Anesthesiology
65:678–683, 1986

Hemodynamic Effects of Diazepam, Flunitrazepam, and Midazolam in Patients with Ischemic Heart Disease: Assessment with a Radionuclide Approach

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Diazepam, flunitrazepam, and midazolam are benzodiazepines extensively used in anesthesia. They have been used to induce anesthesia in patients with myocardial dysfunction.[1–3] Their hemodynamic effects have been studied in normal humans and in patients with coronary artery disease. However, the cardiovascular actions of commonly used doses of these three drugs have not been compared, especially their effects on coronary circulation and contractility.[3,4]

Radionuclide cineangiography effectively reproduces results obtained with contrast angiography in the assessment of left ventricular volumes and function.[5] Application of this relatively noninvasive method provides a complementary tool for assessment of cardiac performance during anesthesia.[6,7]

We compared the consequences of iv bolus doses of diazepam, flunitrazepam, and midazolam on left ventricular function using gated radionuclide (RN) ventriculography in unpremedicated patients with chronic coronary heart disease.

MATERIALS AND METHODS

The trial was approved by our local ethics committee, and informed consent was given by all patients. Forty-two patients of both sexes, aged between 39 and 88 yr, undergoing urologic surgery were randomly assigned after determination of the left ventricular ejection fraction(LVEF > or <55%), to one of three groups receiving diazepam 0.2 $mg \cdot kg^{-1}$, flunitrazepam 0.02 $mg \cdot kg^{-1}$, or midazolam 0.2 $mg \cdot kg^{-1}$. Seven patients in each group had a LVEF equal or greater than 55%, and seven patients a LVEF less than 55%. All patients suffered from angina pectoris secondary to coronary artery disease (CAD). The diagnosis of CAD was based on documentation of previous acute myocardial infarction in 12 patients, followed, in all but one patient, by typical mild-to-moderate angina pectoris. In the remaining 30 patients, the diagnosis of CAD was established by the presence of typical angina pectoris brought on by effort and relieved by rest and nitroglycerin. The diagnosis of these 30 patients was further documented by positive exercise tests. The patient characteristics, the type of CAD, and the treatments are summarized in table 1.

The study was performed in the nuclear medicine laboratory just before surgery. No patients were premedicated, but all received their chronic cardiovascular medications up to and including the morning of surgery to ensure a stable hemodynamic state before the procedure. Each patient was positioned supine on a comfortable table under the camera. An indwelling catheter was inserted into an arm vein. Arterial blood pressure was monitored with a noninvasive arterial pressure monitor (Dinamap Critikon®) during each phase of the study and the ECG (standard limb lead II) was continuously recorded. The patient breathing the room air through a facial mask recorded to a capnometer (47210 A Capnometer, Hewlett-Packard). Respiratory rate and fractional mixed expired CO_2 concentration (FE_{CO_2}) were measured before and during the 3 min following the injection of benzodiazepine and during each phase of the procedure. If apnea occurred, its duration was measured. A baseline study was performed in the 45° left anterior oblique (LAO) position. Diazepam 0.2 $mg \cdot kg^{-1}$, flunitrazepam 0.02 $mg \cdot kg^{-1}$, or midazolam 0.2 $mg \cdot kg^{-1}$ was given iv over a 30-s period. Data acquisitions were serially obtained every 3 min after benzodiazepine administration over the next 15 min. After a last data acquisition at 30 min, the patient was transported to the operating theater.

All patients were studied by RN angiography by means of the ECG gated, equilibrium blood-pool technique[8] using *in vivo* red blood cell labeling with 99 m Technetium (Tc).[9] Lyophilized solution that contained 100 mg of stannouspyrophosphate (TCK 7 CEA) was injected iv. Pretreatment with SN^{++} causes the 99 Tc to bind to the patient's red blood cells with 85–95% efficiency, thus retaining the tracer within the intravascular compartment.

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Received from the Département d'Anesthésiologie et Service de Médecine Nucléaire, Hôtel-Dieu, Centre Hospitalier Universitaire, 44035 Nantes Cedex, France. Accepted for publication July 25, 1986. Supported in part by University of Nantes Institutional Grants Program.
Address reprint requests to Dr. Lepage.
Key words: Hypnotics: diazepam; flunitrazepam; midazolam. Measurement techniques: radionuclide contrast angiography.

