Cardiovascular effects of forskolin and phosphodiesterase-III inhibitors

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Summary

In the first part of this presentation, data is reported on the hemodynamic effects of forskolin given to patients with dilated cardiomyopathy in a concentration of 3 μg/kg/min and 4 μg/kg/min. At the lower dosage, forskolin had no effect on dP/dt_{max}, cardiac index, ejection fraction, or myocardial oxygen consumption. With small dosages of dobutamine, however, an increase of all four parameters has been observed in the same group of patients. Systemic vascular resistance and left ventricular enddiastolic pressure fell with forskolin given at the lower concentration. Forskolin administered at a dosage of 4 μg/kg/min induced an increase in dP/dt_{max} by 19% and a 16% rise in heart rate. However, these changes were associated with symptomatic flush syndromes. Therefore, forskolin may serve as a vasodilating substance in lower concentrations, but cannot be used as a positive inotropic compound because of the subjective symptoms.

In the second part, a study is reported in which an anti-ischemic effect of the phosphodiesterase inhibitor enoximone was observed in patients with proven significant coronary heart disease. With respect to the hemodynamic parameters, the most striking findings were the decreases in left ventricular enddiastolic pressure and systemic vascular resistance. Furthermore, when left ventricular stroke work index was plotted as a function of the left ventricular enddiastolic pressure, enoximone shifted the left ventricular function curve to the left. Therefore, the anti-ischemic effect of enoximone may not only be due to a reduction in preload and afterload but may rather reflect an effect on diastolic compliance. Studies with intracoronary injections of enoximone and animal experiments support this hypothesis.

Introduction

Forskolin, a diterpene derivative of an Indian plant (*coleus forskohlii*), and the phosphodiesterase (PDE) inhibitors currently under investigation are chemically not related and bear no structural similarities. Forskolin is classified as an adenylate cyclase activator, while PDE inhibitors have a direct effect on cyclic AMP [1–3]. The final pathway of effectiveness ultimately leads to changes in the mobilization of Ca^{2+}-ions. However, there are more common features justifying the joint presentation of both substances.

First, the target site of action is not confined to the myocardium, but is rather ubiquitious and wide-spread. Second, based on these prerequisites, there are general effects influencing the cardiocirculatory system. Thus, affecting both the vasculature and the myocardium, vasodilation and positive inotropic stimulation are to be expected when the compounds are administered systemically to healthy volunteers or patients.

Last but not least, the mode of action of both compounds is independent of β-receptors, and therefore cannot be abolished by β-receptor blockers. On the other hand, blockade of their effects by Ca^{2+}-antagonists can be demonstrated. At least for the PDE in-

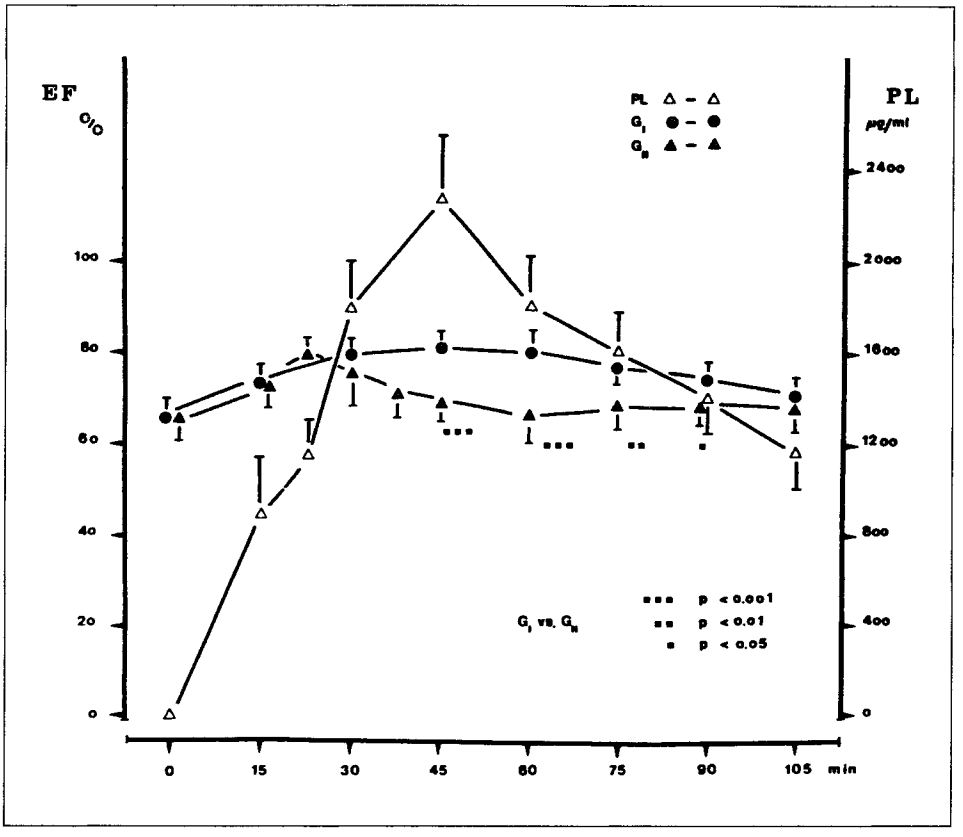

Fig. 1. The graph illustrates sulmazole-induced alterations of ejection fraction (EF) in healthy volunteers and the average serum levels (PL) following infusion of sulmazole 1) without verapamil (group I = G_I) and 2) with the additional application of verapamil (group II = G_{II}).

The conclusions are: 1) In group I alterations of left ventricular performance correspond with the increase of serum levels up to 1800 ng/ml; further elevations do not result in an additional increase in efficiency, i.e., beyond a certain serum level of sulmazole a dosage/efficacy relationship no longer exists; 2) In group II the sulmazole-induced increases in EF are abolished with the influence of verapamil setting in: sulmazole effects are blocked by verapamil

hibitors such a counteraction – induced by verapamil – has been observed when obtaining cardiac parameters after sulmazole infusion at increasing dosage in healthy volunteers [4, 5]. The distinct increase in fractional shortening and ejection fraction and the decrease in the preload- and afterload-independent but rate corrected electromechanical systole (QS_2I) could be abolished when verapamil was added. Looking at the serum levels of sulmazole which were identical in both courses of infusion, it is apparent that the three parameters observed remained at a plateau, although the serum level was still increasing (Fig. 1). Is this a feature inherent to all PDE inhibitors, and can it be assumed that at a certain serum level "target sites" have been totally activated or occupied?

