Mitral valve prolapse—a pervasive condition of uncertain etiology

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Mitral valvular prolapse is a common valvular abnormality, with a incidence of 4% to 15%. Familial incidence and clinical association and pathogenesis are discussed.

Mitral valve prolapse (MVP), the most commonly diagnosed valvular abnormality in human beings,¹ has attracted the attention of some of the greatest names in medicine—Osler, Lewis, DaCosta, Levine, and White, to name a few.² In 1836, Williams³ described a bellow-like sound that occurred in nervous palpitations. This sound, he wrote, is a consequence of a slight regurgitation of blood that accompanies imperfect action of the valves and that is generally “observed in hysteria, females, and hypochondriasis.”

Incidence

Since Williams' description (probably the first) of MVP, there has been mounting fascination with the varying frequency of this condition. Savage and associates¹ cited an incidence of 4% to 17% in the literature, while in their own Framingham study¹ of 2,224 men and 2,743 women, M-mode echocardiography showed age-dependent ranges of 0.7 to 4.4% male incidence and 1.4 to 17% female incidence. In another phonocardiographic and echocardiographic study⁴ of 100 asymptomatic young women, the incidence of MVP was 10%.

Familial association

Many studies also reported familial incidence. Stannard and colleagues⁵ found auscultatory evidence of MVP in one family of three sisters and another of two sisters. Weiss and coauthors⁶ studied 17 index cases and found echocardiograms consistent

with MVP in 27 of 57 first-degree relatives; transmission was to both sexes, but primarily to female subjects. Autosomal dominant inheritance was first proposed by Shell and associates⁷ after phonocardiographic studies of 23 family members in four index cases. Using M-mode echocardiography, Pader⁸ found that a female patient, her mother, and her grandmother all had MVP. This author concluded that MVP has an autosomal dominant pattern, with a sex-dependent mode of expression. The Framingham study found MVP in 9% of offspring of subjects with MVP, with four times as many cases appearing in females as in males.¹

Clinical associations and pathogenesis

Although some patients are asymptomatic, MVP has been proposed to be associated with a number of conditions, including atrial septal defect,⁹ Marfan's syndrome,¹⁰ Ehlers-Danlos syndrome,¹¹ pectus excavatum,¹² straight back,¹³ scoliosis,¹⁴ von Willebrand's syndrome,¹⁵ muscular dystrophy,¹⁶ left ventricular dysfunction,¹⁷ osteogenesis imperfecta tarda,¹⁸ pseudoxanthoma elasticum,¹⁹ pulmonary hypertension,²⁰ right ventricular enlargement,²⁰ hypomastia,²¹ and dermal arches.²²⁻²⁴

Two main unifying theories have been proposed to explain most or all of these associations. The first describes MVP as a developmental defect not merely of the heart valve but of all connective tissue, and even of the entire mesenchymal primordial substance.^{9,10,15,17,19,21,22} Affected tissues in all of these disorders are derived embryologically from mesenchymal cell origins.

The other theory proposes that MVP mostly is a phenomenon produced by altered geometry of the heart, which can be produced directly by atrial septal defect, left ventricular dysfunction, and right ventricular enlargement^{11-14,16}. The geometry of

the heart is altered indirectly via the musculoskeletal system in straight back, Marfan's syndrome, Ehlers-Danlos syndrome, pectus excavatum, scoliosis, and muscular dystrophy. It also is altered indirectly in pulmonary hypertension by the lungs and vascular bed.

Hypomastia

Rosenberg and coresearchers²¹ hypothesized MVP to correlate with hypomastia, because both the mitral valve and mammary gland derive from the mesenchyma, and both differentiate during the sixth week of fetal life. Their study surveyed 27 women with primary hypomastia who presented for augmentation mammoplasty. Postpartum or involutional atrophy patients and postmastectomy patients were excluded from the study. Echocardiography demonstrated MVP in 13 of the 27 women (48%) in the study group, compared with 2 of the 33 (6%) healthy staff members who comprised the control group. A cross-study demonstrated hypomastia (breast size ≤ 200 cc) in 17 of 28 women (61%) with known MVP; 13 women (46%) in this group were found to have one or more skeletal abnormalities (pectus excavatum, scoliosis, or straight back). These findings lend support to the systemic development defect theory of MVP.

