

Dose-Related Hemodynamic and Electrocardiographic Effects of the Calcium Promoter BAY y 5959 in the Presence or Absence of Congestive Heart Failure

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Objectives. The aim of this study was to assess the cardiovascular effects of BAY y 5959, a calcium promoter modulating myocardial calcium channels, in the presence or absence of congestive heart failure.

Background. There is still a clinical need for short-term administration of intravenous positive inotropes. BAY y 5959 was developed as a new approach to increase myocardial performance by selectively enhancing calcium influx in the myocytes.

Methods. Forty-one patients (21 without and 20 with congestive heart failure) were studied in an open label, dose-ranging study. Hemodynamic variables (including left ventricular [LV] angiography) and plasma samples were obtained at baseline and after 20 min of intravenous infusion of BAY y 5959 at doses ranging from 0.25 to 4.5 $\mu\text{g}/\text{kg}$ body weight per min.

Results. In both study groups, BAY y 5959 produced dose-dependent increases in the indexes of inotropic state, without affecting isovolumetric relaxation rate. The magnitude of the response was comparable in patients with or without heart failure (average 38% increase in maximal first derivative of LV pressure

[dP/dt max] at plasma levels of 100 $\mu\text{g}/\text{liter}$). BAY y 5959 also induced mild but statistically significant bradycardia and significantly decreased end-systolic volume while producing a leftward shift of the pressure-volume loop. Mean aortic pressure was unaffected at doses up to 3.0 $\mu\text{g}/\text{kg}$ per min, and cardiac index improved in patients with heart failure at doses of 2.0 $\mu\text{g}/\text{kg}$ per min (+23%, $p < 0.05$). However, at a dose of 4.5 $\mu\text{g}/\text{kg}$ per min, mean aortic pressure and LV systolic wall stress increased, suggesting systemic vasoconstriction. The QT interval was also prolonged significantly at most doses.

Conclusions. BAY y 5959 exhibits positive inotropic effects in patients with and without heart failure. The optimal response—combining bradycardia, reduced preload and improved cardiac output—appeared to be achieved at a dose of ~ 2.0 $\mu\text{g}/\text{kg}$ per min. The impact of QT prolongation with regard to potential antiarrhythmic or proarrhythmic effects is unclear at this time.

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Although the prolonged use of positive inotropic agents in the treatment of congestive heart failure has been seriously questioned because of an increase in mortality (1,2), the short-term administration of intravenous positive inotropes remains a major therapeutic tool in several clinical situations, such as myocardial depression after cardiac bypass surgery or as a bridge in patients with severe heart failure on waiting list for transplantation. The most commonly used agents, such as catecholamines or phosphodiesterase inhibitors, have many

potential drawbacks, including tachycardia, beta-receptor down-regulation and ventricular arrhythmias (1-3). However, it is not yet clear whether the excess mortality is secondary to some direct pharmacologic action of these drugs (i.e., increased intracellular cyclic adenosine monophosphate) or whether they are an unavoidable consequence of inotropic stimulation in this setting (i.e., through energy imbalance or ischemia). Accordingly, new inotropic mechanisms such as calcium sensitization of the contractile proteins or an increase in intracellular calcium availability have recently been investigated. However, earlier attempts to increase myocardium calcium influx by opening the voltage dependent L-type calcium channel were plagued by severe vasoconstriction as well as by proarrhythmia in various experimental models (4).

Recently, new chemical entities with dihydropyridine structure have been identified that show calcium agonistic properties on cardiomyocytes but have little or no functional effect on L-type calcium channels in vascular smooth muscle cells despite their high affinity binding to calcium channels in both tissues. A lead compound in this series, BAY y 5959 [(-)-R-

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Abbreviations and Acronyms

dP/dt	= first derivative of left ventricular pressure
(dP/dt)/DP40	= first derivative of left ventricular pressure measured and normalized at a developed pressure of 40 mm Hg
dP/dt max	= maximal first derivative of left ventricular pressure
ECG	= electrocardiographic
LV	= left ventricle (ventricular)
LVEDP	= left ventricular end-diastolic pressure
NYHA	= New York Heart Association
QTc	= corrected QT interval
T1	= time constant of early isovolumetric pressure decrease

