Comparison of Changes of Body Water Measured by Using Bioelectrical Impedance Analysis between Lercanidipine and Amlodipine Therapy in Hypertensive Outpatients

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Objective: *To compare changes of body water measured by using bioelectrical impedance analysis (BIA), between lercanidipine and amlodipine therapy.*
Material and Method: *This is a prospective randomized open-label study in hypertensive outpatients. Eighty patients were randomized into two groups; 1) amlodipine 5 mg/d and 2) lercanidipine 10 mg/d. Patients were assessed for changes in total body water (TBW), extracellular water (ECW) and intracellular water (ICW) at week 4 and 8 after treatment.*
Results: *At baseline body water in both groups were similar. After treatment, both groups did not have significant changes in body water from baseline. Seven patients in amlodipine group (17.5%) and none of lercanidipine group developed edema; p = 0.012. Among those seven patients, TBW, ECW and ICW all increased significantly from baseline.*
Conclusion: *BIA did not detected changes of body water in most patients. However, in patients who developed edema, TBW, ECW and ICW significantly increased from baseline with the greatest changes seen in extracellular compartment.*

Keywords: *Lercanidipine, Amlodipine, Body water, Peripheral edema, Hypertension, Bioelectrical impedance analysis*

J Med Assoc Thai 2010; 93 (Suppl. 6): S84-S92
Full text. e-Journal: *http://www.mat.or.th/journal*

Hypertension is one of the most common disorders in clinical practice. The estimated prevalence of hypertension is approximately 25% of the global population[1]. In Thailand, previous surveys revealed the prevalence of hypertension to be around 20%[2,3]. Long acting dihydropyridine calcium channel blockers (CCBs) have become the antihypertensive that is commonly used to treat hypertension. They have the advantage of having no adverse effect on glucose and lipid metabolism, can safely be used in patients who have impaired renal function and is recommended by guidelines to be combined effectively with other antihypertensive agents in patients who do not reach their blood pressure goal by using monotherapy. Many previous trials have confirmed their efficacy in terms of blood pressure reduction as well as reduction in cardiovascular events[4-7]. Recent guidelines recommend long acting dihydropyridine CCBs as the first line agents for treating patients with hypertension especially in diabetes or metabolic syndrome patients, patients with high risk for coronary artery disease,

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patients with left ventricular hypertrophy, patients with asymptomatic atherosclerosis, and isolated systolic hypertension[8-10]. Long acting dihydropyridine CCBs have very good safety profile with low incidence of adverse reaction[11-14]. The most common side effect of long acting dihydropyridine CCBs is peripheral edema which is found in 2.8-29% of patients[11-14]. Although, peripheral edema is not a serious side effect, it is the most common reason of discontinuation of long acting dihydropyridine CCBs. It can effect patient's compliance and leads to intolerability and switching of medication in many patients.

The true mechanisms of peripheral edema in patients receiving CCBs still remain unknown. Pedrinelli et al, has postulated that attenuation of postural vasoconstriction by CCBs contributes to the development of peripheral edema[15,16]. However, he also stated that this mechanism could not entirely explain the mechanism of peripheral edema development. Others have reported the evidence that CCBs increase vascular permeability[17,18].

Most of the studies of CCBs-induced peripheral edema used water replacement, or Archimedes, methods to measure the changes in leg volume. Amlodipine is the widely used CCBs in current clinical practice because it is the third generation CCBs that has no effect on heart rate, has no negative inotropic effect and has long half life. However, it is associated with high incidence of peripheral edema[11-13]. Lercanidipine is newer third generation CCBs that has been found in many previous trials, including head-to-head trials with amlodipine[12,19], to have less incidence of peripheral edema[20-22]. Nearly all previous studies used water replacement method to compare the change in leg volume. Whether the main increase in leg volume happens due to increase of water in extracellular space or due to expansion of water in intracellular compartment remains unknown. At present, there has been no previous trial studying the amount of change of water in each compartment of the body after receiving long acting dihydropyridine CCBs.

