Captopril mediated decrease of aortic regurgitation

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SUMMARY The effect of captopril mediated afterload reduction on aortic regurgitation was investigated in 10 patients. Regurgitation was quantitated by means of the regurgitation fraction and the relation of regurgitant volume to end diastolic volume. These variables were derived from gated radionuclide ventriculography. After captopril treatment the blood concentration of angiotensin I rose whereas that of angiotensin II fell significantly. The conversion of angiotensin I to II was reduced to about 50% of the control value. Whereas blood pressure and heart rate did not change significantly, the regurgitation fraction and the regurgitant volume, normalised to end diastolic volume, were significantly reduced by captopril treatment. The ejection fraction remained essentially unchanged. These findings suggest that captopril reduces aortic regurgitation by reducing afterload.

In chronic aortic insufficiency there is long standing volume overload of the left heart chamber. The most prominent haemodynamic alterations are a progressive increase in end diastolic volume and, depending on the extent of the disease, a raised end diastolic pressure. When there is compensated aortic insufficiency stroke volume, ejection fraction, and cardiac output remain essentially unchanged. The heart muscle responds to volume overload by increased replication of sarcomeres and distension of cardiac muscle fibres with consequent hypertrophy of left ventricle^{1,2}; as a result, the normal relation of wall thickness and chamber diameter is maintained.¹

Long term volume overload leads to a progressive dilatation of the left ventricle in late stages of the disease. There are concomitant reductions in forward output, ejection fraction, and regurgitation volume. Pronounced degenerative changes such as fibrosis of cardiac muscle are seen in cases of advanced disease.³ Lower cardiac output, resulting in a reduced coronary perfusion and an increased wall stress, affects cardiac oxygen balance unfavourably.

Chronic volume overload is well tolerated for a surprisingly long time. If decompensated left heart failure develops, however (that is a change from

New York Heart Association stage III to IV) the prognosis is very poor.² The aim of conservative management is to prevent decompensation of left ventricle for as long as possible. The strategy of reducing the afterload on the left ventricle has been applied successfully to patients with chronic aortic insufficiency.⁴⁻⁶ By reducing the difference between diastolic aortic pressure and left ventricular pressure this regimen lessens aortic regurgitation.⁴⁻⁶

Captopril, an angiotensin converting enzyme inhibitor, has been successfully used for afterload reduction in patients with congestive heart failure.⁷ Captopril reduces the production of the potent vasoconstrictor angiotensin II. As well as causing arteriolar dilatation, captopril also reduces production of aldosterone and antidiuretic hormone. Since the renin-angiotensin system is usually stimulated in aortic insufficiency,⁸ this new regimen appears to be a promising treatment for aortic regurgitation.

Patients and methods

Patients—Ten patients with chronic aortic insufficiency (stage I to II, New York Heart Association classification) were examined. Valve disease, other than that affecting the aortic valve, and coronary artery disease were excluded by routine examination including ultrasonography, coronary angiography, and left ventriculography. Patients with aortic insufficiency were examined by gated radionuclide ventriculography before and one hour

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after 25 mg of captopril by mouth. Thus each patient served as his own control.

Renin-angiotensin measurements—Angiotensin I and II and the activity of angiotensin converting enzyme activity were measured by radioimmunoassay or spectrophotometry.⁸ Blood pressure (Riva-Rocci) was measured repeatedly before and after captopril. The average heart rate during radionuclide ventriculography was calculated from the representative heart cycle (see below) before and after captopril.

Gated radionuclide ventriculography—In all patients electrocardiogram gated equilibrium radionuclide ventriculography was performed after injection of 20 mCi of technetium-99m labelled autologous red blood cells. Data in list mode were acquired by means of a LFOV gamma camera connected to a minicomputer. A hardware zoom of 1.5 was applied. Data were collected from the best septal view (30° to 45° left anterior oblique). A high resolution collimator was used. Ten million counts were collected per study. The statistical distribution of the different cardiac cycle lengths during data acquisition was determined and a representative cardiac cycle—usually the one which occurred most frequently—was automatically selected. The cumulative frame sequence was generated exclusively from cycles which fell into the selected range. A frame rate of 50 frames per second was used. The frame size was 64 × 64 pixels. Data on 300 to 500 heart cycles were accumulated per study. End diastolic and systolic frames were identified within the reformatted image sequence. End diastolic images of both ventricles were marked by an operator on the video screen of the computer. A Fourier phase image overlay was used for edge detection of ventricular borders.⁹ Extracardiac background was subtracted from the precordially registered radioactivity. A detailed description of this correction procedure is given below. The volume curves corrected for background radioactivity were used to determine the left and right ventricular ejection fractions and maximal ejection and filling rates.¹⁰ Fourier analysis of the reformatted image sequence was performed as described previously.¹⁰