Dermal arches

Schwartz and coworkers²³ found an increased prevalence in dermal arches in symptomatic patients with MVP, while two subsequent studies had contrary findings. Tay and associates²² found no significant difference in the incidences of dermal arches between an MVP group of school children in Singapore with a control group of children. Kramer-Fox and coworkers²⁴ surveyed 42 subjects with diagnosed MVP, 140 first-degree relatives (48 of whom had MVP), and a control group of their spouses and hospital workers. No significant difference was found in the occurrence of dermal arches among the MVP subjects, the relatives, and the control group.

Atrial septal defect

In an analysis of 200 patients with auscultory evidence of MVP, Pocock and Barlow⁹ found 17 (9%) with secundum-type defects of the atrial septum. Fourteen of these 17 underwent surgical closure. Postoperatively, the murmurs associated with MVP changed sporadically; three disappeared completely, two intensified, and nine did not change. Citing the high incidence of atrial septal defect, the authors proposed an embryologic basis for MVP. The fact that the auscultory findings did not improve with surgical repair was not considered.

They believed that the posterior location of these secundum-type defects would have little effect on the more anteriorly positioned mitral valve.

Ventricular changes

Garcia-Dorado and coauthors²⁰ suggested that changes in left ventricular volume and the geometry of the heart caused MVP in patients with atrial septal defect, pulmonary hypertension, and hypertrophic cardiomyopathy. They evaluated echocardiograms of 176 patients with symptoms of pulmonary hypertension after epidemic poisoning with rapeseed oil. This produced pulmonary hypertension by diffuse vasculitis and vasoconstriction, which led to right ventricular hypertrophy.

The patients were correlated by right ventricle size and the incidence of MVP. Those with borderline or normal-sized ventricles had a 9% incidence of MVP. In those with moderately enlarged ventricles, the incidence was 30%, and those with severe ventricular enlargement had an incidence of 56%. Follow-up echocardiograms were obtained for 12 patients with severe-to-moderate right ventricular hypertrophy on initial study. Of these, eight had had the ventricle size return to normal. Three of these eight had demonstrated MVP on the original echocardiogram, but all three were normal at follow up. These authors proposed that the altered right ventricular geometry, rather than a developmental defect, accounted for MVP in these patients.

Yoshimitsu and coworkers¹⁶ attempted to determine whether the frequent incidence of MVP in progressive muscular dystrophy was due to the changes in left ventricular function or to the altered structure of the thorax. Sixty-nine patients with muscular dystrophy were classified into three groups: Group 1 included 38 persons without MVP; group 2 included 11 persons with MVP confirmed by M-mode echocardiography; and group 3 included 16 patients with MVP on both M-mode and two-dimensional echocardiography.

Left ventricular function, as evaluated by systolic time intervals, did not differ for the three groups. Straight or lordotic spines were found in 32.3%, 100%, and 93.8% of groups 1, 2, and 3, respectively. Inversely, the incidence of MVP in cases with thoracic kyphosis was 4.8%, with straight spines 66.7%, and with lordotic thoracic spines 77.8%.

It was concluded that thoracic geometry, rather than a defect in the myocardium, was the causative agent for MVP in muscular dystrophy. The authors further theorized that all cases of MVP, whether geometric or developmental, cannot be assumed to be from the same cause. Earlier, Yoshimitsu had conducted an unpublished study

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†In pharmacodynamic studies (utilizing 10 mg of enalapril and lisinopril), ACE inhibition was significantly correlated to plasma renin activity and fall in diastolic blood pressure in normal volunteers.³

—adapted from Ajayi et al, p 424²

The clinical significance of pharmacodynamic differences among ACE inhibitors observed in normal volunteers has not been determined in hypertensive patients.