When compounds which exhibit both positive inotropic effects and vasodilating properties are tested clinically, the assessment of inotropy faces several methodological

difficulties. Methods applied should deliver data sufficient to discriminate between pre- and afterload-induced changes of overall cardiac pump function and those caused by true positive inotropic effects, which by definition are load-independent. Most of the parameters which inotropy is judged by in clinical investigations, however, are to some extent, load-dependent, even the so-called contractility parameters. The QS_2 index is load-independent provided heart rate is identical. Pressure/volume diagrams or the endsystolic pressure/volume relationship are able to discriminate between load dependency and inotropic alterations, when the extent of controlled load alterations is used as a measure.

It can be taken as an axiom that with augmentation of inotropy a concomitant increase in oxygen consumption occurs. However, accompanying vasodilation may mask the increase in oxygen consumption so that the net effect may not reflect oxygen-demanding augmentation caused by positive inotropy. Clinical investigations trying to establish positive inotropic effects must therefore be interpreted with caution.

Forskolin

In 1983 Bristow et al. [6] reported on positive inotropic effects of forskolin in membrane preparations derived from failing and normal functioning human left ventricles. There was a dose-related activation of adenylate cyclase, which was 4.38-fold as compared to that caused by maximal isoproterenol application in the normal myocardium and 6.02-fold in the failing heart muscle. The important message from this study, however, was that in a failing myocardium β-receptor density was diminished and that the action of forskolin was independent of this density and could not be abolished by β-receptor blockers. The same investigators [7] also elicited positive inotropic effects in isolated right ventricular papillary muscles from seven failing human hearts and compared these hemodynamic properties of forskolin to isoproterenol in dog experiments. Forskolin increased muscle tension to a lesser degree than isoproterenol, while, in the dog experiments, the effects of forskolin were qualitatively similar to isoproterenol, namely increase in heart rate, cardiac output and dp/dt_{max}, and a decrease in mean arterial pressure, peripheral resistance, and left ventricular filling pressure. However, forskolin proved to be 10- to 100-times less potent on a molar basis, and it appeared to produce relatively greater effects on left ventricular filling pressure. By critically reviewing these investigations, the vasodilator effects were certainly dominating and prevailing over the inotropic effects of forskolin.

In experiments carried out on isolated guinea pig hearts, inotropic action could be studied without interfering with vasodilator effects. It was shown that with increasing doses of forskolin an augmentation of contraction became apparent, while heart rate changes were only minimal. There was an increase in coronary flow and oxygen consumption, although to a much lesser degree than oxygen supplies, pointing to an additional vasodilator effect of this drug on the coronary circulation [8].

There are only few publications dealing with the clinical application of forskolin. Lele et al. [9] reported on observations in which the effects of forskolin were studied by means of a nuclear stethoscope. The cohort of patients in that study was inhomogenous as far as the etiology was concerned. Furthermore, the dosis ranged from 1 μg to 16 μg/kg BW. Following administration of forskolin, there was a statistically significant increase in left ventricular ejection fraction, ejection rate and peak filling rate, and an approximate rise of 15% over the basal values was observed after infusion of 8 μg/kg and 16 μg/kg. Heart rate did not change, cardiac output was elevated and so was stroke volume (in dose-dependent fashion) which amounted to a maximum of 70% following the dosis of 16 μg/kg.

The observed changes showed a large scatter, but it might be suggested that, in addition to an increase in overall pump function, there could have been positive lusitropic effects involved, as indicated by an increase in peak filling rate. As heart rate also increased and no data are given of changes in total peripheral resistance and in arterial pressure, these measurements are not sufficient to discriminate between positive inotropic and vasodilating effects.

Linderer and Biamino [10] likewise studied a group of patients which was etiologically inhomogeneous. In patients with congestive heart failure, mostly due to dilated cardiomyopathy, a 16% increase of dp/dt_{max} was found, systemic vascular resistance was decreased, and coronary blood flow measured by the argon method was either uneffective or even declined in some patients inspite of the increase in dp/dt_{max}. The most striking feature was the drop in left ventricular enddiastolic pressure, which in the author's opinion may explain the reduction in oxygen consumption and the unaltered coronary blood flow due to an improved diastolic compliance of the ventricle.

In our own study, the results were obtained from 15 patients with dilated cardiomyopathy, and the effects of forskolin were compared to those of dobutamine at a rather small dosis of 10 μg/kg infused over 10 min [11]. Since dobutamine has a rather short half-life of only 2.5 min, data after dobutamine application were obtained first and were then followed by a second course of investigation during which forskolin was given at a dosage of 3 μg/kg/min over an infusion period of 10 min. Before and at the end of each infusion period heart rate was maintained constant by atrial pacing. With the dosages applied, heart rate changes were less than 10% and insignificant after both drugs. Left ventricular systolic pressure showed a tendency to fall with forskolin and a slight increase with dobutamine; both changes were insignificant. When patients were divided into two subgroups (Group A with normal resting dp/dt_{max}, and Group B consisting of patients with decreased dp/dt_{max} at rest), dobutamine elicited a significant rise in dp/dt_{max}, while forskolin failed to show a significant increase of this contractility parameter in both subgroups. Cardiac index and EF did not show any increase with either drug. The missing inotropic effect could also be seen by determining myocardial oxygen consumption according to the Bretschneider formula [12, 13]. The slight positive inotropic effect of dobutamine was accompanied by a significant increase in oxygen consumption, whereas forskolin did not induce any alterations in oxygen consumption at all. Left ventricular enddiastolic pressure decreased significantly with both drugs during the infusion period and regained normal values as soon as dobutamine was discontinued. Systemic vascular resistance was decreased with both drugs, but the reduction was more marked with forskolin than with dobutamine. Using the simple compliance index according to Gaasch et al. [14], both drugs exhibited a decrease in this compliance index accompanying the fall in left ventricular enddiastolic pressure. Whether or not this is a specific action of the drug remains speculation (Fig. 2).

