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Effects of Droperidol on Left Ventricular Performance in Humans

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The action of droperidol on left ventricular (LV) performance was examined before angiography in nine unpremedicated patients undergoing cardiac catheterization for stable uncomplicated coronary artery disease. Using local anesthesia, catheters were placed in the left ventricle, thoracic aorta, and pulmonary artery. Cardiac output (CO) and LV pressure derivatives were measured before and 2, 5, 10, 15, and 20 min after intravenous administration of 0.15 mg/kg droperidol. Droperidol administration induced a time-dependent decrease of mean arterial pressure (MAP) (significant at 2, 10, 15, and 20 min) and of cardiac index (CI) (significant at 15 and 20 min) with maximal changes observed at 20 min (−14 per cent for MAP and −15 per cent for CI). In addition, the following changes occurred in variables related to LV performance: 1) a transient increase in both heart rate (HR) (2, 5, and 10 min) and maximum rate of rise of left ventricular pressure/instantaneous left ventricular pressure ($dP \cdot dt^{-1}$ max $\cdot IP^{-1}$) (+15 per cent for HR and +14 per cent for $dP \cdot dt^{-1}$ max $\cdot IP^{-1}$); 2) an early (2 min) and sustained (5, 10, 15, and 20 min) decrease of left ventricular end-diastolic pressure (LVEDP), maximum at 5 min (−30 per cent); 3) no change in systemic vascular resistance (SVR). This study shows that the fall in MAP which occurs after intravenous administration of clinical doses of droperidol is primarily due to decreased CO, secondary to decreased LVEDP and not to changes in cardiac contractility and in SVR. (Key words: Anesthetics, intravenous: droperidol. Heart: cardiac output; contractility.)

DROPERIDOL IS USED in clinical anesthesia for premedication, as a supplement to the potent inhalation agents used during general anesthesia, or in combination with fentanyl for neuroleptanalgesia. A fall in blood pressure has commonly been observed after intravenous administration of droperidol.[1-4] This effect has been attributed to arteriolar vasodilation secondary to partial adrenergic blockade,[5-7] rather than to decreased cardiac output (CO).[1] However, conflicting data regarding the hemodynamic effects of droperidol administration have been reported. For example, paradoxical hypertensive crises just following intravenous administration have been observed in patients with pheochromocytoma.[8,9] These are thought to be due to a brief release of catecholamines.[10] Additionally, data regarding systemic vascular resistances (SVR) determinants of left ventricular (LV) performance, *i.e.*, contractility, heart rate (HR), and preload, have been inconsistent,[2,3,11-13] probably because these data have been collected under varying experimental conditions, using different measurement techniques and in the presence of other drugs. The present study was designed to evaluate, in humans, the effect on LV performance of a clinical dose of droperidol when used alone. The period of observation, the first 20 min after administration, was chosen because the most marked changes in blood pressure are usually observed during this interval.[1-4]

Methods

Nine patients undergoing cardiac catheterization for stable uncomplicated coronary artery disease (New York Heart Association, class 1–2) were studied before angiography. Institutional approval was obtained and all patients gave informed consent. Patients with mitral regurgitation, LV dyskinesia, or arrhythmias were excluded from the study. None were receiving beta-adrenergic blocking drugs or other cardiac medications. Age ranged from 45 to 59 years (mean 53) and mean body weight was 71 ± 4 (SD) kg. All had fasted for more than 12 h and none were premedicated. No more than 100 ml of fluid was given during the procedure.

Using one per cent lidocaine (3–5 ml) for local anesthesia, left and right heart catheterizations were performed, percutaneously. A 7-F Swan-Ganz thermodilution catheter was introduced into the pulmonary artery. A 7-F high-fidelity double micro-tip manometer catheter¶ was placed in the left ventricle through the femoral artery, to simultaneously obtain aortic and LV pressures. Cardiac output was measured in triplicate by the thermodilution method.** Mixed venous and arterial blood O_2 contents were measured by a galvanic cell method.†† Arterial blood *p*H, P_{CO_2} and P_{O_2} were measured with an ABL II blood-gas analyzer.‡‡ Pressures were re-

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¶ PC 770, Millar Instruments, Houston, Texas.
** Cardiac Output Computer, 9520A, Edwards Laboratories, Santa Ana, California.
†† Lex O_2-Con-K, Waltham Instruments, Waltham, Massachusetts.
‡‡ Radiometer, Copenhagen, Denmark.