isopropyl 2-amino-5-cyano-1,4-dihydro-6-methyl-4-(3-phenylquinoline-5-yl)-pyridine-3-carboxylate] is modulating the open and close time of single calcium channels in myocytes. Due to the larger increase in mean open times, the overall effect of BAY y 5959 is increased calcium entry into the cells and prolongation of the action potential, two properties resulting in a positive inotropic effect in various in vitro models (5). These compounds are cardioselective because they only prolong the mean open times of L-type calcium channels at depolarizations beyond $-20/-10$ mV, levels readily achieved during the cardiac action potential but rarely in vascular smooth muscle cells. These promising pharmacologic properties, differing significantly from those of other inotropic agents and coupled with a greater selectivity for the myocytes than for the vascular smooth muscle cells, warranted clinical evaluation of the compound. The present study was therefore undertaken to assess the effects of BAY y 5959 on myocardial contractility, mean arterial pressure and electrocardiographic (ECG) indexes in patients with varying degrees of left ventricular (LV) dysfunction.

Methods

Patient selection. For safety reasons, this evaluation was performed open labeled, starting from low doses and increasing to higher doses when the safety of the previous dose level had been established. Moreover, because the responsiveness to inotropes and the risk of proarrhythmia differ substantially between patients with congestive heart failure and patients with normal or preserved LV function, the study was performed in two steps—study 1, an evaluation in 21 patients with ischemic heart disease and no or only mild heart failure, and study 2, an evaluation in 20 patients with moderate to severe New York Heart Association [NYHA] functional class III to IV heart failure.

Demography. *Study 1.* This study recruited 21 men with coronary artery disease admitted for diagnostic cardiac catheterization. Their ages ranged from 42 to 74 years (mean \pm SD 62 ± 8); 14 men had had a previous myocardial infarction. Twelve were in NYHA functional class I and 9 were in class II. Fourteen suffered from angina pectoris.

Study 2. This study enrolled 17 men and 3 women with congestive heart failure ranging in severity from moderate

(NYHA class III, $n = 11$) to severe (NYHA class IV, $n = 9$). Their ages ranged from 49 to 74 years (mean 62 ± 7). Four patients suffered from idiopathic dilated cardiomyopathy, 2 from alcoholic cardiomyopathy, 13 from ischemic cardiomyopathy (including 10 with one or more previous myocardial infarctions) and 1 from persistent heart failure after mitral valve replacement.

All patients gave written informed consent, and both studies were approved by the local institutional review board. All patients were in sinus rhythm, and all cardiovascular drugs, except angiotensin-converting enzyme inhibitors and diuretic agents, had been discontinued ≥ 24 h before the study.

Study protocol. Left heart catheterization was performed by way of the femoral route, as described in detail previously (6). After diagnostic coronary angiography, an 8F pigtail Millar micromanometer was advanced into the LV, for LV pressure recording and contrast material injection. Arterial pressure was measured in the femoral artery and a standard ECG lead (D_1) was continuously recorded. After baseline hemodynamic and angiographic measurements were obtained, BAY y 5959 was infused intravenously for 20 min before angiographic and hemodynamic data collection was repeated. The doses in study 1 were 0.25, 0.50, 1.0, 2.0 and 3.0 $\mu\text{g}/\text{kg}$ per min, respectively, with four patients completing each dose. In one patient receiving the 2.0- $\mu\text{g}/\text{kg}$ per min dose, infusion was stopped after 15 min because of angina pectoris and the patient was withdrawn from the study. The doses in study 2 were 1.0, 2.0, 3.0 and 4.5 $\mu\text{g}/\text{kg}$ per min, respectively, with five patients per dose. No other adverse events were observed during or after infusion. Plasma samples for assay of BAY y 5959 were also obtained, in study 1, at 20, 30, 45 to 60 min and 4 to 6 h after drug infusion, and in study 2, at 20, 30, 40, 50, 60 min and 4 to 6 h after drug infusion.

Data analysis. Left ventriculography together with the ECG and pressure signals were digitized on-line (DVI Philips, 50 frames/s) and processed off-line (APU Philips, Philips Electronic Instruments). The ventricular silhouettes were digitized frame by frame on a video screen after mask subtraction; the computer system derived the correction factor for X-ray magnification and calculated volumes every 20 ms by applying Simpson's rule. Wall thickness at the LV equator was traced on the last unmasked diastolic frame and was computed for subsequent frames assuming a constant LV mass. Midwall circumferential stress was calculated with the formula of Mirsky (7). Mean systolic wall stress was obtained by averaging data from the start to the end of ejection, and mean diastolic wall stress was obtained by averaging data from the start of diastolic filling to end-diastole. Volume data were normalized by using body surface area, and pressure-volume loops were plotted for each patient. The angiographic cardiac index was calculated as

$$\text{Angiographic stroke volume index} \times \text{Heart rate.}$$

Other hemodynamic data were also continuously digitized on-line every 2 ms and processed off-line to derive the isovolumetric indexes of inotropic state—maximal first derivative of