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Zestril shares the low incidence of side effects characteristic of ACE inhibitors. Additionally, rash or taste disturbance is rarely seen with Zestril. What's more, Zestril is not metabolized by the liver. It is absorbed as the active drug and does not require bioactivation⁷—as needed with prodrugs such as enalapril.^{†5} Absorption of Zestril is unaffected by food.⁸

Evaluation of the hypertensive patient should always include assessment of renal function. (See Dosage and Administration.)

Angioedema has been reported with ACE inhibitors, including Zestril. (See Warnings.)

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Clinical significance has not been determined in hypertensive patients.

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INDICATIONS AND USAGE. Zestril is indicated for the treatment of hypertension. It may be used alone as initial therapy or concomitantly with other classes of antihypertensive agents. In using Zestril, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and that available data are insufficient to show that Zestril does not have a similar risk. (See WARNINGS.) **CONTRAINDICATIONS.** Zestril is contraindicated in patients who are hypersensitive to this product. **WARNINGS.** **Angioedema:** Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including Zestril. In such cases, Zestril should be promptly discontinued, and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, eg, subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) should be promptly administered.** (See ADVERSE REACTIONS.) **Hypotension:** Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of use with Zestril in salt/volume-depleted persons, such as those treated vigorously with diuretics or patients on dialysis. (See PRECAUTIONS, Drug Interactions and ADVERSE REACTIONS.) In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of Zestril and/or diuretic is increased. Similar considerations apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion. **Neutropenia/Agranulocytosis:** Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of Zestril are insufficient to show that Zestril does not cause agranulocytosis at similar rates. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered. **PRECAUTIONS.**

General Impaired Renal Function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including Zestril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death. In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin converting enzyme inhibitor suggests that these increases are usually reversible upon discontinuation of Zestril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy. Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when Zestril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of Zestril and/or discontinuation of the diuretic may be required. **Evaluation of the hypertensive patient should always include assessment of renal function.** (See DOSAGE AND ADMINISTRATION.) **Hyperkalemia:** In clinical trials hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 2.2% of hypertensive patients and 4.0% of patients with congestive heart failure. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in approximately 0.1% of hypertensive patients. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with Zestril. (See Drug Interactions.) **Surgery/Anesthesia:** In patients undergoing major surgery or during anesthesia with agents that produce hypotension, Zestril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion. **Information for Patients.**

