# Anion-Channel Blockade With Alinidine: A Specific Bradycardic Drug for Coronary Heart Disease Without Negative Inotropic Activity?

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**In 14 patients undergoing cardiac catheterization for suspected coronary artery disease, alinidine, 0.6 mg/kg, was administered intravenously to determine its effects on left ventricular (LV) function, coronary blood flow and myocardial oxygen consumption. To assess effects independent of changes in heart rate (HR), measurements were made at spontaneous and matched pacing HRs. At spontaneous HR, alinidine decreased HR from 70 ± 2 to 61 ± 3 beats/min ($p < 10^{-6}$). Peak rate of LV pressure decreased from 1,652 ± 92 to 1,371 ± 80 mm Hg/s ($p < 10^{-5}$) and Vmax decreased from 47 ± 3 to 41 ± 2 $s^{-1}$ ($p < 10^{-4}$). Coronary sinus blood flow decreased from 109 ± 9 to 89 ± 7 ml/min ($p < 0.01$) and myocardial oxygen consumption from 10.9 ± 1.0 to 9.0 ± 0.8 ml $O_2$/min ($p < 0.05$). At a matched pacing HR of 98 ± 3 beats/min before and after alinidine administration, peak rate of LV pressure decreased from 1,984 ± 124 to 1,793 ± 106 mm Hg/s ($p < 10^{-4}$) and Vmax from 60 ± 5 to 56 ± 4 $s^{-1}$ ($p < 0.02$). Coronary sinus blood flow and myocardial oxygen consumption were not significantly changed at matched pacing HRs. The time constant of the first 40 ms of LV isovolumic relaxation was prolonged by alinidine only during spontaneous HR. Thus, alinidine results in a bradycardia-dependent decrease in myocardial oxygen consumption. It has negative inotropic properties independent of changes in HR and so is not a pure bradycardia-specific agent.**

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Alinidine is a new bradycardic agent that acts without β-receptor blockade.[1,2] As such, use of alinidine could avoid limitations associated with potentially undesirable properties of β-receptor blockade.[3] Although its chemical structure is similar to that of clonidine, its pharmacologic spectrum of action is distinctly different with minimal, if any, vasodilating activity.[1] Millar and Vaughan Williams proposed that its bradycardic action may be mediated by a unique mechanism of anion-selective membrane channel blockade.[4,5] In in vitro models, alinidine has slowed the rate of sinus node discharge,[1,4] an in animals, decreased resting myocardial oxygen consumption ($M\dot{V}O_2$).[5,6] In patients with coronary artery disease limited by angina, alinidine decreases heart rate (HR) at rest, prolongs the duration of exercise and increases the level of maximal work without symptoms.[7,8]

Even if alinidine acts through a new mechanism of anion-channel blockade, then it still must be determined whether the drug acts as a unique specific bradycardic agent. Controversy exists over whether alinidine, in humans, has negative inotropic properties as well.[9,10] Because changes in HR alone may alter global left ventricular (LV) function and metabolism, the direct effects of alinidine on the heart, other than bradycardia, are uncertain.

Therefore, we assessed the acute hemodynamic and myocardial effects of an intravenous dose of alinidine in 14 patients undergoing routine catheterization for evaluation of suspected coronary artery disease. Indexes of LV function, $M\dot{V}O_2$ and coronary blood flow were measured before and after administration of the drug. To assess the effects of alinidine independent of changes in HR, measurements were also made at multiple matched atrial paced HRs.

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## Methods

**Study population (Table I):** The mean age of the patients was 54 ± 3 years and mean angiographic ejection fraction was 55 ± 4%. Two patients with atypical chest pain had normal coronary arteries. Beta-blocking and vasodilating drugs were discontinued at least 24 hours before study. Patients were studied after an overnight fast without premedication preceding routine diagnostic angiography.