Table 1. Hemodynamic Data: Study 1

	Mean Baseline (n = 20)	Δ Dose 0.25 (n = 4)	Δ Dose 0.50 (n = 4)	Δ Dose 1.0 (n = 4)	Δ Dose 2.0 (n = 4)	Δ Dose 3.0 (n = 4)	Δ Global (n = 20)
HR (beats/min)	69.5 ± 8.6	-5.0 ± 7.4	-5.6 ± 3.7	-1.6 ± 7.6	-7.0 ± 1.8†	-11.9 ± 4.5*	-6.2 ± 6.0‡
LVEDP (mm Hg)	23.7 ± 5.7	-2.4 ± 2.2	-2.7 ± 1.4*	1.1 ± 2.0	-3.1 ± 4.8	-4.2 ± 4.1	-2.3 ± 3.4†
LVSP (mm Hg)	160.0 ± 20.5	-1.1 ± 4.3	-2.3 ± 6.4	12.2 ± 3.2	2.1 ± 10.7	2.6 ± 2.5	2.7 ± 7.6
Mean AoP (mm Hg)	112.0 ± 13.2	-5.5 ± 5.0	-4.3 ± 5.6	6 ± 3.4	-1.0 ± 2.0	-0.5 ± 7.9	-0.8 ± 6.1
dP/dt max (mmHg/s)	1,612 ± 180	16 ± 72	-19 ± 250	258 ± 96*	322 ± 187*	436 ± 147†	203 ± 232‡
(dP/dt)/DP40 (s ⁻¹)	23.7 ± 2.8	0.7 ± 1.5	1.2 ± 1.9	3.1 ± 2.0	5.2 ± 3.3*	7.9 ± 1.8†	3.6 ± 3.4‡
T1 (ms)	53.5 ± 7.7	0.7 ± 1.8	2.7 ± 6.4	1.5 ± 2.0	0.0 ± 6.1	1.7 ± 6.3	1.3 ± 4.5
QTc (ms)	435 ± 28	-6 ± 23	18 ± 8*	15 ± 34	57 ± 18†	31 ± 36	23 ± 31†

*p < 0.05. †p < 0.01. ‡p < 0.001. Data are expressed as mean value ± SD. AoP = aortic pressure; dP/dt = first derivative of left ventricular pressure; (dP/dt)/DP40 = dP/dt measured and normalized at a developed pressure of 40 mm Hg; dP/dt max = maximal dP/dt; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; LVSP = left ventricular systolic pressure; T1 = time constant of early isovolumetric pressure decrease; QTc = corrected QT interval.

LV pressure (dP/dt max) and first derivative of left ventricular pressure (dP/dt) measured and normalized at a developed pressure of 40 mm Hg [(dP/dt)/DP40 (8)]—and the time constant of early isovolumetric pressure decrease, T1 (9). Systemic vascular resistance was calculated as

$$(\text{Mean aortic pressure}/\text{Angiographic cardiac output}) \times 80.$$

Pharmacokinetic evaluation. BAY y 5959 plasma concentrations were determined by a validated liquid chromatography/mass spectrometry assay. The limit of quantification was 0.1 μg/liter. The coefficients of variation were <10% in the calibration range (0.1 to 100 μg/liter).

For data evaluation a population approach was chosen, using the Nonmem version IV level 2.1 program for model building and subsequent variable estimation. The final population pharmacokinetic model to describe the data was an open two-compartment body model with first-order elimination from the central compartment. The final population pharmacodynamic model was a linear relation between BAY y 5959 concentrations, linked by way of an additional effect site compartment to the central compartment to compensate the equilibrium delay indicated by the observed counterclockwise hysteresis, and the contractility index dP/dt max (percent change from baseline) as effect variable. Individual empiric Bayesian estimates (e.g. for clearance) were obtained from the final population pharmacokinetic model using the “posthoc” feature of the Nonmem program. These estimates were plotted against dose to check for dose-proportional pharmacokinetic behavior and against age and baseline cardiac index to search for a possible relation (10).

