Short Term Evaluation of Captopril in Patients with Chronic Left Sided Valvular Regurgitations

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Abstract

Objective: To evaluate the clinical effects and the changes in cardiac performance of high- and low-dose captopril compared to placebo in patients with chronic symptomatic aortic regurgitation (AR), and/or mitral regurgitation (MR).

Patients and Methods: We randomized patients into three groups, placebo (Group 1), incremental daily doses of 50 mg (Group 2), and 100 mg captopril (Group 3). We compared exercise capacity before and after four-week of treatment.

Results: Treatment was well tolerated with no serious side effects including blood chemistry. There were no significant effects of treatment on left ventricular dimensions nor calculated left ventricular ejection fraction (LVEF) between groups (LVEF change -0.6%, -2.6%, 2.4%, in group 1, 2 and 3 respectively; $p > 0.05$). No difference of exercise duration between treatment and placebo arms (change by 13%, 12.8%, 16.4%, respectively; $p > 0.05$). However, there were trends in the number of the patients who improved in left ventricular performance (absolute LVEF change > 5 % unit = 15%, 16%, and 42% respectively; $p > 0.05$) and exercise performance (exercise time improvement > 75 sec = 50%, 47%, and 68% respectively; $p > 0.05$) in high dose captopril treatment group.

Conclusion: There was no significant improvement of left ventricular performance and exercise capacity after four-weeks' treatment of low and high dose captopril. Further study with a larger sample size, and longer follow-up period may be required.

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Hemodynamic changes in the patient with heart failure is characterized by elevated left ventricular filling pressure and increased systemic vascular resistance which further compromise left ventricular performance[1-3]. The beneficial hemodynamic and clinical effects of angiotensin-converting enzyme (ACE) inhibition in patients with severe congestive heart failure have been documented in large-scale studies[4-6]. This mode of therapy when added to digitalis and diuretics improved survival. ACE inhibitors prevent the formation of the vasoconstrictor peptide, and angiotensin II (AII)[7]. The primary effect of ACE inhibitor in causing vasodilatation of the peripheral vessels and inhibiting aldosterone biosynthesis result in reduction of water and sodium retention[8], the benefit of inhibition of AII synthesis is also believed that in cellular level can limit detrimental cell growth and hypertrophy. Therefore, blockade of AII could be expected to improve the cardiac pumping efficiency of the heart.

Patients with symptomatic aortic or mitral regurgitation may also benefit from decreased cardiac workload due to a reduction in preload. Long term therapy with vasodilating drugs has been shown to reduce left ventricular size and improve performance in chronic aortic regurgitation (AR)[9-12]. Similar trials in mitral regurgitation (MR) have rarely been published[13,14].

Timing of surgery for left sided valvular regurgitation was ambiguous, but it is widely accepted that surgery must be done before development of left ventricular dysfunction[15,16]. A number of various indexes was proposed to allow clinicians to detect and avoid irreversible left ventricular dysfunction[17-19]. Patients have to undergo surgery at an appropriate time, to reduce operative mortality and obtain good long-term survival. While the proper timing for the operations is still being examined, another issue is whether vasodilators, which reduce the regurgitant overload, can delay the onset of ventricular dysfunction and thus also delay surgery.

In Thailand, for socio-economic reasons, valvular replacement surgery is often delayed and there is a large pool of patients with moderate to severe symptomatic aortic and/or mitral regurgitation who are on medical therapy awaiting surgery.

The objective of this study is to assess effects of captopril on left ventricular performance indices in patients with chronic aortic and/or mitral regurgitation. The secondary objective is to measure effect on exercise capacity after the treatment.

METHODS

Patient Selection

The patients eligible in this study have to meet all entry criteria which are :

- 15 to 75 years of age, with evidence of aortic and/or mitral regurgitation confirmed by cardiac Doppler. Written informed consent must be obtained from all patients.
- Patients are in New York Heart Association functional class I to III.
- Left ventricular ejection fraction greater than 40 per cent as determined by 2D echocardiography.
- Maximal exercise test limited by dyspnea and/or fatigue, but not by angina, claudication or arthritic complaints.
- Stable cardiac symptomatology within the previous 60 days.

