Anesthesiology
74:71–76, 1991

Coronary and Left Ventricular Hemodynamic Responses Following Reversal of Flunitrazepam-induced Sedation with Flumazenil in Patients with Coronary Artery Disease

Jean Marty, M.D., Alain Nitenberg, M.D.,† Ivan Philip, M.D.,‡ Jean-Marc Foult, M.D.,§ Dominique Joyon, M.D.,‡ Jean-Marie Desmonts, M.D.**

The effects of reversal of flunitrazepam-induced sedation with flumazenil on coronary hemodynamics, myocardial oxygen consumption ($M\dot{V}_{O_2}$), and left ventricular (LV) performance were investigated, in a double-blind trial, in 12 patients with stable coronary artery disease undergoing cardiac catheterization. Coronary sinus blood flow was measured by continuous thermodilution. Arterial and coronary sinus blood were analyzed for oxygen and lactate contents. The determinants of LV performance were obtained from the cardiac output measured by thermodilution and from left heart catheterization data. To reverse flunitrazepam-induced sedation, patients were randomly allocated to receive placebo or flumazenil (by increment, up to 1 mg) at the end of procedure. In the placebo group, no significant hemodynamic changes were observed. In the flumazenil group, heart rate, cardiac index, maximum velocity of shortening, and relaxation time constant were not significantly altered. By contrast, mean aortic pressure and LV end-diastolic pressure (baselines: 90 ± 5 and 7.3 ± 4.1 mmHg, respectively) increased (9%, $P < 0.05$ and 67%, $P < 0.05$, respectively) after flumazenil administration, but these changes represented mainly a return toward presedation values. $M\dot{V}_{O_2}$ and coronary resistance were not significantly altered, whereas CSBF increased slightly (baseline: 119 ± 20 ml/min; increase 10%, $P < 0.05$). No electrocardiographic evidence of myocardial ischemia was observed during the study. These data show that reversal of benzodiazepine effects with flumazenil is not associated with a major alteration of LV systolic function, relaxation, or coronary hemodynamics in patients with coronary artery disease. Nevertheless, it should be cautiously used when LV end-diastolic pressure is increased at the time of its administration. (Key words: Flunitrazepam, antagonist: flumazenil. Heart: coronary sinus blood flow; myocardial metabolism; left ventricular function: coronary artery disease. Hypnotics, benzodiazepine: flumazenil.)

FLUMAZENIL, a specific antagonist of benzodiazepines, is now proposed for use in clinical anesthesia for reversal of the residual effects of benzodiazepines in the postoperative period.[1,2] Previous reports have demonstrated that reversal with flumazenil is not associated with deleterious effects.[3–5] Thus, the hemodynamic effects of this reversal are considered mild, at least in healthy patients, in contrast to naloxone-induced acute cardiovascular alterations.[6] However, since benzodiazepines are used in patients with coronary artery disease,[7–9] it is important to delineate the hemodynamic effects of reversal with flumazenil in these patients. Therefore, the current study was designed to investigate, in a double-blind, randomized controlled trial, the effects of reversal of flunitrazepam-induced sedation with flumazenil on coronary circulation, myocardial metabolism, and left ventricular (LV) function in patients with coronary artery disease. Flunitrazepam is a long-acting benzodiazepine more potent than diazepam, which is used for sedation or induction of anesthesia.[8] Its pharmacologic effects, including hemodynamic alterations, are similar to those of other benzodiazepines.[8]

Materials and Methods

Twelve patients with stable angina undergoing cardiac catheterization and coronary angiography for coronary artery disease (New York Heart Association class II–III) were randomly allocated into two groups: placebo (P) and flumazenil (F). Institutional approval from our Local Committee for Human Investigation was obtained, and all patients gave informed consent. Patients with valvular heart disease or cardiac arrhythmias were not enrolled in the study. All cardiac medications were continued until the night prior to the procedure. All patients had fasted for more than 12 h, and none was premedicated.

With lidocaine used for local anesthesia, left heart, right heart, and coronary sinus catheterization were performed percutaneously. A 7-Fr pulmonary artery thermodilution catheter was introduced into the pulmonary artery. A 7-F, high-fidelity, double-tipped micromanometer catheter (PC 770, Millar Instruments) was advanced into the left ventricle *via* the femoral artery to permit simultaneous measurements of aortic and LV pressures. A 7-Fr thermodilution catheter (Wilton Webster Laboratories) was inserted *via* the left subclavian vein and positioned in the coronary sinus. Sedation was performed during catheterization and coronary angiography using intravenous flunitrazepam to maintain patients in the sleeping state (no response to verbal command).

