# Calcium Channel Blocker-Related Peripheral Edema: Can It Be Resolved?

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*Calcium channel blocker (CCB)-related edema is quite common in clinical practice and can effectively deter a clinician from continued prescription of these drugs. Its etiology relates to a decrease in arteriolar resistance that goes unmatched in the venous circulation. This disproportionate change in resistance increases hydrostatic pressures in the precapillary circulation and permits fluid shifts into the interstitial compartment. CCB-related edema is more common in women and relates to upright posture, age, and the choice and dose of the CCB. Once present it can be slow to resolve without intervention. A number of strategies exist to treat CCB-related edema, including switching CCB classes, reducing the dosage, and/or adding a known venodilator such as a nitrate, an angiotensin-converting enzyme inhibitor, or an angiotensin-receptor blocker to the treatment regimen. Angiotensin-converting enzyme inhibitors have been best studied in this regard. Diuretics may alter the edema state somewhat, but at the expense of further reducing plasma volume. Traditional measures such as limiting the amount of time that a patient is upright and/or considering use of graduated compression stockings are useful adjunctive therapies. Discontinuing the CCB and switching to an alternative antihypertensive therapy will resolve the edema .*
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Peripheral edema is an uncommon problem in patients with untreated hypertension because local autoregulation by smooth muscle components of precapillary sphincters protects the capillary bed from increased systemic arterial pressures. The onset of persistent peripheral edema in a hypertensive patient should trigger a series of diagnostic considerations, albeit rational ones, to minimize a patient's exposure to unnecessary tests as well as to contain costs. In most cases the diagnostic work-up attempts to identify functional abnormalities in the liver, heart, or kidneys. Without definitive findings in these organ systems, a fail-safe diagnosis is peripheral venous insufficiency, although this should always remain a diagnosis of exclusion.

Two additional important causes of peripheral edema should be considered. In the case of sleep apnea[1] changes in right-sided pressures can slow venous return, prompting the onset of edema. This form of peripheral edema is not typically accompanied by other signs of volume excess and will wax and wane for inapparent reasons that might relate to the fluctuating nature of the sleep apnea itself.[1] This is an uncommon form of peripheral edema.

Drug therapy can also result in peripheral edema. Drug-related edema usually develops gradually and is commonly bilateral, but one limb can exceed the other in size, particularly if venous disease or damage is present more in one limb. The time from the administration of a new drug to the onset of leg edema often provides a helpful clue to a cause-effect relationship. A number of drug classes (other than antihypertensives) have been associated with the onset of peripheral edema in conjunction with weight gain. Nonsteroidal anti-inflammatory drugs (NSAIDs) as well as selective cyclooxygenase inhibitors,[2] such as celecoxib, and rofecoxib, and thiazolidinediones,[3] are two drug classes that may cause edema. Drug-related edema can be expected to subside completely upon withdrawal of the drug, although this may take several days.

Drug therapy causes peripheral edema by two opposing mechanisms. First, as with nonspecific vasodilators such as hydralazine and minoxidil, sodium retention can be of sufficient magnitude to cause edema. The sodium retention caused by these drugs is highly dose-dependent and when present almost always requires diuretic therapy because it seldom remits spontaneously unless the dose of the nonspecific vasodilator is reduced.[4] Other antihypertensives such as β blockers, central α agonists, and peripheral α blockers can also be associated with the development of some peripheral edema, particularly when given in high doses.[5] Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) are rarely associated with peripheral edema. If peripheral edema develops from the use of a calcium channel blocker (CCB), it is not on the basis of salt and water retention because this drug class is intrinsically natriuretic.[6]

This review will focus on the determinants and treatment stratagems of peripheral edema in patients being treated with CCBs. This is a common clinical problem and often is a significant deterrent to continued use of what otherwise is a very effective antihypertensive drug class.

## DEFINITION OF EDEMA

There is no standard definition of peripheral edema in clinical medicine. It is commonly identified by the so-called "pitting" that occurs when pressure is manually placed on various locations in the lower extremities. The physical appearance of peripheral edema is a manifestation of increased interstitial volume.[7] However, interstitial volume must increase significantly before edema becomes evident, and once edema is present small additional changes in interstitial volume can result in a disproportionate increase in the severity of the edema.[8]

Quantifying edema is difficult—both for patient and physician—and is generally reported on a four-point scale. Because of the subjective nature of this scale, the location of the edema—mid-shin or mid-thigh, for example—may provide more practical and reproducible information. Limb asymmetry for edema is also an important qualifying aspect of the edema state because it is often evidence of chronic venous insufficiency. Peripheral edema, which occurs independent of salt and water retention, is troubling but by no means life threatening. The peripheral edema observed with CCBs can differ in appearance from more traditional edema states in that lower extremity redness, warmth, and a non-blanching petechial rash can occur.[9] This is believed to be the result of red blood cell leakage from capillaries and can cause a long-lasting discoloration.