**Data collection:** Catheterization was performed through a right brachial or right femoral approach. In 13 patients, a No. 8Fr double micromanometer-tipped catheter (Millar Instruments) was advanced into the left ventricle. In 1 patient, an 8Fr pigtail micromanometer-tipped catheter (Millar Instruments) was advanced into the left ventricle and briefly pulled back to the central aortic position during coronary blood flow measurements and then reintroduced. LV pressure was analyzed using a previously described on-line system to measure the following variables[11]: HR, LV peak systolic pressure, end-diastolic pressure, peak positive and negative rates of LV pressure change (+dP/dt and −dP/dt), velocity of the contractile element (dP/dt/P) at a total pressure of 40 mm Hg ($Vce_{40}$), peak measured velocity of the contractile element (peak Vce), Vce linearly extrapolated to 0 mm Hg (Vmax), and $T_1$ and $T_2$, the 2 respective time constants for the early first 40 ms and late subsequent phases of LV isovolumic relaxation after the occurrence of peak −dP/dt.[12] Mean aortic pressure (MAP) was determined by digital integration. The systolic pressure-rate product was calculated as HR × LVsys (beats/min·mm Hg).

A coronary sinus thermodilution catheter (Webster) was placed in the coronary sinus for measurement of coronary blood flow, withdrawal of coronary venous samples and atrial pacing. Coronary sinus flow (CSF) was determined by the thermodilution method of Ganz.[13] Coronary vascular resistance (R) was calculated as MAP/CSF. Aortic arterial (Ao) and coronary sinus (CS) oxygen saturation were measured by oximetry. $M\dot{V}O_2$ was calculated as CSF × (Ao − CS) × hemoglobin concentration (in g/dl) × 0.0136. Alinidine serum concentration was measured by radioimmunoassay by the method of Arndts and Ståhle.[14]

**Protocol:** After placement of catheters, stable repeated LV pressures were measured and control coronary blood flow, oxygen saturations, and aortic pressure measurements were made. Control LV pressure measurements were then obtained at spontaneous HR followed by increasing atrial paced HRs with increments of 5 to 10 beats/min between measurements. A maximal HR approximately 30 beats/min greater than the heart rate at rest was chosen to provide a range of HRs and minimize the likelihood of angina pectoris or atrioventricular block. At the maximal paced HR, coronary blood flow, oxygen saturations, and aortic pressures were determined. Pacing was discontinued and repeat control measurements made at a spontaneous HR. Alinidine, 0.6 mg/kg, was then administered by a slow intravenous infusion over 3 minutes. LV measurements were made every 30 seconds for 4 minutes, coronary blood flow, oxygen saturations, and aortic pressures were determined, and a final set of spontaneous HR-LV measurements were made. An arterial sample was withdrawn to measure alinidine serum concentration. Patients were again atrial paced at increasing HRs with increments of 5 to 10 beats/min with measurements made at each HR up to an identical maximal paced HR as during the pacing measurements before alinidine. At this rate, coronary blood flow, oxygen saturations and aortic pressure were finally determined.

**Analysis:** Pressure measurements suitable for analysis were recorded in 13 patients. In each patient, comparisons before and after the administration of alinidine were made at the spontaneous HR and at the minimal (low matched pacing, $P_1$) and maximum (high matched pacing, $P_2$) identical paced rates obtained before and after the drug. Coronary blood flow and $M\dot{V}O_2$ could be measured in 12 patients and were compared at spontaneous HR and matched maximal paced rate.

**Statistics:** Results are expressed as the mean ± standard error of the mean. Group data before and after alinidine administration were compared by a paired Student *t* test. A p value <0.05 was considered statistically significant.

