Negative Inotropic Effect of Lidocaine in Patients with Coronary Arterial Disease and Normal Subjects*

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The effect of administration of lidocaine on left ventricular performance was studied using systolic time intervals in nine normal subjects, eight patients with stable angina, and 15 patients with acute myocardial infarction. The greatest response in systolic time intervals occurred at three minutes after intravenous injection of lidocaine (100 mg), with values returning to baseline at 10 to 15 minutes. Administration of lidocaine produced a significant prolongation of the pre-ejection period (PEP) corrected for heart rate in all groups and a prolongation of the ratio of PEP to left ventricular ejection time (PEP/LVET) in patients with angina. The group with acute myocardial infarction exhibited a hyperadrenergic state, as shown by a short baseline QS. The QS I was lengthened by administration of lidocaine in all groups, but this was more profound in those with acute myocardial infarction. These changes in systolic time intervals were still present at two hours after injection in six patients with acute myocardial infarction in whom an infusion of lidocaine followed the initial bolus. The effect of administering lidocaine after intravenous injection of propranolol (5 mg) was also studied in six normal subjects. Although propranolol therapy alone prolonged the PEP/LVET, a further significant prolongation followed subsequent injection of lidocaine.

Although lidocaine is a widely used antiarrhythmic drug, its effect on left ventricular performance is not well understood. Lidocaine has been shown to have a dose-dependent negative inotropic effect in isolated canine and human cardiac muscle and in experimental animals. In our laboratory, studies of dogs with experimentally produced acute myocardial infarction have shown that administration of lidocaine produces a significant negative inotropic effect manifest by a decrease in left ventricular dP/dt and in the acceleration of velocity of flow (dQ/dt) unpublished data). We have also shown that ST-segment elevation in acute myocardial infarction was decreased significantly following administration of lidocaine. These findings are consistent with a significant negative inotropic effect; however, in clinical studies, few and often variable hemodynamic effects have been reported. This study was therefore undertaken to evaluate the effect of administration of lidocaine on left ventricular performance as judged by systolic time intervals. To do so, we have studied patients with acute myocardial infarction, patients with chronic stable angina pectoris, and normal subjects. In addition, we have studied the effect of administering lidocaine before and after β-adrenergic blockade in normal subjects, since this is not an uncommonly employed therapeutic combination.

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MATERIALS AND METHODS

Fifteen normal volunteers (age 21 to 28 years [mean, 24 years]; weight, 61 to 85 kg [mean, 77 kg]), 15 patients with acute myocardial infarction (age 40 to 64 years [mean, 52 years]; weight, 59 to 82 kg [mean, 70 kg]), and eight patients with stable angina (age 46 to 62 years [mean, 56 years]; weight, 57 to 78 kg [mean, 68 kg]) were studied. Informed consent was obtained in all cases. The normal subjects were comprised of apparently healthy medical students or nurses, four women and 11 men. The diagnosis of acute myocardial infarction was based upon clinical history, electrocardiographic findings, and characteristic enzymatic changes. All...
patients with acute myocardial infarction were studied between the second and fourth day after onset of symptoms. All were without chest pain and had normal left ventricular performance as measured from the systolic time intervals prior to the study. Six of the patients with acute myocardial infarction had premature ventricular beats, and an infusion of lidocaine was started immediately following the study. The presence of angina was confirmed either by a documented previous acute myocardial infarction or a luminal obstruction greater than 70 percent in one or more major coronary arteries demonstrated on coronary angiographic studies. None of the patients with angina was receiving drugs, and all had stable angina during the study. None of the patients with acute myocardial infarction or angina had evidence of heart failure, either by physical examination or chest x-ray film.

Systolic time intervals were demonstrated from rapid-speed simultaneous recordings of the carotid pulse tracing, phonocardiogram, and electrocardiogram and were corrected for heart rate using the regression equations of Weissler et al. Systolic time intervals were measured from ten consecutive sinus beats, including inspiratory and expiratory beats. The ratio of the preejection period (PEP) to the left ventricular ejection time (LVET), or PEP/LVET, and the PEP corrected for heart rate (PEPI) were used as indices of left ventricular performance and the QS2 I was used as an index of adrenergic activity. The studies were performed either at the bedside or in a special procedure room, as the clinical situation dictated.

