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Assessment of the bradycardic and inotropic properties of ST 567 using a new scheme of administration

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In 10 patients undergoing diagnostic cardiac catheterisation a bolus of 15 mg ST 567 was administered intravenously in 1·5 min followed by a 30 min infusion of 7·5 mg. The maximal plasma level was 343 ± 131 ng ml^{-1} (mean ± s.d.) 1 min after bolus injection and stabilised around 179 ng ml^{-1} thereafter. Heart rate decreased from 71 ± 10 beats min^{-1} at baseline to 66 ± 10 beats min^{-1} at the end of the bolus injection (−7%). This decrease in heart rate persisted during the whole observation period. Also there was an 8% reduction in peak positive first derivative of LV pressure. Cardiac output measured by thermodilution during atrial pacing decreased from 5·9 ± 1·1 l min^{-1} to 5·3 ± 0·7 l min^{-1} ($P < 0·02$). In 3 patients with the largest decrease in cardiac output, the end diastolic LV pressure at the end of the observation period decreased, which may reflect a decrease in pre-load. Only in 1 patient the decrease in end diastolic LV pressure exceeded twice the standard deviation of the random error component of duplicate measurements. Thus, although normal therapeutic plasma levels were achieved, ST 567 demonstrated negative inotropic properties independent of changes in heart rate with this scheme of administration.

Introduction

ST 567 (alinidine, N-allyl-clonidine) is a bradycardic drug that restricts anionic current[1,2] and interacts with the pacemaker current i_f[3,4].

It has been claimed that alinidine has a specific bradycardic action without concomitant negative inotropic effects[5]. However, Schamhardt *et al.*[6], using 0·57 ± 0·07 mg kg^{-1} (mean ± s.e.m.) alinidine intravenously, showed a 22% reduction in max LV *dP/dt* and a 5% lowering of cardiac output in ischaemic open-chest pigs after adjustment of heart rate by atrial pacing.

Recently Jaski and Serruys[7] reported a 13% reduction is spontaneous heart rate together with 9 to 12% reduction in isovolumic indices of contraction after a 3 min intravenous infusion of 0·6 mg kg^{-1} alinidine in patients with coronary artery disease. However, in some of the patients with the most pronounced depression of contractility the plasma alinidine levels were excessively high (see Fig. 1).

