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Disproportionate Effects of Regional Hypokinesis on Radionuclide Ejection Fraction: Compensation using Attenuation-Corrected Ventricular Volumes

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This study evaluates the potential effects of regional hypokinesis on measurements of global ejection fraction (EF) as determined by radionuclide angiographic techniques. Studies were performed in a two-compartment left-ventricular (LV) model that allowed simulation of global, anterior-region, or posterior-region hypokinesis in a torso chamber with heart-to-background activity similar to that in clinical studies. Radionuclide techniques accurately measured changes in EF during global hypokinesis but progressively underestimated true EF during increasing anterior-region hypokinesis, and progressively overestimated true EF during increasing posterior hypokinesis. When EF (y-axis) was plotted against true EF (x-axis) for a 240-ml model, from linear regression equations, the slopes and intercepts were significantly different for anterior and posterior hypokinesis. The disproportionate effects of regional hypokinesis increased with LV size. Accurate EF was computed during regional hypokinesis by determining absolute LV volumes from count rates corrected for attenuation, depth, background activity and blood-pool activity. Thus, the disproportionate effects of regional hypokinesis on EF were corrected by considering differential count attenuation.

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The measurement of ejection fraction (EF) by the radionuclide angiographic (RA) technique is based on the concept that radionuclide counts in the left-ventricular (LV) region are proportional to LV volume, and that, consequently, fractional changes in counts are proportional to fractional changes in volume. Green et al., however, have emphasized that the count rate measured from the precordial area is not absolutely proportional to LV radioactivity (*1*). They noted that since the LV blood and surrounding tissue absorb and scatter photons as a function of depth, the source points farther from the gamma detector are shielded by larger amounts of tissue, so that a gradient in detector sensitivity exists along the line of sight through the ventricle. Similarly, there should be differences in photon attenuation between end-diastole and end-systole (*2*). The present study tests the hypothesis that nonuniform contraction resulting from regional hypokinesis in the anterior wall (near the detector) or inferior wall (farther from the detector) may cause differential effects on global count changes, and thus on the EF measurement.

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METHODS

Model studies of RA ejection fraction. Models were constructed to simulate left ventricles of two sizes and with varying degrees of global and regional hypokinesis. Each LV model consisted of a pair of balloons fastened to opposite sides of a $\frac{1}{8}''$ sheet of plexiglas so that they shared a common fixed base (Fig. 1). One model ac-

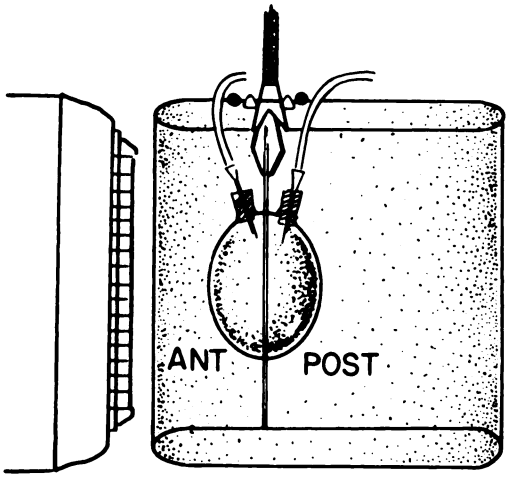

FIG. 1. Diagram of two-compartment heart model consisting of 2 balloons simulating anterior (ant) and posterior (post) LV regions. Model is held by clamp in water-filled torso chamber positioned in front of gamma camera.

commodated volumes of 25 to 50 ml in each balloon, and a second model accommodated 50 to 120 ml in each. The volume of each balloon could be serially adjusted by injecting water through an airtight stopper.

Models were placed vertically in a water-filled torso chamber with the plexiglas base fixed parallel to, and 6 cm from, the collimator's front face (Fig. 1). One balloon (anterior) was thus directly in front of the other balloon (posterior). The anterior balloon simulated the portion of a ventricular chamber that is nearer the gamma detector; the posterior balloon simulated a more distant region.

The maximum total volume placed into each heart model defined a constant "end-diastolic" volume (V_{ed}). Smaller volumes were used to represent a range of "end-systolic" volumes (V_{es}). Ventricular hypokinesis was simulated by progressively increasing V_{es} in three patterns: (a) global hypokinesis was initiated by symmetric increases in V_{es} in both anterior and posterior balloons; (b) posterior regional hypokinesis by increases in V_{es} in only the posterior balloon; and (c) anterior regional hypokinesis by increases in V_{es} in only the anterior balloon.