Exclusion criteria are :

- Myocardial infarction or coronary bypass surgery within the past 60 days.
- Symptoms of angina pectoris within 1 month of entry.
- Cardiac arrhythmias except controlled atrial fibrillation.
- Hypertension requiring additional therapy
- Treatment with angiotensin converting enzyme inhibitors within 4 weeks of entering the study.
- Serum creatinine concentration > 2.0 mg/dL.
- Pulmonary disease which limits exercise capacity.
- Inability to perform treadmill exercise test.
- Obstructive cardiac valvular disease.
- Systolic blood pressure < 100 mmHg or > 220 mmHg.
- Severe hepatic disease (SGOT or SGPT > 2 folds upper limit of normal).
- History of collagen vascular or auto-immune disease.
- Leukopenia (WBC < 3500 /mm^3) or neutropenia (< 1500 /mm^3).
- Previously demonstrated hypersensitivity to angiotensin converting enzyme inhibitors.
- Known renal artery stenosis.
- Treatment with vasodilators, calcium channel blockers or beta blockers.

Randomization and Dose Titration

Patients who met the entry criteria were randomized to receive placebo (Group 1, n = 21) or captopril 25 mg bd (Group 2, n = 19) or captopril 50 mg bd (Group 3, n = 20) after captopril testing dose. Diuretics were withheld on the day of captopril testing dose. Eligible patients were given a 6.25 mg test dose of captopril in hospital clinic, heart rate and seated blood pressure will be taken every 15 minutes for 1 hour. If the patients did not have hypotension with a drop of systolic > 10 mmHg from baseline or systolic blood pressure fell below 100 mmHg, then the patients were randomized to 1 tablet of placebo bd in Group 1, to therapy at 6.25 mg bd increasing to 25 mg bd in Group 2 and to 50 mg bd in Group 3.

Study Assessment

The patients returned to the clinic at the end of the week. Compliance was checked with brief physical examination. If the patients had symptoms of hypotension or systolic blood pressure < 100 mmHg then the dose of captopril would be reduced to the level of the lowest tolerated dose.

The duration of study was four weeks including 1 week dose titration and 3 weeks therapy of the target dose.

At baseline the following assessments were accomplished; complete medical history and physical examination, chest X-ray and 12 lead ECG, baseline laboratory profiles, concomitant medications, New York Heart Association (NYHA) functional class, and 2D echocardiography including Doppler echocardiography to determine left ventricular end-diastolic dimension index (LVEDI), left ventricular end-systolic volume index (LVESVI), Stroke volume index (SVI), and left ventricular ejection fraction (LVEF) in triplicate measurements (3 readings at one sitting). Treadmill exercise test was performed, using a continuous multi-stage modified Naughton protocol. The exercise was terminated if dyspnea and/or fatigue developed.

At the end of therapy (week 4) patients returned to the clinic for the following procedures: compliance check, complete medical history and physical examination, 12 lead ECG, laboratory profiles, concomitant medications, NYHA class, follow-up echocardiography, and the treadmill exercise test.

The following concomitant medications were permitted: diuretics, digoxin, nitrates, anticoagulant or anti-platelet aggregation medication.

Criteria for Discontinuing Treatment

The following events were reasons for discontinuing treatment with the study medication:

1. serious adverse events due to the study drug.
2. conditions requiring therapeutic intervention.
3. heart failure requiring treatment.
4. myocardial infarction.
5. laboratory findings fulfilling the exclusion criteria i.e. serum creatinine > 2.5 mg/dL.
6. withdrawal of consent
7. pregnancy.
8. patients not 80 per cent compliant at week 1 determined by pill count.
9. any other situation where in the opinion of the investigator, continued participation in the study would not be in the best interests of the patient.

Statistical Analysis

$P \leq 0.05$ was considered statistically significant. For all discrete data, summarization was presented in form of per cent, and the differences were analyzed with Pearson's chi-square or Fisher's exact test for small sample. Means and standard deviation were used to present continuous data with normal distribution. One way ANOVA was performed on comparison of baseline normally distributed data, and Kruskal-Wallis rank test was performed for the same purposes for data with non-normal distribution. Furthermore repeated measurement method or Friedman two-way ANOVA was used for multivariate comparison of variables which were measured repeatedly on time.

All data analysis was performed with two statistical package; STATA version 4.0 and SPSS version 7.0.

RESULTS

There were sixty eligible (after test dose) patients with aortic and/or mitral regurgitation enrolled and randomized in this study, 21 in Group 1, 19 in Group 2, and 20 in Group 3. The majority of patients were in New York Heart Association functional class IIs and IIm. Clinical characteristics and baseline functional class in the three treatment groups were similar as presented in Table 1. The number of patients who took digitalis and diure-

Table 1. Clinical characteristics of patients with asymptomatic chronic valvular regurgitation comparing between groups.