To further establish genuine and therefore load-independent positive inotropic effects, left ventricular pressure/volume loops were recorded in all patients. Volume was determined by scintigraphic methods and left ventricular pressure by tip manometer [11]. For volume determinations 250–300 heart beats were mandatory; both signals were digitized and computer-assisted pressure/volume curves were obtained. With dobutamine the endsystolic pressure/volume relationship is shifted to the left and downwards. Lack of slope-k deviations proved that the alterations appearing after the administration of forskolin were due to changes in pre- and afterload exclusively and positive inotropic effects were lacking.

To provoke a more pronounced inotropic stimulation, the dosage of forskolin was increased to 4 μg/kg/min in a pilot study. This resulted in an average increase of dp/dt_{max}

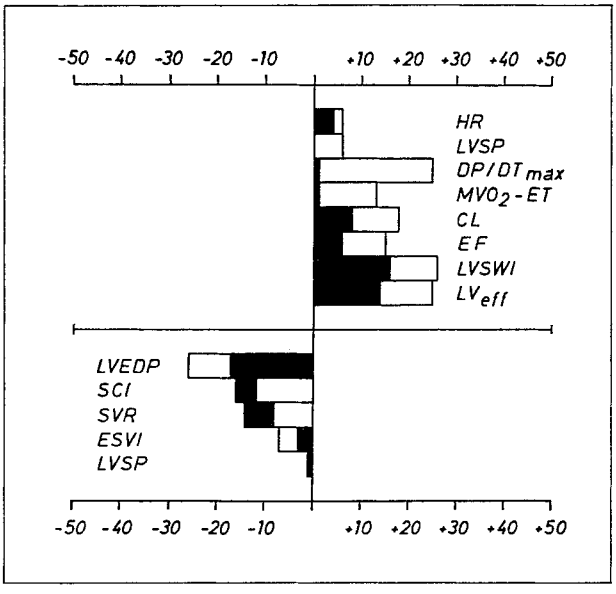

Fig. 2. Maximal percentile parameters alterations of left ventricular function during forskolin intervention (black columns) and dobutamine (white columns).

Abbreviations: HR = heart rate, LVSP = left ventricular systolic pressure, MVO_2-ET = myocardial oxygen consumption (indirectly assessed), CI = cardiac index, EF = ejection fraction, LVSWI = stroke work index, LV_{eff} = left ventricular efficiency, LVEDP = left ventricular enddiastolic pressure, SCI = compliance index according to GAASCH, SVR = systemic vascular resistance, ESVI = endsystolic volume index

by 19%, but was accompanied by a 20% decrease in arterial pressure and a 16% rise in heart rate. Clinically, these hemodynamic changes were associated with symptomatic flush snydromes. For these reasons, further investigations with an increased dosage were delayed. As far as preliminary conclusions can be drawn from our results, we comment that the main effect of forskolin is vasodilation and that, in order to achieve positive inotropic effects, the drug would have to be administered in dosages which are not tolerable for the patient, leading to a fall in blood pressure and systemic vascular resistance and concomitantly to undue subjective symptoms.

To our present knowledge, no further clinical investigations have been carried out in patients with failing hearts. Although the mode of action is sound by principle and certainly valed in theory as regards treatment of the failing heart, we are still in search of a cardiospecific adenylate cyclase activator whch can be used safely and with inotropy as prevailing effect.

PDE Inhibitors

With the exception of amrinone, all PDE inhibitors are still on clinical trial. While favorable effects with short- and long-term treatment of patients with congestive heart failure have been published [15–23], there have been conflicting reports as to whether the ben-

eficial effects were due to vasodilatory or true positive inotropic action of these drugs [24–27]. Wilmshurst et al. deny any positive action of amrinone and claim only vasodilating properties [28].

In a study carried out in patients with dilated cardiomyopathy, pressure-volume curves were obtained to distinguish between vasodilating and positive inotropic effects [29]. Using the conductance catheter technique [30], the required rapid load changes were achieved by either pharmacological intervention with nitroprusside and phenylephrine or by temporary balloon occlusion of the inferior caval vein. Atrial pacing was used to obtain pressure-volume diagrams at comparable heart rates. According to the severity of left ventricular impairment, patients were divided into two subgroups. In patients of Group A with a minor degree of left ventricular impairment, amrinone was given at a low i.v. dosage of 0.5 mg/kg BW. The drug-induced slope k of the endsystolic pressure-volume relationship did not deviate from the slope of either controls, vasodilation with nitroprusside or vasoconstriction with phenylephrine. The isometric maxima all appear