**TABLE I Patient Characteristic Data**

| Pt | Age (yr) & Sex | EF | No. of Vessels with >50% Stenoses |
|---|---|---|---|
| 1 | 27M | * | 3 |
| 2 | 47M | 0.54 | 1 |
| 3 | 40F | 0.60 | 1 |
| 4 | 70F | * | 2 |
| 5 | 47M | 0.69 | 0 |
| 6 | 54M | 0.56 | 1 |
| 7 | 69M | 0.36 | 3 |
| 8 | 51F | 0.65 | 0 |
| 9 | 49M | 0.64 | 3 |
| 10 | 73F | 0.16 | 3 |
| 11 | 48M | 0.47 | 2 |
| 12 | 57M | 0.66 | 3 |
| 13 | 69F | 0.59 | 3 |
| 14 | 60M | 0.64 | 3 |

* No EF available because of ventricular ectopic activity during left ventriculoangiogram.
EF = ejection fraction.

## Results

**Spontaneous heart rate (Tables II and III):** A mean of 9.3 ± 0.4 minutes after administration, HR decreased from 70 ± 2 to 61 ± 3 beats/min (−12.9%, $p < 10^{-6}$). LV systolic pressure decreased from 146 ± 5 to 140 ± 6 mm Hg (4.1%, $p < 0.05$) and LV end-diastolic pressure increased slightly, from 17.8 ± 2.2 to 19.2 ± 2.4 mm Hg (7.9%, $p < 0.05$). The rate-pressure product decreased from 10.2 ± 0.4 to 8.6 ± 0.6 × $10^3$ beats/min·mm Hg (−15.7%, $p < 10^{-5}$).

LV peak + dP/dt fell from 1,652 ± 92 to 1,371 ± 80 mm Hg/s (17.0%, $p < 10^{-5}$). $Vce_{40}$ decreased 15.6%, peak Vce decreased 17.1%, and Vmax decreased 12.8%; all of these changes were statistically significant compared with control. LV peak −dP/dt decreased from 1,950 ± 96 to 1,845 ± 106 mm Hg/s (6.1%, $p < 0.01$). The time constants of isovolumic relaxation, $T_1$ and $T_2$, increased 12.2% ($p < 0.001$) and 10.5% ($p < 0.01$), respectively.

During CS flow measurements, CS flow fell from 109 ± 9 to 89 ± 7 ml/min (−18.3%, $p < 0.02$). $M\dot{V}O_2$ decreased significantly, from 10.9 ± 1.0 to 9.0 ± 0.8 ml $O_2$/min (17.4%, $p < 0.05$).

Mean alinidine serum concentration determined preceding the final atrial pacing in 12 patients was 790 ± 112 ng/ml.

**Matched atrial pacing (Tables II and III):** *Low matched pacing rate ($P_1$):* At a matched pacing rate of 74 ± 3 beats/min before and after alinidine administration, LV +dP/dt decreased from 1,681 ± 89 to 1,479 ± 76 mm Hg/s (12.0%, $p < 10^{-5}$). LV −dP/dt decreased