Bioelectrical impedance analysis (BIA) measures the opposition of body tissues to the flow of a small (less than 1 mV) alternating current. It is a simple, non-invasive investigation that has been shown in many previous studies to be accurate in assessing amount of body water compared to standard methods (*e.g.* dual energy X-ray absorptiometry (DEXA))[23]. BIA has been used in many clinical setting, however, there has been no clinical trial comparing changes in body water by using BIA in patients who receive lercanidipine and amlodipine. The objective of this study is to compare the change of total body water (TBW), extracellular water (ECW) and intracellular water (ICW) between patients receiving lercanidipine versus amlodipine by using BIA measurement.

Material and Method

This is a prospective, randomized, open-label, blinded to endpoint (PROBE) study in hypertensive outpatients. The patients were recruited into the study if they were more than 50 years old, and had indication to receive antihypertensive medication according to JNV VII guidelines. The exclusion criteria included secondary hypertension; severe hypertension or hypertensive crisis; pregnancy or lactation; history of peripheral edema; history of heart failure, liver disease, kidney dysfunction, malnutrition and deep vein thrombosis; concurrent use of medications that may cause edema (*i.e.* steroids, NSAIDs, thiazolidinediones, oral contraceptive pills); concurrent use of medications or substance that may affect blood pressure; body mass index > 30 kg/m2; concurrent use of other calcium channel blockers; and allergy to CCBs. The patients, whom BIA could not be performed, for example, patients with cardiac arrhythmia and amputated patients, were also excluded. All patients gave written informed consent.

The baseline demographic data were obtained and thorough physical examination was performed in all patients. Blood pressure was measured using standard recommended technique using automatic blood pressure monitor (BP 3BT0-A, Microlife®, Switzerland). The blood pressure measurement was performed in both arms and the arm with the higher value of each individual patient was used for baseline and for all follow-up measurements. The blood pressure was measured three times and the mean value of two closest readings was used.

BIA was measured using Maltron Bioscan 916 Analyser. The equipment had been calibrated with calibration device (MCR-1204) at the beginning of the study. The total body water (liter), extracellular water (liter) and intracellular water (liter) and other results of BIA measurements were recorded using the standard recommended protocol[23].

The patients were then randomized using block randomization into two groups (40 patients in each group). The control group received amlodipine 5 mg/d and the study group received lercanidipine 10 mg/d. Both groups were advice to take the study medication in the morning. Both groups received similar

advices regarding lifestyle modifications using identical advice protocol. Investigators called each individual patient weekly to monitor adverse reaction. The patients were scheduled to come in at week 4 and week 8 for physical examination, and for BP and BIA measurement. The primary endpoint of the study was the absolute change of TBW, ECW and ICW from baseline. The secondary endpoints included the incidence of peripheral edema, and the efficacy of each treatment regimen defined as percent of patients who achieved goals according to JNC 7 at the end of study. Peripheral edema was diagnosed from physical examination by single investigator and was confirmed by patient's physician. Patients were assessed for (1) changes in total body water, extracellular water and intracellular water (2) incidence of peripheral edema (3) correlation between clinical edema and body water after 4 and 8 weeks of treatment. The assessments were conducted by investigators who were blinded to the patients' medications. After 4 weeks of treatment, the dose of medication was doubled in patients who did not achieve their blood pressure goals according to JNC VII.

Statistical analysis

Data were analyzed using statistical software (SPSS version 11.5, USA). Descriptive statistics for all numeric variables, including means and standard deviations (SD), together with the proportions of all categorical variables were calculated. Depending on these, Chi-square tests or Fisher's exact test (for categorical variables) and ANOVA or Unpaired t-test (for continuous variables) were used to assess difference between lercanidipine and amlodipine groups. One-way repeated measures ANOVA was used for within group comparison. An intention-to-treat analysis was substituted for any missing values. $P<0.05$ was considered to be statistically significant.

Results

There were 80 patients included in the study. Baseline demographic data were shown in Table 1. The mean age of population was 61.81 $\pm$ 9.72 years. Fifty five percent (44/80) were female. The mean body weight and height were 67.03 $\pm$ 10.13 kilograms and 158.52 $\pm$ 7.91 centimeters, respectively. The mean BMI in the studied population was 26.59 $\pm$ 1.14 kg/m^2. Nearly all patients (95%) were non-smoker and only few patients (10%) had history of alcohol consumption. Around seventy percent of the studied population performed regular exercise. The most common co-morbid disease was dyslipidemia which affected around three-quarter of the patients. One-third of patients were diabetes.