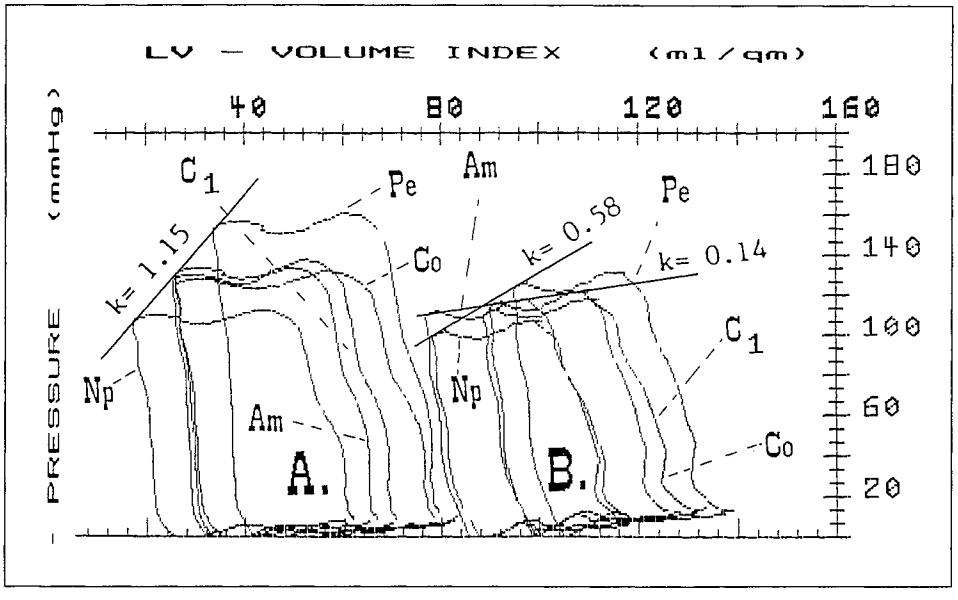

Fig. 3. Amrinone effects as analyzed by endsystolic pressure-volume relationships (ESPVR). Rapid load changes were induced pharmacologically by 1) nitroprussid (Np) and 2) phenylephrine (Pe); pacing for constant heart rates was kept up during the entire investigation. The computer print out demonstrates the ESPVR of the five representative investigational phases, displayed as summation loops for 1) group A with smaller ventricular volumes and 2) group B with larger volumes. Am marks the phase of maximal amrinone effects at a dosage of 1.5 mg/kg and C1 the control during pacing.

Thus, improved LV-pump function in group A was achieved by load changes and not by inotropy: the Am-induced leftward motion of the loop of the ESPVR occurs along the endsystolic interventional line C1-Am which is identical with the endsystolic load line Np-Pe; slope k is 1.15 mm Hg/ml.

In group B patients with larger ventricles a minor (not significant) Am-induced change in inotropy can be assumed since the leftward motion (representing the interventional line C-1-Am) shows a noticeable deviation form the loading line Np-Pe

on one line; vasoactivity of the drug is indicated, but no change in contractility. In the patients of Group B with severely impaired left ventricular function characterized by larger volumes and dp/dt_{max} reduced to a range of 1000 mm Hg/s, amrinone shifted the loop of the endsystolic pressure/volume relationship slightly to the left with a minor deviation of slope k, indicating tendencies towards positive inotropic action induced by amrinone at a low i.v. dosage of 1.5 mg/kg (Fig. 3).

This becomes more apparent, when, in a different cohort of patients with equally impaired left ventricular function, the dosage of amrinone was increased to 2.5 mg/kg, and the required rapid load changes were achieved by temporary balloon occlusion of the vena cava inferior. Without medication the slope k was 0.52 mm Hg/ml, and deviated with amrinone increasing to 0.69 mmHg/ml, while the summarized loop shifted leftwards. When dobutamine (10 μg/kg/min) was infused additionally at this point, slope k deviated to 0.80 mm Hg/ml, thus contributing to the mild inotropic effects of amrinone [29]. A mild, but distinct inotropic action of amrinone can, therefore, be expected. However, it apparently exhibits stronger effects on the more severely impaired cardiac function (Fig. 4).

The same behavior, namely a stronger cardiotonic effect, was obtained when enoximone was studied. Of 27 patients with dilated cardiomyopathy and a cardiac index of about or below 2 l/min/m^2, enoximone was administered in 13 patients at a dosage of 0.5–1 mg/kg, and in 14 patients at a dosage of 1.5–2.0 mg/kg. There was a dose-related

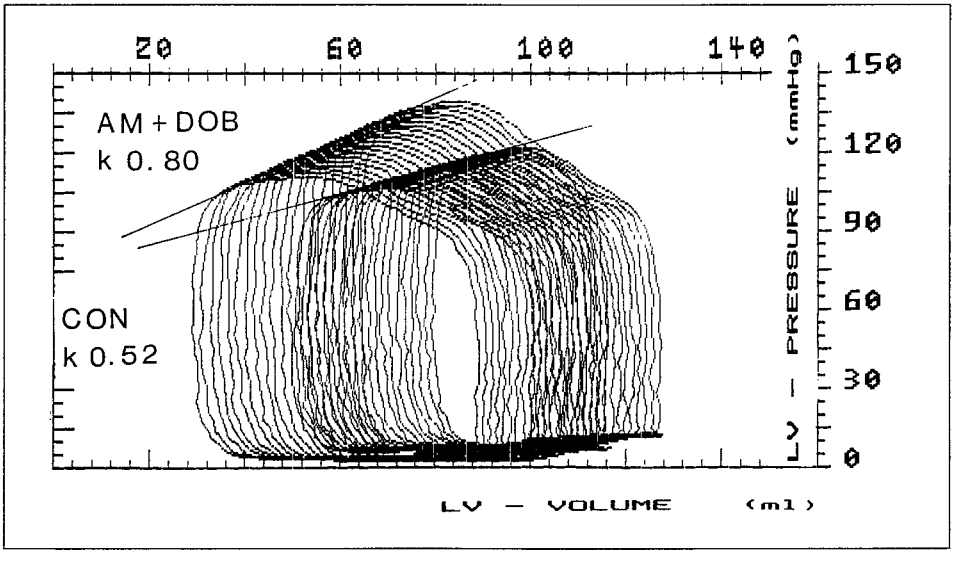

Fig. 4. Depicted are amrinone effects as analyzed by endsystolic pressure-volume relationships (ESPVR) in patients with ventricular impairment. The required load changes were (in contrast to those in Fig. 3) induced by temporary balloon occlusion of the vena cava inferior.