* Professor of Anesthesia.
† Professor of Physiology.
‡ Assistant Professor of Anesthesia.
§ Assistant Professor of Physiology.

Received from the Département d'Anesthésiologie, Service d'explorations fonctionnelles, Hopital Bichat, Unité d'Enseignement et de Recherche Xavier Bichat, Université Paris VII and Produits Roche, Neuilly, France. Accepted for publication September 19, 1990. Presented in part at the Annual Meeting of the American Society of Anesthesiologists, San Francisco, California, October 1988.

Address reprint requests to Dr. Marty: Département d'Anesthésie–Réanimation, Hopital Bichat, 46 rue Henri Huchard, 75018 Paris, France.

Hemodynamic parameters were obtained from catheterization data. Cardiac output was measured in triplicate by the thermodilution method (Cardiac Output Computer 9520A, Edwards Laboratories) and values were introduced at the time of pressure recording in a catheterization data analysis system (5600 M, Hewlett-Packard), which performed on-line analysis of LV and aortic pressures on nine beats to average out respiratory variations. This system calculated left ventricular end-diastolic pressure (LVEDP), systolic arterial pressure (SAP), mean aortic pressure (MAP), diastolic arterial pressure (DAP), stroke index (SI), systemic vascular resistance (SVR), and maximum velocity of shortening (V_{max}). V_{max} was obtained by extrapolating the downslope of the curve of dP/Kdt *versus* pressure back to zero pressure.[10] The relaxation time constant (T) was determined on curves of LV pressures recorded at a speed of 100 mm.s^{-1} according to the method of Weiss *et al.*[11] Coronary sinus blood flow (CSBF) was measured by continuous thermodilution (AHS, France).[9] Coronary vascular resistance (CVR) was calculated from LVEDP, MAP, and CSBF as (MAP − LVEDP ÷ CSBF).

Mixed venous, arterial, and coronary sinus blood oxygen contents were measured by a galvanic cell method (Lex-O_2-Con K, Waltham Instruments). Arterial, venous, and coronary sinus blood *p*H, Pa_{CO_2}, and Pa_{O_2} were measured with an ABL2 blood gas analyzer (Radiometer). Whole-body oxygen consumption ($\dot{V}O2$) was calculated by multiplying the difference between arterial and mixed venous oxygen by cardiac output (CO), and $M\dot{V}_{O_2}$ was obtained by multiplying the difference between arterial and coronary sinus oxygen contents by CSBF. Arterial and coronary sinus plasma lactate concentrations were measured with an enzymatic method. Lactate extraction was obtained by dividing the difference between the arterial and coronary plasma lactate concentrations by the arterial plasma lactate concentration. ECG was monitored during the entire study with the use of eight leads—I, II, III, aVR, aVL, AVF, V2, and V5. Quality of reversal was evaluated by one of us using a four-degree scale, where 1 = excellent effect and 4 = no effect.

All measurements were obtained during steady-state sedation (control) and 5, 10 and 15 min after flumazenil or an equal volume of placebo (administered by increment every 30 s up to 1 mg [0.3, 0.3, 0.3 and 0.1 mg], until an excellent [grade-1] effect was achieved). In addition, presedation measurements were performed in six patients.

Mean values and SD were calculated. Difference between postinjection data and values obtained during steady-state sedation were examined by analysis of variance (ANOVA) with the Bonferroni method for paired *t* test comparison. Differences between the two groups also were evaluated with ANOVA. Nonparametric tests (chi-squared and contingency analysis) were used for categorical data. A $P < 0.05$ was considered significant.

TABLE 1. Demographic Data in the Flumazenil and the Placebo Groups

	Placebo (n = 6)	Flumazenil (n = 6)
Age (yr)	52 ± 10	48 ± 9
Weight (kg)	75 ± 21	78 ± 16
Sex (M/F)	5/1	5/1
Previous myocardial infarction	4	3
Treatment		
Nitrates	5	6
Beta-adrenergic blocking drugs	1	1
Calcium-channel blocking drugs	5	6
Dose of flunitrazepam (mg)	2.3 ± 0.7	2.4 ± 1.3
Duration of sedation (min)	30 ± 10	26 ± 9

Mean ± SD.