**TABLE II Left Ventricular Function During Control and After Alinidine Administration**

| | | Control | Alinidine | Δ% | p Value |
|---|---|---|---|---|---|
| HR (beats/min) | S | 70 ± 2 | 61 ± 3 | −12.9 | $<10^{-6}$ |
| | P1 | 74 ± 3 | 74 ± 3 | 0 | NS |
| | P2 | 98 ± 3 | 98 ± 3 | 0 | NS |
| LVsys (mm Hg) | S | 146 ± 5 | 140 ± 6 | −4.1 | <0.05 |
| | P1 | 147 ± 5 | 141 ± 5 | −4.1 | <0.02 |
| | P2 | 143 ± 6 | 138 ± 5 | −3.5 | <0.077 = NS |
| LVEDP (mm Hg) | S | 18 ± 2 | 19 ± 2 | +7.9 | <0.05 |
| | P1 | 15 ± 2 | 16 ± 2 | +2.6 | NS |
| | P2 | 10 ± 2 | 11 ± 2 | +6.9 | NS |
| HR × LVsys (beats/min-$mm_3$ Hg × $10^3$) | S | 10 ± 0.4 | 9 ± 0.6 | −15.7 | $<10^{-5}$ |
| | P1 | 11 ± 0.5 | 10 ± 0.6 | −4.6 | <0.005 |
| | P2 | 14 ± 0.6 | 14 ± 0.6 | −3.5 | NS |
| LV +dP/dt (mm Hg/s) | S | 1,652 ± 92 | 1,371 ± 80 | −17 | $<10^{-5}$ |
| | P1 | 1,681 ± 89 | 1,479 ± 76 | −12 | $<10^{-5}$ |
| | P2 | 1,984 ± 124 | 1,793 ± 106 | −9.6 | <0.001 |
| $Vce_{40}$ ($s^{-1}$) | S | 32 ± 2 | 27 ± 2 | −15.6 | $<10^{-5}$ |
| | P1 | 33 ± 2 | 29 ± 2 | −12.1 | $<10^{-4}$ |
| | P2 | 41 ± 3 | 38 ± 3 | −7.3 | <0.005 |
| Peak Vce ($s^{-1}$) | S | 35 ± 3 | 29 ± 2 | −17.1 | <0.001 |
| | P1 | 38 ± 3 | 29 ± 2 | −10.5 | <0.001 |
| | P2 | 52 ± 5 | 48 ± 5 | −7.7 | <0.02 |
| Vmax ($s^{-1}$) | S | 47 ± 3 | 41 ± 2 | −12.8 | $<10^{-4}$ |
| | P1 | 49 ± 3 | 44 ± 3 | −10.2 | <0.001 |
| | P2 | 60 ± 5 | 56 ± 4 | −6.7 | <0.02 |
| LV −dP/dt (mm Hg/s) | S | 1,965 ± 96 | 1,845 ± 106 | −6.1 | <0.02 |
| | P1 | 2,017 ± 103 | 1,897 ± 116 | −5.9 | <0.02 |
| | P2 | 2,147 ± 123 | 2,098 ± 121 | −2.3 | NS |
| T1 (ms) | S | 49 ± 5 | 55 ± 5 | +12.2 | <0.001 |
| | P1 | 48 ± 5 | 51 ± 5 | +6.2 | <0.05 |
| | P2 | 44 ± 5 | 44 ± 5 | 0 | NS |
| T2 (ms) | S | 38 ± 3 | 42 ± 4 | +10.5 | <0.01 |
| | P1 | 37 ± 4 | 37 ± 3 | 0 | NS |
| | P2 | 31 ± 4 | 33 ± 4 | +6.5 | NS |

Values are mean ± standard error of the mean (n = 13).
HR = heart rate; HR × LV sys = rate-pressure product; LVsys = left ventricular systolic pressure; LVEDP = left ventricular end-diastolic pressure; LV +dP/dt = peak positive first derivative of LV pressure; LV −dP/dt = peak negative dP/dt; NS = not significant; $P_1$ = low matched pacing; $P_2$ = high matched pacing; Peak Vce = peak measured Vce; S = spontaneous; $T_1$,$T_2$ = time constants from biexponential fitting of the LV isovolumic pressure decay; $Vce_{40}$ = velocity of the contractile element at 40 mm Hg total pressure; Vmax = Vce extrapolated to P = 0.

from 2,017 ± 103 to 1,897 ± 116 mm Hg/s (5.9%, p <0.02). $Vce_{40}$ decreased 12.1% (p $<10^{-4}$), peak Vce 10.5% (p <0.001) and Vmax 10.2% (p <0.001). $T_1$ decreased slightly (6.2%, p <0.05) and $T_2$ did not change.

*High matched pacing rate ($P_2$):* At a matched pacing rate of 98 ± 3 beats/min before and after alinidine administration, LV +dP/dt decreased from 1,984 ± 124 mm to 1,793 ± 106 mm Hg/s (9.6%, p <0.001). $Vce_{40}$ decreased 7.3% (p <0.005), peak Vce 7.7% (p <0.02), and Vmax 6.7% (p <0.02). There were no significant changes in either LV − dP/dt or $T_1$ and $T_2$. Coronary flow and $M\dot{V}O_2$ did not change during matched pacing (Fig. 1, 2 and 3).