Statistical analysis. Because the primary objective of this open study was safety, and because it did not include a placebo-controlled group, each group was analyzed separately, and the p values presented (based on paired t test calculations) are considered explorative. To account for multiple comparisons, the t test in each group was performed only if a global test showed a statistically significant change from baseline for the selected variable regardless of the group selected. This global test was performed by using an analysis of variance. Because of the multiple comparisons and relatively small sample sizes, the

possibility of a type I error needs to be considered. Thus, for a more conservative evaluation of the effects, one might rely only on the overall comparisons and use the Bonferroni correction. Even with this conservative approach, all values <0.001 in Tables 1 to 3 would remain statistically significant.

Results

Study 1. Tables 1 and 2 summarize the hemodynamic and angiographic changes. Overall, BAY y 5959 infusion at doses ranging from 0.25 to 3.0 μg/kg per min decreased heart rate and slightly increased stroke volume index with minimal effects on LV end-diastolic pressure, LV systolic pressure, mean aortic pressure or angiographic cardiac index (3.67 ± 0.84 to 3.40 ± 0.85 liters·min⁻¹·m⁻²; p = NS). The indexes of inotropic state increased and the increases were significant at doses ≥2.0 μg/kg per min, without affecting the time constant of isovolumetric pressure decrease. Despite the dose-dependent bradycardia, averaging -11.9 beats/min at 3.0 μg/kg per min, end-diastolic volume index tended to decrease and there was a significant reduction in end-systolic volume index at the highest dose. This reduction in end-systolic volume was accompanied by a leftward shift of the pressure-volume loop (Fig. 1), further supporting the conclusion that myocardial contractility had increased. At these dose levels, afterload estimated either as mean systolic wall stress (-10 kdynes/cm²; p = NS), as mean aortic pressure (-0.5 mm Hg; p = NS) or as systemic vascular resistance (1,283 ± 390 to 1,385 ± 381 dynes·s·cm⁻⁵; p = NS) did not change. The corrected QT interval (QTc) tended to increase at doses above 0.25 μg/kg per min but, as shown in Table 1 and Fig. 2, the relation between plasma concentration of BAY y 5959 and changes in dP/dtmax was more linear than with the QTc prolongation, which reached a plateau earlier. In addition, both relations exhibited hysteresis.

Study 2. The effects of BAY y 5959 on changes in heart rate and indexes of inotropic state in patients with moderate to severe heart failure paralleled those observed in study 1 (Tables 1 and 3, Fig. 3), but the overall decrease in LVEDP was more marked than in study 1. Stroke volume index increased significantly at the three highest dose levels but

Table 2. Angiographic Data

	Study 1						
	Mean Baseline (n = 20)	Δ Dose 0.25 (n = 4)	Δ Dose 0.50 (n = 4)	Δ Dose 1.0 (n = 4)	Δ Dose 2.0 (n = 4)	Δ Dose 3.0 (n = 4)	Δ Global (n = 20)
EF (%)	47 ± 12	4.5 ± 5.3	5.3 ± 3.1*	10.5 ± 12.8	7.0 ± 10.8	11.3 ± 13.0	7.7 ± 9.2†
EDVI (ml/m ²)	114 ± 20	2.5 ± 4.8	0.5 ± 7.3	-3.8 ± 8.0	-3.8 ± 9.4	-10.5 ± 12.9	-3.0 ± 9.1
ESVI (ml/m ²)	61 ± 22	-2.8 ± 4.1	-4.8 ± 6.5	-13.5 ± 11.7	-10.5 ± 9	-17.0 ± 9.6*	-9.7 ± 9.4‡
SVI (ml/m ²)	53 ± 7	5.3 ± 2.2	5.3 ± 3.2	9.7 ± 5.9	6.7 ± 5.0	6.5 ± 4.5	6.7 ± 4.5
MSS (kdynes/cm ²)	326 ± 76	-7 ± 11	6 ± 33	-33 ± 18	-37 ± 32	-10 ± 54	-16 ± 34*
MDS (kdynes/cm ²)	63 ± 29	-10 ± 8	-8 ± 12	-8 ± 6	-21 ± 24	-29 ± 4‡	-15 ± 14‡