Of 80 patients, forty patients were randomly assigned to receive lercanidipine and the other forty patients were assigned to amlodipine group. The baseline BMI in both groups were similar (26.12 $\pm$ 1.40 kg/m2 vs. 27.05 $\pm$ 1.10 kg/m2, $p = 0.305$). The baseline systolic blood pressure (SBP) and diastolic blood pressure (DBP) in lercanidipine (159.69 $\pm$ 10.47 mmHg, 93.10 $\pm$ 10.18 mmHg) and in amlodipine groups (159.15 $\pm$ 12.33 mmHg, 92.10 $\pm$ 9.55 mmHg) were not statistically different. Twelve patients in lercanidipine group and eight patients in amlodipine group received only study medication monotherapy for treating hypertension ($p = 0.439$). Both groups had similar rate of using other concomitant anti-hypertensive medications (Table 1).

After 4 weeks of treatment, 7 patients who received amlodipine developed peripheral edemas which were confirmed by physicians. All of them were female aged from 53-83 years. Five of seven patients required discontinuation of amlodipine. The symptom of peripheral edema disappeared completely in all five patients after discontinuation of amlodipine for 1-2 weeks. No patient in lercanidipine group experienced peripheral edema. There was no additional report of peripheral edema between week 4 and week 8 in both groups.

After 4 weeks of treatment, the mean SBP and DBP in lercanidipine group (137.50 $\pm$ 12.80mmHg/ 82.48 $\pm$ 10.75 mmHg) were similar to amlodipine group (135.80 $\pm$ 17.13 mmHg/ 80.10 $\pm$ 12.13 mmHg), $p > 0.05$. After 8 weeks, the mean SBP and DBP were also not different in both groups;133.12 $\pm$ 13.62 mmHg/ 77.89 $\pm$ 10.93 mmHg in lercanidipine group and 133.35 $\pm$ 10.08 mmHg/ 79.36 $\pm$ 8.96 mmHg in amlodipine group, $p > 0.05$. At the end of study, the percent of patients who achieved their blood pressure goals in lercanidipine and amlodipine were 57.5% vs. 50%, respectively, $p = 0.248$.

At baseline, the total body water (TBW), extracellular water (ECW) and intracellular water (ICW) in lercanidipine group were 34.68 $\pm$ 6.58 L, 15.05 $\pm$ 2.86 L and 19.63 $\pm$ 3.98 L, respectively, which were similar to those of amlodipine group (35.13 $\pm$ 6.86 L, 15.15 $\pm$ 2.85 L and 19.62 $\pm$ 4.30 L, respectively), all $p > 0.05$ (Table 2). After 4 weeks of treatment, TBW, ECW and ICW in lercanidipine group were 34.50 $\pm$ 6.41 L, 14.78 $\pm$ 2.59 L and 19.72 $\pm$ 4.08 L, respectively, which were not different from those of amlodipine group; 35.17 $\pm$ 6.58 L, 15.16 $\pm$ 2.73 L and 20.00 $\pm$ 4.20 L, respectively, all $p > 0.05$. There had been no significant changes of water in all compartments from baseline after 4 and 8 weeks of both treatment regimens. The mean body weights of the

patients in both groups were also unchanged.

In 7 patients who developed clinically significant peripheral edema, there had been significant increases in body water. The mean TBW, ECW and ICW in those 7 patients at baseline were 30.72 ± 4.50 L, 13.34 ± 1.55 L, and 17.38 ± 3.29 L and significantly increased to 32.18 ± 4.72 L, 14.20 ± 1.81 L and 17.98 ± 3.36 L after 4 weeks of treatment. The mean increase in TBW was 1.46 ± 1.04 L which was 4.75% increase of TBW from baseline. Most of the increase in body water was in extracellular compartment (0.86 ± 0.82 L) which was 6.45% increase from baseline ECW. The water in intracellular compartment also significantly increased from baseline in those 7 patients but the amount of change (0.59 ± 0.39 L, 3.39% of baseline ICW) was less than the change observed in extracellular compartment (Table 3). The mean body weight of those 7 patients increased from 64.06 kg to 64.41 kg after 4 weeks of treatment.