TABLE 1. Hemodynamic Data (Means ± SE)

	Control	2 min	5 min	10 min	15 min	20 min
MAP (mmHg)	100 ± 4	93 ± 5†	95 ± 4	88 ± 3‡	86 ± 3‡	86 ± 3‡
CI ($l \cdot min^{-1} \cdot m^{-2}$)	3.0 ± 0.3	2.9 ± 0.2	2.8 ± 0.3	2.7 ± 0.2	2.6 ± 0.3*	2.6 ± 0.2*
HR ($beats \cdot min^{-1}$)	70 ± 6	80 ± 6‡	80 ± 6‡	73 ± 6*	71 ± 6	69 ± 6
$dP \cdot dt^{-1}$ max $\cdot IP^{-1}$ (s^{-1})	19 ± 1	22 ± 1‡	21 ± 1‡	20 ± 1‡	20 ± 1‡	19 ± 1
LVEDP (mmHg)	9.7 ± 1.0	7.0 ± 0.8‡	6.6 ± 0.7‡	7.2 ± 0.8‡	7.7 ± 0.7‡	8.1 ± 0.9‡
SI ($ml \cdot m^{-2}$)	45 ± 5	37 ± 4†	35 ± 3†	38 ± 3†	38 ± 3†	39 ± 4†
SVR (units)	18 ± 3	17 ± 3	20 ± 3	18 ± 4	18 ± 3	19 ± 2

* $P < 0.05$. † $P < 0.01$. ‡ $P < 0.001$.

corded on an eight-channel recorder at a paper speed of 100 mm/s. Left ventricular end-diastolic pressure (LVEDP), mean arterial pressure (MAP), and maximum rate of rise of LV pressure (LV $dP \cdot dt^{-1}$ max) were obtained from the recordings. Derived measurements included cardiac index (CI), stroke index (SI), the maximum rate of rise of LV pressure/instantaneous LV pressure ($dP \cdot dt^{-1}$ max $\cdot IP^{-1}$) and SVR; the latter was calculated as the quotient of MAP and CO. Arteriovenous blood oxygen difference (a-$\bar{v}$ O_2D) was calculated from O_2 contents and whole body oxygen consumption ($\dot{V}_{O_2}$) was calculated from the Fick relationship.

Control measurements were obtained in each patient 15 min after insertion of the catheters. At this time, pulse rate and blood pressure had returned to precatheterization levels. Taking care not to alert the subjects, an intravenous bolus injection of droperidol (0.15 mg/kg) was then administered. All hemodynamic measurements were repeated 2, 5, 10, 15, and 20 min after drug injection. Arterial blood-gas measurements and mixed venous and arterial blood O_2 contents were obtained during the control period and 20 min after injection of droperidol.

Mean values and standard error of the mean (SE) were calculated. Time-dependent regressions were calculated for the hemodynamic data. Differences between postinjection data and control values were examined using analysis of variance. Significance was considered present if $P < 0.05$.

Results

Clinical sedation was observed in all patients 5 to 10 min after administration of droperidol. Hemodynamic data are summarized in table 1 and in figure 1. Droperidol administration resulted in a time-dependent decrease of MAP ($r = -0.62$; $P < 0.001$) and of CI ($r = -0.33$; $P < 0.02$). MAP was significantly lower than control at 2, 10, 15, and 20 min with the maximal decrease observed at 20 min (−14 per cent). Cardiac index was significantly lower only at 15 and 20 min (−15 per cent).

Heart rate, $dP \cdot dt^{-1}$max $\cdot IP^{-1}$, LVEDP, and SI changes occurred in all patients at approximately the same times. Heart rate increased significantly at 2, 5, and 10 min, and $dP \cdot dt^{-1}$ max $\cdot IP^{-1}$ was increased at 2, 5, 10, and 15 min, following which they returned to control values. Maximal changes were present at 2 min (+15 and +14 per cent, respectively). Left ventricular end-diastolic pressure was significantly lower than control during the entire study with the maximal reduction noted at 5 min (−30 per cent). Stroke index decreased at 2, 5, 10, 15, and 20 min with the maximal change at 5 min (−22 per cent). No significant change was observed in SVR.