Thirty minutes later, the *in vivo* preparation containing 30 to 35 mCi of 99 m Tc pertechnetate (Technetium CEA Elumat 300) was injected through the indwelling catheter. After 2 min at equilibrium of the RN in the blood pool, data were collected up to a preset total of 300 kilocounts per frame, which usually took 2.5 min to acquire. The study was performed using a commercial scintillation camera equipped with an all-purpose, medium-resolution, medium-sensitivity collimator. The data were extracted from the modified LAO (40–45° from anterior, 10–15° caudal tilt) projection, adjusted for maximal separation of the left ventricle from all other cardiac chambers and optimal visualization of septum. The data synchronized with ECG were transferred to a computer for processing and displayed on a color monitor for visualization and photographic recording. Cardiac cycles that varied more than 10% from the mean in length were excluded. Each cumulative cycle was framed into 16 intervals beginning at the R wave. Using diastole, systole, and Fourier transforms, one of the authors (J.H.), who did not know which benzodiazepine was given, manually assigned regions of interest corresponding to the left ventricle in the LAO position and the automatically computed periventricular background. At the beginning of the acquisition, actual time per frame was determined by the computer, and the total number of cycles used for the acquisition of the 300 kilocounts was registered for each study. A time activity curve throughout the cardiac cycle was produced by subtraction of background counts and normalized with respect to ventricular area. Ejection fraction was calculated by the computer from background-corrected end-diastolic and end-systolic counts using the standard formula in which counts are substituted for volumes:

$$\text{LVEF} = (\text{EDC} - \text{BKCD}) - (\text{ESC} - \text{BKCD})/(\text{EDC} - \text{BKCD})$$

where EDC = end-diastolic counts; ESC = end-systolic counts; and BKCD = background. To determine left ventricular RN volume equivalents, formula 1 of Slutsky *et al.*,[10] was considered to be the simplest for the purpose of this study. According to this formula:

$$V = (\text{EDC or ESC}/\text{Nb of heart beats}) \times 0.04\,\text{s}/\text{actual time per frame}$$

where V = volume; heart beats = the number of cycles required for data acquisition; and actual time per frame = the time for acquisition of counts during each of the 16 frames. The value obtained from this and the following equations using RN studies does not represent actual volumes in milliliters, but rather, RN volume equivalents that are reasonably well correlated with contrast angiographic volumes.[10] Because each patient served as his own control, changes in volumes and in ejection fraction from baseline obtained by this equation are valid for this study.

TABLE 1. Characteristics of the Patients

	Diazepam n = 14	Flunitrazepam n = 14	Midazolam n = 14
Age (yr)	71 (51–79)	68 (39–81)	69 (49–88)
Weight (kg)	66 (46–81)	68 (53–80)	69 (47–85)
Type of coronary disease			
Angina pectoris			
NYHA 1	3	4	5
NYHA 2	7	6	6
NYHA 3	4	4	3
Myocardial infarction	5	4	3
Congestive heart failure	3	3	4
Hypertension	4	3	5
Treatment			
Nitrates	14	14	14
Ca channel blocker	5	6	5
β adrenergic blocker	3	5	3
Digoxin	3	3	4
Diuretics	6	3	2
Amiodarone	3	2	2
Antihypertensive agents	5	3	5

NYHA = New York Heart Association classification system.

The following equations were used to determine relative changes from baseline in each patient: Stroke volume equivalent: SV = EDV − ESV, where EDV and ESV = end-diastolic and end-systolic volume equivalents; cardiac output equivalent: CO = SV × HR, where HR = heart rate measured at the beginning of each stage of the procedure; systemic vascular resistance equivalent: SVR = MAP/CO, where MAP = mean arterial blood pressure measured at the beginning of each stage of the procedure.

All data are given as mean ± SEM. Multiple comparison has been made by using a multivariate analysis of variance. $P < 0.05$ was considered as significant.

