Effect of the Vasodilator Therapy in Regurgitant Valvular Disease

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The hemodynamic response to afterload reduction by sodium nitroprusside was assessed in 5 patients with mitral regurgitation and in 7 with aortic regurgitation. The drug significantly lowered left ventricular systolic pressure, end-diastolic pressure and end-diastolic volume. In patients with mitral regurgitation, significant decreases in regurgitant volume (74 ± 10 to 44 ± 7 ml) and regurgitant fraction (60 ± 4 to $41 \pm 5\%$) were associated with substantial increases in cardiac output (4.18 ± 1.18 to 5.43 ± 1.18 L/min) and forward stroke volume (49 ± 10 to 64 ± 9 ml). In patients with aortic regurgitation, vasodilator therapy was effective in increasing forward output only in 2 patients who had an initially elevated end-diastolic pressure which was reduced only to levels slightly above normal with nitroprusside. In patients with a lower level of end-diastolic pressure, further reduction in the filling pressure resulted in no benefit or rather a fall in forward stroke volume, despite a significant increase in pump function (ejection fraction being augmented from 55 ± 4 to $61 \pm 5\%$).

Experiments in dogs confirmed that nitroprusside reduced the amount of mitral regurgitation by virtue of diminishing the regurgitant orifice size, as a result of the reduction in size of the left heart chamber. These observations also support the concept that it is ultimately important to maintain filling pressure at an optimal level during administration of a vasodilating agent, otherwise effects due to afterload reduction tend to be offset.

RECENTLY the importance of vasodilator therapy for the treatment of cardiac failure has been emphasized by many investigators. The concept of clinical application of this therapy is based on the experimental findings that defined the inverse relationship between force and velocity or extent of muscle shortening at a constant muscle lengths.^{1,2} In the intact failing

ventricle, it would be expected that ventricular ejection could be augmented by reducing the level of afterload, provided that the venous return is maintained.^{3,4}

Vasodilator therapy with nitroprusside exerts significantly favorable effects in patients with mitral regurgitation⁵⁻⁷ Mechanisms of the reduction of regurgitant volume have been postulated to be related to an increased competence of the mitral apparatus due to a decrease in left ventricular chamber size as well as to the decrease in the resistance to ejection of blood into the aorta. Recently, vasodilator therapy was also applied for the treatment of chronic aortic regurgitation

Key Words:

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TABLE I

Pt	Age	Sex	Dx	HR (beat/min)		LVSP (mmHg)		LVEDP (mmHg)		CO (L/min)		FSV (ml/beat)		EDV (ml)		ESV (ml)		TSV (ml)		EF (%)		RV (ml)		RF (%)		
				C	NP	R	C	NP	C	NP	C	NP	C	NP	C	NP	C	NP	C	NP	C	NP	C	NP	C	NP
Patients with Mitral Regurgitation																										
M.H.	37	F	RC	60	63	NSR	141	107	16	12	2.70	3.19	45	51	158	143	38	33	120	110	76	77	75	59	62	54
T.A.	64	M	RHD	92	88	AF	154	115	10	6	4.98	6.36	54	73	139	108	25	18	114	90	82	83	83	35	61	35
Y.O.	37	M	RHD	79	85	AF	127	115	31	24	2.79	5.03	35	59	226	199	104	82	122	117	54	59	87	58	71	50
S.N.	32	F	RC	100	100	NSR	157	133	11	7	7.99	9.00	80	90	233	183	70	54	163	129	70	70	83	39	51	30
H.W.	59	M	PMD/CAD	80	80	NSR	110	110	32	20	2.43	3.56	30	45	241	222	171	150	70	72	29	32	40	27	57	38
Mean				82	83		138	116	20	14	4.18	5.43	49	64	199	171	82	67	118	104	62	64	74	44	60	41
SEM				8	7		10	5	5	4	1.18	1.18	10	9	24	23	29	26	17	11	11	10	10	7	4	5
p				NS			<0.05		<0.05		<0.05		<0.01		<0.01		<0.01		NS		NS		<0.01		<0.01	
Patients with Aortic Regurgitation																										
M.S.	48	M	Post IE	78	71	NSR	166	107	36	17	3.46	4.06	44	58	253	237	127	84	126	153	50	65	82	95	65	62
M.H.	45	M	RHD	62	65	NSR	174	108	13	9	5.40	5.72	87	88	248	222	98	68	150	154	60	69	63	66	42	43
H.I.	27	M	RHD	75	78	NSR	134	104	20	9	6.85	6.49	91	83	299	278	156	151	143	127	46	46	52	44	36	35
K.Y.	62	F	HT	69	85	NSR	188	118	13	8	5.40	6.94	78	82	164	151	58	48	106	103	65	68	28	21	26	21
K.S.	56	F	RHD	60	68	NSR	182	115	27	16	4.09	5.55	68	82	225	215	87	55	138	160	61	74	70	78	51	49
K.K.	38	M	ARD	75	94	NSR	154	129	11	7	6.30	6.20	84	66	416	340	237	182	179	158	43	46	95	92	53	58
M.U.	26	M	RHD	71	90	NSR	128	110	10	5	9.40	8.24	122	91	245	180	96	69	149	111	61	62	27	20	18	18
Mean				70	79		161	113	19	10	5.84	6.17	82	79	264	232	123	93	142	138	55	61	60	59	42	41
SEM				3	5		9	3	5	2	0.80	0.53	10	5	32	26	24	21	9	10	4	5	11	13	7	7
p				= 0.05			<0.01		<0.01		NS		NS		<0.05		<0.01		NS		<0.05		NS		NS	