Discussion

To our knowledge, this is the first report of the changes in TBW, ECW, and ICW in patients receiving long acting dihydropyridine CCBs. The previous researches of CCBs-induced peripheral edema monitor changes in leg volume by using water

Table 1. Baseline demographic data of patients

Demographic data	All patients Number (%) n = 80	Number (%)		p-value
		Lercanidipine n = 40	Amlodipine N=40	
1. Gender				
Male	36 (45.0)	18 (45.0)	18 (45.0)	1.000
Female	44 (55.0)	22 (55.0)	22 (55.0)	
2. Age (mean ± SD, year)	61.81 ± 9.72	59.93 ± 8.95	63.70 ± 10.20	0.083
3. Body weight (kg)	67.03 ± 10.13	66.30 ± 9.48	67.75 ± 9.82	0.602
4. Height (cm)	158.52 ± 7.91	159.06 ± 7.75	157.99 ± 8.13	0.547
5. Body mass index (kg/m^2)	26.59 ± 1.41	26.12 ± 1.40	27.05 ± 1.10	0.305
6. Heart rate (beats/min)	69.74 ± 13.27	72.45 ± 13.98	67.03 ± 12.09	0.067
7. SBP (mmHg)	159.42 ± 11.37	159.69 ± 10.47	159.15 ± 12.33	0.834
8. DBP (mmHg)	92.60 ± 9.82	93.10 ± 10.18	92.10 ± 9.55	0.652
9. Underlying disease				
- ischemic heart disease	5 (6.2)	2 (5.0)	3 (7.5)	1.000[a]
- stroke	7 (8.8)	4 (10.0)	3 (7.5)	1.000[a]
- diabetes	27 (33.8)	12 (30.0)	15 (37.5)	0.636
- dyslipidemia	61 (76.2)	33 (82.5)	28 (70.0)	0.293
10. Family history of heart disease	6 (7.5)	4 (10.0)	2 (5.0)	0.675[a]
11. Smoking	4 (5.0)	2 (5.0)	2 (5.0)	1.000[a]
12. Exercise				
- regularly	57 (71.2)	29 (72.5)	28 (70.0)	1.000
- occasionally	17 (21.3)	8 (20.0)	9 (22.5)	
- rarely	6 (7.5)	3 (7.5)	3 (7.5)	
13. alcoholic consumption	8 (10.0)	6 (15.0)	2 (5.0)	0.263[a]
14. Anti-hypertensive medication				
- beta-blockers	32 (40.0)	15 (37.5)	17 (42.5)	0.819
- ACEIs	30 (37.5)	17 (42.5)	13 (32.5)	0.488
- diuretics	33 (41.2)	15 (37.5)	18 (45.0)	0.650
- ARBs	16 (20.0)	5 (12.5)	11 (27.5)	0.162
- □-blockers	6 (7.5)	2 (5.0)	4 (10.0)	0.675[a]
- None	20 (25.0)	12 (30.0)	8 (20.0)	0.439

[a] Fisher's Exact test

SBP = systolic blood pressure, DBP = diastolic blood pressure, ACEIs = angiotensin converting enzyme inhibitors, ARBs = angiotensin receptor blockers

replacement (water submersion), or Archimedes, method[15, 24, 25]. Although this technique is simple and non-invasive, it is very inconvenience and cumbersome and rarely been used in real clinical practice. It also does not provide information whether the main increase in leg volume happens due to increase of water in extracellular space or due to expansion of water in intracellular compartment.

BIA is a commonly used method to estimate body composition. BIA provides the estimate of total body water[26,27]. The value of TBW derives from BIA is used to estimate body composition (*e.g.* fat-free mass and body fat). BIA is a simple, non-invasive, inexpensive, accurate and portable device. BIA has been found to be accurate when compared with other standard technique for measuring TBW[28]. BIA has the potential for monitoring change in body water and makes it an interesting investigation for detecting change in TBW, ECW and ICW in patients receiving long acting dihydropyridine CCBs.