Background correction—Count rates registered over the heart chambers that were not emitted by the ventricle's blood pool (background) were determined for the area difference between the end diastolic and the end systolic contours of both ventricles. The background count rates were standardised for the respective end diastolic area of the ventricles. Left and right ventricular count rates were corrected for background radioactivity by subtraction of the normalised count rates derived from the area difference between end diastolic and end

systolic left and right ventricular images.

Regurgitation fraction (RF) was calculated from the background corrected count rates according to the method of Sørensen, *et al*¹¹ as modified by Alderson¹²: $RF(\%) = (LV \text{ count} - 1.02 \times RV \text{ count} \times LV \text{ count}) \times 100$. The calibration factor of 1.02 had been determined in our laboratory.⁹ A typical example of end diastolic and end systolic images and their respective regurgitation fractions is shown in Fig. 1.

We also determined the ratio of regurgitant volume (RGV) to end diastolic volume (EDV). This ratio is a major determinant of the reversibility of functional impairment of compromised left ventricular performance in aortic insufficiency.¹³

Control of regurgitation measurements—To check the validity of measuring regurgitation by radionuclide ventriculography 19 patients with coronary heart disease (established by coronary angiography) with normal heart valves and 10 patients with chronic aortic or mitral regurgitation (reflux) were examined before and after valve replacement.⁹ Virtually no regurgitation was found in patients with coronary heart disease (4.1(3.4)% of left ventricular

Fig. 1 End diastolic (left) and end systolic (right) radionuclide ventriculographic images before and after captopril treatment in a patient with aortic regurgitation. The regurgitation fraction was reduced from 42% to 27%.

Fig. 2 Arterial blood pressure and heart rate (mean (SD)) before and after captopril treatment in 10 patients with aortic insufficiency.

stroke volume (mean (SD))). In contrast, in patients with chronic aortic or mitral regurgitation there was considerable regurgitation across the respective valves (59(18.6)%).⁹ The angiographically determined grade of regurgitation correlated significantly with the amount of regurgitation as assessed by radionuclide ventriculography.⁹ After valve replacement considerably reduced or virtually no regurgitation (reflux) was found. (3.7(8.2)%).⁹ Together with results reported from other laboratories, these findings demonstrate the validity of determining valvar regurgitation by radionuclide ventricu-

Fig. 3 Effect of captopril on regurgitation fraction (RF) and ejection fraction (EF) (mean (SEM)) in 10 patients with aortic insufficiency. EDV, end diastolic volume; ESV, end systolic volume.

Fig. 4 Effect of captopril on regurgitant volume in 10 patients with aortic insufficiency (mean (SD)). RGV, regurgitant volume; EDV, end diastolic volume.

lography in patients with aortic or mitral insufficiency.^{11,14}

Results

Neither heart rate nor blood pressure were significantly influenced by captopril (Fig. 2). The left ventricular ejection fraction was also essentially unchanged (Fig. 3) (ejection fraction 60% before captopril *vs* 66% after captopril). In contrast the regurgitation fraction decreased from 54% before captopril to 37% after captopril (p < 0.0001). The ratio of regurgitant volume to end diastolic volume also showed a significant decrease from 33% before captopril to 24% after captopril (p < 0.01) (Fig. 4).

Fig. 5 Inhibition by captopril of conversion of angiotensin I (AI) to angiotensin II (AII) in 10 patients with aortic insufficiency (mean (SEM)).

Conversion: traditional units to SI—
 Angiotensin I: 1pg/ml = 0.771 pmol/l.
 Angiotensin II: 1pg/ml = 0.9561 pmol/l.