The computer print out demonstrates the ESPVR, displayed as summation loop-series, before and after amrinone (AM), 2.5 mg/kg plus dobutamine (DOB). Under the influence of both drugs a leftward shift of the loops was achieved, with the slope "k" of the ESPVR increasing from 0.52 mmHg/ml to 0.8 mmHg/ml. This indicates an amrinone-induced increase of inotropy which can be enhanced by applying additionally dobutamine

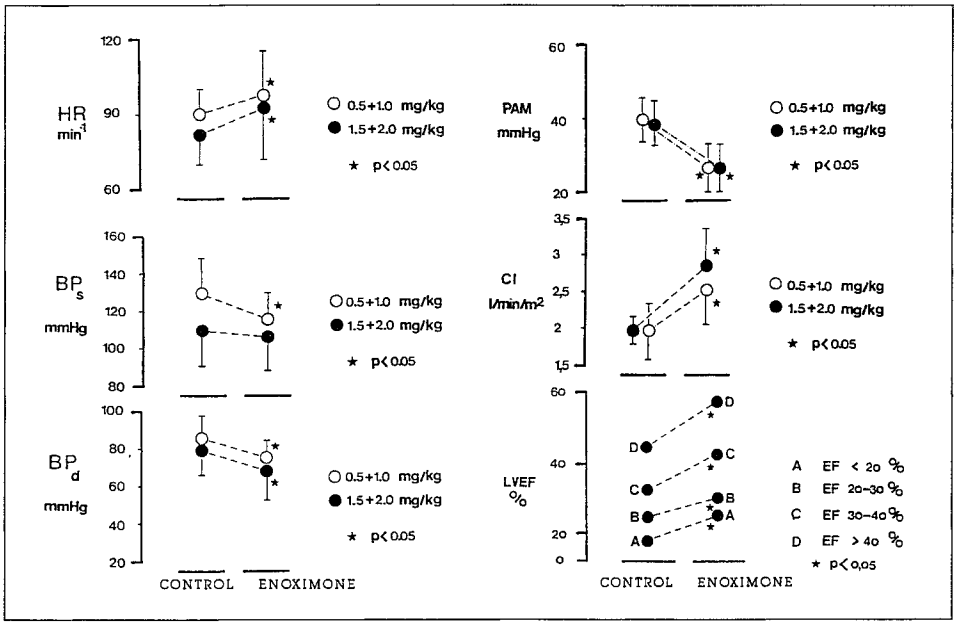

Fig. 5. Dose-related hemodynamic alterations with enoximone, intravenously applied. For details see text.

Abbreviations: BP_s = systolic blood pressure, BP_d = diastolic blood pressure, PAM = pulmonary artery pressure mean, CI = cardiac index, LVEF = left ventricular ejection fraction

increase in cardiac index, statistically significant with both dosages. Concomitantly the pathologically elevated mean pulmonary artery pressure fell from a level of about 40 mm Hg to normal levels of about 25 mm Hg. Twenty-one of these patients were selected and subdivided according to their left ventricular ejection fraction determined by pool-gated technetium scintigraphy. After administration of 1.5 mg/kg given intravenously over a period of 5 min, there was a statistically significant rise of left ventricular ejection fraction in all subgroups (Fig. 5; [21]).

In another cohort of 14 patients with dilated cardiomyopathy (NYHA II) and cardiac indices within normal limits, enoximone, given at a dosage of 1.0 mg/kg, did not alter cardiac index under resting conditions. On exercise, however, there was a statistically significant increase in cardiac index, and the pathological augmentation of mean pulmonary artery pressure with exercise was significantly abolished by enoximone. An improved cardiac pump function is achieved by a decrease in filling pressure, shifting the functional curve of the left ventricle to the left (Fig. 6; [31]).

Again, these data do not allow discrimination between vasodilatory and positive inotropic effects. Whether or not this relationship is in the same range for all PDE inhibitors under investigation has not been established. Pharmacological research has furnished evidence for a compound-specific profile of PDE inhibitors as far as the relationship between vasodilation and inotropy is concerned. The investigations were carried out in anesthetized dogs in which PDE inhibitors were applied by bolus injection. Inotropy was graded by the increase of dp/dt/P; total peripheral resistance (TPR) was calculated and cardiac output (CO) determined by thermodilution.

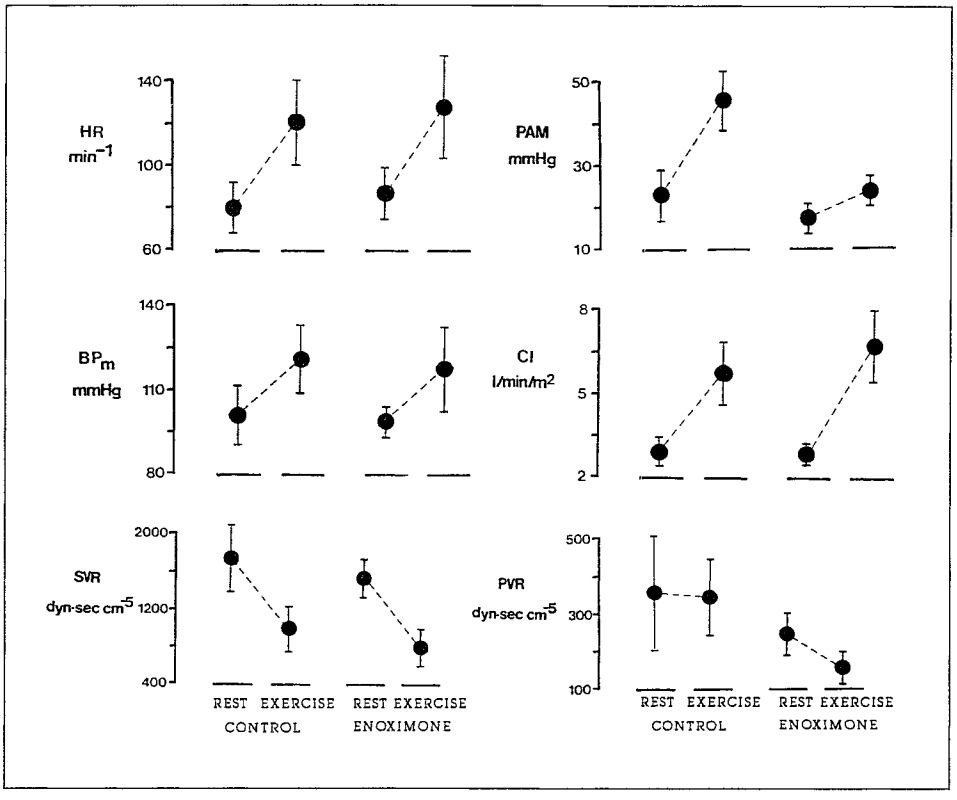

Fig. 6. Enoximone (1.0 mg/kg)-induced hemodynamic changes in 14 patients with dilated cardiomyopathy, under resting conditions and during exercise. For details see text.