TABLE 2. Hemodynamic Data Before and During Sedation

	Before	During
SAP (mmHg)	123 ± 19	109 ± 20*
DAP (mmHg)	73 ± 10	69 ± 11*
MAP (mmHg)	94 ± 12	87 ± 14*
CI (l·min^{-1}·m^{-2})	2.6 ± 0.6	2.4 ± 0.5
HR (beats per min)	69 ± 7	74 ± 7
V_{max} (s^{-1})	1.4 ± 0.3	1.5 ± 0.3*
LVEDP (mmHg)	10.7 ± 3.9	7.5 ± 3.4
SVR (dyn·cm^{-5}·s^{-1})	17.1 ± 2.5	16.8 ± 1.8
CSBF (ml/min)	131 ± 15	145 ± 31
CVR (units)	0.65 ± 0.12	0.56 ± 0.14
MV_{O_2} (ml/min)	15.5 ± 2.4	15.4 ± 2.8

Mean ± SD; n = 6 patients.
* $P < 0.05$ *versus* before sedation.
See text for abbreviations.

Results

Relevant clinical data are summarized in the table 1. The two groups did not differ with regard to average age,

TABLE 3. Hemodynamic Data Before Reversal in Both Groups

	Group F	Group P
SAP (mmHg)	115 ± 12	108 ± 30
DAP (mmHg)	70 ± 6	67 ± 15
MAP (mmHg)	90 ± 5	85 ± 21
CI (l·min^{-1}·m^{-2})	2.8 ± 0.5	2.4 ± 0.5
HR (beats per min)	71 ± 9	79 ± 12
V_{max} (s^{-1})	1.4 ± 0.3	1.6 ± 0.3
LVEDP (mmHg)	7.3 ± 4.1	7.7 ± 3.8
SVR (dyn·cm^{-5}·s^{-1})	17.6 ± 5	17.9 ± 3.5
CSBF (ml/min)	119 ± 20	135 ± 23
CVR (units)	0.67 ± 0.17	0.58 ± 0.15
MV_{O_2} (ml/min)	13.2 ± 2.8	14.1 ± 3.1

Mean ± SD.
No significant difference was found between the two groups.
See text for abbreviations.

TABLE 4. Blood Gas Tensions and Oxygen Data in the Two Groups

	Placebo				Flumazenil			
	C	5	10	15	C	5	10	15
*p*Ha	7.36 ± 0.01	7.34 ± 0.01	7.36 ± 0.01	7.36 ± 0.01	7.39 ± 0.01	7.4 ± 0.01	7.39 ± 0.01	7.39 ± 0.01
Pa_{CO_2} (mmHg)	42 ± 4.5	40 ± 6*	42 ± 6	42 ± 6	40 ± 1.5	38 ± 2*	39 ± 3	39 ± 2
Pa_{O_2} (mmHg)	68 ± 6	73 ± 7.5	75 ± 9*	79 ± 10*	69 ± 9	80 ± 6*	81 ± 9*	83 ± 8*
AV_{O_2} (ml/100 ml)	3.9 ± 0.7	4.3 ± 0.7	4.2 ± 0.5	4.6 ± 0.7	3.7 ± 1.1	4.1 ± 0.5	3.7 ± 1	4.1 ± 0.8
V_{O_2} (ml/min)	181 ± 71	191 ± 76	207 ± 115	215 ± 103	186 ± 74	199 ± 53	179 ± 61	182 ± 50
A-CS_{O_2} (ml/100 ml)	10.5 ± 1.4	10.5 ± 1.4	10.2 ± 1.1	10.4 ± 1.3	10.5 ± 1.9	10.9 ± 1.6	10.6 ± 1.7	11 ± 1.8
Pcs_{O_2} (mmHg)	25 ± 2	25 ± 2	26 ± 2	25.5 ± 1.5	23 ± 3.5	23 ± 3	24 ± 2	24 ± 2

Mean ± SD.
* $P < 0.05$ *versus* C.

See text for abbreviations.

sex ratio, history of myocardial infarction, or cardiac medications, or with average duration of procedure or doses of flunitrazepam used. Administration of flunitrazepam induced sleep in all cases. Hemodynamic alterations related to the injection of flunitrazepam, presented in table 2, were similar to those previously reported.[8] Before reversal, no difference was found in hemodynamic (table 3) and blood gas data (table 4) between the two groups.