Captopril treatment significantly increased blood concentrations of angiotensin I to 240% of control (range 120–630%) and significantly reduced concentrations of angiotensin II (range 5.7–42.6%, $p < 0.01$). There was a 27% decrease of angiotensin converting enzyme activity in peripheral blood ($p < 0.01$). Rate of conversion of angiotensin I to angiotensin II, calculated from blood concentrations, decreased to 50% of that of controls (range 28–86%, $p < 0.01$) (Fig. 5).

Discussion

Captopril significantly suppresses the renin-angiotensin system in patients with aortic regurgitation, as shown by an increase in concentration of angiotensin I and a decrease in concentration of angiotensin II. Accordingly the rate of conversion of angiotensin I to II was significantly reduced and, as expected, the activity of angiotensin converting enzyme was considerably reduced. Reflex tachycardia, which is often seen after treatment with arteriolar dilators, was not observed after captopril. This finding may be explained by a reduction in the angiotensin II mediated component of sympathetic tone.¹⁵ Also, unlike some other vasodilators, captopril does not stimulate the renin-angiotensin system and thus some unfavourable haemodynamic effects are avoided.

Systolic and diastolic blood pressure were essentially unchanged after captopril. In contrast Froer *et al* noted a slight decrease in systolic blood pressure and little change in diastolic blood pressure.¹⁶ In their study mean systolic pressure decreased by about 15% after captopril.¹⁶ The different response of systolic blood pressure to captopril in our study may be explained by the fact that our patients were classified as New York Heart Association stage I or II and those of Froer *et al*¹⁶ as stage III.

The most important haemodynamic consequences of captopril treatment were a pronounced reduction of aortic regurgitation with an unchanged ejection fraction. Similar findings were reported when afterload was reduced in patients with aortic insufficiency by means of sodium nitroprusside or hydralazine.^{4,5} Froer *et al* reported an increase in forward output and concluded from their data that the regurgitant volume through the aortic valve had decreased.¹⁶ Our findings support this interpretation and show that the ratio of the volume being regurgitated through the aortic valve to the total stroke volume is significantly reduced by captopril. This effect is most prominent when the 30% reduction of normalised regurgitant volume is considered.

This haemodynamic improvement is probably

caused by a reduction in systemic vascular resistance.¹⁶ This change might be accomplished by reducing the pressure difference between aorta and left ventricle, by increasing cardiac output, or by a combination of both effects. Because the left ventricular ejection fraction remains essentially unchanged and regurgitation is reduced, an increase of stroke volume and (since heart rate remains constant) cardiac output may indeed occur. Alternatively the captopril induced improvement in haemodynamic variables may be explained by a reduction of end diastolic and end systolic ventricular volumes with an unchanged stroke volume. Such a reduction of preload and afterload achieved without a change in cardiac output suggests that a smaller expenditure of energy would be required to perform the same amount of cardiac work. If this effect is substantiated in future studies, it may provide an approach to long term conservative management of patients with aortic regurgitation and better preservation of myocardial function which will increase the success of eventual cardiac surgery.

Non-invasive accurate measurement of end diastolic and end systolic ventricular volumes and cardiac output is now possible by several techniques based on radionuclide ventriculography.^{17–19} Thus it should be possible to determine the principal mechanism (increased cardiac output or decreased ventricular volumes) responsible for captopril induced haemodynamic changes. Repeated assessment of absolute ventricular volume is especially important because patients with progressive left ventricular dilatation and decreasing aortic regurgitation have a very poor prognosis.¹³ Accurate and repeated haemodynamic measurements may be obtained by radionuclide ventriculography without causing undue patient discomfort and such measurements may be used to monitor conservative treatment or to select patients for valve replacement.