Characteristic	Group 1 n = 21 number (%)	Group 2 n = 19 number (%)	Group 3 n = 20 number (%)	p - values
Sex				
male	11 (52.38)	7 (36.84)	9 (45.0)	} 0.61
female	10 (47.62)	12 (63.16)	11 (55.0)	
Age (years)	38.7 ± 17.6	35.8 ± 19.8	35.9 ± 16.58	0.73
Systolic blood pressure (mmHg)	135.1 ± 24.2	126.6 ± 18.4	134.8 ± 22.0	0.69
Diastolic blood pressure (mmHg)	62.6 ± 15.6	68.0 ± 13.6	60.4 ± 14.6	0.51
Baseline functional class*				
class I (no limitation)	1 (4.76)	4 (21.05)	3 (15.00)	}0.119
class IIS (slight limitation)	15 (71.43)	7 (36.84)	15 (75.0)	
class IIM (moderate limitation)	4 (19.05)	6 (31.58)	2 (10.0)	
class III (inability on any activity)	1 (4.76)	2 (10.53)	0 (0.0)	
Medications at baseline				
digitalis	13 (61.9)	17 (89.5)	7 (62.7)	0.004
diuretic	14 (66.9)	16 (84.2)	8 (42.1)	0.026
ISDN	1 (4.8)	3 (15.8)	1 (5.0)	0.51
amiodarone	1 (4.8)	0	1 (5.0)	1.0
ASA and anticoagulant	0	1 (5.3)	1 (5.0)	0.53
Exercise time (sec)	602.3 ± 204	800.4 ± 278.9	997.7 ± 296.3	0.59
BUN (mg/dl)	14.5 ± 4.7	16.2 ± 4.8	14.27 ± 3.6	0.77
Creatinine (mg/dl)	1.0 ± 0.0	2.2 ± 70.3	0.9 ± 0.1	0.4
Number of patient with predominant MR	11 (52.4)	14 (73.7)	9 (45.0)	} 0.173
Number of patient with predominant AR	10 (47.6)	5 (26.3)	11 (55.0)	
LVH by voltage criteria of ECG	20 (95)	19 (100)	19 (95)	0.8

ISDN = isosorbide dinitrate; ASA = aspirin; MR = mitral regurgitation; AR = aortic regurgitation;
LVH = left ventricular hypertrophy
* New York Heart Association Functional Classification

Table 2. Comparison of standing blood pressure and laboratory data between baseline and week-4.

Parameter		Mean ± SD Group 1	Group 2	Group 3
SBP(mmHg)	week 0	135.1 ± 24.2	126.6 ± 18.4	134.8 ± 22.0
	week 4	133.0 ± 26.0	125.0 ± 17.2	126.7 ± 38.0
DBP (mmHg)	week 0	62.6 ± 15.6	68.0 ± 13.60	60.4 ± 14.6
	week 4	62.0 ± 11.3	64.7 ± 11.8	57.4 ± 11.0
BUN (mg/dL)	week 0	14.5 ± 4.7	16.2 ± 4.8	14.3 ± 3.6
	week 4	15.4 ± 4.4	17.7 ± 6.5	14.3 ± 3.5
Creatinine (mg/dL)	week 0	1.0 ± 0.0	2.2 ± 0.3	0.9 ± 0.1
	week 4	1.0 ± 0.0	1.1 ± 0.3	1.0 ± 0.3
Uric acid (mg/dL)	week 0	6.6 ± 1.6	6.6 ± 1.9	6.0 ± 2.0
	week 4	6.6 ± 2.2	6.5 ± 1.7	6.1 ± 2.2
Potassium (mEq/l)	week 0	4.1 ± 0.4	4.0 ± 0.54	4.2 ± 0.6
	week 4	4.3 ± 0.9	4.3 ± 0.6	4.4 ± 0.6
Magnesium (mEq/l)	week 0	2.4 ± 0.5	2.7 ± 0.7	2.8 ± 1.2
	week 4	2.5 ± 0.9	2.6 ± 8.2	2.5 ± 1.6
SGOT (mg/dL)	week 0	26.7 ± 18.0	26.4 ± 10.4	23.3 ± 8.2
	week 4	34.8 ± 18.1	26.0 ± 6.0	21.3 ± 8.1
SGPT (mg/dL)	week 0	29.4 ± 22.1	22.8 ± 13.6	13.7 ± 9.9
	week 4	29.8 ± 21.0	22.5 ± 11.0	13.0 ± 8.9

All p - value > 0.05 (ANOVA)
SBP = systolic blood pressure; DBP = diastolic blood pressure; BUN = blood urea nitrogen;
SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase.