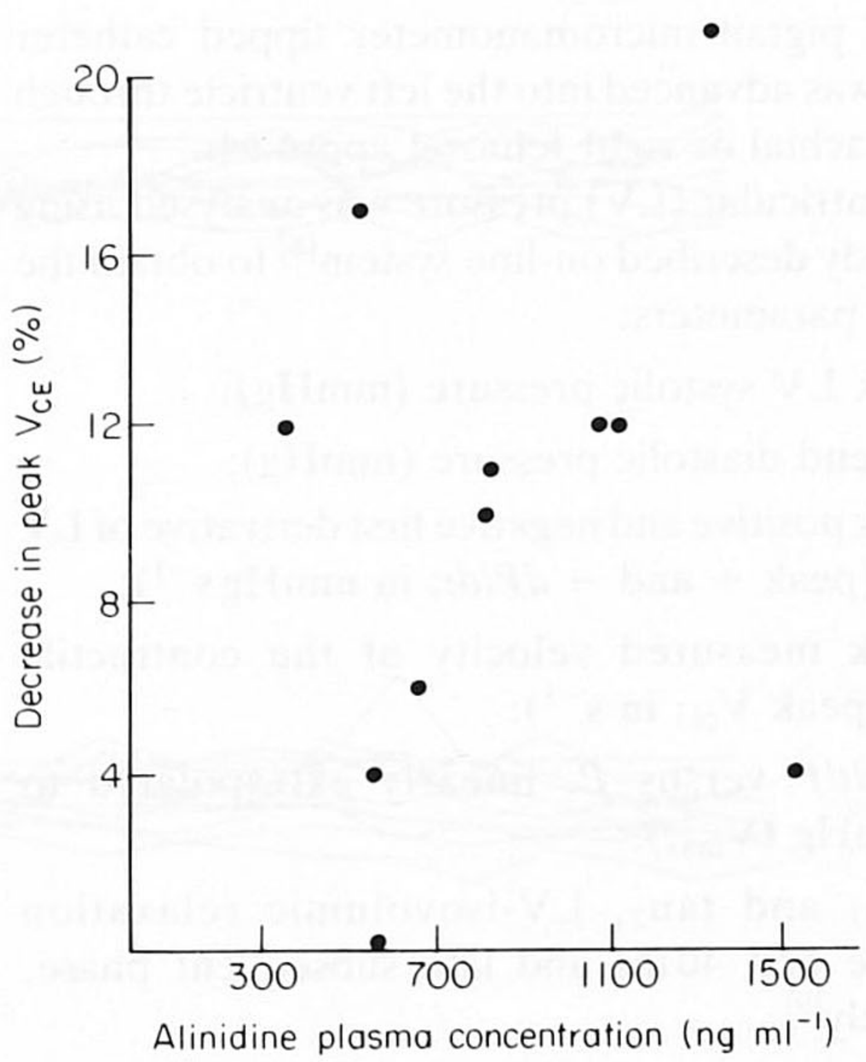

Figure 1 The relation between the alinidine plasma concentration and peak measured velocity of the contractile element (peak V_{ce}) in the patients studied by Jaski and Serruys[7].

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Therefore we tested a new scheme of administration and investigated the relation between the plasma levels and the effect on heart rate and left ventricular (LV) function.

In the present study four questions were formulated:

1. Does a bolus of 15 mg ST 567 followed by 7·5 mg infused in 30 minutes result in stable therapeutic ST 567 plasma levels without excessive high peak values in patients with coronary artery disease?

2. Is there a lowering of heart rate with this dose regimen?

3. Is there still a negative inotropic effect associated with this scheme of administration?

4. Are the negative inotropic and the negative chronotropic effects concomitant?

Methods

STUDY POPULATION

Ten patients undergoing diagnostic heart catheterisation for suspected coronary artery disease gave informed consent. The mean age was 61 years (range 52–74). Drugs with known bradycardic effect (i.e. beta-blocking agents and diltiazem) were stopped one week before catheterisation. Vasodilating drugs (i.e. nifedipine and nitrates) were stopped 12 to 24 hours before the investigation.

DATA COLLECTION

An 8 F pigtail micromanometer tipped catheter (Philips) was advanced into the left ventricle through a right brachial or right femoral approach.

Left ventricular (LV) pressure was analysed using a previously described on-line system[8] to obtain the following parameters:

1. Peak LV systolic pressure (mmHg);

2. LV end diastolic pressure (mmHg);

3. Peak positive and negative first derivative of LV pressure (peak + and − dP/dt; in mmHg s^{-1});

4. Peak measured velocity of the contractile element (peak V_{ce}; in s^{-1});

5. $dP/dt/P$ versus P, linearly extrapolated to $P = 0$ mmHg (V_{max});

6. Tau_1 and tau_2, LV-isovolumic relaxation during the first 40 ms and late subsequent phase, respectively[9].

Cardiac output was measured by thermodilution using a Swan–Ganz thermodilution catheter. A bipolar pacing catheter was positioned high in the right atrium.

PROTOCOL

After positioning of the catheters, heart rate was recorded at 30 second intervals over a period of 6 min to provide a baseline heart rate. Before and during drug administration the heart was intermittently paced at a rate 2 beats min^{-1} higher than the highest heart rate recorded during the baseline period. Two baseline values were recorded for the LV pressures and contractility parameters to provide a baseline. Three control cardiac outputs were determined at the paced heart rate. Then a bolus of 15 mg ST 567 was administered in one and a half minutes in the pulmonary artery, followed by an infusion of 7·5 mg ST 567 administered over 30 minutes. LV pressure and derived indices were averaged and computed on-line after a period of data aquisition of 20 seconds either at spontaneous heart rate (2, 4, 6, . . . min after the bolus of ST 567) or at paced heart rate (1, 3, 5, . . . min after the bolus injection). Cardiac output measurements were repeated at 15 and 29 minutes after completion of the alinidine bolus. Blood samples were drawn from the right atrium after 1, 7, 13, 19, 25 and 31 minutes for ST 567 plasma level determination (radioimmuno assay, method of Arndts and Stahle[10]).