RESULTS

The age, weight, coronary artery disease, and treatment did not differ significantly in the different patient groups. Sleep, as defined by the lack of response to vocal command, was observed in all patients within 50 s (mean 30 ± 14) after the administration of the three benzodiazepines and persisted throughout the 30-min study period. No statistical significant change in respiratory rate and FE_{CO_2} value were noticed after the first min following the administration of the drugs when compared with the control point. In four patients apnea (which did not last more than 20 s) occurred just after the injection of diazepam for two patients, flunitrazepam for one patient, and midazolam for one patient. Hemodynamic data are

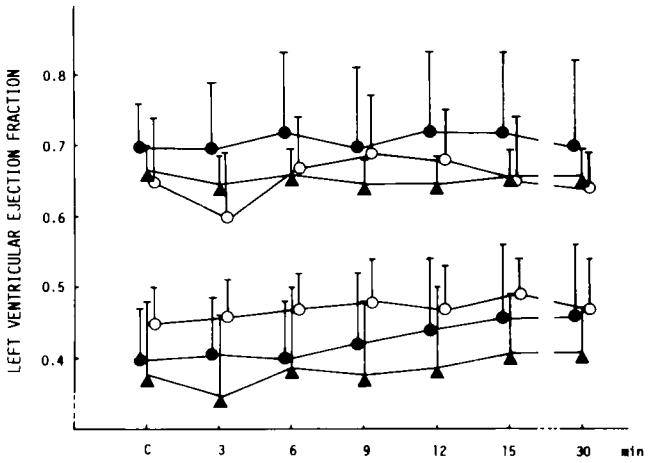

FIG. 1. LVEF radionuclide measurements in patients with chronic ischemic heart disease after iv bolus administration of doses of diazepam 0.2 mg·kg^{-1} (●), flunitrazepam 0.2 mg·kg^{-1} (▲), and midazolam 0.2 mg·kg^{-1} (○). No significant change from control was noticed whether LVEF is ≥0.55 or <0.55.

summarized in figures 1–3. The trend of change was the same in all groups. The LVEF values (fig. 1) did not diverge significantly from control, whether they were in the >55% group or the <55% group. The MAP, systolic arterial blood pressure (SAP), diastolic arterial blood pressure (DAP), and heart rate did not change significantly. EDV and ESV were constant so that no significant changes were observed in stroke volume, cardiac output, and systemic vascular resistance equivalents. No ECG modification was observed during the entire procedure in any patient. Finally, the regional ejection fraction histograms were never significantly modified, particularly for the pixel numbers < 0% and the pixel numbers 0 to 40% (fig. 4).

DISCUSSION

RN ventriculography has been validated as a reliable, relatively noninvasive technique for investigating ventricular function.[10,11] Its accuracy for assessment of left ventricular function has been demonstrated in studies in which contrast media is used as a standard for comparison.[12,13] LVEF determined by both methods are well correlated at rest, during exercise, and during change from exercise to rest. Reproducibility in the same patient by the same observer is extremely high. Finally, the meth-