Abbreviations: Pt = patient, Dx = diagnosis, HR = heart rate, LVSP = left ventricular peak systolic pressure, CO = cardiac output, FSV = forward stroke volume, EDV = end-diastolic volume, ESV = end-systolic volume, TSV = total stroke volume, EF = ejection fraction, RV = regurgitant volume, RF = regurgitant fraction, C = control, NP = with nitroprusside, RC = rupture of chordae tendineae, RHD = rheumatic heart disease, PMD = papillary muscle dysfunction, CAD = coronary artery disease, IE = infectious endocarditis, HT = hypertension, ARD = aortic route disease, NSR = normal sinus rhythm, AF = atrial fibrillation, R = rhythm, NS = not significant

Fig.1. Left ventricular and pulmonary capillary wedge pressure tracing before (left panel) and during (right panel) nitroprusside infusion in patient T.A. Reduction in peak left ventricular systolic pressure is associated with a dramatic decrease in the magnitude of the peak *v* wave as well as a decrease in left ventricular end-diastolic pressure during nitroprusside infusion.

which showed a general improvement in the hemodynamics by reducing aortic regurgitation or improving ventricular pump function.⁸ However, there was an evident heterogeneity of response in some patients and such was likely to be related to the extent of the reduction in the preload.

The present study was designed to examine more precisely the variability in response to afterload reduction in the two different valvular lesions and to elucidate the possible factors responsible for the improvement of regurgitation in both clinical and experimental settings.

MATERIALS AND METHODS

Clinical Study

The study population consisted of 7 patients with aortic regurgitation of valvular origin and 5 patients with mitral regurgitation, 2 of which were related to a valvular lesion and 3 to a defect in subvalvular apparatus. The clinical profile of the patient group is shown in Table I.

Cardiac catheterization was performed with the patients in a fasting state and after light premedication with diazepam 10 mg im. Right heart catheterization was carried out with a No 7F Swan-Ganz balloon tipped thermodilution catheter. Left heart catheterization was performed using No 8F NIH closed tip catheter with multiple sideholes either percutaneously through

a femoral artery or *via* a right brachial arteriotomy. All the pressures were recorded using Statham P23Db transducers. Cardiac output was measured in triplicate by the thermodilution technique using Nihon Koden MCL 4100 cardiac output computer.