## FREQUENCY OF EDEMA WITH CCB THERAPY

The frequency with which CCB treatment is accompanied by peripheral edema is both compound-specific and dose-dependent. Therefore, a more potent CCB like amlodipine will be associated with higher rates of edema development than a somewhat lower-potency CCB like diltiazem.[10] Reported frequency rates for peripheral edema with CCB therapy are quite varied in the literature in part because of the dose-dependent nature of the phenomenon, and can range from 5% to as high as 70%.[11–15]

Several considerations should be accounted for when attempting to determine the purported frequency of CCB-related edema. First, the reporting system for peripheral edema varies from study to study. The reported frequency of edema is clearly influenced by the method of diagnosis. Edema frequency can be determined from patient self-report,[13] but self-report can overestimate edema frequency because a simple sense of fullness in the lower extremities often is registered as a positive patient response. Edema frequency can also be determined by simple yes/no responses to standardized questions. If this process is repeated several times during a clinical trial, the repetitive nature of the process can result in a learned response pattern. This may be the basis for positive edema reports with either placebo or active therapy that otherwise would not be associated with edema.[12] Finally, edema rates can be ascertained by physical examination combined with careful questioning with slotting into categories of mild, moderate, or severe edema by prospectively established criteria.[12]

A study by Kloner et al.[12] illustrates the difficulty of accurately reporting edema frequency and severity: "The degree of peripheral edema was assessed at each visit by applying gentle pressure to elicit 'pitting' and was ranked as mild, moderate, or severe according to the following criteria. *Mild*: edema was present on examination, but the patient was not aware of it (asymptomatic); the edema did not interfere with daily living, and the patient was willing to continue study medication. *Moderate*: edema was present on examination, and the patient was aware of it (symptomatic); the edema did or did not interfere with daily living, and the patient was willing to continue study medication. *Severe*: edema was present on examination, and the patient was aware of it (symptomatic); the edema interfered with daily living, and the patient was unwilling to continue study medication." Although objective criteria were used for determining the presence of edema in that study, the category assignment was extremely subjective.

Each of these modes of frequency ascertainment also falls short in that the background frequency of peripheral edema before the start of CCB therapy is rarely identified. Transient peripheral edema is

quite common in the general population relating to posture, climactic conditions, and age.[7]

## PATHOPHYSIOLOGY OF EDEMA

The pathophysiology of edema with CCB therapy has no relationship to salt and water retention. In fact, CCBs are intrinsically natriuretic—a process related to a direct tubular effect of CCBs.[6,16] This latter phenomenon is the probable explanation for the occasional reports of polyuria in patients receiving CCB therapy.[17] However, CCB-related edema can occur with pre-existing volume expanded forms of edema, in which case the edema can be severe. CCB-related edema is caused by preferential arteriolar or precapillary dilation without commensurate dilation in the venous or postcapillary circulation.[18,19]

In addition, the reflex rise in precapillary resistance that ordinarily occurs with upright posture is effectively blocked by CCBs.[20,21] This further compounds the problem.

This discrepancy in resistance values increases precapillary pressures to a degree that plasma is literally forced from the intravascular compartment into the interstitium—the origin of peripheral edema with CCB therapy. Under these circumstances the continuous nature of transcapillary fluid movement must exceed the capacity of the lymphatic system for edema to be clinically evident. The issue of CCBs specifically modifying capillary permeability as an additional cause of edema has been debated with no definitive conclusions.[22] In addition, if specific CCBs increase angiotensin-II concentrations it can be expected that venoconstriction might occur with the potential for worsening of the peripheral edema.[6,23]

Several factors will influence the onset and/or severity of peripheral edema with CCB therapy. The individual CCB classes have differing capacities to decrease vascular resistance, with dihydropyridine CCBs being more potent arteriolar dilators than the nondihydropyridine CCBs such as verapamil and diltiazem. Thus, dihydropyridine CCBs are more commonly associated with peripheral edema.[10,17] Peripheral edema rates increase in tandem with dose escalation for all CCBs but not necessarily in an exact, dose-proportional manner.[13,15] Modifiers of CCB-related edema are well characterized and include upright posture,[24] warmth,[24] older age,[25] and female gender. Although female gender is often cited as a risk for peripheral edema with CCBs[26,27] most studies fail to report edema rates on a gender-specific basis.[11–15]

Upright posture provides an additional gravitational contribution to the already increased hydrostatic forces in CCB-treated patients with peripheral edema.[24] On occasion, in an otherwise edema-free CCB-treated patient, peripheral edema can develop if there is a change in the daily postural pattern so that an upright posture is maintained for longer periods of time.