After reversal, sedation scores were significantly lower in the flumazenil group (fig. 1). No significant change in LV function, coronary circulation, or myocardial metabolism was observed in the placebo group during the entire study period (figs. 2–5). Flumazenil administration did not significantly alter heart rate, cardiac index, V_{max}, or T (figs. 2–5). By contrast, SAP, DAP, MAP, SVR, and LVEDP increased significantly (12, 7, 9, 12, and 67%, respectively), 5 min after the administration of flumazenil. Individual alterations of LVEDP in the two groups, 5 min after reversal, are presented in figure 6. The increase in LVEDP was observed in all patients in the flumazenil

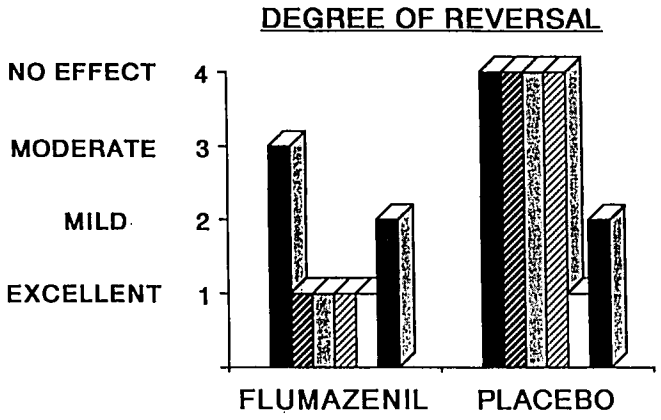

FIG. 1. Quality of reversal 5 min after administration of flumazenil or placebo described on a four-degree scale. Reversal was significantly better after administration of flumazenil ($P < 0.05$ *versus* placebo).

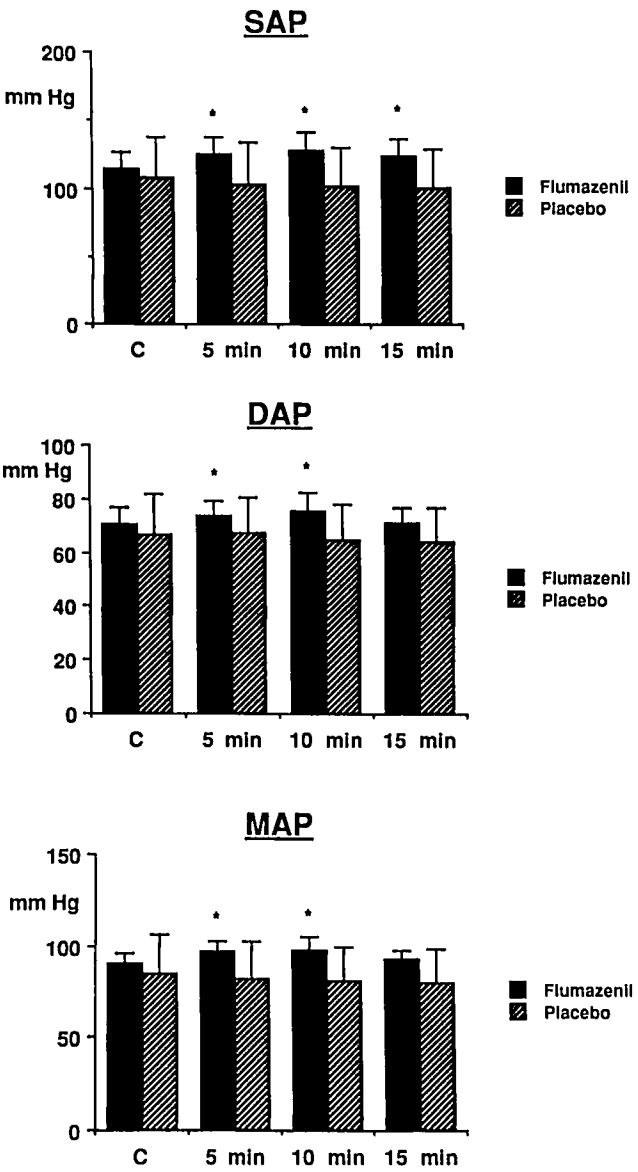

FIG. 2. Mean (± SD) values of SAP, DAP, and MAP in the two groups. * $P < 0.05$ *versus* before reversal (C).