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of Zestril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician. **Symptomatic Hypotension:** Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patient should be told to discontinue the drug until they have consulted with the prescribing physician. All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with their physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician. **Neutropenia:** Patients should be told to report promptly any indication of infection (eg, sore throat, fever) which may be a sign of neutropenia. **NOTE:** As with many other drugs, certain advice to patients being treated with Zestril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. **Drug Interactions. Hypotension—Patients on Diuretic Therapy:** Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with Zestril. The possibility of hypotensive effects with Zestril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with Zestril. If it is necessary to continue the diuretic, initiate therapy with Zestril at a dose of 5 mg daily, and provide medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS, and DOSAGE AND ADMINISTRATION.) When a diuretic is added to the therapy of a patient receiving Zestril, an additional antihypertensive effect is usually observed. Studies with ACE inhibitors in combination with diuretics indicate that the dose of the ACE inhibitor can be reduced when it is given with a diuretic. (See DOSAGE AND ADMINISTRATION.) **Indomethacin:** In a study in 36 patients with mild to moderate hypertension where the antihypertensive effects of Zestril alone were compared to Zestril given concomitantly with indomethacin, the use of indomethacin was associated with a reduced effect, although the difference between the two regimens was not significant. **Other Agents:** Zestril has been used concomitantly with nitrates and/or digoxin without evidence of clinically significant adverse interactions. No clinically important pharmacokinetic interactions occurred when Zestril was used concomitantly with propranolol or hydrochlorothiazide. The presence of food in the stomach does not alter the bioavailability of Zestril. **Agents Increasing Serum Potassium:** Zestril attenuates potassium loss caused by thiazide-type diuretics. Use of Zestril with potassium-sparing diuretics (eg, spironolactone, triamterene or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. **Carcinogenesis, Mutagenesis, Impairment of Fertility.** There was no evidence of a tumorigenic effect when lisinopril was administered for 105 weeks to male and female rats at doses up to 90 mg/kg/day (about 56 times* the maximum recommended daily human dose) or when lisinopril was administered for 92 weeks to (male and female) mice at doses up to 135 mg/kg/day (about 84 times* the maximum recommended daily human dose). *Based on patient weight of 50 kg. Lisinopril was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. It was also negative in a forward mutation assay using Chinese hamster lung cells. Lisinopril did not produce single strand DNA breaks in an in vitro alkaline elution rat hepatocyte assay. In addition, lisinopril did not produce increases in chromosomal aberrations in an in vitro test in Chinese hamster ovary cells or in an in vivo study in mouse bone marrow. There were no adverse effects on reproductive performance in male and female rats treated with up to 300 mg/kg/day of lisinopril. **Pregnancy, Pregnancy Category C:** Lisinopril was not teratogenic in mice treated on days 6-15 of gestation with up to 1,000 mg/kg/day (625 times the maximum recommended human dose). There was an increase in fetal resorptions at doses down to 100 mg/kg; at doses of 1,000 mg/kg this was prevented by saline supplementation. There was no fetotoxicity or teratogenicity in rats treated with up to 300 mg/kg/day (188 times the maximum recommended dose) of lisinopril at days 6-17 of gestation. In rats receiving lisinopril from day 15 of gestation through day 21 postpartum, there was an increased incidence in pup deaths on days 2-7 postpartum and a lower average body weight of pups on day 21 postpartum. The increase in pup deaths and decrease in pup weight did not occur with maternal saline supplementation. Lisinopril, at doses up to 1 mg/kg/day, was not teratogenic when given throughout the organogenic period in saline supplemented rabbits. Saline supplementation (physiologic saline in place of tap water) was used to eliminate maternotoxic effects and enable evaluation of the teratogenic potential at the highest possible dosage level. The rabbit has been shown to be extremely sensitive to angiotensin converting enzyme inhibitors (captopril and enalapril) with maternal and fetotoxic effects apparent at or below the recommended therapeutic dosage levels in man. Fetotoxicity was demonstrated in rabbits by an increased incidence of fetal resorptions at a dose of lisinopril at 1 mg/kg/day and by an increased incidence of incomplete ossification at the lowest dose tested (0.1 mg/kg/day). By whole body autoradiography, radioactivity was found in the placenta following administration of labeled lisinopril to pregnant rats, but none was found in the fetuses. There are no adequate and well-controlled studies in pregnant women. Zestril should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers:** Milk of lactating rats contains radioactivity following administration of ¹⁴C lisinopril. It is not known whether this drug is excreted in human milk.

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Because many drugs are excreted in human milk, caution should be exercised when Zestril is given to a nursing mother. **Pediatric Use:** Safety and effectiveness in children have not been established. **ADVERSE REACTIONS:** Zestril has been found to be generally well tolerated in controlled clinical trials involving 2003 patients and subjects. The most frequent clinical adverse experiences in controlled trials were dizziness (6.3%), headache (5.3%), fatigue (3.3%), diarrhea (3.2%), upper respiratory symptoms (3.0%), and cough (2.9%), all of which were more frequent than in placebo-treated patients. For the most part, adverse experiences were mild and transient in nature. Discontinuation of therapy was required in 6.0% of patients. In clinical trials, the overall frequency of adverse experiences could not be related to total daily dosage within the recommended therapeutic dosage range. For adverse experiences which occurred in more than 1% of patients and subjects treated with Zestril or Zestril plus hydrochlorothiazide in controlled clinical trials, comparative incidence data are listed in the table below.