Our study did not find significant changes of body water from baseline, measured by using BIA, in both lercanidipine and amlodipine groups. The result differed from other previous study that used water replacement technique[19]. In those studies, amlodipine was associated with significant increase of leg volume and the degree of increase was greater than that of lercanidipine. There are many possible explanation of the negative result from our study. First, the population in our study represented the patients with very low risk of developing edema. Patients with previous history of peripheral edema from any causes, patients who had

Table 2. Water in each body component measured by BIA

Body water	Lercanidipine	Amlodipine	p- value[a]
1. TBW (mean ± SD,L)			
week 0 (n = 80)	34.68 ± 6.58	35.13 ± 6.86	0.769
week 4 (n = 80)	34.50 ± 6.41	35.17 ± 6.58	0.644
week 8 (n = 73)[b]	34.67 ± 6.60	35.48 ± 6.29	0.577
p-value[d] (0 vs. 1, 0 vs. 2)[c]	0.138, 1.000	1.000, 0.928	
2. ECW (mean ± SD,L)			
week 0 (n = 80)	15.05 ± 2.86	15.15 ± 2.85	0.877
week 4 (n = 80)	14.78 ± 2.59	15.16 ± 2.73	0.528
week 8 (n = 73)[b]	15.00 ± 2.78	15.28 ± 2.73	0.653
p-value[d] (0 vs. 1, 0 vs. 2)[c]	0.166, 1.000	1.000, 1.000	
3. ICW (mean ± SD,L)			
week 0 (n = 80)	19.63 ± 3.98	19.62 ± 4.30	0.995
week 4 (n = 80)	19.72 ± 4.08	20.00 ± 4.20	0.759
week 8 (n = 73)[b]	19.67 ± 4.08	20.19 ± 3.83	0.553
p-value[d] (0 vs. 1, 0 vs. 2)[c]	0.966, 1.000	0.957, 0.450	

TBW= total body water, ECW=extracellular water, ICW=intracellular water, SD = standard deviation, L= liter
[a] Using ANOVA test
[b] At week 8 use mean of group for the missing data
[c] Week 4 and 8 compared with week 0
[d] Using repeated measures one-way ANOVA

Table 3. Details of Bioelectrical impedance analysis (BIA) measurement in patients who developed clinical edema

Body water (n = 7)	Week 0	Week 4	Absolute change (Median)	p-value [a]
1. TBW (mean) ± SD,L)	30.72 ± 4.50	32.18 ± 4.72	1.46 ± 1.04 (1.80)	0.010*
2. ECW (mean ± SD,L)	13.34 ± 1.55	14.20 ± 1.81	0.86 ± 0.82 (1.02)	0.032*
3. ICW (mean ± SD,L)	17.38 ± 3.29	17.98 ± 3.36	0.59 ± 0.39 (0.58)	0.007*

[a] Paired-Samples T test
*Statistically significant, $p < 0.05$

conditions that might cause edema and patients who were taking medications that affected edema were all excluded. The mean change of body water might have been more prominent, if we chose to study the population with higher incidence of peripheral edema. Second, BIA may not be sensitive or accurate tool for detecting changes in body water in patients receiving CCBs. Although many studies showed the accuracy of BIA in several clinical setting[28-30], the accuracy of BIA remained limited in many conditions[31-35]. Third, BIA detected the change in whole body and may not be sensitive enough to monitor change in lower limbs area. The use of segmental BIA may be more accurate or more sensitive in detecting any changes in the area interested but more researches are needed to confirm this possibility.

The results of our study were consistent with previous studies in terms of blood pressure control[12,36-40]. Both lercanidipine and amlodipine were effective in reducing blood pressure. The final SBP and DBP after treatment and also the percent of patients achieved blood pressure target were not different in both groups.

The definite mechanism of CCBs induced peripheral edema remains inconclusive. Studies of skin blood flow using laser Doppler flowmetry suggested that attenuation of postural vasoconstriction by CCBs may play a pivotal role in the development of peripheral edema. Others have reported the evidence that CCBs increase vascular permeability[17,18].

The incidence of clinical edema in our study was low. No one in lercanidipine group develop peripheral edema, the finding that was similar to previous study[14, 22]. The incidence of peripheral edema in amlodipine group was also comparable to previous studies[12]. All 7 patients who developed clinical edema were female and were in amlodipine group. Other investigators also reported more frequent peripheral edema in female[41] and in patients taking amlodipine compared to lercanidipine[19,42]. The reasons for gender preference in development of peripheral edema were unknown. The reason of less edema with lercanidipine may be explained by the fact that, unlike amlodipine that has main vasodilatory effect on pre-capillary arterioles, lercanidipine has the balance effect on both pre- and post-capillary vessels.