Table 3. Comparison of echocardiographic analysis in patients treated in each group.

Parameters	Mean ± SD		
	Group 1	Group 2	Group 3
LVEDD (mm)			
baseline	60.9 ± 8.2	63.3 ± 9.2	62.3 ± 16.8
week 4	59.3 ± 9.0	60.6 ± 15.3	61.3 ± 15.6
p-values	0.15	0.4	0.17
LVEDS (mm)			
baseline	39.2 ± 7.8	41.9 ± 7.4	40.0 ± 11.3
week 4	38.9 ± 9.6	43.0 ± 7.9	39.5 ± 9.3
p-values	0.88	0.36	0.17
LVEDVI (ml/m^2)			
baseline	124.2 ± 34.0	147.0 ± 51.7	150.0 ± 56.5
week 4	114.5 ± 42.7	139.2 ± 37.5	141.3 ± 57.0
p-values	0.14	0.22	0.28
LVESVI (ml/M^2)			
baseline	45.7 ± 18.7	53.2 ± 23.6	50.2 ± 20.4
week 4	46.8 ± 24.6	55.8 ± 26.0	55.8 ± 26.0
p-values	0.76	0.89	0.28
LA dimension (mm)			
baseline	43.8 ± 12.1	52.1 ± 12.4	47.2 ± 11.4
week 4	46.4 ± 9.6	52.7 ± 16.3	44.5 ± 13.3
p-values	0.2	0.56	0.15
LVEF (%)			
baseline	63.7 + 9.2	63.7 + 8.6	66.0 ± 12.1
week 4	63.1 + 11.2	61.1 + 9.4	68.4 ± 9.3
p-values	0.76	0.24	0.15

tics was significantly higher in Group 2 than other groups.

There was no significant difference of blood pressure in each group at baseline and after treatment. (Table 2.)

Echocardiographic analysis

Serial changes over time of left ventricular end-diastolic (LVEDD) and end-systolic dimension (LVEDS), and volume index, and ejection fraction (LVEF) were assessed in all patients (Table 3). There were no significant changes in all echocardiographic parameters during 4-weeks' follow-up including calculated ejection fractions between groups.

Using improvement of 5 per cent of LVEF after treatment, there was still no significant number of patients in each of the three groups who had improved LVEF. (Fig. 1)

Exercise capacity

The exercise duration among placebo group, Group 2, and Group 3 showed no significant changes after 4-weeks' follow-up (Table 4). There were more patients who had improvement at least 75 seconds of exercise duration in Group 3 than in the other two groups (Fig. 2). However, there was no statistical significance.

Function capacity

There were changes in functional class during follow-up in each group. There was more trend of improvement in the functional class in both captopril treatment arms, especially in high dose captopril group, but without statistical significance. (Fig. 3)

Adverse effects

There was one patient in each Group 1

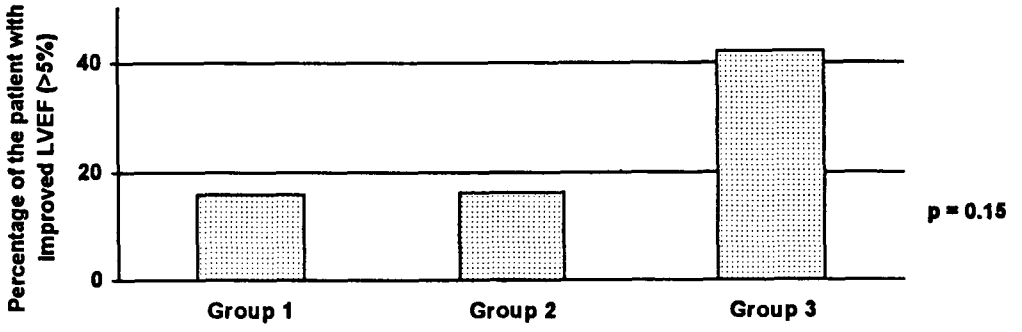

Fig. 1. Comparison of the numbers of patients with improvement of LVEF between groups.

Table 4. Comparison of exercise time in patients treated in each group.