A common pattern with CCB-related peripheral edema is that edema is worse at the end of the day and improves and/or disappears after a patient has remained recumbent throughout the overnight hours. Warm conditions—be they seasonal or work-related—can independently vasodilate the arteriolar circulation and worsen edema. Age is an additional determinant of edema in that interstitial tissue typically serves a barrier role to hydrostatically driven edema formation and the counterbalancing nature (to prevent edema) of such tissue diminishes with age.[25]

Although the principle is sound to support the notion that edema formation with CCB therapy is more common in the elderly, not all reports break edema formation rates out based on age.[25] Finally, edema rates are suggested to be higher in women than men.[26,27] The basis for this has been suggested to relate to the lower threshold for women to report cosmetic changes (such as edema) that might go unrecognized by males.[27] This is a curious supposition and not one that has been formally evaluated. A more interesting possibility for this may be pharmakokinetic. For example, with equivalent doses of the CCB verapamil, women will attain much higher plasma levels for this compound than men.[26] Because peripheral vasodilation relates directly to plasma levels of CCBs, it can be inferred that the higher the plasma levels of verapamil, the greater the tendency to develop edema. The pharmacokinetics of other CCBs have not been determined on a gender basis to permit a generalization of this concept.

## TREATMENT OF CCB-RELATED EDEMA

There have been inconsistent findings when switching from one dihydropyridine CCB to another or when switching to different formulations of the same drug to lessen or resolve peripheral edema.[29–31] Edema will diminish upon conversion from a dihydropyridine CCB to a nondihydropyridine CCB such as verapamil or diltiazem. In addition, the newer, third-generation dihydropyridine CCBs such as lacidipine,[32,33] manidipine,[34] and lercanidipine[32–35] are regularly reported to cause less peripheral edema. Also, there is some suggestion that nocturnally administered CCBs carry a reduced risk of edema development.[36,37]

Diuretic therapy has been offered as one mode of treatment for CCB-related peripheral edema despite the fact that this form of peripheral edema is not related to volume overload per se. When carefully studied, some change in limb volume, a more precise marker of CCB-related vasodilation effect, can be

demonstrated with thiazide-type diuretics.[26] However, the manner by which diuretic therapy improves CCB-related peripheral edema may not be physiologically correct. It is ill advised to routinely diurese patients with CCB-related peripheral edema for the sole purpose of correcting the edema state.

Another strategy useful for the resolution of CCB-related edema is providing a venodilator drug as a means to reducing the venous hypertension that characterizes this phenomenon.[13,37–39] Several drug classes have relevant venodilating potential and, in addition, can further reduce blood pressure. This includes ACE inhibitors, ARBs, and nitrates.[40] ACE inhibitors have been the best studied of this group. They have been shown in several trials to improve edema rate and severity when administered to patients with edema from CCBs.[38,39] However, several questions still remain: What is the optimal venodilating dose of an ACE inhibitor for a specific CCB?, and, Do intraclass differences exist among the several ACE inhibitors? Until such information becomes available, ACE inhibitors should be empirically dosed according to blood pressure considerations and any venodilating effect accepted as a secondary benefit. It should also be appreciated that addition of an ACE inhibitor to a CCB further reduces blood pressure and may permit reduction in the dose of the CCB. This will also aid in resolution of the peripheral edema.

ARBs should behave similarly to ACE inhibitors. However, limited information is available in the published literature to allow substantiation of this hypothesis. Nitrates offer some venodilating potential but require a stop-start regimen to forestall nitrate tolerance. Thus, the dosing regimen becomes fairly complicated if their use is contemplated as a means to modifying the peripheral edema seen with CCB.

## CONCLUSIONS

Peripheral edema is probably the most troubling side effect of CCB therapy. The mechanisms of its development are understandable, so treatment strategies can be developed. A prospective evaluation of treatment strategies has not been undertaken. An approach to peripheral edema that empirically employs dose reduction, interclass shifting of medication, and/or ACE inhibitor or ARB therapy is quite reasonable. Failing conventional treatment, discontinuation of the CCB will ultimately resolve the issue.

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