## Discussion

These findings show that alinidine acts both as a negative chronotropic and negative inotropic agent in patients with coronary artery disease. After alinidine administration, spontaneous HR consistently decreased, accompanied by decreases in indexes of contractility, coronary blood flow, and $M\dot{V}O_2$. When patients were paced at both low and high matched HRs, the decrease in multiple indexes of contractility persisted. $M\dot{V}O_2$ measured at the higher pacing rate, however, no longer differed significantly from matched pacing control. Coronary vascular resistance was unchanged during spontaneous or paced HRs.

Kobinger et al[1] first reported in 1979 that in animal models, alinidine acts as a "specific" bradycardic agent in that its negative chronotropic effect appeared more prominent than its other cardiovascular effects. Millar and Vaughan Williams[4] showed that alinidine decreased the spontaneous beating rate in isolated rabbit atria. By comparison, in this model, clonidine led to either no change or a slight increase in rate.[15] This bradycardic action was not related to cholinergic, adrenergic, calcium channel or fast inward current activity.[4,5] Alterations in alinidine's effects by replacement of extracellular chloride with other anions and intracellular sinoatrial recordings showing a reduction in the slope of slow diastolic depolarization were consistent with a mechanism of anion-selective channel blockade. In man, Kasper et al[16] showed that a 40-mg dose of alinidine led to a 23% increase in PP cycle length with no change in PA, AH or HV intervals or QRS duration.

Brutsaert et al[17] identified an additional effect of alinidine in rat ventricular cardiac cells that theoretically could account for a change in myocardial performance. In rat ventricular cardiac cells, alinidine delayed the release of calcium from the intracellular membranous system with only minor effects on the total amount

**TABLE III Coronary Flow and Myocardial Oxygen Consumption During Control and After Alinidine Administration**

| | | Control | Alinidine | Δ% | p Value |
|---|---|---|---|---|---|
| HR (beats/min) | S | 69 ± 2 | 61 ± 3 | −11.6 | <0.001 |
| | P2 | 97 ± 3 | 97 ± 3 | 0 | NS |
| Ao (mm Hg) | S | 108 ± 3 | 100 ± 3 | −7.4 | <0.002 |
| | P2 | 116 ± 3 | 109 ± 3 | −6.0 | <0.02 |
| CBF (ml/min) | S | 109 ± 9 | 89 ± 7 | −18.3 | <0.02 |
| | P2 | 122 ± 9 | 110 ± 8 | −9.8 | <0.071 (NS) |
| CVR (mm Hg ml/min) | S | 1.08 ± 0.10 | 1.20 ± 0.08 | +11.1 | NS |
| | P2 | 1.03 ± 0.10 | 1.05 ± 0.08 | +2.9 | NS |
| Art-CS $O_2$ (ml/liter) | S | 99 ± 3 | 101 ± 3 | +1.8 | NS |
| | P2 | 97 ± 3 | 100 ± 3 | +3.8 | NS |
| $MVO_2$ (ml/min) | S | 11 ± 1 | 9 ± 1 | −17.4 | <0.05 |
| | P2 | 11 ± 1 | 11 ± 1 | −6.7 | NS |

Values are mean ± standard error of the mean (n = 12).
Art-$CSO_2$ = arterial-coronary sinus difference in oxygen content; CBF = coronary sinus blood flow; CVR = coronary vascular resistance; HR = heart rate; MAP = mean aortic pressure; $MVO_2$ = myocardial oxygen consumption; NS = not significant; $P_2$ = high matched pacing; S = spontaneous.

of calcium released or on calcium reuptake, a phenomenon they named activation stabilization. This selective delay in the kinetics of myocardial calcium release could lead to a mechanical asynergy in myocardial function equivalent to the effective decrease in LV performance associated with a diffuse intraventricular conduction defect.[18] With no effect on electrical recordings, it is possible that a heterogeneous prolongation in the intracellular onset of mechanical activation could lead to a global change in the synergy of LV contraction and, thus, effectively reduce inotropic state.