	Study 2					
	Mean Baseline (n = 20)	Δ Dose 1.0 (n = 5)	Δ Dose 2.0 (n = 5)	Δ Dose 3.0 (n = 5)	Δ Dose 4.5 (n = 5)	Δ Global (n = 20)
EF (%)	17 ± 8	2.6 ± 1.5*	4.4 ± 5.9	6.6 ± 4.8*	12.8 ± 10.5	6.6 ± 7.2‡
EDVI (ml/m ²)	203 ± 54	-6.4 ± 10.3	-6.6 ± 22.2	-8.8 ± 10.7	-3.8 ± 15.5	-6.4 ± 14.3
ESVI (ml/m ²)	170 ± 55	-10.2 ± 7.1*	-12.2 ± 17.1	-19.2 ± 14.5*	-24.4 ± 19.1*	-16.5 ± 15.1‡
SVI (ml/m ²)	33 ± 17	3.8 ± 3.3	5.6 ± 4.2*	10.4 ± 5.0*	20.6 ± 7.2*	10.1 ± 6.7‡
MSS (kdynes/cm ²)	342 ± 57	-17 ± 31	11 ± 60	4 ± 66	20 ± 63	4 ± 54
MDS (kdynes/cm ²)	121 ± 40	-27 ± 25	-22 ± 23	-31 ± 19*	-18 ± 31	-25 ± 24‡

*p < 0.05. †p < 0.01. ‡p < 0.001. Data are expressed as mean value ± SD. EDVI = end-diastolic volume index; EF = ejection fraction; ESVI = end-systolic volume index; MDS = mean diastolic wall stress; MSS = mean systolic wall stress; SVI = stroke volume index.

because of the bradycardia, the changes in cardiac index were less pronounced. Angiographic cardiac index tended to increase at doses of 2.0 (+23 ± 13%; p < 0.05), 3.0 (+11 ± 6%; p = NS) and 4.5 (+8 ± 13%; p = NS) μg/kg per min. There was also some evidence of unfavorable hemodynamic effects when the dose was increased from 3.0 to 4.5 μg/kg per min. Indeed, at the highest dose and despite further increase in inotropic state, LV systolic pressure, mean aortic pressure and mean systolic wall stress all tended to increase, as did systemic vascular resistance (+5 ± 13% at 4.5 μg/kg per min vs. -14 ±

9% and -7 ± 11% at the dose of 2.0 and 3.0 μg/kg per min, respectively), suggesting that BAY y 5959 could exert some vasoconstriction at the highest dose level.

Pharmacokinetic measurements. There was a good correlation between total dose administered and total exposure, and no significant difference in pharmacokinetics was detected between the patients of studies 1 and 2 (Fig. 4). Neither age nor baseline cardiac index had an influence on BAY y 5959 pharmacokinetics. A population pharmacokinetic/pharmacodynamic modeling combining the data from the two studies supports a linear relation between BAY y 5959 plasma concentrations and dP/dt max for the observed concentration range of up to 200 μg/liter. A BAY y 5959 steady state concentration of ~100 μg/liter will result in a 38% change in dP/dt max.

Figure 1. Typical changes in LV pressure-volume loop after infusion of BAY y 5959 at a dose of 3.0 μg/kg per min in a patient with preserved LV function. There was a leftward shift in end-systolic pressure-volume data and a slight downward shift of the diastolic pressure-volume data.

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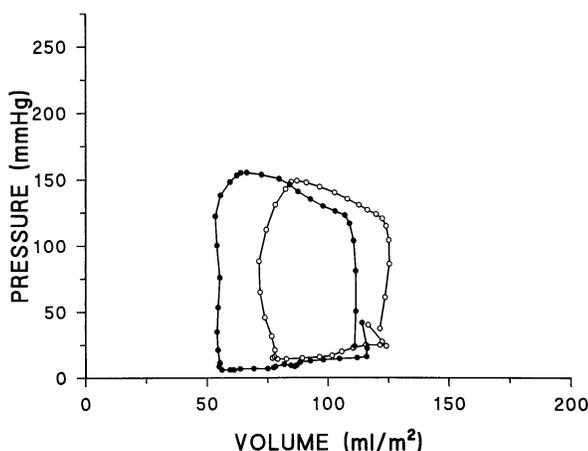


Figure 2. Typical relation between plasma concentration and dP/dt max or QTc prolongation during and immediately after cessation of infusion of BAY y 5959 at a dose of 3.0 μg/kg per min. Although both relations exhibited some hysteresis, dP/dt max increased almost linearly with plasma concentration, whereas QTc prolongation maintained a plateau (same patient as in Fig. 1). l = liter.