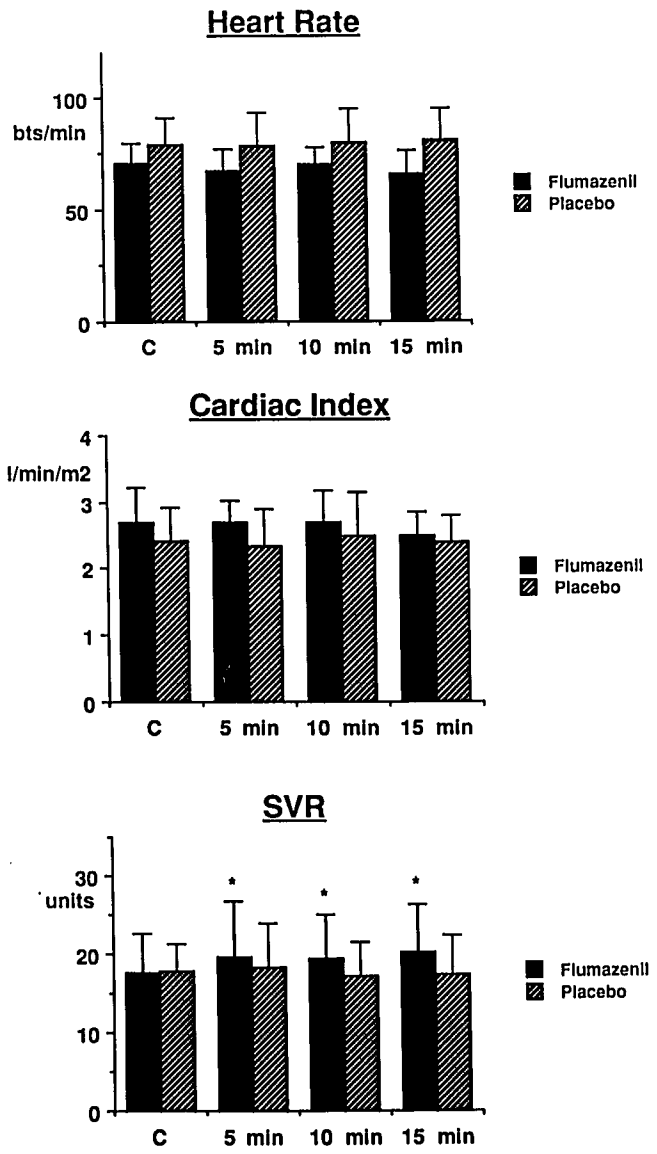

FIG. 3. Mean (± SD) values of heart rate, cardiac index and systemic vascular resistances (SVR) in the two groups. * $P < 0.05$ *versus* before reversal (C).

group, and consisted mainly of a return toward presedation values (fig. 6).

$M\dot{V}_{O_2}$ was not significantly modified, whereas CSBF increased slightly after flumazenil administration (figure 5). Myocardial lactate extraction was not affected, but one patient in each group had lactate production at one period. However, no ECG change was observed during the study in any group.

Time course of arterial blood gas tensions and $\dot{V}O2$ were similar in the two groups (table 4).

No significant differences between the two groups was observed at any time of the study.

Discussion

The current study shows that reversal of flunitrazepam-induced sedation by flumazenil is not associated with major alterations of LV function or coronary circulation in patients with coronary artery disease. However, the observed increase in LV end-diastolic pressure should be emphasized, since it might be detrimental in some patients.

Previous studies regarding circulatory effects of the reversal of benzodiazepine-induced anesthesia or sedation reported usually moderate or no changes.[12] However, the