Left ventriculography (60 frames/sec) was performed at the 30 degree right anterior oblique projection with injection of 25 to 40 ml of contrast medium (80% Angioconray[®]) at a rate of 10 to 14 ml/sec. After completion of all the control studies, sodium nitroprusside in concentrations ranging from 25 to 100 μ g/min were infused to lower the peak systolic pressure by approximately 30% in aortic regurgitation and by 20% in mitral regurgitation. When stability of the desired pressure was confirmed for 10 min, all hemodynamic and angiographic measurements were repeated (Fig. 1).

Left ventricular volumes were calculated using the area length method which was modified for single plane cineangiography.⁹ Total stroke volume was divided by the end-diastolic volume yielding the left ventricular ejection fraction. Forward left ventricular stroke volume was derived from the cardiac output by the thermodilution divided by the heart rate. The regurgitant volume was calculated by subtracting the forward stroke volume from the total stroke volume. The regurgitant fraction was expressed

Fig.2. Changes from control (C) in left ventricular systolic pressure (LVSP), left ventricular end-diastolic pressure (LVEDP) and forward stroke volume (FSV) during nitroprusside (NP) infusion. Individual values for 5 patients with mitral regurgitation (left panel) and for 7 patients with aortic regurgitation (right panel) are shown. The heavy solid circle indicates the mean value of each group of measurements, bracket the standard error of mean.

Fig.3. Individual changes from control (C) in end-diastolic volume (EDV), ejection fraction (EF) and regurgitant fraction (RF) by nitroprusside (NP) infusion for 5 patients with mitral regurgitation (left panel) and for 7 patients with aortic regurgitation (right panel). The heavy solid circle indicates the mean value of each group of measurements, bracket the standard error of the mean.

as the regurgitant volume divided by the total stroke volume.

Experimental Study

Mongrel dogs were anesthetized with sodium pentobarbital. Respiration was controlled by a Harvard pump delivering room air *via* an endotracheal tube; a thoracotomy was performed in the fifth left intercostal space and the pericardium was opened. A high fidelity pressure micromanometer (Königsberg P-22) was inserted at the left ventricular apex. A pair of ultrasonic crystals was then implanted to measure the instantaneous transverse diameter of the left atrium and the left ventricular segment length.¹⁰

A flow probe was placed around the ascending aorta and forward stroke volume was recorded using a Narco RT500 electromagnetic flowmeter.

After control recordings, mitral regurgitation was produced by the following two approaches: one was by sectioning the chordae tendineae through the transventricular route,^{10,11} the other was by external bypass circuit which permitted blood to flow from the left ventricle to the left atrium during systole.¹² When the stable state was obtained after the induction of mitral regurgitation, we infused nitroprusside at a rate of 5 $\mu\text{g}/\text{kg}/\text{min}$. Recordings were repeated when systolic pressure decreased 20% below the control level.

Fig.4. The instantaneous transverse diameter of the left atrium and left ventricular free wall segment length were measured throughout the cardiac cycle in an anesthetized dog using ultrasonic dimension gauges (upper panel). The alternatively measured aortic blood flow is shown in the lower panel. Following the control recording (left panel), the severe mitral regurgitation was produced by sectioning the chordae tendineae. The left atrial and the left ventricular chamber were both enlarged remarkably. The magnitude of atrial motion was severely decreased while the left ventricular shortening increased (middle). Nitroprusside caused an augmentation of forward stroke volume associated with a decrease in the end-diastolic dimension of the left ventricular and left atrial chambers. V wave of the atrial pressure was essentially abolished (right panel).