Whole body oxygen consumption was significantly lower than control at 20 min (−19 per cent); pH_a, Pa_{CO_2} and Pa_{O_2} did not change (table 2).

Discussion

This study confirms that there is a progressive fall in blood pressure following intravenous injection of droperidol. Furthermore, it permits delineation of the factors which may be involved in this phenomenon, namely the determinants of LV performance and SVR. In brief, droperidol administration resulted in two main effects: 1) it caused a transient increase in both HR and $dP \cdot dt^{-1}$ max $\cdot IP^{-1}$; and 2) it led to an early and sustained decrease in LVEDP. There was no effect on SVR.

Our results also indicate that droperidol administration, in humans, at clinical doses, does not depress LV function, confirming previous animal work.[11,13] Transient enhancement of $dP \cdot dt^{-1}$ max $\cdot IP^{-1}$ was present early but did not persist. The alteration of $dP \cdot dt^{-1}$ max $\cdot IP^{-1}$ reflects an increase in contractility, this index being one of the better estimates of myocardial function[14] in intact animal or humans. It is likely that the increase in contractility was due only to the increase in HR as changes in these two parameters were parallel.[15] A baroreflex response increasing HR and contractility could have occurred, but if that were the case, it should have persisted until the end of the study since MAP remained low throughout. Another possible explanation is that droperidol had a direct chronotropic effect, but recent

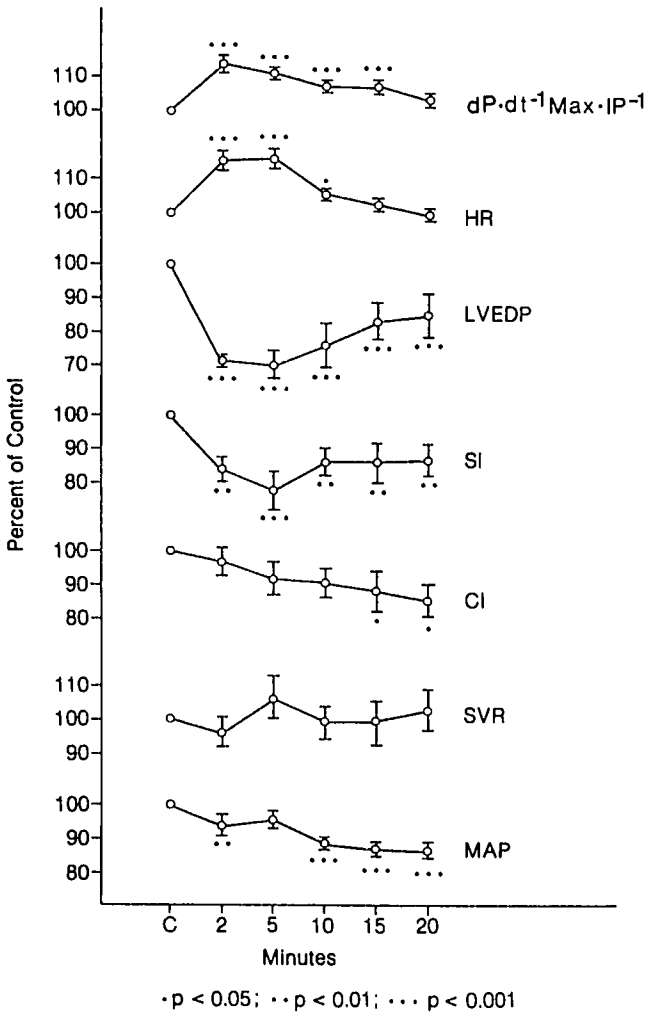

FIG. 1. Hemodynamic data expressed as a percentage of the control value (±SE) of the measured and derived variables, plotted against time after intravenous administration of 0.15 mg/kg droperidol. Abbreviations: C = control period; others—see text.