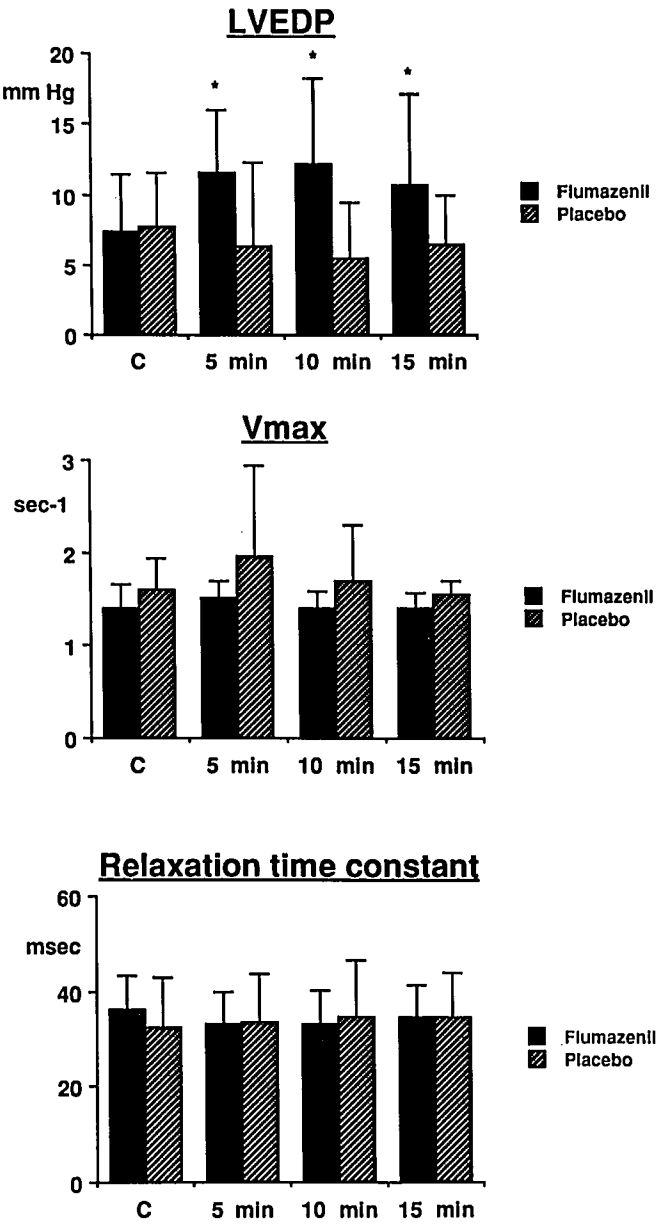

FIG. 4. Mean (± SD) values of LVEDP, V_{max}, and relaxation time constant in the two groups. * $P < 0.05$ *versus* before reversal (C).

