

CLINICAL INVESTIGATION PROTOCOL

I. Activity: Division of Nuclear Medicine, Department of Radiology and Department of Internal Medicine, Naval Hospital, NMCNCR, Bethesda, MD 20814

II. Title: Effects of Oral Therapy with Verapamil upon Left Ventricular Diastolic Function in Hypertensive Patients.

III. Investigators

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ENCLOSURE (3)

IV. Identification of drugs and devices to be used in this study:

Stannous pyrophosphate and Sodium Tc-99m pertechnetate for labeling of RBC pool.

Verapamil hydrochloride tablets (Calan Tablets, Isoptin Oral Tablets)

V. Manufacturing Information:

A. Source: Stannous pyrophosphate: standard supplier  
Sodium Tc-99m pertechnetate: standard supplier  
Verapamil  
Calan: Searle & Co.  
Isoptin: Knoll Pharmaceutical Co.

B. Dosage form

Stannous pyrophosphate: 25 mg IV  
Sodium Tc-99m pertechnetate: 29.9 mCi IV  
Verapamil: standard oral doses

C. FDA forms: Not required

D. Cost to the CID for drugs and devices: No costs to be incurred outside Naval Supply System

VI. Preclinical information and pharmacology: Not required.

VII. Clinical Information:

A. Objectives:

1. To demonstrate the effects of oral therapy with Verapamil upon left ventricular diastolic function in hypertensive patients.

B. Background:

Radionuclide studies have consistently demonstrated left ventricular diastolic dysfunction in hypertension, as manifested by impairment of LV relaxation and diastolic filling. Diastolic dysfunction may occur in an isolated fashion before there is impairment of systolic performance. While most hypertensive patients are asymptomatic, impaired diastolic relaxation and filling have been associated with exertional dyspnea and objective evidence of congestive heart failure. It remains controversial whether available drug therapy can reverse diastolic dysfunction in hypertension. In work by Fouad et al. and by Inouye et al. beta-blocking drugs, a calcium channel blocking agent (Diltiazem), and diuretics failed to produce

consistent improvement in diastolic function. In other conditions characterized by diastolic dysfunction, however, such as hypertrophic cardiomyopathy and coronary artery disease, calcium channel blockers have been shown to improve diastolic function. Early work by Bonow et al. showed that long-term treatment with oral Verapamil significantly increased LV peak filling rate in patients with hypertrophic cardiomyopathy without affecting systolic performance. The same group reported similar results in patients with CAD and associated diastolic dysfunction. To date the effect of long-term therapy with calcium channel blockers upon the diastolic dysfunction of hypertension has been less well-studied. Betocchi et al. have recently reported improvement in diastolic peak filling rate in hypertensive patients receiving IV Verapamil. However, in view of the known differential effects of IV and oral Verapamil upon LV systolic function and other hemodynamic parameters. These findings cannot be directly applied to long-term oral therapy,

Because the long-term effects of hypertension, (including left atrial enlargement, atrial fibrillation, and congestive heart failure) may be related to diastolic dysfunction, reversal of diastolic filling abnormalities with anti-hypertensive therapy is an important goal. To that end we propose to study the effects of long-term oral therapy with Verapamil upon diastolic function in hypertensive patients.

C. Investigational drugs: none

D. Protocol design:

Patients with untreated or recently diagnosed hypertension (defined for purposes of study as diastolic BP consistently greater than 95 mm Hg) will be referred by Internal Medicine and Hypertension Clinics. In all cases the selection of a calcium channel blocker for initial control of blood pressure shall have been considered by the referring physician. Duration of hypertension will be established by review of patient's record. Patients with any of the following complicating factors will be excluded from the study:

1. Clinical or electrocardiographic evidence of ischemic heart disease
2. Evidence of valvular heart disease
3. Evidence of cardiomyopathy unrelated to hypertension (e.g. alcoholic cardiomyopathy, history of myocarditis, IHSS)
4. Peripheral vascular disease
5. Diabetes mellitus
6. Contra-indication to the use of Verapamil, e.g. biventricular block, second or third degree AV block, atrial fibrillation with evidence of accessory conduction pathway.