In patients with coronary artery disease and impaired LV function, Löllgen et al[9] observed a 16% decrease in HR at rest after a 20-mg intravenous dose of alinidine. Cardiac output remained unchanged as pulmonary wedge pressure decreased 19%. Systolic pressure decreased 7 to 8% and systemic vascular resistance did not change. With exercise, alinidine, compared with control, led to increases in stroke volume and cardiac output and a 28% decrease in pulmonary wedge pressure. Löllgen et al concluded that alinidine had no significant negative inotropic effects and improved cardiac performance during exercise.

Most of our patients did not have significant LV dysfunction, so it is difficult to compare our results to these data. In addition, we did not measure cardiac output to allow computation of stroke volume.

In patients with unstable angina or myocardial infarction, Simoons and Hugenholtz[10] found that with intravenous doses of up to 40 mg, alinidine led to a 13%

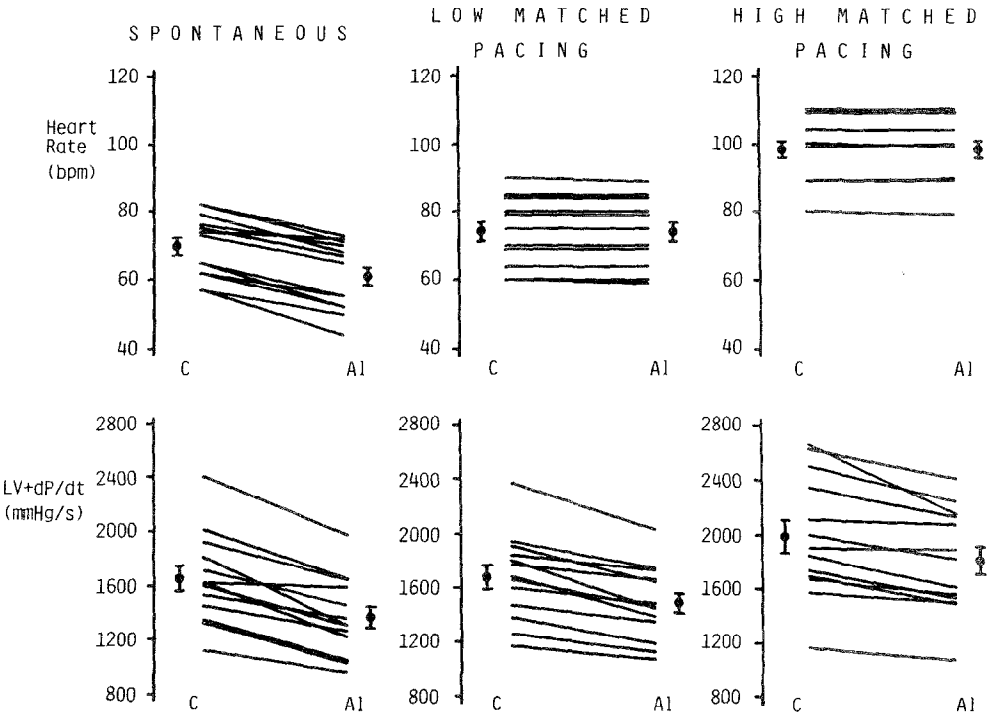


**FIGURE 1.** Individual and group mean changes in heart rate (HR) and peak positive left ventricular dP/dt (LV + dP/dt) at spontaneous, low matched pacing, and high matched pacing heart rates after alinidine (Al) administration. LV + dP/dt was significantly lower after alinidine at all heart rates. C = control.