STATISTICS

Results are expressed as the mean ± s.d. Analysis of variance was performed on the data with and without inclusion of the baseline values. Two-sided P values are reported. A paired Student t-test was used to assess the significance of serial changes once a trend was identified by the analysis of variance.

Results

Baseline characteristics and data of the catheterisation procedure are given in Table 1.

The dose that we used in the present study resulted in a ST 567 peak level of 343 ± 131 ng ml^{-1} at 1 min after the bolus injection (see Fig. 2 and Table 2). Thereafter a stable alinidine plasma level was achieved around a mean of 179 ng ml^{-1}. The plasma levels of clonidine were 0·01 ng ml^{-1} or less in nearly all blood samples. In patient 1, however, unexplained high clonidine plasma levels were found (0·88 ng ml^{-1} at 1 min, increasing to 0·94 ng ml^{-1} in the 31 min sample). The clonidine plasma levels at 25 and 31 min samples increased to 0·15 ng ml^{-1} in patients 3 and 8 and to 0·26 ng ml^{-1} in patient 9.

Individual plots of changes in ST 567 plasma level, spontaneous heart rate and peak positive dP/dt, relative to the baseline measurements, are given in Fig. 2. The peak positive dP/dt is at a paced heart rate.

Table 1 Patient characteristic data

Patient	Age (years)	Sex	Angina NYHA Class	Clinical history	LV ejection fraction	No. of vessels with diam. stenosis ⩾ 50%
1	62	M	II	PTCA	0·30–0·50*	2
2	55	F	III	AMI	0·61	1
3	56	M	II	—	0·70	1
4	66	M	II	AMI	0·57	3
5	66	M	III	AMI	0·38	2
6	52	F	II	—	>0·50*	0
7	64	M	III	AMI, CABG	0·52	3
8	58	M	II	AMI	0·50	2
9	54	M	II	CABG, PTCA	>0·50*	2
10	74	M	II	AMI, PTCA	0·47	0

M = male, F = female, NYHA = New York Heart Association classification, diam. = diameter, PTCA = percutaneous transluminal coronary angioplasty, CABG = coronary artery bypass grafting, AMI = acute myocardial infarction. *Technical quality did not allow quantitative analysis.