RESULTS

Clinical Study

Table I summarizes the hemodynamic effects of nitroprusside in the 5 patients with mitral regurgitation and 7 patients with aortic regurgitation. In all patients with mitral regurgitation, the same directional changes were observed. Heart rate did not change significantly (from 82 to 83/min). The average peak left ventricular systolic pressure (LVSP) fell significantly (-16%) as did the left ventricular end-diastolic pressure (LVEDP) (-32%) (Fig. 2). In 2 cases, measurement of pulmonary capillary wedge pressure was repeated during nitroprusside infusion in which a dramatic decrease in v wave was observed (Fig. 1). In one patient (HW), LVSP remained unchanged, presumably because a substantial increase in forward stroke volume

(FSV) which occurred along with a decrease in systemic vascular resistance counteracted a fall in aortic pressure. Nitroprusside infusion produced a significant increase in cardiac output ($+29\%$) and forward stroke volume ($+31\%$) (Fig. 2). End-diastolic and end-systolic volumes decreased by 14% and 18% , respectively. Total stroke volume tended to decrease but the changes were not statistically significant. Thus, the observed increase in the forward stroke volume was almost entirely the result of decreases in regurgitant volume (-60%) and in regurgitant fraction (-69%). Ejection fraction was not affected by nitroprusside (Fig. 3).

In patients with aortic regurgitation, nitroprusside infusion produced a significant reduction in LVSP and LVEDP. Five of these 7 patients had an elevated peak systolic pressure in the resting state (more than 150 mmHg), and 3

exhibited abnormally high resting LVEDP (more than 20 mmHg). The heart rate increased significantly on the average from 69 to 79 beats/min, but in one patient (MS), there was a reduction in heart rate during nitroprusside infusion. FSV was augmented in 2 patients (MS, KS), unchanged in 2 (MH, KY) and decreased in 3 (HI, KK, UM) (Fig. 2).

With regard to left ventricular volumes, the end-diastolic and end-systolic volumes decreased by 12% and 23%, respectively, with an insignificant change in the total stroke volume. Ejection fraction increased from 55 to 62%. There was no consistent change in regurgitant volume. Regurgitant fraction remained unchanged (Fig. 3).

In 2 patients (MS, KS), in whom there was an increase in FSV, the LVEDP which was initially elevated was reduced but to levels slightly above normal. Hereby, end-diastolic volume was reduced by 6% in one (MS) and 7% in the other (KS), accompanied by substantial augmentations of the total stroke volume and ejection fraction. Thus, these favorable effects in improving FSV were mostly the result of an increase in pump function. In the patients with relatively low levels of LVEDP, further reduction in filling pressure with vasodilator therapy resulted in no benefit or rather a fall in FSV.

Experimental Studies

Acute onset of mitral regurgitation in the canine heart induced initially an augmentation of atrial shortening with chamber dilation as a result of an optimal use of the Frank-Starling mechanism of atrial muscle. As mitral regurgitation was progressively increased, the extent of the atrial shortening and expansion was diminished, despite the geometrical advantage of a further increase in atrial diameter (Fig. 4). The left atrial pressure was markedly elevated with an abbreviation of the x descent and striking increase in v wave with early onset of its ascent. The left ventricular cavity continuously enlarged with resultant increase in wall shortening. Despite this enhanced pump function, FSV was appreciably diminished (Fig. 4). With nitroprusside, there was a significant fall in LVSP and in atrial pressure with a marked reduction in v wave. The atrial diameter decreased with restoration of active atrial shortening. Left ventricular size was also remarkably decreased accompanied by the reduction of LVEDP. FSV was substantially augmented (Fig. 4). All of these findings indicated a reduction in the regurgitant volume.

In mitral regurgitation induced by the external bypass circuit, there was a considerable acceleration of systolic pressure fall in the early phase of ventricular ejection. LVEDP was elevated. Left ventricular and left atrial chamber sizes were significantly enlarged with a resultant enhancement of myocardial shortening. In this preparation, nitroprusside infusion was started before regurgitation became extremely severe as in the case with chordal rupture, which resulted in a substantial fall in FSV associated with definite reduction in end-diastolic dimension of the left ventricular and left atrial chambers (Fig. 5).