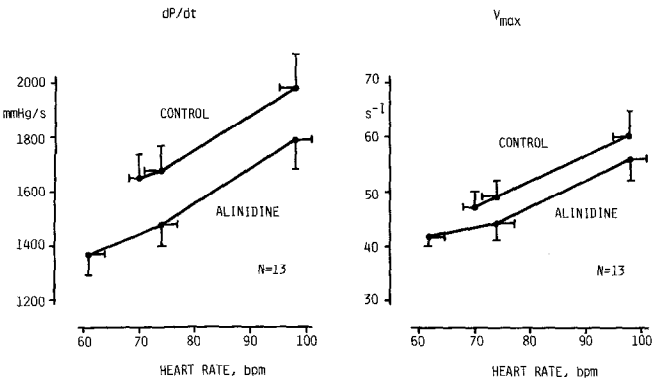


**FIGURE 2.** Effects of alinidine on indexes of systolic function. Despite matched pacing heart rates, both peak positive left ventricular dP/dt (LV + dP/dt) and Vmax remained significantly lower after alinidine administration.

decrease in HR. Although mean stroke volume and LV filling pressure did not change, in 3 patients drug-associated signs of heart failure developed, for which the drug was discontinued.

In our study, spontaneous HR decreased 12.9% after a 0.6-mg/kg intravenous dose of alinidine, a decrease similar to that reported by other studies. This reduction in HR was accompanied by a 15.7% decrease in the rate-pressure product and 17.4% decrease in $M\dot{V}O_2$.

At matched paced HRs, in almost all patients, multiple indexes of contractility were reduced. The 12.1 and 9.6% decrease in peak +dP/dt observed at low and high matched pacing rates, respectively, is similar to that after intravenous administration of 0.15 mg/kg of propranolol in patients with coronary artery disease at a constant atrial paced HR.[19] These changes occurred with no change in LV end-diastolic pressure. At the low matched rate, peak LV systolic pressure and mean aortic pressure were slightly lower. At the high matched rate, peak LV systolic pressure was unchanged and mean aortic pressure was slightly lower. Peak +dP/dt is insensitive to changes in afterload[20] and should not be significantly affected by these minimal decreases in pressure. The uniform decrease in "load-independent" indexes of systolic function also supports the conclusion that the change in systolic function occurred independent of changes in loading.

At spontaneous HR, alinidine decreased the peak rate of LV pressure decline (−dP/dt) and prolonged the time constants of both early and late isovolumic relaxation. These results would be anticipated from a reduction in HR or inotropic state. When compared at matched HRs, however, there were no differences in these indexes of relaxation with alinidine. This possible dissociation between the effect on LV contractility and relaxation would be unlike that observed with other negative inotropic agents such as calcium channel blockers,[21] and could be consistent with the drug's alternative mode of action.

That the decrease in contractility at matched pacing HRs was not associated with a significant decrease in $M\dot{V}O_2$ is not surprising. Beta blockers also lead to no change in $M\dot{V}O_2$ at matched paced HRs.[22,23] This finding is consistent with the hypothesis that the anticipated decrease in $M\dot{V}O_2$ after a decrease in inotropic state may be offset by an increase in ventricular diameter and systolic wall tension.[24]

Why Löllgen et al[9] failed to observe a negative inotropic effect with alinidine in patients with coronary artery disease and LV dysfunction is uncertain. The methods used in their study (right-sided cardiac catheterization) are much less sensitive than those used in