	Percent of Patients in Controlled Studies		
	Zestril (n = 2003†) Incidence (discontinuation)	Zestril/Hydrochlorothiazide (n = 644) Incidence (discontinuation)	Placebo (n = 207) Incidence
Dizziness	6.3 (0.6)	9.0 (0.9)	1.9
Headache	5.3 (0.2)	4.3 (0.5)	1.9
Fatigue	3.3 (0.2)	3.9 (0.5)	1.0
Diarrhea	3.2 (0.3)	2.6 (0.3)	2.4
Upper Respiratory Symptoms	3.0 (0.0)	4.5 (0.0)	0.0
Cough	2.9 (0.4)	4.5 (0.8)	1.0
Nausea	2.3 (0.3)	2.5 (0.2)	2.4
Hypotension	1.8 (0.8)	1.6 (0.5)	0.5
Rash	1.5 (0.4)	1.6 (0.2)	0.5
Orthostatic Effects	1.4 (0.0)	3.4 (0.2)	1.0
Asthenia	1.3 (0.4)	2.0 (0.2)	1.0
Chest Pain	1.3 (0.1)	1.2 (0.2)	1.4
Vomiting	1.3 (0.2)	1.4 (0.0)	0.5
Dyspnea	1.1 (0.0)	0.5 (0.2)	1.4
Dyspepsia	1.0 (0.0)	1.9 (0.0)	0.0
Paresthesia	0.8 (0.0)	2.0 (0.2)	0.0
Impotence	0.7 (0.2)	1.6 (0.3)	0.0
Muscle Cramps	0.6 (0.0)	2.8 (0.6)	0.5
Back Pain	0.5 (0.0)	1.1 (0.0)	1.4
Nasal Congestion	0.3 (0.0)	1.2 (0.0)	0.0
Decreased Libido	0.2 (0.0)	1.2 (0.0)	0.0
Vertigo	0.1 (0.1)	1.1 (0.2)	0.0

†Includes 420 patients treated for congestive heart failure who were receiving concomitant digitalis and/or diuretic therapy.