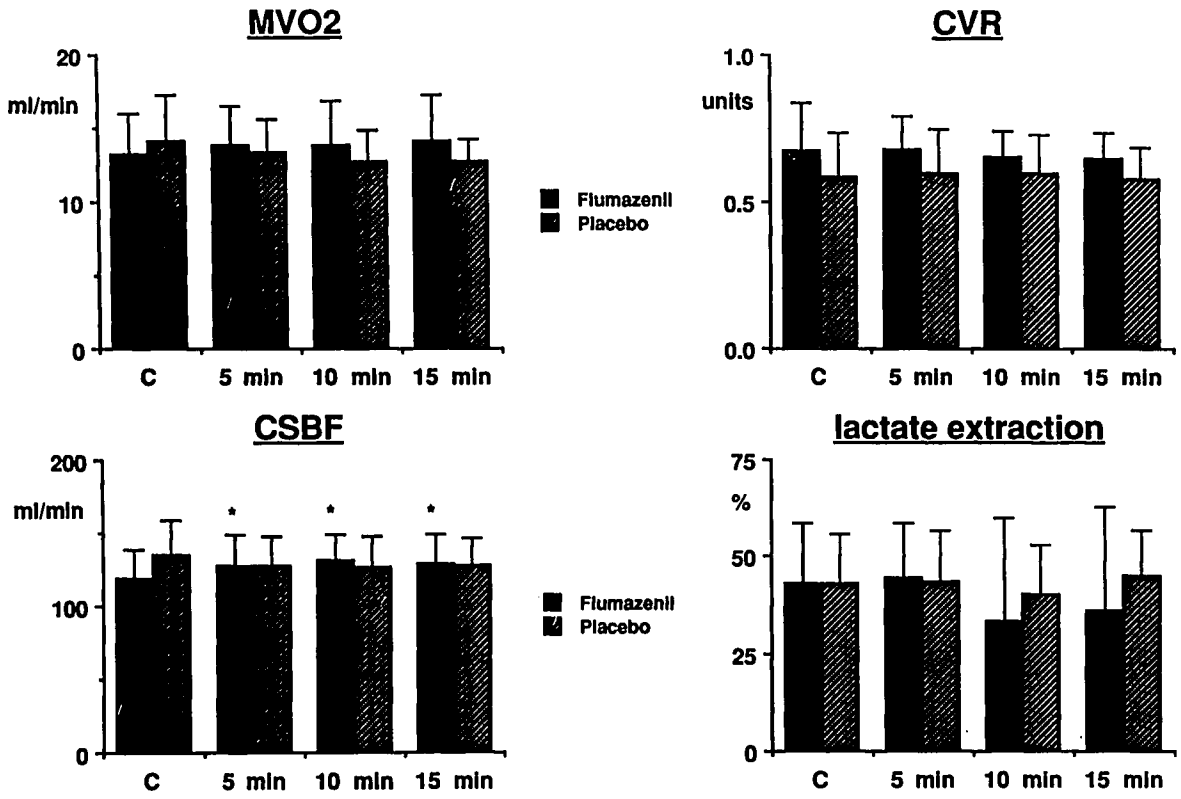

FIG. 5. Mean (± SD) values of CSBF, CVR, MV_{O_2}, and lactate extraction in the two groups. * $P < 0.05$ *versus* reversal (C).

conditions of the patients and the methods of the investigations may have influenced the results. Flumazenil by itself has no hemodynamic effects in volunteers[13] and in patients with ischemic heart disease.[14] In addition, it suppresses the midazolam-induced hemodynamic changes if it is given prior to midazolam administration.[13] No hemodynamic alterations were observed when flumazenil was administered for reversal of benzodiazepine sedation,[3-5] and no evidence of adrenergic activation was reported.[5] Similar results have been reported when flumazenil was used for reversal of midazolam-supplemented general anesthesia.[12] Nevertheless, an increase in blood pressure without a change in heart rate has sometimes been observed when flumazenil administration was associated with stress and anxiety during emergence, particularly after cardiac surgery.¶ In the current study, a slight but significant increase in arterial blood pressure was observed but was not clinically relevant.

However, the absence of marked alterations in blood pressure or heart rate does not necessarily imply that LV function or coronary circulation are not altered. No previous study has examined the effects of flumazenil on these parameters. In fact, in surgical patients, flumazenil may induce hemodynamic alterations, by two mechanisms. The first mechanism would be related to a direct antagonism of the pharmacologic effects of benzodiazepines on the determinants of LV function. This is likely the case for the changes of LV end-diastolic pressure we observed, since benzodiazepines used in anesthesia induce a marked decrease of LV filling pressure.[7-9,15,16] In the current study, the degree of increase in LV end-diastolic pressure after flumazenil administration corresponded to a return toward presedation levels. However, this response was present whatever the value of LV end-diastolic pressure before reversal. Since benzodiazepines have been reported to attenuate increases of filling pressures, it is preferable to carefully use flumazenil when the preadministration level of LVEDP is high. The second mechanism possibly involved in hemodynamic changes related to flumazenil administration would be cardiovascular responses to the recovery itself. Indeed, several factors, such as emergence, shivering, and extubation, may contribute simultaneously to circulatory alterations. In similar conditions, naloxone induces marked hemodynamic responses.[6] However, the design of our study avoided the confounding influence of nonspecific cardiovascular responses to postanesthetic

¶ Louis M, Forster A, Suter PM, Gemperle M: Clinical and hemodynamic effects of a specific benzodiazepine antagonist (Ro 15-1788) after open heart surgery (abstract). ANESTHESIOLOGY 61:A61, 1984.

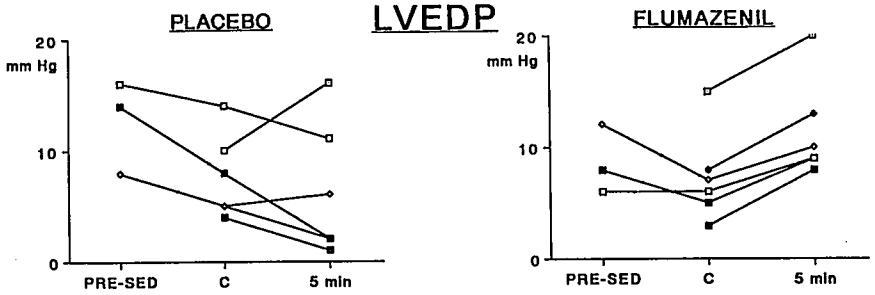

FIG. 6. Individual values of LVEDP before sedation (PRE-SED), at baseline (C), and 5 min after reversal in the two groups. All patients in the flumazenil group experienced an increase in LVEDP.

recovery. In addition, comparison with placebo in a controlled randomized trial allows the evaluation of the specific effects of reversal.