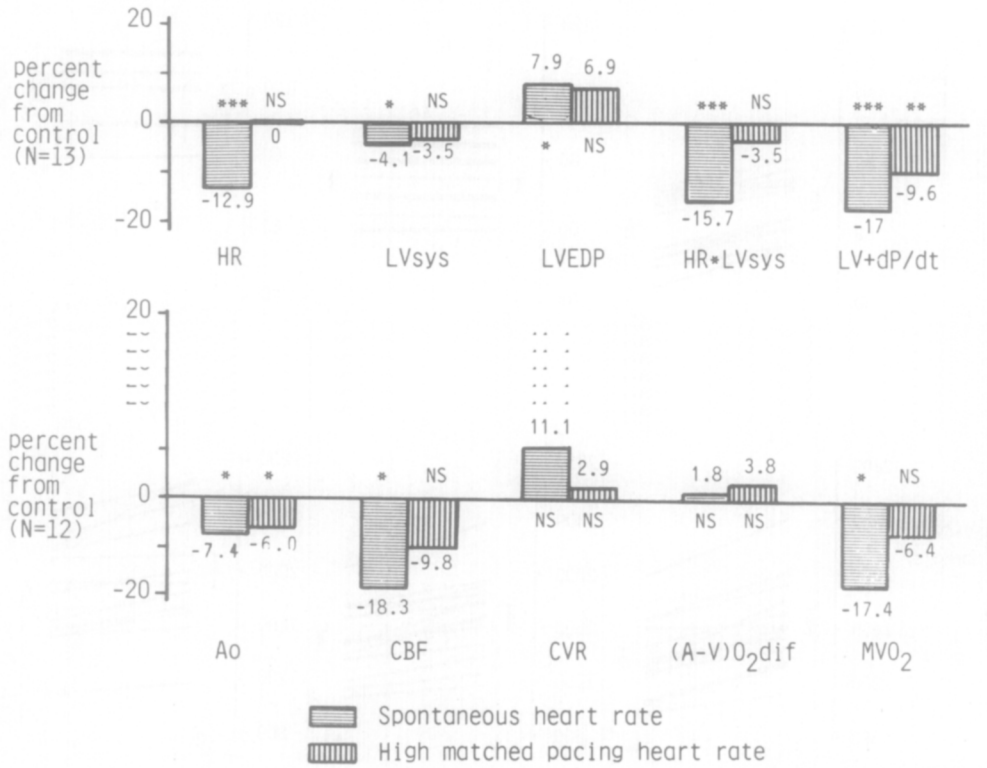


**FIGURE 3.** Summary of comparative changes in left ventricular (LV) function and coronary hemodynamics after alinidine administration at spontaneous at high matched pacing heart rates (HR). Although changes in indexes of LV function persisted at matched HR, there was no significant change in either coronary blood flow or myocardial oxygen consumption ($M\dot{V}O_2$). Ao = mean aortic pressure; $(A\text{-}V)O_2$ diff = arterial–coronary sinus difference in oxygen content; CBF = coronary blood flow; CVR = coronary vascular resistance; HR·LVsys = product of HR·LV peak systolic pressure; LV + dP/dt = peak rate of LV pressure; NS = not significant.

the present study. That the negative inotropic property may nonetheless be important is confirmed by the finding of Simoons and Hugenholtz[10] that alinidine did lead to clinical heart failure in several patients with acute severe ischemic heart disease.

Administration of alinidine leads to detectable levels of the metabolite clonidine after 3 hours that reach low peak levels in 8 to 9 hours.[25,26] This would not affect the results obtained from this acute study, but could have a pharmacologic effect on sympathetic activity with chronic use.

In stable patients, alinidine could offer an alternative to β-blocking drug therapy in the presence of atrioventricular block, obstructive lung disease or potential hypoglycemia. In an initial report, when alinidine was compared to the β-blocker metoprolol in patients with chronic stable angina, both similarly reduced angina symptoms and increased maximal workload with no limiting side effects encountered with either drug.[27] Alinidine, however, led to a smaller reduction in HR at rest, maximal exercise HR and maximal exercise rate-pressure product. The role of the metabolite clonidine will also have to be assessed, because this agent has also been reported to be beneficial in patients with angina pectoris.[28]

Whether patients with LV dysfunction can tolerate alinidine better than β-blocking drugs is uncertain. Theoretically, in patients with severe heart failure requiring inotropic support with catecholamines, alinidine could prevent an undesired tachycardia while relatively preserving inotropic augmentation.[29] In general, however, any bradycardic and negative inotropic agent is contraindicated in patients critically dependent on sympathetic stimulation in whom cardiac output is maintained by an increased HR.

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