DISCUSSION

Chatterjee et al.⁵ first demonstrated favorable effects of nitroprusside on hemodynamics in patients with mitral regurgitation due to dysfunction of the subvalvular mitral apparatus. In the situation when the ventricle is subjected to acute severe volume overloading, the Frank-Starling reserve becomes exhausted and the left ventricle is forced down a maximally shifted force-velocity-length relationship due to the increased afterload with enhanced systolic pressure, cardiac dilatation, and wall thinning, all determinants of wall stress.¹³ Thus, left ventricular failure may be the result of the acute afterload mismatch with depressed stroke volume due to severe mechanical overload in the face of a fully utilized preload reserve, despite an unaltered contractile state of myocardium.^{3,4}

Afterload reduction in this condition will exert a dramatic effect on improving pump function by simple correction of afterload mismatch. However, when we applied nitroprusside to the ventricle with severe mitral regurgitation in both clinical and experimental settings, no significant augmentation of the total pump function was observed. When the left ventricular end-diastolic volume was reduced to a relatively low level after nitroprusside, total stroke volume substantially fell.

With the onset of mitral regurgitation in the dogs, the peak left ventricular pressure declined accompanied by a significant change in the contour of the tracing, i.e., the pressure reached its peak in early systole and declined rapidly during ejection. Left ventricular chamber size was also reduced more rapidly during the pre-ejection phase of systole due to regurgitation of blood into the left atrium, as a consequence of mitral incompetence.¹⁴ Since wall tension is a

Fig.5. Following the control recordings as in the Fig. 4 (left panel), the mitral regurgitation was induced by the external bypass circuit (middle panel). Nitroprusside infusion resulted in a fall in forward stroke volume with definite reduction in end-diastolic dimension of the left ventricular and left atrial chambers.

function of both ventricular pressure and radius, the combination of a decrease in left ventricular pressure and an acceleration in reduction in the ventricular volume results in a precipitous decline in tension during the course of ejection. Thus, the left ventricle is already in an unloaded state with occurrence of mitral regurgitation and further reduction in systemic resistance induced by a vasodilating agent is not likely to improve pump function of the left ventricle but rather will redistribute the left ventricular output so that a greater portion is directed forward by virtue of its selective lowering of aortic impedance!^{11,15}

According to the hydraulic formula of Gorlin and Dexter,¹⁶ the amount of regurgitation is dependent on the area of the regurgitant mitral orifice, the pressure gradient across it and the duration of ventricular systole. Because the square route of pressure is used in the equation, it is reasonable to assume that factors which alter the regurgitant orifice size affect the regurgitation relatively more than would similar changes in the pressure gradient. Importance of orifice size in reducing regurgitant volume has been well

demonstrated in the experiments of Yoran et al.^{17,18} in which phasic transmitral flow was directly measured by an electromagnetic flow probe placed around the mitral annulus, together with a aortic flow to calculate filling volume, stroke volume and regurgitant volume, on a beat to beat basis. They demonstrated that when norepinephrine was given, systolic transmitral pressure gradient increased by 50% but regurgitant volume actually decreased by 12%, reducing the regurgitant fraction by 20%. If the regurgitant area had been fixed, the increase in systolic pressure gradient would have resulted in an increase of regurgitant volume by 6%.¹⁷

Borgenhagen et al.¹⁹ using an angiographic method demonstrated that the mitral area for regurgitation was not fixed but was actively determined by ventricular dynamics, and they speculated that factors which tend to reduce ventricular size are responsible for a reduction in mitral regurgitation, largely independent of changes in transvalvular gradients. Our study demonstrated that in patients with mitral regurgitation, left ventricular systolic and end-diastolic pressures were similarly reduced with nitroprus-

Fig. 6. Diagram showing relations between the left ventricular end-diastolic pressure (EDP) and left ventricular end-diastolic volume (EDV) at the resting state (upper panel) and those between the extent of ventricular shortening (stroke volume [SV]) and afterload (aortic pressure [AoP]) (lower panel). In the ventricle in which the limit of preload reserve is approached (point A), afterload mismatch can be corrected by vasodilator therapy provided venous return is maintained (point B). In the ventricle operating at relatively compliant portion of its passive pressure-volume curve (point C), actual fall in stroke volume may occur when afterload is reduced if the preload is also allowed to fall (point D).

side which rendered changes in systolic pressure gradient to be minimal. Thus, the diminished mitral orifice size is more likely to account for the significant reduction in regurgitation.