Abbreviations: HR = heart rate, BP_m = blood pressure mean, PAM = pulmonary artery pressure mean, CI = cardiac index, SVR = systemic vascular resistance, PVR = pulmonary vascular resistance

When dp/dt/P was measured at a 10% fall of TPR, and TPR and cardiac output at a level of 60% increase of dp/dt/P, a compound-specific profile in the vasodilator to inotropic effects could be established, ultimately leading to a classification of PDE inhibitors into three classes:

Class I drugs in which the increase of dp/dt/P was predominating, while vasodilator effects were only weak;

Class II drugs showed a profile with only slightly prevailing positive inotropy, and

Class III drugs with a balanced ratio of cardiotonic and vasodilating effects or slightly accentuated vascular activity (Fig. 7; [32]).

Since positive inotropy feeds on increased myocardial oxygen consumption, it has to be questioned whether these drugs might provoke ischemia in patients with coronary artery disease.

In a recent publication, patients have been reported to experience angina pectoris when enoximone was applied. This did not only occur in patients with proven coronary artery disease, but, given at relatively high dosage, also in patients suffering from idio-

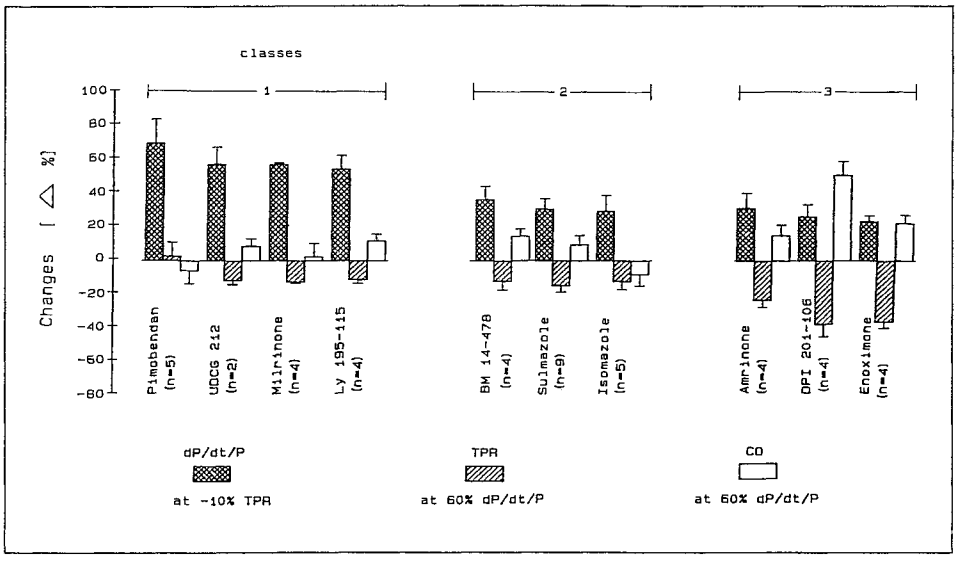

Fig. 7. Relative changes of cardiotonic activity, vasodilation and cardiac output in anesthetized beagle dogs (courtesy Drs. H. J. Schliep and J. Harting, Dept Pharmacol, E Merck/Darmstadt, FRG). For details see text.

Abbreviations: TPR = total peripheral resistance, CO = cardiac output, dp/dt/P = index of contractility

pathic dilated cardiomyopathy [33]. When we first investigated the effects of sulmazole, the drug was applied in 17 patients with angiographically proven 2– or 3-vessel disease in stable angina. Ischemia could be provoked by ventricular pacing as evidenced by lactate production and loss of regional wall motion. The patients received 2 mg/kg BW of sulmazole intravenously over 5 min, and the acute effects were studied at rest and after 9, 14, and 19 min after administration of the compound. Heart rate slightly increased by 19%, left ventricular systolic pressure fell by 13%, and ventricular enddiastolic pressure by 42%. There was a rise in dp/dt_{max} by 27%, systemic vascular resistance was reduced by 24% and cardiac index increased by 30%. Coronary sinus flow was augmented by 39%, coronary vascular resistance declined by 37%, and myocardial oxygen consumption, as calculated by the Bretschneider formula [12, 13], was enhanced by 35%. None of the patients, however, experienced angina pectoris [34].

When ischemia was induced by ventricular pacing (stimulation rate 170 over 75 s) and the procedure repeated 10 min after i.v. administration of 2.5 mg/kg BW of sulmazole, no ischemic patterns could be elicited by the pacing maneuver. An increased pump function was observed and, with the abolition of pacing-induced ischemia, ventricular wall motion considerably improved [35].

Because of these apparently anti-anginal effects of PDE inhibitors, enoximone was investigated with regard to its anti-ischemic effects. In these consented studies, patients with proven significant coronary stenoses and stable angina were investigated. In all, angina could be provoked by either exercise or ventricular pacing. Prior to the investigation, all anti-anginal drugs, with the exception of nitrates, were withdrawn for a period of 5 half-lives, and nitrates were withheld 8–12 h before examinations.

Seventeen patients were exercised on a bicylce ergometer in supine position applying a modified Bruce protocol. A five-lead ECG was recorded, pulmonary-artery and PC-pressures and cardiac output were measured by Swan Ganz catheter. Systemic blood pressure was obtained by the Riva-Rocci method, and resistances were calculated. In addition, lactate, potassium and pH were determined in blood samples taken from the pulmonary artery. Exercise load was individually adjusted and terminated when at least two of the following three criteria were fulfilled: 1) occurrence of angina, 2) ST-segment depression in at least two leads exceeding 0.2 mV, and 3) an elevated mean pulmonary artery pressure above 30 mm Hg. Immediately after termination of exercise, measurements were taken and the patients were allowed to rest for 30 min. Then 0.75 mg of enoximone/kg BW were infused over 10 min; after another 15 min measurements were carried out at rest and after exercise which was repeated for exactly the same time at an identical work load. At the end, all parameters were again taken and calculated. The alterations in pH, lactate and potassium were only slightly altered by enoximone. The lesser decrease in pH and potassium seen after exercise and enoximone can probably be attributed to an increased peripheral blood flow due to the vasodilatory properties.