In 7 patients who developed clinical peripheral edema, BIA detected significant changes of body water in all compartments. The mean increase of TBW was 1.46 ± 1.04 L. We observed greater amount of changes of water in the extracellular compartment (0.86 ± 0.82L or 6.45% increase from baseline) than in the intracellular compartment (0.59 ± 0.39L or 3.39% increase from baseline). Our group was the first to report of changes in TBW, ECW and ICW in patients who developed CCBs induced peripheral edema. The percent increase of ICW from baseline was nearly 50% less than the percent increase in ECW; however, the increase in ICW was clearly significant. Our finding of significant increase in ICW could not be explained by any of the previously mentioned mechanisms. Further studies are needed to explore the effect of CCBs and intracellular water in order to have better understanding of the mechanisms of CCBs induced peripheral edema.

There were few limitations in our study. First, the number of patients in our study was small. Although it was comparable to previous comparative studies of CCBs and was statistically sufficient, the number may be too small for subgroup analysis. Second, prospective randomized open label, blind to endpoints (PROBE) was used in our study because it was more convenience than double-blinded randomized control trial. The patients were equally randomized into each group, objective measurements (BIA measurements) were used for endpoints, and the endpoint measurements were made without knowing the patient's treatment. However, the possibility of bias could not be completely excluded. Third, we used whole body BIA because it was widely used, was available in clinical practice, and had a lot of data support. Using segmental BIA technique to measure only the lower extremities could yield the different results and future studies are needed.

Conclusions

There was no significant change of body water, measured by using BIA, in patients after 4 to 8 weeks of lercanidipine and amlodipine treatment. Amlodipine was associated with higher incidence of clinical peripheral edema. In patients who developed peripheral edema, there were significant increases of body water in all compartments (TBW, ECW, and ICW) with the greatest change seen in the extracellular compartment.

Acknowledgements

We would like to thank Pannipa Tengtrakulcharoen for manuscript preparation.

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การเปรียบเทียบการเปลี่ยนแปลงปริมาณน้ำในร่างกายหลังได้รับการรักษาด้วยยาเลอร์คานิดิปีนและแอมโลดิปีนในผู้ป่วยนอกโรคความดันโลหิตสูง

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วัตถุประสงค์: *เพื่อศึกษาการเปลี่ยนแปลงของปริมาณน้ำในร่างกายหลังได้รับการรักษาด้วยยาเลอร์คานิดิปีนเทียบกับยาแอมโลดิปีน*

วัสดุและวิธีการ: *ทำการวิจัยเชิงทดลองชนิดสุ่มไปข้างหน้าแบบเปิดในผู้ป่วยโรคความดันโลหิตสูง 80 คน ได้รับการสุ่มแบ่งเป็น 2 กลุ่ม คือกลุ่มได้รับยาแอมโลดิปีน ขนาด 5 มิลลิกรัมวันละครั้ง และกลุ่มได้รับ ยาเลอร์คานิดิปีน 10 มิลลิกรัมวันละครั้ง ทำการศึกษาการเปลี่ยนแปลงของน้ำในร่างกายของทั้งสองกลุ่มโดยใช้ bioelectrical impedance analysis ที่ 4 และ 8 สัปดาห์*

ผลการศึกษา: *ผู้ป่วยทั้งสองกลุ่มมีข้อมูลพื้นฐานไม่แตกต่างกัน ผลการศึกษาพบว่าผู้ป่วยทั้งสองกลุ่มมี ปริมาณน้ำในร่างกายไม่ต่างกันอย่างมีนัยสำคัญและไม่เปลี่ยนแปลงเมื่อเทียบกับค่าตั้งต้น มีผู้ป่วยเกิดการบวม 7 คน ในผู้ป่วย 7 คนที่เกิดการบวม พบการเพิ่มขึ้นของปริมาณน้ำในร่างกายอย่างมีนัยสำคัญ*

สรุป: *ไม่พบการเปลี่ยนแปลงของปริมาณน้ำในร่างกายในผู้ป่วยส่วนใหญ่ที่ได้รับการรักษาด้วยยาเลอร์คานิดิปีนและยาแอมโลดิปีน ในผู้ป่วยที่เกิดการบวมพบมีการเพิ่มขึ้นของปริมาณน้ำในร่างกาย โดยเฉพาะในส่วนของปริมาณน้ำนอกเซลล์*