On the other hand, the balance between forward cardiac output and regurgitant flow is strongly influenced by aortic impedance to left ventricular outflow. Greenberg et al²⁰ reported that hydralazine which selectively acts on the arteriolar resistance bed was also effective in reducing mitral regurgitation. Unlike nitro-

prusside, this drug did not alter left ventricular end-diastolic volume or end-diastolic pressure. Accordingly, augmentation of cardiac output was considered to be related solely to the reduction in aortic impedance. Arteriolar effects may play a primary role in cases with a fibrous or calcified valve orifice, however, in most patients with mitral regurgitation, the valve orifice is rarely fixed. The direct effect of preload reduction by nitroprusside on regurgitant orifice size is no doubt the primary mechanism for improvement of regurgitation.

Contrary to the consistent reduction in regurgitant volume in mitral regurgitation, with no significant change in pump function (as reflected by unchanged ejection fraction), vasodilator therapy in aortic regurgitation induced some heterogeneity in response. In 2 patients, improvement of forward stroke volume was achieved by substantial rise in the ejection fraction which was brought about by a reduction in impedance to ejection, while maintaining a relatively high filling pressure. Thus, in these patients, forward cardiac output was enhanced by virtue of increased total stroke volume, at the expense of increased regurgitant volume, the regurgitant fraction being maintained unchanged. In 3 patients, nitroprusside induced a substantial decrease in forward stroke volume associated with an extreme fall in end-diastolic pressure and end-diastolic volume. The importance of maintaining filling pressure at an optimal level in vasodilator therapy for regurgitant valvular disease with fixed regurgitant orifice is exemplified by an animal experiment in which mitral regurgitation was induced by an external bypass circuit with a fixed caliber. In this experimental model, afterload reduction to the same extent as in the mitral regurgitation due to chordal rupture, resulted in a decrease in total excursion with diminished chamber size.

A framework for understanding these divergent responses of the ventricle with aortic regurgitation to vasodilator therapy is shown in Fig. 6. The failing heart with markedly elevated end-diastolic pressure is assumed to be operating at a high and steeper portion of the passive pressure-volume curve (Fig. 6, point A) where considerable decrease in end-diastolic pressure is associated with only small change in end-diastolic volume (Fig. 6, point B). In such a ventricle with an almost fixed preload, the afterload reduction directly enhances the ejection, according to the simple expression of force-shortening relation-

ship (from point A to point B in the lower panel of Fig. 6). On the contrary, the heart with end-diastolic pressure of normal range is operating at the lower flat portion of the passive pressure-volume curve (point C in the upper panel of Fig. 6), where marked reduction in end-diastolic volume with less change in end-diastolic pressure is induced by a reduction in venous return (point D). Thus, with nitroprusside, the ventricle shifts to a new force-shortening curve displaced downward, hereby, any effects due to afterload reduction tend to be offset (point D in lower panel).

In summary vasodilator therapy is uniformly effective in reducing mitral regurgitation and in increasing forward stroke volume primarily by decreasing the regurgitant orifice size as a result of the reduction in left heart chamber size. The afterload reduction in patients with aortic regurgitation yields a variable response depending on the accompanying change in preload. The patients who have pump failure with elevated end-diastolic pressure are likely to benefit from afterload reduction by correcting afterload mismatch, provided venous return is maintained, while a reduction in mean circulatory pressure with inadequate maintenance of venous return in patients with a lower level of end-diastolic pressure may induce no change or actual fall in forward stroke volume, despite an enhanced cardiac function.

