrombosis in veins and arteries has been studied extensively, many unknowns remain. Genome-wide analyses in 2019 revealed that venous diseases and cardiovascular diseases share more genetic factors than previously thought, providing new insights into their interconnected pathophysiology.[22]

4. Emerging Impacts of Chronic Venous Insufficiency on Systemic (Cardiac) Health

Jürgen H. Prochaska has suggested that while shared risk factors may partially explain how CVI directly influences cardiovascular disease (CVD), unexplored risk factors, such as physical inactivity, and unknown interactions may also play a role.[4]

Several studies have investigated the potential impact of CVI on coronary arteries and cardiac function from different perspectives. Rusinovich Y et al. reported, using echocardiographic studies, that patients with C6 CVI exhibited inferior vena cava diastolic dysfunction and impaired active

diastolic filling of the right ventricle compared to C2 patients.[23] Aykan AC et al. found that patients with CVI had higher mean arterial pressure and cardio-ankle vascular index (CAVI) compared to controls. They suggested that CVI should be considered as a form of vascular sclerosis and that arterial and venous diseases should not be separated in analysis.[24]

Functional arterial resistance may increase due to chronic venous hypertension, leading to irreversible pathological changes. After venous surgery, reduced venous hypertension may decrease functional arterial resistance. Chronic venous insufficiency may elevate both preload and afterload on the heart, potentially impairing cardiac function. Elevated BNP levels in patients with varicose veins before surgery provide indirect support for this hypothesis.[10]

Edema has traditionally been classified as systemic or localized, with CVI considered a cause of localized edema. However, our research using InBody770 to measure extracellular water ratios has demonstrated that varicose veins can also cause systemic edema.[25] Post-surgical reductions in extracellular water ratios were accompanied by improvements in clinical symptoms attributed to edema, such as facial and hand swelling, contralateral leg swelling, and nocturia.[26]

These findings suggest a novel mechanism through which CVI may adversely impact systemic (including cardiac) health. The direct causal relationship between CVI and atherosclerotic disease remains unclear and requires further investigation.

5. Addressing the Relationship Between Chronic Venous Insufficiency and Cardiovascular Diseases

Considering the extensive reports on shared risk factors and pathophysiology between CVI and CVD, it is natural to heed Hamburg NH's call to seriously address these relationships.[11] Inflammation control is a critical area of research, and clinical studies abroad have actively explored the use of vasoactive drugs such as micronized purified flavonoid fractions (MPFF).[27] However, these are not yet covered by insurance in Japan.

In clinical practice, strategies for diagnosing and managing cardiovascular diseases in patients with CVI have not been thoroughly studied. Coronary artery calcium scoring (CACS), a simple CT-based method, can stratify coronary calcium and guide treatment strategies. Elevated CACS has been associated with increased risk of angina and all-cause mortality.[28]

Our outpatient screenings for chronic venous disease routinely include CT imaging, during which CACS is also measured.[29] Among 246 asymptomatic CVI patients, 35% had a CACS ≥100, and 3.5% underwent coronary interventions. Despite visiting for leg-related complaints, discussing asymptomatic cardiac concerns remains uncommon, leading to low utilization rates for cardiac CT or myocardial scintigraphy. Notably, 17.6% of patients who underwent myocardial scintigraphy received subsequent treatment, suggesting that many high-risk patients remain undiagnosed.

CACS ≥1000 is associated with a high probability of cardiovascular events within a few years. Further analysis showed that CVI itself might be an independent risk factor for coronary artery calcified plaques.[30] In a study comparing CVI patients and matched controls, CVI patients had significantly higher CACS values (214 ± 578 vs. 64.8 ± 233) and greater proportions of CACS >100 (35% vs. 12%). Multivariate analysis identified CVI, age, hypertension, and dyslipidemia as independent risk factors for coronary artery calcification.

In settings without CT access, CVI patients with advanced age (≥75 years), hypertension, or dyslipidemia should be identified as asymptomatic ischemic heart disease risk groups. Such patients should either consult a cardiologist or consider optimal medical therapy (OMT) targeting LDL levels below 70 mg/dL in collaboration with their primary care physician.

6. Introduction of an Interesting Case and a Review on the Association Between Chronic Venous Insufficiency and Cardiovascular Disease

A case of an 88-year-old male is presented. The patient was 157 cm tall and weighed 78 kg (BMI 32). He lived alone and presented to our outpatient clinic with the chief complaint of chest pain. Upon arrival, he was asymptomatic. He had a history of obesity, untreated hypertension, untreated dyslipidemia, and inactivity. He also had a history of smoking. His Cardio Ankle Vascular Index (CAVI) was 10. No elevated liver enzymes were found, and there were no changes in his electrocardiogram. The patient had a three-year history of treatment for a venous ulcer (C6), for which he was scheduled for admission to a dermatology department at another hospital three days later. During his outpatient visit, coronary artery CT was performed, revealing a coronary artery calcium score (CACS) of 2456 and a 99% stenosis in the left anterior descending artery (LAD). Despite this, his condition remained stable, and he proceeded with the planned hospitalization at the other hospital. However, one week later, he developed unstable angina and was transported by ambulance to our hospital. Fortunately, he underwent percutaneous coronary intervention (PCI) and was discharged seven days later. The venous ulcer healed after three months. Although the patient had regular follow-ups with his primary care physician, his hypertension and dyslipidemia were not

treated. Had the abnormal CACS been identified during screening, this situation could have potentially been avoided.

In 2022, Gianesini et al. summarized the relationship between chronic venous insufficiency and cardiovascular disease at the UIP symposium[27]. Chronic venous insufficiency (CVI) is considered a cardiovascular disease, as patients with CVI are prone to both arterial (atherosclerosis) and venous (thromboembolism) diseases. The common pathophysiological features of CVI and cardiovascular disease include endothelial injury, hypercoagulability, and systemic inflammation. In CVI, inflammation mainly affects the microcirculation, leading to changes in capillary permeability, remodeling of the venous walls and valves, and an increase in oxidative stress. Once symptoms or signs of CVI appear, patients tend to reduce their physical activity, which can increase the risk of cardiovascular disease. The presence of CVI is associated with an increased risk of cardiovascular events, including peripheral artery disease and heart failure (HF), and as the severity of CVI increases, the risk of cardiovascular events also rises. Management of CVI requires a multidisciplinary approach to assess risk factors related to both the venous and arterial systems. Focusing on resolving endothelial inflammation may be a promising treatment option to control both CVI and cardiovascular diseases.

Conclusion

Chronic venous insufficiency shares pathophysiological and risk factors with cardiovascular disease, as accumulated research has demonstrated that CVI impacts life expectancy. Chronic venous insufficiency should no longer be regarded as solely a problem of the lower limbs but as a cardiovascular disease that warrants attention. It is essential to raise awareness and educate both the general public and healthcare professionals. To deepen understanding in this field, collaboration among researchers from various medical disciplines, such as cardiology, vascular surgery, phlebology, radiology, and rehabilitation medicine, is indispensable.

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Disclosure Statement

Shinji Tomita has no conflict of interest

Author contributions

- Study conception: ST
- Manuscript preparation: ST
- Critical review and revision: ST
- Final approval of the article: ST
- Accountability for all aspects of the work: ST

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