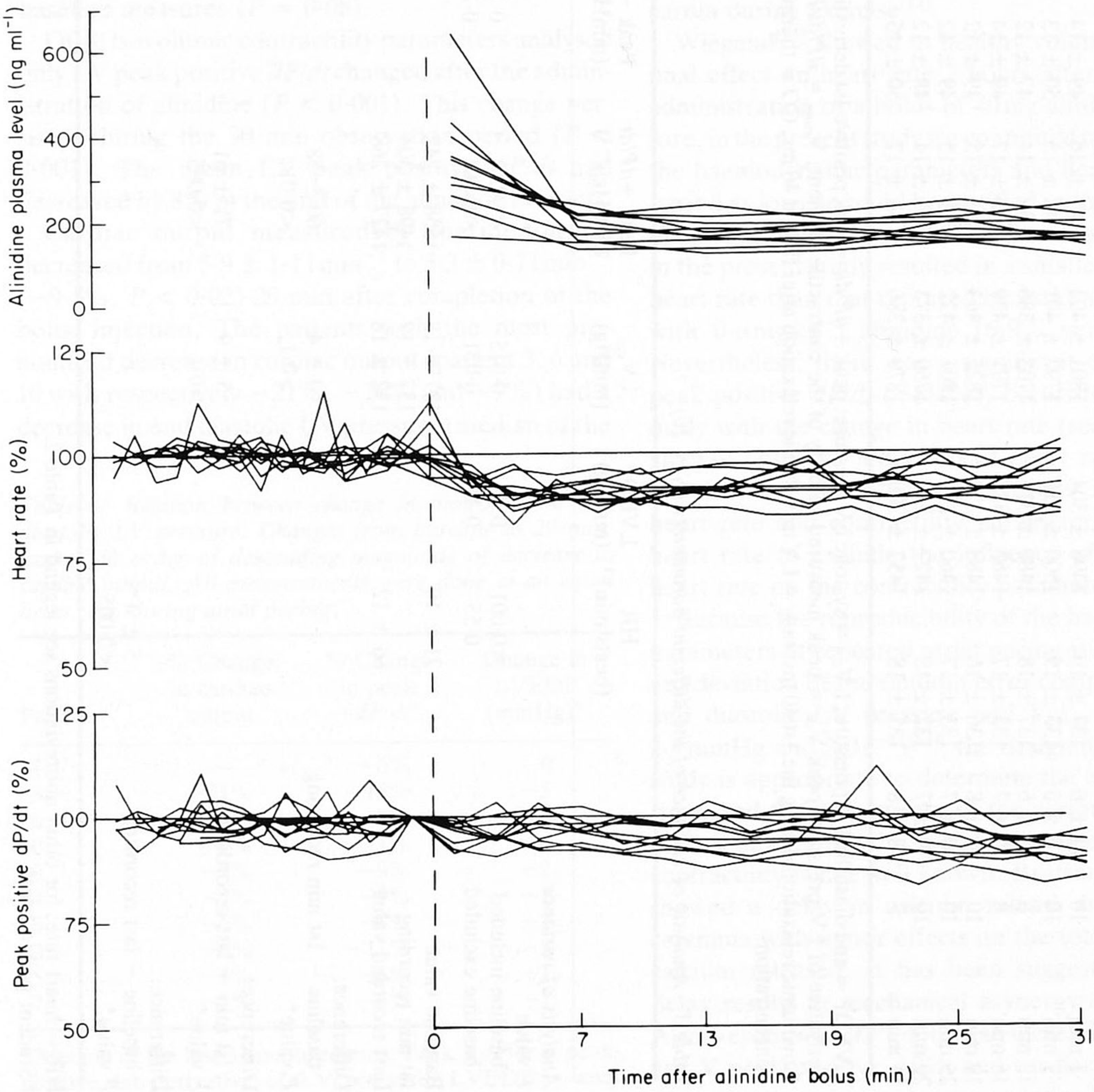

Figure 2 Individual plots of changes in alinidine plasma levels, spontaneous heart rate, and peak positive *dP/dt*, relative to the mean of the baseline values. The peak positive *dP/dt* measurements are at a constant, paced heart rate.

Table 2 Mean (± s.d.) of the different parameters during cardiac pacing (time is measured in minutes from completion of the bolus injection of alinidine)

	N	LVEDP (mmHg)	LV_{sys} (mmHg)	Peak $+dP/dt$ ($mmHg\,s^{-1}$)	Peak $-dP/dt$ ($mmHg\,s^{-1}$)	Peak V_{ce} (s^{-1})	V_{max} (s^{-1})	Tau_1 (ms)	Tau_2 (ms)	CO (min^{-1})	ST 567 ($ng\,ml^{-1}$)
Baseline	10	11 ± 7	137 ± 18	1558 ± 342	1834 ± 430	42 ± 15	51 ± 14	48 ± 15	32 ± 13	5·9 ± 1·1	—
1 min	10	11 ± 6	137 ± 19	1498 ± 304	1801 ± 404	41 ± 16	49 ± 14	48 ± 13	31 ± 14	—	343 ± 131
7 min	10	10 ± 8	133 ± 19	1500 ± 315	1797 ± 401	42 ± 15	50 ± 13	48 ± 13	33 ± 13	—	189 ± 35
13 min	8	12 ± 6	137 ± 18	1486 ± 315	1703 ± 386	39 ± 14	47 ± 12	52 ± 14	36 ± 11	—	173 ± 34
15 min	8	10 ± 7	133 ± 17	1463 ± 325	1791 ± 439	41 ± 17	49 ± 14	48 ± 16	33 ± 14	5·6 ± 0·6	—
19 min	10	11 ± 8	136 ± 16	1488 ± 278	1825 ± 463	41 ± 15	49 ± 12	49 ± 14	32 ± 13	—	173 ± 30
25 min	10	10 ± 7	133 ± 17	1460 ± 293	1801 ± 422	41 ± 15	49 ± 12	47 ± 14	31 ± 14	—	186 ± 34
29 min	10	9 ± 7	132 ± 18	1427 ± 268	1750 ± 373	41 ± 14	48 ± 12	49 ± 15	31 ± 14	5·3 ± 0·7	—
31 min	7	8 ± 8	135 ± 18	1457 ± 300	1870 ± 386	44 ± 17	50 ± 15	45 ± 15	29 ± 17	—	172 ± 37