	Mean±SD		
	Group 1	Group 2	Group 3
Exercise time at baseline (sec)	802.0 ± 240.0	800.4 ± 279.0	997.0 ± 298.0
Exercise time at week 4 (sec)	911.0 ± 297.4	903.3 ± 251.0	1161.0 ± 295.0

$p > 0.05$

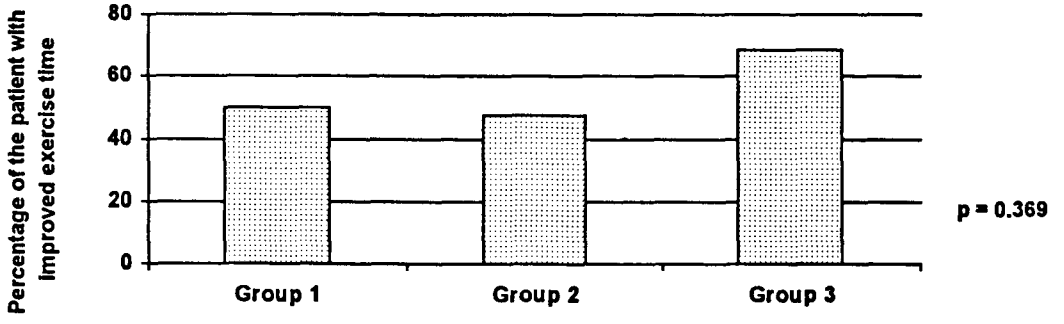

Fig. 2. Comparison of the numbers of patients with improvement of exercise time (>75 sec) between group.

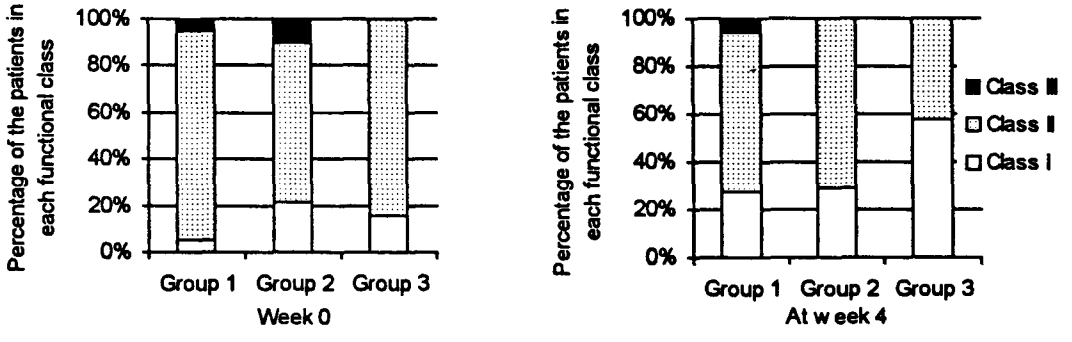

Fig. 3. Functional class changes comparing between each treatment group.

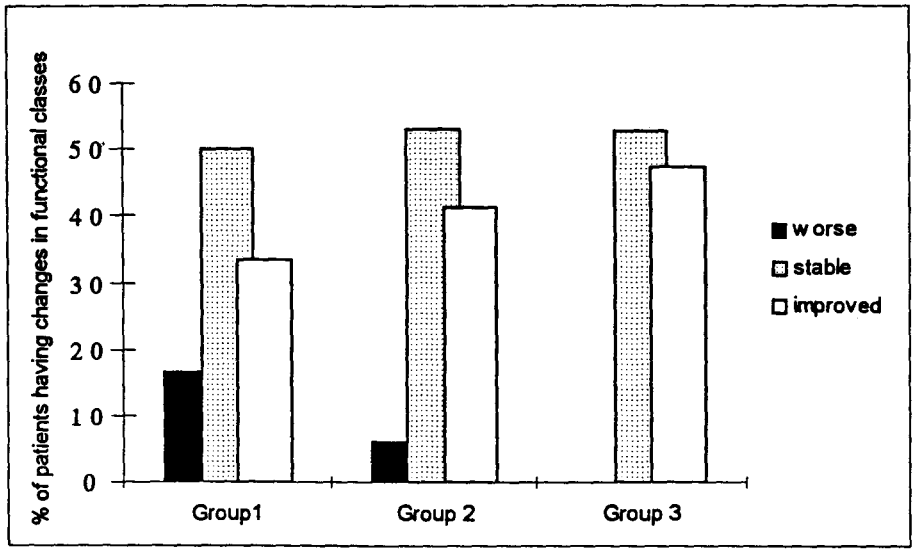

Fig. 4. Percentage of the patients according to functional class changes (> 1 class) comparing between each treatment group.

and 2, and two patients in Group 3, who developed a cough. All except one in Group 3 were able to continue treatment until the end of the study.