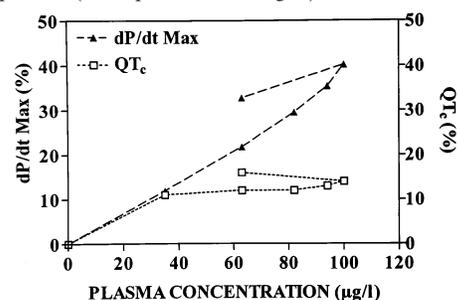


Table 3. Hemodynamic Data: Study 2

	Mean Baseline (n = 20)	Δ Dose 1.0 (n = 5)	Δ Dose 2.0 (n = 5)	Δ Dose 3.0 (n = 5)	Δ Dose 4.5 (n = 5)	Δ Global (n = 20)
HR (beats/min)	84.7 ± 16.2	-11.1 ± 7.8*	-6.2 ± 4.8*	-8.9 ± 7.7	-11.9 ± 7.2*	-9.5 ± 6.8‡
LVEDP (mm Hg)	29.3 ± 8.5	-8.6 ± 6.7*	-2.0 ± 7.0	-7.0 ± 2.9†	0.2 ± 3.9	-4.3 ± 6.2†
LVSP (mm Hg)	124.5 ± 21.3	-3.7 ± 10.2	6.2 ± 10.3	9.5 ± 11.1	23.3 ± 9.7†	8.8 ± 13.7†
Mean AoP (mm Hg)	94.4 ± 13.0	-3.3 ± 6.2	1.3 ± 9.6	0.2 ± 11.6	7.4 ± 8.0	1.4 ± 9.2
dP/dt max (mm Hg/s)	1,005 ± 266	10 ± 103	166 ± 152	255 ± 185*	462 ± 107‡	223 ± 212‡
(dP/dt)/DP40 (s ⁻¹)	13.4 ± 4.0	2.1 ± 1.4*	2.6 ± 3.9	5.8 ± 3.6	7.5 ± 2.4†	4.5 ± 3.6‡
T1 (ms)	73.6 ± 14.3	2.7 ± 6.2	-1.9 ± 12.3	-7.2 ± 11.0	14.4 ± 12.3	2.0 ± 12.8
QTc (ms)	478 ± 50	18 ± 26	49 ± 32*	79 ± 69	83 ± 44*	57 ± 50‡

*p < 0.05. †p < 0.01. ‡p < 0.001. Data are expressed as mean value ± SD. Abbreviations as in Table 1.

Discussion

The aim of the study was to explore the tolerability and hemodynamic effects of the new calcium promoter BAY y 5959 in the presence or absence of congestive heart failure. Overall, the drug was well tolerated during and after the infusion period. Only one patient, in study 1, with a history of anterior myocardial infarction 10 years before the study and recent onset of chest pain, was withdrawn prematurely because of typical angina after 15 min of infusion. Diagnostic coronary arteriography and baseline ventriculography had revealed three-vessel disease and an ejection fraction of 37%. The relation between angina and the drug infusion is difficult to interpret, but a contribution of BAY y 5959 cannot be ruled out. This patient recovered fully. No other adverse events attributable to the study drug were noted up to 30 days after study.

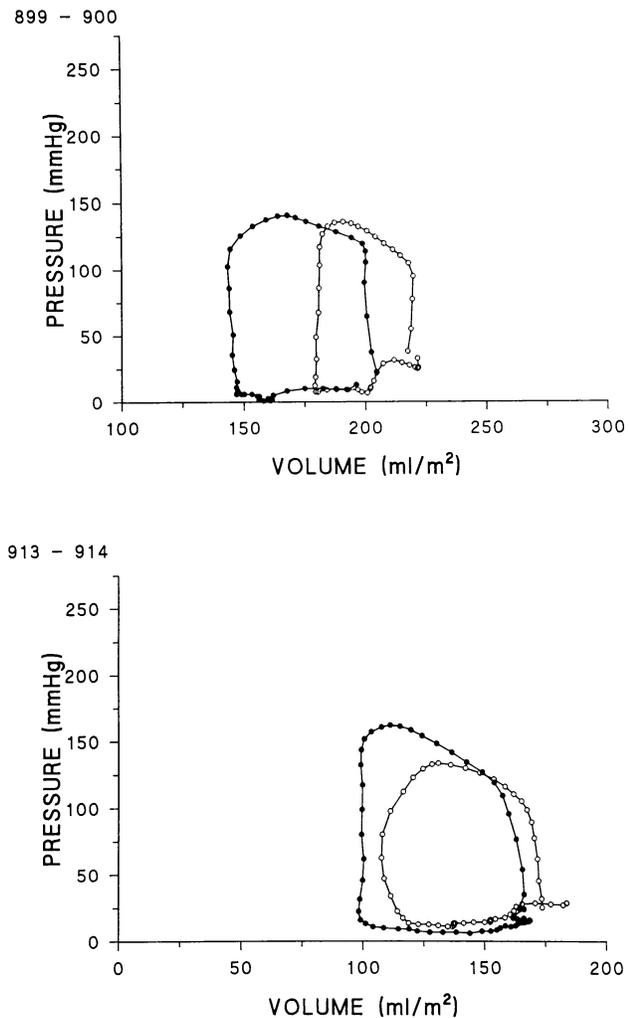
Three other aspects of the effects of BAY y 5959 are also worth reviewing in detail: the inotropic and lusitropic actions, the overall effect on LV pump function and effects on heart rate and QT interval.