LVEDP = end diastolic LV pressure; LV_{sys} = systolic LV pressure; peak $+dP/dt$ = peak positive 1st derivative of LV pressure; peak $-dP/dt$ = peak negative 1st derivative of LV pressure; peak V_{ce} = peak measured velocity of the contractile element; $V_{max} = dP/dt/P$ linearly extrapolated to $P = 0$ mmHg; tau_1 = LV isovolumic relaxation during the 1st 40 ms; tau_2 = LV isovolumic relaxation after the 1st 40 ms; CO = thermodilution cardiac output; ST 567 = alinidine plasma concentration.

Table 3 Analysis of variance of the different parameters (N = 10)

	HR (beats min^{-1})	LVEDP (mmHg)	LV_{sys} (mmHg)	Peak $+dP/dt$ ($mmHg\ s^{-1}$)	Peak $-dP/dt$ ($mmHg\ s^{-1}$)	Peak V_{ce} (s^{-1})	V_{max} (s^{-1})	Tau_1 (ms)	Tau_2 (ms)
Analysis of variance									
P value									
baseline included	<0·001	0·08	0·015	<0·001	0·11	0·26	0·13	0·30	0·77
baseline excluded	0·55	0·14	0·031	<0·001	0·22	0·29	0·60	0·36	0·76
Baseline value	71 ± 10		137 ± 18	1558 ± 342					
1st min recording			137 ± 19	1498 ± 304					
Last recorded value	66 ± 12		132 ± 18	1427 ± 268					
Difference:									
baseline − 1st min recording			0 ± 4	60 ± 58					
P value*			>0·1	<0·01					
Difference:									
1st min − last recording			5 ± 9	71 ± 61					
P value*			>0·1	<0·005					
Difference:									
baseline − last recording	5 ± 4								
P value*	<0·005								

HR = heart rate; for other abbreviations see legend in Table 2.
* Student paired *t*-test.

Grouped data, expressed as mean ± s.d., are shown in Table 2 for the paced values. Table 3 gives an overview of the analysis of variance for all parameters.

The spontaneous heart rate was substantially lower during the 30 min observation period than during the baseline period ($P < 0{\cdot}001$). This decrease in heart rate occurred immediately after the bolus injection of ST 567; during the observation period there was no further decrease in heart rate.

The heart rate decreased from 71 ± 10 beats min^{-1} at baseline to 66 ± 10 beats min^{-1} (−7%) 2 min after completion of the bolus injection.

The mean LV systolic pressure remained unchanged during the entire investigation (see Table 3). The end diastolic LV pressure did not change after the administration of alinidine compared to the baseline measures ($P = 0{\cdot}08$).

Of all isovolumic contractility parameters analysed only LV peak positive *dP/dt* changed after the administration of alinidine ($P < 0{\cdot}001$). This change persisted during the 30 min observation period ($P < 0{\cdot}001$). The mean LV peak positive *dP/dt* had decreased by 8% at the end of the alinidine infusion.

Cardiac output measured by thermodilution decreased from 5·9 ± 1·1 l min^{-1} to 5·3 ± 0·7 l min^{-1} (−9·5%, $P < 0{\cdot}02$) 29 min after completion of the bolus injection. The patients with the most pronounced decrease in cardiac output (patient 3, 6 and 10 with respectively −21%, −16% and −9%) had a decrease in end diastolic LV pressure (median of the last 3 measurements respectively −5 mmHg, −2 mmHg and −6 mmHg) (see Table 4). The decrease in end diastolic LV pressure exceeded twice the standard deviation of the random error component of duplicate measurements (s.d. = 2·9 mmHg[14]) in only 1 patient. Three patients without a decrease in end diastolic LV pressure demonstrated nevertheless a decrease in contractility.