In summary, it can be assumed that the work load compared by these rough parameters was almost identical. However, systolic and diastolic blood pressure did not change; heart rate increased slightly, but significantly, at rest, but did not do so during exercise. Calculating myocardial oxygen consumption by the double product and the pressure work volume index (Rooke and Feigl [36]), there was only a slight increase in the double product at rest, while the values as calculated by both formulas were not altered on exercise. Cardiac output was increased during exercise and after enoximone. But the most striking feature was a pronounced fall in mean pulmonary pressure and pulmonary capillary pressure, accordingly lowering pulmonary vascular resistance. At an identical workload and with probably identical oxygen consumption, mean pulmonary artery was kept at normal levels compared to pathological levels of about 40 mm Hg during exercise without enoximone. ST-segment depression as a sum of all ST-segment depressions and elevations in the five leads was almost completely abolished, while it was pronounced under exercise without the drug (Fig. 8; [37]). To explain these findings, one could reason that a marked reduction of preload caused by enoximone, which became more apparent under exercise, is responsible for the elevation of the anginal threshold, since all of these patients experienced angina without enoximone and none did so after the drug had been adminsitered. Have we been dealing with just a better nitrate preparation?

Almost identical anti-ischemic effects were seen in another cohort of patients in whom enoximone was given as a single oral dose of 150 mg. The maximal effects were found 2 h after application of the drug showing a strong correlation between plasma levels, hemodynamic improvement at rest and after exercise, and anti-ischemic action [38].

To further evaluate the possible role of intracavitary pressure and reduction of ventricular size and volume, another cohort of 12 patients was studied during routine cardiac catheterization [39]. The same protocol as outlined with sulmazole [35] was applied to these patients, i.e., ventricular pressure recordings were taken at rest and after pacing with and without enoximone and three biplane ventriculograms were performed under the same conditions. On the average, there was an increase of dp/dt_{max} of 20% after post-pacing enoximone as compared to post-pacing without the drug. The oxygen consumption measured on-line by the Bretschneider formula and the Rooke and Feigl formula [12, 13, 36] was identical with and without enoximone. Left ventricular effectiveness was increased by 17%. There were only insignificant changes in heart rate, but, again, the most striking feature was the decrease in left ventricular enddiastolic pressure by 37% and the fall in systemic vascular resistance by 31%. Ejection fraction, which fell under

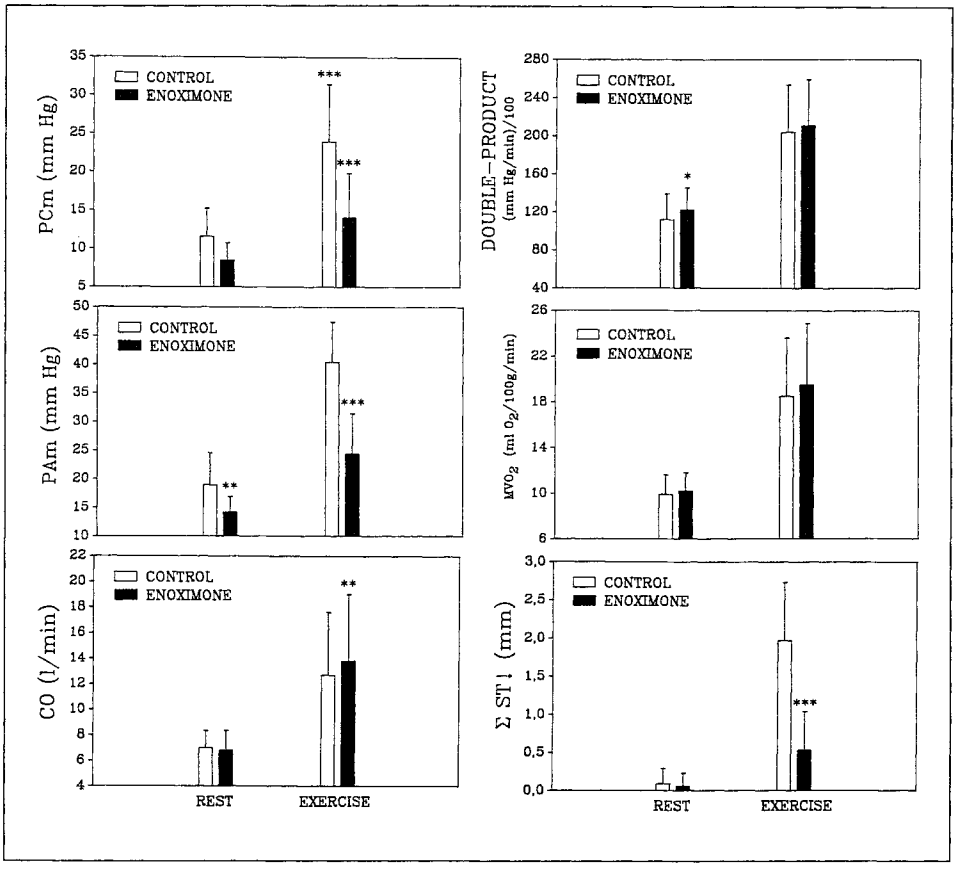

Fig. 8. Enoximone-induced hemodynamic changes in 17 patients with ischemic coronary artery disease at rest and during exercise. Note that cardiac output increased significantly with enoximone only during exercise and that exercise-induced ischemia was abolished by the influence of enoximone. For further details see text. (Abbreviations as in Figs. 2, 5, and 6)

the pacing procedure without enoximone, returned to control values, when the drug had been administered. It is certainly unconventional to average regional wall motion in patients with a different pattern of stenotic lesions in the coronary system. But doing so, it turned out that the loss in regional wall motion which was seen in the five segments in RAO- and LAO-projections and which occurred after the pacing procedure without enoximone, was completely compensated when the pacing procedure was repeated after application of enoximone (Fig. 9; [39]).