The experimental procedure was as follows: a slow intravenous infusion of a 5-percent solution of dextrose in water was started. After a rest period of 30 minutes, three systolic time intervals were recorded every five minutes as controls, and the results were averaged. A 100-mg bolus of lidocaine was then injected intravenously over a period of one minute. The systolic time intervals were then recorded at 1, 3, 5, 10, 15, and 30 minutes after injection of lidocaine. In six patients with acute myocardial infarction who had premature ventricular contractions, an infusion of lidocaine (1 to 3 mg/min) was started in addition to the bolus, and the systolic time intervals were recorded two hours after the onset of the infusion. No arrhythmia was noted during the period of infusion.

The effect of the administration of lidocaine on left ventricular performance following β-adrenergic blockade was studied in six normal subjects. Baseline values for systolic time intervals were recorded prior to an intravenous injection of 5 mg of propranolol. The systolic time intervals were then recorded at 5, 10, 15, and 30 minutes after injection. Thirty minutes following the injection of propranolol, 100 mg of lidocaine was injected, and systolic intervals were measured at one, three, five, and ten minutes after the injection of lidocaine.

The heart rate and blood pressure were measured simultaneously with systolic time intervals throughout the study. Statistical analyses were accomplished using analysis of variance with repeating measurements with the aid of a computer-calculator (Hewlett-Packard 9100B).

RESULTS

The greatest change in the systolic time intervals following a 100-mg intravenously administered bolus of lidocaine occurred at three minutes. Consequently, the three-minute values will be employed hereafter. In Figure 1, it is seen that the effect on the systolic time intervals gradually returns to the baseline by 10 to 15 minutes after injection.

The PEP/LVET was prolonged significantly following administration of lidocaine in the patients with angina and in normal subjects. The ratio was not significantly changed in the patients with acute myocardial infarction (Table 1). Patients with acute myocardial infarction had the shortest initial QS2 I and showed a significant lengthening of the QS2 I. Significant lengthening of the QS2 I was also observed in patients with angina and in normal

![Graph](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/20989/ on 06/26/2017)
Table 1—Effect of Intravenous Administration of 100 mg of Lidocaine on Systolic Time Intervals, Heart Rate, and Blood Pressure

<table>
<thead>
<tr>
<th>Group and Time**</th>
<th>QS1, msec</th>
<th>LVETI, msec</th>
<th>PEPI, msec</th>
<th>PEP/LVET</th>
<th>Heart Rate, beats per minute</th>
<th>Blood Pressure, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myocardial infarction (n = 15) Before</td>
<td>502 ± 5</td>
<td>383 ± 5</td>
<td>120 ± 4</td>
<td>0.36 ± 0.02</td>
<td>83</td>
<td>122/72</td>
</tr>
<tr>
<td>After</td>
<td>523 ± 6</td>
<td>388 ± 6</td>
<td>127 ± 4</td>
<td>0.38 ± 0.01</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>P &lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.05</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Angina (n = 8) Before</td>
<td>512 ± 3</td>
<td>380 ± 5</td>
<td>132 ± 4</td>
<td>0.40 ± 0.01</td>
<td>76</td>
<td>107/64</td>
</tr>
<tr>
<td>After</td>
<td>522 ± 4</td>
<td>384 ± 4</td>
<td>139 ± 3</td>
<td>0.43 ± 0.01</td>
<td>78</td>
<td>112/68</td>
</tr>
<tr>
<td>P &lt; 0.025</td>
<td>NS</td>
<td>&lt; 0.05</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Normal subjects (n = 9) Before</td>
<td>539 ± 4</td>
<td>406 ± 3</td>
<td>132 ± 1</td>
<td>0.36 ± 0.02</td>
<td>84</td>
<td>127/78</td>
</tr>
<tr>
<td>After</td>
<td>547 ± 4</td>
<td>403 ± 3</td>
<td>143 ± 4</td>
<td>0.43 ± 0.02</td>
<td>84</td>
<td>127/78</td>
</tr>
<tr>
<td>P &lt; 0.05</td>
<td>NS</td>
<td>&lt; 0.025</td>
<td>&lt; 0.025</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

*Table values are means ± SE. NS, Not significant.
**Before and after administration of lidocaine.