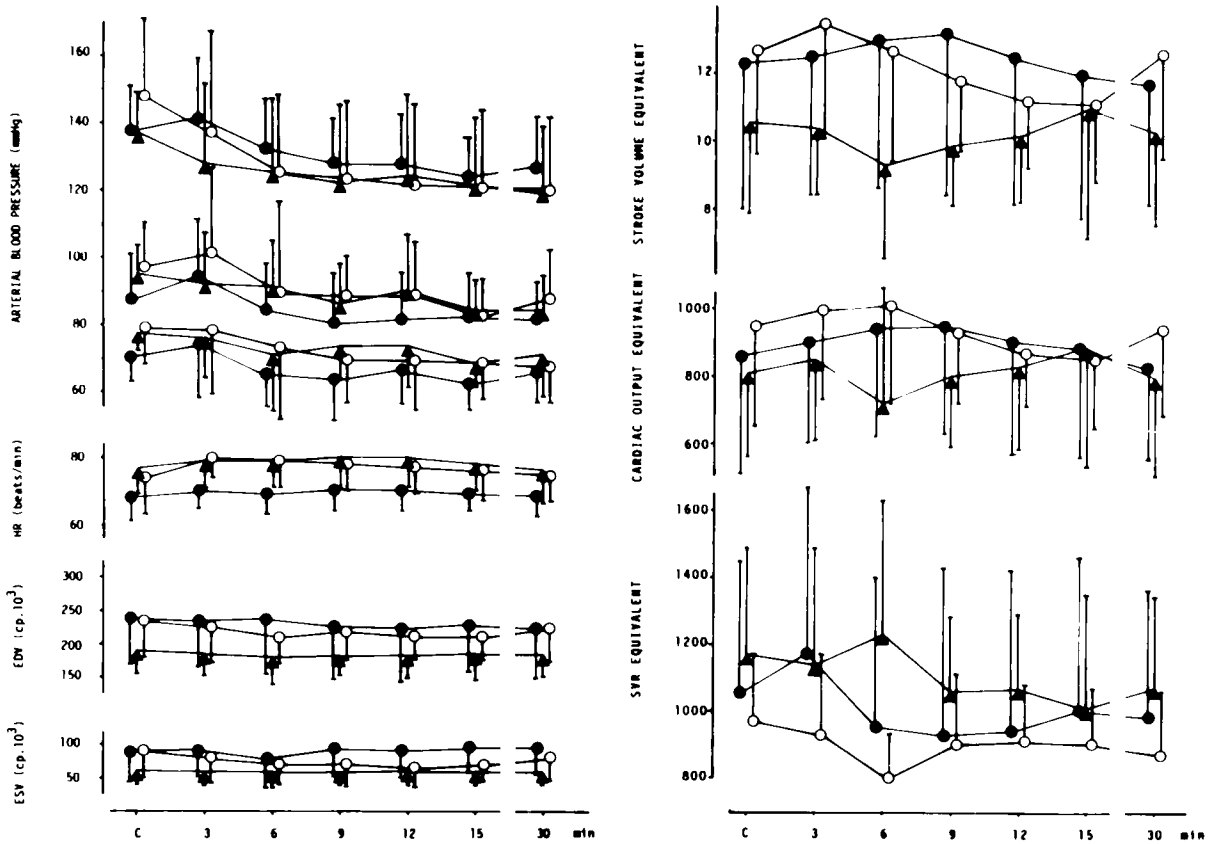

FIG. 2. Evolution of hemodynamic variables in chronic ischemic heart disease patients with radionuclide measured LVEF ≥ 0.55 after iv bolus administration of doses of diazepam 0.2 mg·kg^{-1} (●), flunitrazepam 0.02 mg·kg^{-1} (▲), and midazolam 0.2 mg·kg^{-1} (○). No significant change was noted when any measurement was compared with its control value or the comparable value for the other benzodiazepines.

