SANAMED
2024; 19(3): 263–265
ISSN-1452-662X

DOI: 10.5937/sanamed0-52781
UDK: 616.12-085
ID: 160164873
Letter to editor

CARVEDILOL: A BETA BLOCKER OF CHOICE FOR THE TREATMENT OF PATIENTS WITH REYNAUD'S PHENOMENON AND CARDIOVASCULAR DISEASES

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Primljen/Received: 15. 08. 2024. Prihvaćen/Accepted: 29. 09. 2024. Published online first: 09. 10. 2024.

Reynaud's phenomenon (RP) is characterized by vasospasm of the digital arteries, leading to episodic color changes. It is named after Maurice Raynaud, who first described this phenomenon in 1862 in a female patient presenting with transient digital ischemia (1). The discoloration of the affected area is typically triphasic: the skin first becomes white due to vasospasm (ischemic phase), then purple (cyanotic phase), and finally red (hyperemic phase). RP is often precipitated by cold exposure or emotional stress and can be accompanied by pain and paresthesia. Its prevalence in the general population is around 5% (2), and it can be classified as primary ("idiopathic") or secondary (SRP). Primary RP is an isolated vasospastic disorder driven by vascular functional abnormalities that typically do not cause permanent damage to the skin.

In contrast, SRP is prevalent in many rheumatic diseases (RD), particularly in connective tissue diseases like systemic sclerosis (SSc) and systemic lupus erythematosus (SLE). The pathogenesis of SRP is complex, involving various vascular structural and functional abnormalities (1). If untreated, SRP can progress to ulceration, gangrene, and scarring, especially in patients with SSc.

Cardiovascular diseases (CVD) are common in patients with RD. Rheumatoid arthritis (RA) patients have a 48% increased risk of cardiovascular events (3), while 20-30% of deaths in SSc patients are attributed to cardiovascular causes (4). Furthermore, the relationship between SLE and atherosclerosis is well established, with these patients at higher risk for coronary artery disease (CAD), cerebrovascular, and peripheral vascular diseases (5). Traditional risk factors like arterial hypertension (HTN) and dyslipidemia cannot solely account for the increased risk of CVD in patients with RD. It is likely that inadequate immune and inflammatory responses in RD contribute to endothelial dysfunction, leading to atherosclerosis and CVD (6).

The most prevalent CVDs in patients with RD include HTN, CAD, and heart failure (HF). Treatment for these CVDs usually involves beta blockers (BBs) (7, 8, 9). Their effectiveness in preventing cardiovascular morbidity and mortality in HF, CAD, and HTN patients is well documented in large randomized studies. However, beta blockers can exacerbate RP (10), with prevalence rates of RP in patients receiving beta-blocker therapy reaching up to 15% (11). It is assumed that by blocking β-adrenoceptors, BBs mimic the norepinephrine-induced vasoconstriction of digital arteries via α1-adrenoceptors. Nevertheless, the exact mechanism by which BBs worsen RP remains unclear.

Consequently, when faced with a patient who has RP and, for example, HF, clinicians may hesitate to prescribe BBs, fearing they might worsen RP, despite knowing that these medications prevent premature mortality in such patients (7). The resolution to this common clinical dilemma lies in recognizing the heterogeneity within the beta blocker class. Indeed, indications and contraindications differ among beta blockers, as they exhibit several distinct pharmacological activities (12, 13). In this context, initiating treatment with a drug that blocks both α-receptors and β-receptors appears logical. However, to date, only one medication with these specific properties has been investigated—labetalol (14).

Labetalol is a non-selective BB that acts as a competitive antagonist of β-receptors and postsynaptic α-receptors (15). Its β-adrenoceptor-blocking activity leads to a reduction in heart rate (HR), while α-adrenoceptor blockade reduces systemic vascular resistance (SVR), resulting in vasodilation and lower blood pressure (BP). Due to this dual blocking activity, labetalol is widely used for treating HTN, especially during hypertensive crises (9). In the previously mentioned study, labetalol demonstrated clinical improvement in patients with RP (14). However, its role in treating CVD is limited to HTN management (9).

Carvedilol, similar to labetalol, is a non-selective beta blocker with β-adrenoceptor antagonist and α_1-adrenoceptor antagonist activity, but it also possesses antioxidative and antiproliferative effects (16). While it primarily lowers BP by reducing SVR through its alpha-1-blocking activity (17), its effect on HR is less pronounced than that of other (selective) BBs (17). The beneficial effects of carvedilol are well established, not just in HTN but also in HF and CAD (7,8,9, 17). The COPERNICUS trial demonstrated that carvedilol administration significantly reduces the risk of death and hospitalizations due to HF in patients with HF and reduced ejection fraction (18). Furthermore, the CAPRICORN study found that administering carvedilol after myocardial infarction significantly reduces all-cause mortality in these patients (19). Therefore, carvedilol exhibits similar effects to labetalol but offers additional benefits (antioxidative and antiproliferative properties), a broader range of indications, and proven beneficial effects on CVDs, as demonstrated in numerous randomized clinical trials.

RP is common in RD, often accompanied by CVD, necessitating the use of BBs in therapy. Carvedilol emerges as a reasonable choice due to its documented benefits in patients with CVD and its dual adrenoreceptor antagonist activity, suggesting it may reduce RP episodes. However, no research has been published on this topic to date. Perhaps a well-designed randomized clinical trial will determine whether carvedilol is the appropriate choice for patients with RP and CVD, and we advocate for this research.

Conflict of Interests: The authors declare no conflicts of interest related to this article.

Funding: No.

Author contribution: All authors have contributed equally

Note: Artificial intelligence was not utilized as a tool in this study.

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***How to cite this article**:* Stojanović M, Nedović J, Ilić S. Carvedilol: a beta blocker of choice for the treatment of patients with Reynaud's phenomenon and cardiovascular diseases. Sanamed. 2024; 19(3): 263-265. doi: 10.5937/sanamed0-52781.