The PEPI was significantly lengthened by administration of lidocaine in all three groups. The LVET corrected for heart rate (LVETI) did not change significantly in the normal subjects or the group with angina but significantly lengthened in the group with acute myocardial infarction (Table 1). No changes in duration of the QRS complex were observed with administration of lidocaine.

In the six patients with acute myocardial infarction in whom systolic time intervals were measured following a two-hour infusion of lidocaine, there was a persistence of the effect of lidocaine (Fig 2).

The effect of β-adrenergic blockade upon the action of lidocaine in normal subjects is illustrated in Figure 3. Although administration of propranolol alone caused a significant prolongation of the PEPI and the PEP/LVET, there was further significant prolongation of the PEP/LVET following administration of lidocaine. Of interest, the LVETI, which was unchanged after administration of lidocaine alone, shortened significantly when lidocaine was given after propranolol.

There were no changes in blood pressure throughout this study (Table 1). The blood pressure readings before and after administration of propranolol and after administration of lidocaine in six normal subjects was 112/69 mm Hg, 109/67 mm Hg, and 110/69 mm Hg, respectively. The heart rate significantly decreased after administration of propranolol (61 ± 4 from 70 ± 5 beats per minute; P < 0.05) but was not further changed by administration of lidocaine (63 ± 2 beats per minute).

**DISCUSSION**

The relationship between the effect of lidocaine and its plasma concentration has been well established; the therapeutic range of plasma levels has been reported as 1.2 μg/ml to 5.5 μg/ml. The effects reported here are assumed to be related to the plasma level; however, no measurements of the plasma concentration were made. There were no changes in blood pressure throughout this study (Table 1). The blood pressure readings before and after administration of propranolol and after administration of lidocaine in six normal subjects was 112/69 mm Hg, 109/67 mm Hg, and 110/69 mm Hg, respectively. The heart rate significantly decreased after administration of propranolol (61 ± 4 from 70 ± 5 beats per minute; P < 0.05) but was not further changed by administration of lidocaine (63 ± 2 beats per minute).
plasma concentrations of lidocaine were made. From the pharmacokinetic model proposed by Rowland and co-workers, it is possible to estimate the plasma levels one might anticipate following the bolus and infusions of lidocaine administered in this investigation. Figure 4 shows a computer simulation of the plasma level of lidocaine vs time following both administration of a single 100-mg bolus and from the administration of a 100-mg bolus followed by a constant infusion of 2 mg/min. It can be seen that levels fall very rapidly following the initial bolus. At three minutes following the single bolus, the plasma levels are approximately 2.1 μg/ml. The plasma levels of patients receiving a single bolus plus an infusion are seen to drop rapidly to a low level at about 20 minutes after administration of the bolus and then begin to rise again. The plasma level at 120 minutes is predicted to be 1.6 μg/ml. Without initiating an infusion, it can be seen that plasma levels are below the therapeutic range (0.5 μg/ml) by 15 minutes following administration of the bolus alone.

This study demonstrates a negative inotropic effect of a 100-mg bolus of lidocaine injected into normal subjects, patients with angina, and patients with acute myocardial infarction. Consistent with the previously shown pharmacokinetic model, the negative inotropic effect of administration of lidocaine is manifested with therapeutic plasma levels. The maximum changes in the systolic time intervals occurred at approximately three minutes after injection, with values returning to baseline by 10 to 15 minutes. The significant negative inotropic effect was manifest by a prolongation of the PEPI and an increase in PEP/LVET. The PEP was not subdivided into isovolumic contraction time and electromechanical delay. The fact that the duration of the QRS complex was unchanged with administration of lidocaine makes unlikely the possibility that the changes in PEPI were related to an increase in the electromechanical delay.