When left ventricular stroke work index is plotted against left ventricular enddiastolic pressure, it becomes apparent that less cardiac work is performed at higher left ventricular enddiastolic pressure during pacing-induced ischemia, and that after enoximone left ventricular stroke work index is back to resting values, but this was now achieved at a lower enddiastolic pressure, shifting the functional curve of the left ventricle to the left (Fig. 10).

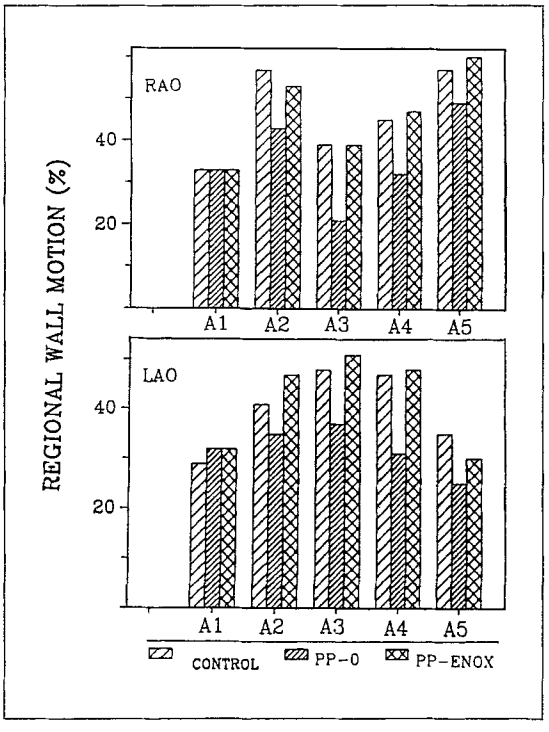

Fig. 9. Group-percentile changes in regional wall motion (RWM) for the 5 segments in both angiographic positions, comparing the postpacing phase with (PP-ENOX) and without enoximone (PP-O). Although this type of demonstration ignores the non-uniformity of individual coronary lesions, the general impression is that with the exception of the septal and postero-basal area, RWM is greatly reduced in PP-O and RWM is improved in PP-ENOX up to and/or above resting levels

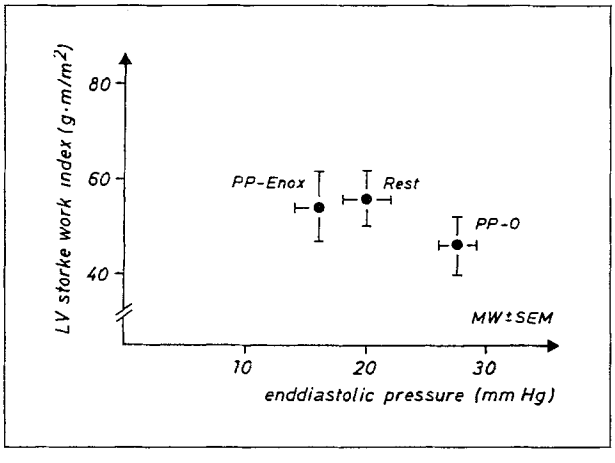

Fig. 10. For 12 patients (same group as in Fig. 9) the changes in left ventricular pump function are defined by the relation of left ventricular stroke work index (LVSWI) versus enddiastolic pressure (LVEDP): In the postpacing phase without medication (PP-O) ischemia was produced, so that LVSWI declined while LVEDP rose (rightward motion down). In the enoximone-medicated postpacing phase (PP-ENOX), LVSWI improved by 18% while LVEDP decreased by 37% (leftward motion, up) and myocardial ischemia was no longer present (PP-ENOX vs PP-O: $p < 0.05$)

Again, when interpreting these findings the question arises as to whether the abolition of the ischemic patterns after enoximone is only due to a predominant preload and possible afterload reduction; or is there a myocardial factor influencing diastolic compliance and, hence, extracoronary coronary flow impairment, responsible for the decrease of intraventricular pressure and elevation of ischemic threshold?

These problems have to be investigated, and valid solutions are not at hand at this time. It could be demonstrated in pilot studies that intracoronary administration of enoximone had similar anti-ischemic effects. Patients in these studies received a 10-min-infusion of 0.075 mg/kg BW of enoximone into a stenosed coronary vascular bed. With these dosages given intravenously, no systemic effects were seen, and serum levels after intracoronary administration of the said dosages were below therapeutic levels and hardly detectable.

Intracoronary application, however, decreased normal and elevated LVEDP. As compared to ventricular pacing before i.c. administration of enoximone, the stimulation procedures were unable to elicit ischemic patterns after i.c. application of the drug.

With a newly developed echo contrast agent which can safely be infused into the coronary arteries, the washout time of the bubbles (T½) from the myocardium can be measured. In animal experiments and investigations in patients, it could be demonstrated that T½ is flow-dependent and is markedly prolonged when LVEDP is increased in consequence to eliciting ischemia by ventricular pacing [40, 41]. When this method was applied in studying the effects of enoximone i.c., not only did the pacing procedure fail to elevate LVED or to cause angina, but T½ was significantly decreased as compared to control values and measurements obtained after pacing without the application of the drug. LVEDP was decreased, but arterial pressures were not altered at all, i.e., identical perfusion pressures.

In animal experiments, Taira [42] demonstrated vasodilation of the epicardial coronary arteries after amrinone i.c. In interpreting our results, a similar mechanism of enoximone can be assumed. But this assumption does not explain the marked drop in LVEDP or the lacking increase after pacing procedures, responsible for ischemia without the drug. Preliminary echocardiographic and Doppler investigations point to a better filling property of the ventricle and a positive lusitropic effect of enoximone after intracoronary application has to be considered, possibly contributing to the beneficial anti-ischemic effects of PDE inhibitors. This ultimately leads to a marked fall in enddiastolic pressure, and this fall, in turn, takes off the burden of an extravascular flow impairment in the coronary circulation.

The findings so far obtained need to be clarified by further studies, which hopefully may lead to a better understanding of the undoubtedly existing anti-ischemic effects of PDE inhibitors, but may also shed new light on the pathophysiological mechanisms of ischemic events.

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