Table 4 Relation between change in inotropy and end diastolic LV pressure. Changes from baseline to 29 min, ranked in order of descending magnitude of decrease in cardiac output. All measurements were done at an equal heart rate, during atrial pacing

Patient	% Change in cardiac output	% Change in peak $+dP/dt$*	Change in LVEDP (mmHg)*
1	—	−6%	0
3	−21%	−15%	−5
6	−16%	−7%	−2
10	−9%	−1%	−6
9	−7%	−9%	−2
4	−7%	−9%	−1
8	−6%	−8%	+1
2	−6%	−11%	−3
5	−4%	−5%	+1
7	−2%	−6%	−1

* Median of the last 3 measurements. Peak $+dP/dt$ = peak positive 1st derivative of LV pressure; LVEDP = end diastolic LV pressure.

Discussion

The dose used in the present study is based on computer simulated plasma concentration curves made by Boehringer Ingelheim, and based on a pharmacokinetic study reported by Arndts[11]. The aim was to obtain alinidine plasma levels just above 100 ng ml^{-1}, which have been shown to be effective in lowering heart rate in normal volunteers with tachycardia during exercise[12].

Wiegand[13] showed in healthy volunteers a maximal effect on heart rate 2 hours after intravenous administration of a bolus of 40 mg alinidine. Therefore, in the present study we continued registration of the haemodynamic parameters and heart rate for a period as long as could be justified in the setting of a diagnostic catheterisation. The dose of alinidine used in the present study resulted in a smaller decrease in heart rate than that reported by Jaski and Serruys[7] with 0·6 mg kg^{-1} alinidine (6·9% versus 12·9%). Nevertheless, there was a significant effect on LV peak positive *dP/dt* (−8·4%), occurring simultaneously with the change in heart rate (see Fig. 2). To analyse both the reduction of heart rate and contractility we recorded alternatingly spontaneous heart rate and contractility parameters at a paced heart rate to exclude the influence of decrease in heart rate on the contractility parameters.

Because the reproducibility of the haemodynamic parameters at repeated atrial pacing is good (standard deviation of the random error component of the end diastolic LV pressure and V_{max}, respectively 2·9 mmHg and 3·0 s^{-1})[14], the design of the present study is appropriate to determine the effect on inotropy and the time course of the various effects.

The mechanism by which alinidine affects the contractility is not well known. Brutsaert *et al.*[15,16] showed a delay in calcium release from the sarcolemma with minor effects on the total amount of calcium released. It has been suggested that this delay results in mechanical asynergy of the heart. Also Verdouw *et al.*[17] found an increasing reduction in LV peak positive *dP/dt* and cardiac output with increasing cumulative doses up to 6 mg kg^{-1} in dom-

estic pigs, despite correction of heart rate by atrial pacing. The change in spontaneous heart rate was proportional to the change in contractility.

In the present study the effect on contractility was seen in isovolumic contraction parameters as well as in cardiac output measured by thermodilution. However, the decrease of cardiac output measured by thermodilution must be interpreted cautiously: the patients with the most pronounced decrease in cardiac output also showed a decrease in end diastolic LV pressure.

It is impossible to conclude from this study to what extent alinidine is responsible for decrease in cardiac output, because cardiac output is affected by changes in preload reflected by changes in end diastolic LV pressure. Because the decrease of LV peak positive dP/dt followed immediately after the bolus injection (Figure 2 and Table 3), while the effect on end diastolic LV pressure was seen later during the 30 min observation (Table 2), it is likely that in this study the decrease in LV peak positive dP/dt is caused by other factors than preload, e.g. alinidine.

A possible explanation for the decrease in end diastolic LV pressure is a lowering in adrenergic tone during the 30 min follow up. Theoretically, this could be the result of diminished psychological stress at the end of the catheterisation procedure or the effect of a metabolite of alinidine: clonidine[12,18], a drug that is well known to lower plasma cathecholamine levels[19]. However, the clonidine plasma levels in this study were low. This is not surprising since it has been demonstrated in healthy volunteers that the peak plasma level of clonidine occurs 4·8 ± 2·5 h (mean and s.d.) after the peak alinidine plasma concentration following an intravenous bolus of 40 mg alinidine[18].

Since reducing heart rate *per se* may induce heart failure in patients with poor ventricular function, bradycardic agents are, *a priori*, not suitable for these patients. The clinical relevance of the negative inotropic effect that we found, therefore, remains to be established. Furthermore it is unclear whether ST 567 is superior to beta-blockers as a bradycardic agent.

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