The hemodynamic changes that were observed had no detrimental effects on systolic function (V_{max}) and relaxation (T) of the left ventricle in patients with coronary artery disease. In addition, they had no significant consequences on $M\dot{V}_{O_2}$ and coronary hemodynamics. No evidence of ischemia related to the use of flumazenil was observed. Nevertheless, the small number of patients included in this study does not allow us to establish definitely the safety of flumazenil in patients with coronary artery disease, especially those in other circumstances, such as major surgery. Furthermore, some differences may be expected depending on the specific benzodiazepine used for sedation, even if hemodynamic effects of benzodiazepines are roughly similar.[8,9]

In conclusion, the current study demonstrates that flumazenil may be used safely in patients with coronary artery disease to reverse residual effects of flunitrazepam. However, it should be used especially carefully in patients with increased LV end-diastolic pressure.

References

1. Darragh A, Lambe R, Brick I: Reversal of benzodiazepine-induced sedation by intravenous Ro 15-1788. Lancet 2:1042–1045, 1981.
2. Ricou B, Forster A, Bruckner A, Chastonnay P, Gemperle M: Clinical evaluation of a specific benzodiazepine antagonist (Ro 15-1788). Br J Anaesth 58:1005–1011, 1986.
3. Sage DJ, Close A, Boas RA: Reversal of midazolam sedation with anexate. Br J Anaesth 59:459–464, 1987.
4. Alon E, Baitella L, Hossli G: Double-blind study of the reversal of midazolam supplemented general anesthesia with Ro 15-1788. Br J Anaesth 59:455–458, 1987.
5. White PF, Shafer A, Boyle WA, Doze VA, Duncan S: Benzodiazepine antagonism does not provoke a stress response. ANESTHESIOLOGY 70:636–639, 1989.
6. Desmonts JM, Bohm G, Couderc E: Hemodynamic effects of low doses of naloxone after narcotic nitrous oxide anesthesia. ANESTHESIOLOGY 49:12–16, 1978.
7. Samuelson PN, Reves JR, Kouchoukos NT, Smith LR, Dole KM: Hemodynamic responses to anesthetic induction with midazolam or diazepam in patients with ischemic heart disease. Anesth Analg 60:802–809, 1981.
8. Nitenberg A, Marty J, Blanchet F, Zouioueche S, Baury A, Desmonts JM: Effects of flunitrazepam on left ventricular performance, coronary haemodynamics and myocardial metabolism in patients with coronary artery disease. Br J Anaesth 55:1179–1184, 1983.
9. Marty J, Nitenberg A, Blanchet F, Zouioueche S, Desmonts JM: Effects of midazolam on the coronary circulation in patients with coronary artery disease. ANESTHESIOLOGY 64:206–210, 1986.
10. Pollack GH: Maximum velocity as an index of contractility in cardiac muscle. Circ Res 26:111–127, 1970.
11. Weiss JL, Frederiksen JW, Weisfeldt F: Hemodynamic determinants of time course of fall in canine left ventricular pressure. J Clin Invest 58:751–760, 1976.
12. Marty J, Joyon D: Haemodynamic responses following reversal of benzodiazepine-induced anaesthesia or sedation with flumazenil. Eur J Anaesth (Suppl) 2:167–171, 1988.
13. Rouiller M, Forster A, Gemperle M: Assessment of the efficacy and tolerance of a benzodiazepine antagonist (Ro 15-1788). Ann Fr Anesth Réan 6:1–6, 1987.
14. Croughwell ND, Reves JG, Will CJ, Kasson BJ, Hawkins E. Safety of flumazenil in patients with ischemic heart disease. Eur J Anaesthesiol Suppl 2:177–182, 1988.
15. Cote P, Campeau L, Bourassa M: Therapeutic implications of diazepam in patients with elevated left ventricular filling pressure. Am Heart J 91:747–751, 1976.
16. Reves JG, Samuelson PN, Linnan M: Effects of midazolam maleate in patients with elevated pulmonary occluded pressure, Trends in Intravenous Anesthesia. Edited by Aldrete JA, Stanley TH. Chicago, Year Book Medical Publishers, 1980, pp 253–252.