There was no significant difference in baseline and week 4 electrolytes, renal and liver functions among the three groups except lower serum glutamic-pyruvic transaminase (SGPT) in Group 3. (Table 2)

DISCUSSION

In severe MR, short-term treatment with vasodilators including intravenous nitroprusside and intravenous or oral hydralazine reduces systemic vascular resistance and wedge pressure and increases cardiac output[20]. Trial of hydralazine in asymptomatic moderate to severe AR found controversial results[10,21]. Similar 12-month trial of nifedipine in asymptomatic AR, gave a potential value for long-term treatment[22]. Since long-term oral treatment with hydralazine in AR was complicated by frequent adverse effects[10]. There are few studies using vasodilator in symptomatic AR. Angiotensin converting enzyme inhibitor has been used to improve left ventricular volume, mass and function in chronic mild symptomatic AR. No long-term studies in MR have been conducted. Recently, a small trial revealed captopril given in single moderate dose did not improve hemodynamics or ventricular performance in symptomatic patients with severe MR (LVEF 0.52±0.12, 0.49± 0.11 in pre- and post captopril treatment respectively, p = NS)[23]. The study of single-dose therapy was not applicable to clinical practice.

In this study, we attempted to evaluate the short-term efficacy of captopril in continuous treatment in patients with valvular regurgitations. The results showed neither significant improvement in echocardiographic variables nor exercise duration in treatment groups compared to placebo. The lack of differences is probably due to considerable limitations in this study. The short observation time and the limited number of patients. Using group comparison rather than self control and using fixed dosage rather than flexible dosage, e.g., maximal tolerable dosage, may also cause insufficient different between drugs and placebo. In addition, there is imbalance in randomization between baseline characteristics, particularly the underlying valvular lesions - number of patients with AR which was higher in Group 3. However, by Doppler findings, most of our patients had mixed aortic and mitral regurgitation with one predominant lesion. Realizing that each valvular lesion has different hemodynamic changes, future trials should attempt to differentiate which is pre-

dominate lesion and study each group separately. The number of concomitant drugs treated in each group were also different which might represent different severity of disease in each group. Finally this is only a short-term study. Further study with a large sample size, and longer follow-up period is required.

SUMMARY

This study, short term captopril in low and high doses did not result in changes of ventricular performance and exercise capacity in the combined patients of mildly symptomatic chronic severe AR and MR. The drug was well tolerated with few side effects.

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การประเมินผลทางคลินิกของแค็พโทพริล ในผู้ป่วยลิ้นหัวใจห้องซ้ายรั่วเรื้อรัง

เกรียงไกร จิรสิริโรจนากร, พ.บ., นิธิ มหานนท์, พ.บ.**, พยงค์ จูฑา, พ.บ.*, ศุภชัย ไชยธีรพันธ์, พ.บ.**, กาญจนา หวานสนิท, พย.บ.**, วิภาวิน วัฒนประการชัย, พย.บ.***

ได้ศึกษาผู้ป่วยลิ้นหัวใจไมตรัลและลิ้นหัวใจเอออร์ติกรั่วเรื้อรัง จำนวน 60 คน เพื่อประเมินประสิทธิภาพและผลข้างเคียงของ captopril โดยให้ผู้ป่วยรับประทานยา 50 มก.ต่อวัน หรือ 100 มก.ต่อวัน เป็นเวลา 4 สัปดาห์ ภายหลังจากได้รับ captopril ไม่พบการเปลี่ยนแปลงของขนาดช่องหัวใจห้องซ้าย หรือการเปลี่ยนแปลงความสามารถในการบีบตัวของกล้ามเนื้อหัวใจ (left ventricular ejection fraction) ระหว่างกลุ่มผู้ป่วยที่ได้ยา captopril เทียบกับกลุ่มควบคุม และไม่มีการเปลี่ยนแปลงสมรรถภาพในการออกกำลังกายบนสายพานได้อย่างชัดเจน แต่มีแนวโน้มจะทำให้ความสามารถในการบีบตัวของกล้ามเนื้อหัวใจดีขึ้นในกลุ่มที่ได้ captopril ขนาด 100 มก.ต่อวัน การศึกษานี้ไม่พบผลข้างเคียงรุนแรงจากยา

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