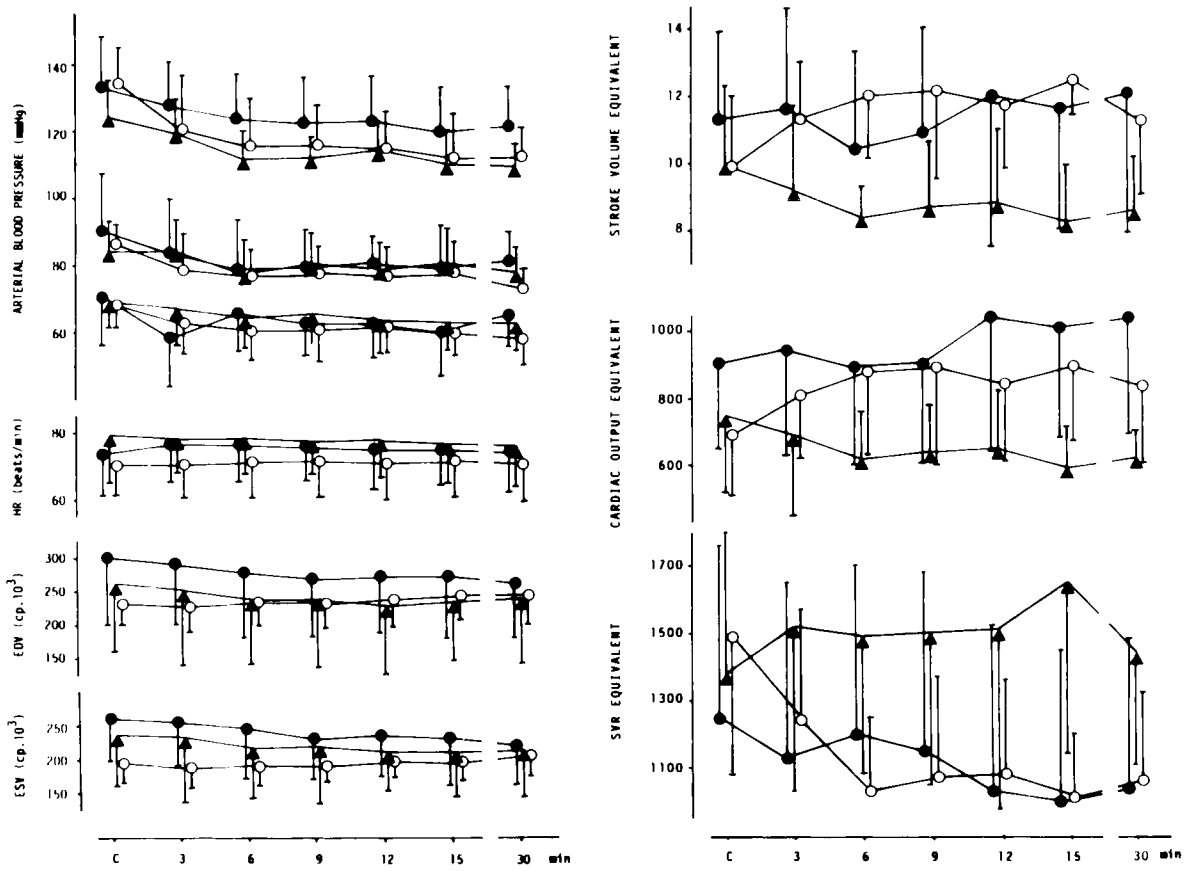

FIG. 3. Evolution of hemodynamic variables in chronic ischemic heart disease patients with radionuclide measured LVEF < 0.55 after iv bolus administration of doses of diazepam 0.2 mg · kg^{-1} (●), flunitrazepam 0.02 mg · kg^{-1} (▲), and midazolam 0.2 mg · kg^{-1} (○). No significant change was noted when any measurement was compared with its control value or the comparable value for the other benzodiazepines.

odologic error of the RN-based ejection fraction is approximately 5%.[14,15] The use of equilibrium method allows prolonged study because the isotope remains in the intravascular pool during 6 h or more with adequate activity for imaging.[15] This method seems to be particularly well suited for studying the rapid changes in left ventricular function and dimensions that may occur after administering drugs with potential cardiocirculatory effects without introducing the myocardial depression associated with radioopaque contrast techniques.[16] The use of RN angiography with a mobile gamma camera to monitor intraoperative ventricular function has been reported.[6] Our study emphasizes that RN angiography is of particular value for diagnostic, choice of appropriate management in anesthesia, and assessment of efficacy or risk of drugs.[17,18]

Ejection fraction is a nonspecific indicator of left ventricular function, but decrease in LVEF, especially during exercise, constitutes a reasonable sensitive detector of ischemia in pertinent CAD.[15] Therefore, one would expect that the deleterious effect on coronary circulation and myocardium induced by anesthetic drugs should be detected by RN angiography. LVEF is obviously the most feasible quantitative parameter,[11] but supplementary information about ventricular dysfunction associated with ischemia is provided by the nongeometric, count-based RN angiography, allowing quantitative assessment of regional dysfunction and minimizing difficulties for its visual detection.[6,15] Finally, the preoperative LVEF is a useful guideline for the choice of preoperative monitoring and a useful prediction of postoperative alterations.[19,20] Uncomplicated anesthesia and surgery are generally associated in CAD with LVEF greater than 0.55.[20]

This study demonstrated that the iv administration of diazepam, flunitrazepam, or midazolam, when used solely, did not modify the LVEF and did not induce regional myocardial dysfunction in patients with chronic CAD. However, the extrapolation of these data to clinical anesthesia may be questioned because of the conditions of the study. The doses employed for diazepam are rather sedative than anesthetic; but the doses employed for flunitrazepam[2] and midazolam[3] are the doses often recommended for induction of anesthesia. In any event, sleep was obtained in all patients all along the procedure in the