The changes in the LVETI after administration of lidocaine were not constant. Indeed, a significant negative inotropic effect of lidocaine could be present without changes in LVET. Studies in dogs with experimentally produced acute myocardial infarction in our laboratory have shown that admin-
istration of lidocaine produced a negative inotropic effect manifest by a significant decrease in left ventricular dP/dt and dQ/dt and by prolongation of the PEP, while no significant effect on the aortic flow, ejection time, or blood pressure was found (unpublished data). Thus, the negative inotropic effect of lidocaine using systolic time intervals is best detected by the lengthening of the PEP. This was consistently noted in all of the groups we studied.

Adrenergic tone appears to be an important determinant of the effect of administration of lidocaine on the LVETI. Thus, the response in systolic time intervals to administration of lidocaine was different before and after propranolol administration in normal subjects, and was different in patients with acute myocardial infarction than in the other groups studied. The patients with acute myocardial infarction had a short baseline Q-S; this has previously been shown to be due to a hyperadrenergic state. Since administration of lidocaine appears to have minimal influence on the stroke volume, its effect to decrease the velocity of fiber shortening lengthens the LVETI in the patients with acute myocardial infarction. When normal adrenergic tone is present, administration of lidocaine produces no significant change in LVETI. Only when adrenergic tone is blunted (as in the normal subjects who were pretreated with propranolol) does the LVETI shorten with administration of lidocaine. Presumably, in this setting the stroke volume decreased.

Combined therapy with both propranolol and lidocaine is common in patients with angina and acute myocardial infarction. The studies of normal subjects in which both drugs were administered indicate that lidocaine has a negative inotropic effect which is additive to that of propranolol, often producing severely abnormal systolic time intervals in healthy medical students. Hammermeister and co-workers studied the negative inotropic effect of various common antiarrhythmic drugs employing the Vmax of isolated cat papillary muscle and concluded that the negative inotropic effect of lidocaine was equal to propranolol at drug concentrations equal to the maximal human therapeutic level.

Previous human studies have shown either a transient decrease or no effect upon myocardial performance following administration of lidocaine; however, many studies were performed in patients with acute myocardial infarction, or the measurements were performed after the expected maximal effect of lidocaine.

In conclusion, this study indicates that administration of lidocaine has a negative inotropic effect in normal subjects, in patients with angina, and in patients with acute myocardial infarction. When given as a bolus, the effect is of short duration but can persist with an infusion. When a hyperadrenergic state is present, such as with acute myocardial infarction, the negative inotropic effect may be partially masked. This effect is additive to that of propranolol. We, therefore, conclude that lidocaine should be used with caution in patients who are receiving propranolol and in patients with poor left ventricular function.

Finally, since it has been suggested that drugs with negative inotropic effects may decrease the size of myocardial infarctions in humans with uncomplicated acute myocardial infarction, the negative inotropic effect of lidocaine may prove beneficial in such patients.

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Maya-Toltec Culture

At some time around AD 1,000 the Itza people, a part of the Toltec race, descended on Maya territory and conquered the local population and thus the Maya-Toltec culture was born. The city of Chichen, now called Chichen Itza after its conquerors, was the cultural and artistic centre of this civilization. At Chichen Itza the Toltec stylistic elements are particularly obvious in the use of columns to support the beam roofs, and in the design of circular-based temples with serpent-shaped columns at their entrances. The jaguar motif is a common decorative element as are the feathered serpent and the bird of prey holding a human heart in its claws, and fresco paintings showing Toltec rituals of human sacrifice. Stone sculpture included the figures of the standard-bearer, the large anthropomorphic figures and more frequently the Chac Mool. The Castillo is a pyramid built in nine stages, with staircases leading up each of the four sides to a low temple on the summit.

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NEGATIVE INOTROPIC EFFECT OF LIDOCAINE 175

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