Inotropic effects of BAY y 5959. Although all isovolumetric indexes have some limitations, in that they can be affected by heart rate, preload and afterload, it is noteworthy that the increases in dP/dt max and in (dP/dt)/DP40 occurred in most cases despite slight reductions in heart rate and LV end-diastolic pressure. This is good evidence for an increase in myocardial contractility, a conclusion further supported by the leftward shift of the end-systolic pressure-volume data (Figs. 1 and 3). The effects on dP/dt max appeared relatively linear within a plasma concentration range of 20 to 100 μg/liter (Fig. 2). Few effects were observed at an infusion rate <1.0 μg/kg per min. At doses that overlap between studies 1 and 2 (1.0, 2.0 and 3.0 μg/kg per min), the responsiveness of the failing ventricle to BAY y 5959 appeared to be well maintained. This observation is consistent with data recently reported in conscious dogs with heart failure (11). The mean changes in end-diastolic and end-systolic volume indexes observed at doses of 2.0 and 3.0 μg/kg per min were also of the same magnitude in studies 1 and 2, although ejection fraction tended to improve more in patients with preserved systolic function.

There appeared to be no significant effect on the rate of myocardial relaxation, estimated by T1 (9), although the

beginning of relaxation was probably delayed, given the prolongation in the QT interval. In light of the multiple feedback mechanisms that regulate sarcoplasmic reticulum function and

Figure 3. Typical changes in pressure-volume loop observed in patients with moderate to severe heart failure during infusion of BAY y 5959 at a dose of 3.0 μg/kg per min (**top**) and at a dose of 4.5 μg/kg per min (**bottom**). Although both doses decreased end-systolic volume, 4.5 μg/kg per min produced a substantial increase in systolic pressure.



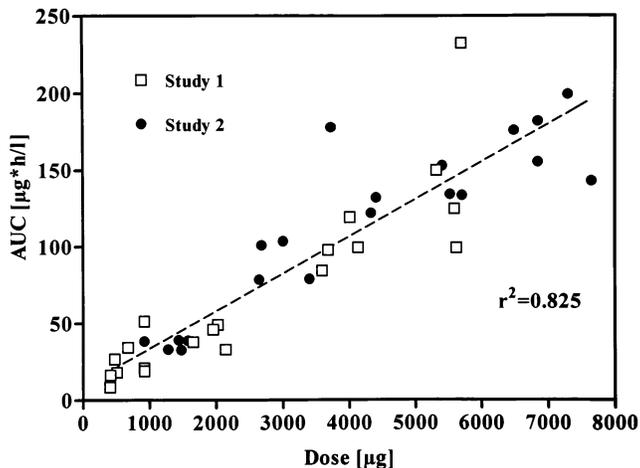


Figure 4. Relation between total dose of BAY y 5959 administered and the area under the curve (AUC) in patients with or without heart failure. BAY y 5959 exhibits linear pharmacokinetics that does not appear to be affected by the presence of heart failure. l = liter.

the sensitivity of contractile proteins to calcium, one can only speculate about the lack of slowing in relaxation rate. One hypothesis, which could be verified in isolated myocardium, is that BAY y 5959 does not cause a net increase in intracellular calcium stores, the increased influx in systole being compensated by an efflux of similar magnitude during each diastole. Furthermore, LVEDP decreased, and the diastolic pressure-volume relation tended to be shifted downward. Here, also, several factors such as changes in right ventricular size due to the inotropic stimulation could explain this observation (12), and mean diastolic wall stress decreased significantly in both groups at the dose of 3.0 $\mu\text{g}/\text{kg}$ per min. Thus, although BAY y 5959 promotes calcium entry into the myocardium, there was no evidence for an impairment in diastolic function similar to that seen in other types of calcium overload (e.g., ischemia, toxic doses of digoxin).