studies do not support this hypothesis.[16,17] A more likely mechanism, because of the brief duration of the effects, would be that the change in heart rate was a consequence of a beta-adrenergic effect, secondary to a brief catecholamine discharge. Such a mechanism has been shown to occur experimentally at the adrenergic synapses of the saphenous vein of dogs.[10]

The second main action of droperidol was that it decreased LVEDP. This may have been due to an increase in HR or in contractility, causing a fall in end-diastolic volume. However, in this study, $dP \cdot dt^{-1}$ max $\cdot IP^{-1}$ returned to control value at 20 min and HR at 15 min, whereas LVEDP remained lower than the control value throughout. The transient increase of contractility could account for the initial drop in LVEDP but then another explanation would be necessary for the periods when HR had returned to control value. A direct action of droperidol on the venous bed, increasing venous capacitance, should be considered; it would explain a fall in venous return and LV filling. Such an effect previously has been reported in anesthetized dogs with Innovar,[11] but in that case the contributory action of fentanyl may have been a factor. Indeed, Hsu *et al.*[18] have shown that morphine increased venous capacitance in humans for at least 15 min following intravenous injection. The action of fentanyl on venous capacitance in humans has not been studied, but Waller *et al.*[19] did not find any significant hemodynamic change following intravenous administration of 10 μg/kg of fentanyl. The present study suggests that droperidol, when administered alone, acts on the venous bed, either by an alpha-blocking action on venous adrenergic receptors[10] or by a direct venodilator effect.

If one were to have predicted the action of droperidol on SVR, one might have expected a decrease because, *in vitro*, droperidol acts as an alpha-blocking drug on arterial adrenergic receptors.[5,7] Furthermore, Whitwam and Russel[1] have shown that droperidol, administered either directly into the oxygenator during cardiopulmonary bypass or into the abdominal aorta during translumbar aortography, produced an immediate fall in blood pressure which could only have been due to direct action on the arterial bed. Indeed, SVR has been shown to be decreased in studies in which droperidol was injected intravenously in combination with fentanyl[11,12] or morphine.[2] However, the action of the narcotics used in these investigations probably accounted for the major part of the change. This is suggested by the results of Hsu *et al.*[18] who showed that morphine induced an early drop in SVR. From our study, it appears that the effect of clinical doses of droperidol on SVR, following intravenous administration, are negligible.

Rather than directly effecting SVR, it is the summation of the effects of droperidol on preload, contractility, HR, and afterload which account for the modifications that were observed in CO and MAP. Just after administration of droperidol there was a decrease in preload (LVEDP) which was compensated for, at least in part, by enhanced HR without a change in SVR. Thus, CO was not altered significantly. Later, preload reduc-

TABLE 2. Oxygen and Blood-gas Data (Means ± SE)

	Control	20 min
$\dot{V}_{O_2}$ (ml·min^{-1}·m^{-2})	138 + 11	112 ± 7*
a-$\bar{v}$ O_2 D (ml/100 ml)	4.6 + 0.2	4.5 ± 0.2
pH_a	7.41 ± 0.01	7.39 ± 0.01
Pa_{O_2} (mmHg)	75 ± 3	75 ± 3
Pa_{CO_2} (mmHg)	39 ± 1	39 ± 1
Arterial hematocrit (%)	41 ± 2	39 ± 2

* $P < 0.05$.

tion was the only determinant of the fall in CO, as HR had returned to control values. This decrease in CO, moreover, was consistent with the lowered $\dot{V}_{O_2}$ which likely resulted from the sedative effect of droperidol.

In conclusion, this work shows that 0.15 mg/kg of droperidol induced a marked decrease in preload which led to a reduction in MAP; there was no effect on SVR. The early changes in left ventricular function may be attributed to a brief release of catecholamines. The clinical consequences are that droperidol should be used with caution in hypovolemic patients and that its use in patients with stable ischemic heart disease may be of value especially in combination with morphine or fentanyl.

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Erratum

There was an error in the title of the article which appeared on page 380 of the May 1982 issue of the Journal. The correct title should read, "Binding of Halothane Free Radicals to Fatty Acids Following UV Radiation." The hyphen between the words halothane and free should not have appeared in the title.