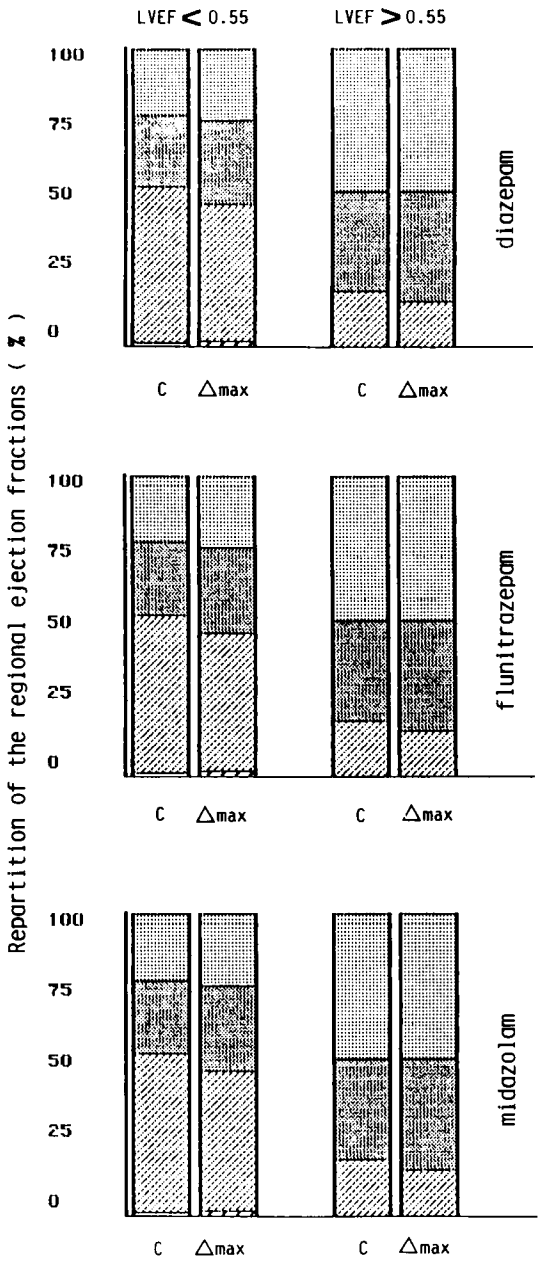

FIG. 4. Repartition in per cent of the regional ejection fractions. Ejection fractions are computed in pixels and ranged in four classes (percentage of pixels with a <0 EF ; percentage of pixels with a 0–40 EF ; percentage of pixels with a 40–60 EF ; percentage of pixels with a >60 EF). Each class is expressed in percentage of total number of left ventricular area before (C) and after (maximal change from control = Δ max) benzodiazepine administration.

absence of nociceptive stimulations. This study represents a basis for further investigations on the hemodynamic effects of clinical anesthesia by using the association of benzodiazepine, narcotics, and muscle relaxants, because there is some potential for hemodynamic depression when benzodiazepines are used in combination with other anesthetic drugs[21,22]—which mechanism remains unclear. The patients were not premedicated and, consequently, the existence of basal rest conditions at the control point may be disputed because the patients rested at least 30 min during pretreatment with SN^{++}. The patients took their cardiac medication until the moment of the procedure, so that might have influenced the hemodynamics. FE_{CO_2} remained unchanged in our study, which did not preclude variations in Pa_{CO_2} as far as the relationship between end-tidal CO_2 and the tension of CO_2 in arterial blood is influenced by a number of hemodynamic and respiratory parameters, the only one of which measured in our noninvasive study was the respiratory rate. It has been demonstrated elsewhere that an increase in Pa_{CO_2} might occur in relation to the respiratory depressant effect of the benzodiazepines.[23] That could be a bias in our study in regard to the hypercarbia influence on coronary circulation.[24]

Still, our findings are consistent with previous reports.[4,25,26] In unpremedicated patients with CAD the MAP decreases from 5 to 10% with diazepam,[25] and 5 to 20% with flunitrazepam[4] and midazolam.[26] Heart rate is unchanged with diazepam[26] and slightly increased with the other drugs.[4,26] Variations of stroke volume, cardiac output, and systemic vascular resistance equivalents are in accordance with the published data where cardiac output is determined by means of the dilution method.[4,25,26] Abnormalities of wall motion or determination of coronary sinus blood flow and myocardial oxygen consumption cannot be evaluated in our study. Nevertheless, the assessment of regional ejection fraction allowed indirect appreciation of ischemic influence on myocardial contraction. Absence of variation in the distribution of regional ejection fractions is one more argument along with studies on coronary circulation to prefer benzodiazepine for induction in patients with ischemic heart disease.

In summary, RN angiography applied for assessment of cardiovascular effects of the three benzodiazepines used in anesthesia demonstrates their slight influence on LVEF. Besides these results, hemodynamic interactions of diazepam, flunitrazepam, and midazolam with the other drugs employed in anesthesia remain to be investigated. In this respect, extension of nuclear technique could provide a reliable method for nonivasive determination of cardiac action of the main anesthetic agents.

The authors are indebted to Roche Laboratories, Neuilly sur Seine, France, for supplies of midazolam.

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