Effects on global left ventricular pump function. In patients with preserved LV function, the mean cardiac index was normal at baseline (3.6 liters/min per m^2). In this setting, BAY y 5959 produced only insignificant changes in cardiac index; stroke volume increased slightly but, because of the decrease in heart rate, overall output remained unchanged. This observation is not surprising as it is well known (13) that at rest, in the absence of pump failure, cardiac output is more dependent on venous return than on myocardial contractility. One could have expected, however, to observe a relatively large decrease in LVEDP, because with inotropic stimulation the ventricle is expected to achieve similar or greater stroke work at a lower end-diastolic volume. Only slight decreases in end-diastolic volume and pressure were seen at doses of 2.0 and 3.0 $\mu\text{g}/\text{kg}$ per min ($p = \text{NS}$). It is possible that at these infusion rates, inotropic stimulation is still very modest when compared, for example, with sympathetic stimulation during exercise and that the decrease in heart rate also contributed to minimize the changes in LVEDP.

In contrast, in patients with heart failure, cardiac index was slightly reduced at baseline (2.7 liters/min per m^2) and increased at infusion rates of 2.0 and 3.0 $\mu\text{g}/\text{kg}$ per min (by $23 \pm 13\%$ and $11 \pm 6\%$, respectively) despite the slight bradycardia. At doses between 1.0 and 3.0 $\mu\text{g}/\text{kg}$ per min, LVEDP also decreased, but again the inotropic stimulation was relatively modest, as estimated by the percent increase in dP/dt max, and there was little change in afterload, as assessed by mean aortic pressure, calculated systemic vascular resistance or mean systolic wall stress. It is therefore not surprising that at this level of inotropic stimulation the overall hemodynamic benefit was less than with drugs like dopamine or amrinone, which combine positive inotropic and vasodilator properties. Moreover, at the highest infusion rate, the increase in cardiac index was no longer significant ($8 \pm 13\%$) and there was a substantial increase in LV systolic pressure (Table 3; Fig. 3, bottom). These findings suggest that, at this infusion rate, some degree of smooth muscle selectivity is lost and that BAY y 5959, like the classic calcium agonist BAY k 8644, may start producing some systemic vasoconstriction. Indeed, systemic vascular resistance reached a minimum at the 2.0- $\mu\text{g}/\text{kg}$ per min rate ($-14 \pm 9\%$; $p < 0.05$), was insignificantly reduced at 3.0 $\mu\text{g}/\text{kg}$ per min ($-7 \pm 11\%$; $p = \text{NS}$) and started to rise at 4.5 $\mu\text{g}/\text{kg}$ per min ($+5 \pm 13\%$; $p = \text{NS}$).

Effects on heart rate and QT interval. At doses beginning at 2.0 $\mu\text{g}/\text{kg}$ per min, BAY y 5959 produced a mild reduction in sinus rhythm. Although agents that prolong action potential may slower the sinus rate, Sato et al. (14) observed in dogs that the bradycardia in response to BAY y 5959 was abolished after ganglionic blockade. This finding suggests a role of the baroreceptor reflex in the bradycardia, but such a conclusion would require confirmation in humans. By its pharmacologic action, BAY y 5959 increased the action potential duration; hence, the QT/QTc interval would also be expected to increase in vivo. In theory, this corresponds to a class III antiarrhythmic effect. However, QT prolongations have been linked to afterpotential generation and torsade de pointes, a life-threatening ventricular arrhythmia. Female patients and patients with congestive heart failure are, among others, particularly at risk for this complication (15). In the present study, no proarrhythmia was observed, and it also appeared that the QT prolongation tended to reach a plateau faster than the increase in contractility (Fig. 2). However, the number of patients was very small and, given the risk observed with all agents that prolong the QT interval, careful monitoring will continue to be necessary and further studies will be needed to assess the electrophysiologic effects of this class of agents in patients.

In summary, the new calcium promoter BAY y 5959 exhibits bradycardic and positive inotropic properties that are preserved in patients with heart failure. The optimal response—combining bradycardia, reduced preload and improved cardiac output—appeared to be achieved at a dose of ~ 2.0 $\mu\text{g}/\text{kg}$ per min. The impact of QT prolongation with regard to potential antiarrhythmic or proarrhythmic effects is unclear at this time. This compound, which appeared to be well tolerated and

exhibited predictable kinetics, deserves further clinical evaluations in patients with heart failure.

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