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REFERENCES

1. SONNENBLICK EH: Force-velocity relations in mammalian heart muscle. *Am J Physiol* **202**: 931, 1962
2. SONNENBLICK EH: Implications of muscle mechanics in heart. *Fed Proc* **21**: 975, 1962
3. ROSS JJr: Afterload mismatch and preload reserve: A conceptual framework for the analysis of ventricular function. *Progr Cardiovasc Dis* **18**: 255, 1976
4. ROSS JJr, FRANKLIN D, SASAYAMA S: Preload, afterload, and the role of afterload mismatch in the descending limb of cardiac function. *Europ J Cardiol* **4**: 77, 1976
5. CHATTERJEE K, PARMLEY WW, SWAN HJC, BERMAN G, FORRESTER J, MARCUS HS: Beneficial effects of vasodilator agents in severe mitral regurgitation due to dysfunction of subvalvular apparatus. *Circulation* **48**: 684, 1973
6. GOODMAN DJ, ROSSEN RM, HOLLOWAY EL, ALDERMAN EL, HARRISON DC: Effect of nitroprusside on left ventricular dynamics in mitral regurgitation. *Circulation* **50**: 1025, 1974
7. HARSHOW CW, GROSSMAN W, MUNRO AB, McLAURIN LP: Reduced systemic vascular resistance as therapy for severe mitral regurgitation of valvular origin. *Ann Intern Med* **83**: 312, 1975
8. BOLEN J, ALDERMAN EL: Hemodynamic consequences of afterload reduction in patients with chronic aortic regurgitation. *Circulation* **53**: 879, 1976
9. KENNEDY JW, TRENHOLME SE, KASSER IS: Left ventricular volume and mass from single-plane cineangiocardigram. A comparison of antero-posterior and right anterior oblique methods. *Am Heart J* **80**: 343, 1970
10. SASAYAMA S, TAKAHASHI M, OSAKADA G, HIROSE K, HAMASHIMA H, NISHIMURA E, KAWAI C: Dynamic geometry of the left atrium and left ventricle in acute mitral regurgitation. *Circulation* **60**: 177, 1979
11. SASAYAMA S, KUBO S, KUSUKAWA R: Hemodynamic and angiocardigraphic studies on cardiodynamics: Experimental mitral insufficiency. *Jpn Circul J* **34**: 513, 1970
12. ROSS J Jr, COOPER T, LOMBARDO CR: Hemodynamic observations in experimental mitral regurgitation. *Surg* **47**: 795, 1960
13. McGRAGOR DC, COVELL JW, MAHLER F, DILLEY RB, ROSS JJr: Relations between afterload, stroke volume, and descending limb of Starling's curve. *Am J Physiol* **223**: 820, 1974
14. URSCHER CW, COVELL JW, SONNENBLICK EH, ROSS JJr, BRAUNWALD E: Myocardial mechanics in aortic and mitral valvular regurgitation: The concept of instantaneous impedance as a determinant of the performance of the intact heart. *J Clin Invest* **47**: 867, 1968
15. SASAYAMA S, TAKAHASHI M, KAWAI C: Left atrial function in acute mitral regurgitation. *Herz* **6**: 156, 1981
16. GORLIN R, DEXTER L: Hydraulic formula for the calculation of the cross sectional area of the mitral valve during regurgitation. *Am Heart J* **43**: 188, 1952
17. YORAN C, YELLIN EL, BECKER RM, GABBAY S, FRATER RWM, SONNENBLICK EH: Dynamic aspects of acute mitral regurgitation: Effects of ventricular volume, pressure and contractility on the effective regurgitant orifice area. *Circulation* **60**: 170, 1979
18. YORAN C, YELLIN EL, BECKER RM, GABBAY S, FRATER RWM, SONNENBLICK EH: Mechanism of reduction of mitral regurgitation with vasodilator therapy. *Am J Cardiol* **43**: 773, 1979
19. BORGENTHAGEN DM, SERUR JR, GORLIN R, ADAMS D, SONNENBLICK EH: The effects of left ventricular load and contractility on mitral regurgitant orifice size and flow in the dog. *Circulation* **56**: 106, 1977
20. GREENBERG BH, MASSIE BM, BRANDAGE BH, BOTVINICK EH, PARMLEY WW, CHATTERJEE K: Beneficial effects of hydralazine in severe mitral regurgitation. *Circulation* **58**: 273, 1978