Clinical adverse experiences occurring in 0.3% to 1.0% of patients in the controlled trials and rarer, serious possibly drug related events reported in uncontrolled studies or marketing experience include: BODY AS A WHOLE: Chest discomfort, fever, flushing, CARDIOVASCULAR: Angina pectoris, orthostatic hypotension, rhythm disturbances, tachycardia, peripheral edema, palpitation, DIGESTIVE: Abdominal pain, anorexia, constipation, flatulence, METABOLISM: Gout, MUSCULOSKELETAL: Joint pain, shoulder pain, NERVOUS SYSTEM/PSYCHIATRIC: Depression, somnolence, insomnia, stroke, RESPIRATORY SYSTEM: Bronchitis, sinusitis, pharyngeal pain, UROGENITAL: Oliguria, progressive azotemia, acute renal failure, OTHER: Blurred vision, pruritus, urinary tract infection, vasculitis of the legs. **ANGIOEDEMA:** Angioedema has been reported in patients receiving Zestril (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with Zestril should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.) **HYPOTENSION:** In hypertensive patients, hypotension occurred in 1.2% and syncope occurred in 0.1% of patients. Hypotension or syncope was a cause of discontinuation of therapy in 0.5% of hypertensive patients. (See WARNINGS.) In patients with congestive heart failure, hypotension occurred in 5.0% and syncope occurred in 1.0% of patients. These adverse experiences were causes for discontinuation of therapy in 1.3% of these patients. **Clinical Laboratory Test Findings. Serum Electrolytes:** Hyperkalemia (See PRECAUTIONS.) **Creatinine, Blood Urea Nitrogen:** Minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 2.0% of patients with essential hypertension treated with Zestril alone. Increases were more common in patients receiving concomitant diuretics and in patients with renal artery stenosis. (See PRECAUTIONS.) Reversible minor increases in blood urea nitrogen and serum creatinine were observed in approximately 9.1% of patients with congestive heart failure on concomitant diuretic therapy. Frequently these abnormalities resolved when the dosage of the diuretic was decreased. **Hemoglobin and Hematocrit:** Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.4 g% and 1.3 vol% respectively) occurred frequently in patients treated with Zestril but were rarely of clinical importance in patients without other cause of anemia. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia. **Other (Causal Relationship Unknown):** Rarely, elevations of liver enzymes and/or serum bilirubin have occurred. Overall, 2.0% of patients discontinued therapy due to laboratory adverse experiences, principally elevations in blood urea nitrogen (0.6%), serum creatinine (0.5%), and serum potassium (0.4%). **OVERDOSEAGE:** The oral LD₅₀ of lisinopril is greater than 20 g/kg in mice and rats. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of normal saline solution. **DOSAGE AND ADMINISTRATION. Initial Therapy:** In patients with uncomplicated essential hypertension not on diuretic therapy, the recommended initial dose is 10 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 20 to 40 mg per day administered in a single daily dose. The antihypertensive effect may diminish toward the end of the dosing interval regardless of the administered dose, but most commonly with a dose of 10 mg daily. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, an increase in dose should be considered. Doses up to 80 mg have been used but do not appear to give greater effect. If blood pressure is not controlled with Zestril alone, a low dose of a diuretic may be added. Hydrochlorothiazide, 12.5 mg has been shown to provide an additive effect. After the addition of a diuretic, it may be possible to reduce the dose of Zestril. **Diuretic Treated Patients:** In hypertensive patients who are currently being treated with a diuretic, symptomatic hypotension may occur occasionally following the initial dose of Zestril. The diuretic should be discontinued, if possible, for two or three days before beginning therapy with Zestril to reduce the likelihood of hypotension. (See WARNINGS.) The dosage of Zestril should be adjusted according to blood pressure response. If the patient's blood pressure is not controlled with Zestril alone, diuretic therapy may be resumed as described above. If the diuretic cannot be discontinued, an initial dose of 5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Drug Interactions.) Concomitant administration of Zestril with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium. (See PRECAUTIONS.) **Use in Elderly:** In general, blood pressure response and adverse experiences were similar in younger and older patients given similar doses of Zestril. Pharmacokinetic studies, however, indicate that maximum blood levels and area under the plasma concentration time curve (AUC) are doubled in older patients so that dosage adjustments should be made with particular caution. **Dosage Adjustment in Renal Impairment:** The usual dose of Zestril (10 mg) is recommended for patients with creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance > 10 mL/min < 30 mL/min (serum creatinine > 3 mg/dL), the first dose is 5 mg once daily. For patients with creatinine clearance < 10 mL/min (usually on hemodialysis) the recommended initial dose is 2.5 mg. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Renal Status	Creatinine-Clearance mL/min	Initial Dose mg/day
Normal Renal Function to Mild Impairment	> 30	10
Moderate to Severe Impairment	≥ 10 ≤ 30	5
Dialysis Patients	< 10	2.5*

*Dosage or dosing interval should be adjusted depending on the blood pressure response. Rev G 5/88

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in which MVP was produced in six open-chested dogs by direct pressure of the left ventricle.

Comment

It is necessary to consider both the developmental and geometric concepts of MVP pathogenesis until further studies appear. Therefore, a patient with a systolic click and mid-to-late systolic murmur must be examined carefully for developmental anomalies. Patients with scoliosis, straight back, thoracic lordosis, or pectus excavatum should undergo echocardiography.

Although MVP usually has a benign course,²⁵ the possibility of arrhythmias, embolic phenomena, or endocarditis must be considered. As MVP receives more attention and more data are assembled, the pathogenesis will become apparent.

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