Additionally, patients should not previously have been treated

with a calcium channel blocker. Any potentially pregnant female will be studied in the first 10 days of her menstrual cycle as required by Nuclear Medicine Clinic policy.

In all cases a resting gated cardiac blood pool study will be performed in standard fashion in the Nuclear Medicine Clinic prior to institution of antihypertensive therapy. Technique will employ acquisition parameters appropriate for evaluation of diastolic function. Additionally, supine and erect BP will be recorded as well as a resting 12-lead EKG.

Patients will then be placed on verapamil in an initial total daily dose of 120 mg. Adjustment of dose will be supervised by the referring physician to achieve satisfactory BP control, which will be defined as diastolic blood pressure consistently less than 90 mm Hg. Blood pressure measurement is to be performed with patient sitting and before administration of the morning dose of verapamil. One month after initiating therapy with verapamil resting gated cardiac blood pool study will be performed as before 1-2 hours after AM dose of verapamil. BP and resting EKG will again be recorded. A one month period is considered sufficient to establish blood pressure response to the medication. Any patient failing to achieve adequate blood pressure control with usual doses of verapamil will be excluded from the study and appropriate medication adjustment made by the referring physician. The duration of oral therapy required to influence diastolic function has not been established. With intravenous administration of verapamil, however, a measurable effect on diastolic function has been shown after a single dose.

In each instance ejection fraction will be calculated by a standard algorithm as well as at least 2 parameters of diastolic function--peak filling rate and time to peak filling rate. Time-activity curves will be subjected to a four-harmonic Fourier transform in a manner previously reported to be optimal for evaluation of diastolic function.

A control population for establishment of diastolic parameters in normal individuals will consist of patients with no history of hypertension or other complicating conditions who have been referred to Nuclear Medicine Clinic for evaluation of LV function in anticipation of chemotherapy for unrelated conditions. Resting gated cardiac blood pool studies will be performed and evaluated in the same manner as for experimental patients.

#### E. Possible toxicities:

The radiation absorbed doses for radionuclide ventriculography with Tc-99m-labeled RBC's are as indicated below. There are no known reactions to stannous pyrophosphate.

	rads/mCi
Whole body	0.015-0.057
Heart	0.06-0.08
Lungs	0.03-0.13
Spleen	0.03-0.23

Ovaries	0.02
Testes	0.012
Blood	0.058

By comparison, ambient cosmic radiation in the Washington, DC area is approximately 100 mrem per year.

Serious adverse reactions associated with the usual oral doses of Verapamil are rare. Some of the reported adverse reactions are listed.

#### Verapamil

Cardiovascular:	Hypotension (2.9%)
	Peripheral edema (1.7%)
	Complete AV block (0.8%)
	Bradycardia (less than 50 bpm) (1.1%)
	CHF or pulmonary edema (0.9%)
CNS:	Dizziness (3.6%)
	Headache (1.8%)
	Fatigue (1.1%)
GI:	Constipation (6.3%)
	Nausea (1.6%)
	Elevated LFT's (uncommon)

VIII. Statistical analysis, justification of sample size, and data analysis:

Sample Size Calculation: The goal is to demonstrate differences in one or more parameters of diastolic function (e.g. peak filling rate and time to peak filling rate) in hypertensive patients before and after administration of a calcium channel blocker. For this purpose each experimental subject will serve as his own control. Additionally, a difference in baseline function between groups of hypertensive and normotensive patients is to be demonstrated.

For the case of pooled subjects,

$$n = (z / d)^2$$

where n is required sample size

z is 1.96 for p equal to 0.05

d is estimated difference to detect

is standard deviation for normal population  
(approximately 1 EDV/sec for peak filling rate)

If we select d = 0.5 EDV/sec, then n = 15.4

Twenty patients will be assigned to the experimental group and twenty to the control group (40 patients total).