References

- 1 Braunwald E. Valvular heart disease. In: Braunwald E, ed. *Heart disease*. Philadelphia: WB Saunders, 1980: 1095–165.
- 2 Bolte HD, Hort W. Erworbene Herzklappenfehler. In: Riecker G, ed. *Klinische Kardiologie*. Heidelberg: Springer Verlag, 1982: 217–26.
- 3 Maron BJ, Ferrans VJ. Ultrastructural features of hypertrophied human ventricular myocardium. *Prog Cardiovasc Dis* 1978; 21: 207–38.
- 4 Bolen JL, Alderman EL. Hemodynamic consequences of afterload reduction in patients with chronic aortic regurgitation. *Circulation* 1976; 53: 879–83.
- 5 Greeberg BH, De Mots H, Murphy E, Rahimtoola SH. Mechanism for improved cardiac performance with arteriolar dilators in aortic insufficiency. *Circulation*

- 1981; **63**: 263–8.
- 6 Fioretti P, Benussi B, Scarditi S, Klugmann S, Brower RW, Camerini F. Afterload reduction with nifedipine in aortic insufficiency. *Am J Cardiol* 1982; **49**: 1728–1732.
- 7 McKay CR, Nanna M, Elkayam U, Kawanishi D, Chandraratna PAN, Rahimtoola SH. Long-term vasodilator treatment of chronic aortic regurgitation: preliminary evidence of hemodynamic and functional improvement [Abstract]. *Circulation* 1983; **68** (suppl III): 300.
- 8 Heck I, Mattern H, Fricke G, Krück F. Aktivierungszustände des Renin-angiotensin-Systems (RAS) bei Aorten- und Mitralklappen vor und nach Klappenersatz. *Z Kardiologie* 1983; **72** (suppl 1): 20.
- 9 Kropp J, Biersack HJ, Janson R, Reske SN, Bähre M, Winkler C. Regurgitations index bei Herzklappenfehlern: Vergleichende Untersuchungen an Patienten vor und nach chirurgischer Korrektur. In: Schmidt HAE, Adam WE, eds. *Nuklearmedizin*. Stuttgart: Schattauer, 1984: 236–9.
- 10 Knopp R, Breuel HP, Schmidt H, Winkler C. Funktionsszintigraphie des Herzens. 1. Datentechnische Grundlagen und Methodik. *ROFO* 1978; **128**: 44–7.
- 11 Sörensen S, O'Rourke RA, Chaudhuri TK. Non-invasive quantitation of valvular regurgitation by gated equilibrium radionuclide angiography. *Circulation* 1980; **62**: 1089–98.
- 12 Alderson PO. Radionuclide quantification of valvular regurgitation. *J Nucl Med* 1982; **23**: 851–5.
- 13 Levine HJ, Gaasch WH. Ratio of regurgitant volume to end-diastolic volume: a major determinant of ventricular response to surgical correction of chronic volume overload. *Am J Cardiol* 1983; **52**: 406–10.
- 14 Rigo P, Alderson PO, Robertson RM, Becker LC, Wagner HN, Jr. Measurement of aortic and mitral regurgitation by gated cardiac blood pool scans. *Circulation* 1979; **60**: 306–12.
- 15 Bertel O. Pathophysiologische Bedeutung des Renin-Angiotensin-Systems bei Herzinsuffizienz. In: Gross F, ed. *Hemmung des Angiotensin-Konversionsenzym (ACE). Ein neues Prinzip in der Behandlung der Hypertonie und der Herzinsuffizienz*. Munich: MMW Medizinverlag, 1983: 11–9.
- 16 Froer KL, Hall D, Deming K. Captopril bei valvulärer Herzerkrankung. In: Gross F, ed. *Hemmung des Angiotensin-Konversionsenzym (ACE). Ein neues Prinzip in der Behandlung der Hypertonie und der Herzinsuffizienz*. Munich: MMW Medizinverlag, 1983: 64–70.
- 17 Dehmer GJ, Firth BG, Hillis LD, Nicod P, Willerson JT, Lewis SE. Nongeometric determination of right ventricular volumes from equilibrium blood pool scans. *Am J Cardiol* 1982; **49**: 78–84.
- 18 Links JM, Becker LC, Shindler JG, et al. Measurement of absolute left ventricular volume from gated blood pool studies. *Circulation* 1982; **65**: 82–91.
- 19 Seiderer M, Böhm J, Büll U, Kleinhans E, Rienmüller R, Strauer BE. Optimierte Bestimmung des linksventrikulären enddiastolischen Volumens mit der Äquilibrium-Radionuklid-Ventrikulographie. *Nuklearmedizin* 1981; **20**: 257–64.