The true EF was calculated in each case as:

$$\text{true EF} = \frac{V_{ed} - V_{es}}{V_{ed}}. \quad (1)$$

The experiments were performed by filling each balloon to its maximum volume, either 50 or 120 ml; counts were determined by standard RA techniques as a measure of V_{ed}. The volume was then reduced in each balloon to a minimum volume, either 25 or 50 ml, to provide a minimum V_{es}; this resulted in a maximum EF value. A range of hypokinesis was then produced by progressively increasing the V_{es} in both balloons to produce global hypokinesis, or in one balloon to produce regional hypokinesis (Table 1).

To simulate heart-to-background ratios in patient studies, [Tc-99m]pertechnetate was distributed in the "ventricle" and "body" in a 10:1 concentration ratio (heart 10 μCi/ml; torso, 1 μCi/ml). Static images were obtained using a mobile scintillation camera with a high-resolution parallel-hole collimator interfaced to a computer. Data were acquired in word mode without magnification, in a 64 × 64 matrix of 150,000 counts per study. For each study, a region of interest (ROI) was assigned for the heart model using an operator-assisted semiautomatic method that involves a combined second derivative and count-threshold algorithm. A background region was manually generated, encircling the heart model approximately 10 pixels from the edge. Background and decay-corrected count rates were computed.

Since background-corrected count rates in the model's ROI are considered proportional to volume, the RA EF was calculated as:

$$\text{EF} = \frac{N_{ed} - N_{es}}{N_{ed}}, \quad (2)$$

where N_{ed} and N_{es} are background-corrected count rates derived by imaging the "end-diastolic" and "end-systolic" volumes, respectively.

Multiple linear regression analyses were performed to compare true EF determined from the measured volumes of solution with RA EF during the conditions of global and anterior and posterior regional hypokinesis.

Subsequently, the same experiments and analyses were performed with the heart model placed so that the plexiglas base was fixed at an increased distance from the detector (10 cm rather than 6), and also with no background activity in the torso. Finally, the heart models were imaged with the gamma camera repositioned lateral to the torso, with the detector's axis in the plane of the plexiglas base, so that the anterior and posterior balloons were equidistant from the detector. This permitted calculation of attenuation-corrected volumes.

The following analysis describes the calculation of LV volume by considering the effects of attenuation on counts (*3–5*). The volume-derived or volumetric EF is defined as:

$$\text{volumetric EF} = \frac{\nu_{ed} - \nu_{es}}{\nu_{ed}} \quad (5)$$

where ν_{ed} and ν_{es} are the ventricular volumes (ml) at end-diastole and end-systole, respectively. The volumetric EF is calculated using an attenuation compensation procedure to compute ν_{ed} (and ν_{es}) from multigated blood-pool count rates using the formulation of Jaszczak et al. (*4,5*):

TABLE 1. STUDIES OF REGIONAL HYPOKINESIS IN HEART MODEL

V_{ed}* (ml)	N_{ed}†	V_{es}‡ (ml)	true EF§	Global hypokinesis V_{es} (ml) Ant¶	Post**	N_{es}	RNA EF	Posterior hypokinesis V_{es} (ml) Ant	Post	N_{es}	RNA EF	Anterior hypokinesis V_{es} (ml) Ant	Post	N_{es}	EF
240	2467	100	58	50	50	884	64	50	50	978	60	50	50	922	63
		110	54	55	55	967	61	50	60	1026	58	60	50	1106	55
		120	50	60	60	1103	55	50	70	1124	54	70	50	1244	50
		130	46	65	65	1246	49	50	80	1134	54	80	50	1406	43
		140	42	70	70	1320	46	50	90	1232	50	90	50	1567	36
		150	38	75	75	1477	40	50	100	1270	49	100	50	1708	31
		160	33	80	80	1589	36	50	110	1364	45	110	50	1869	24
		170	29	85	85	1689	32	50	120	1430	42	120	50	1993	19
100	1021	50	50	25	25	504	51	25	25	480	53	25	25	475	53
		55	45	27.5	27.5	538	47	25	30	513	50	30	25	528	48
		60	40	30	30	585	43	25	35	537	47	35	25	590	42
		65	35	32.5	32.5	675	34	25	40	594	42	40	25	665	35
		70	30	35	35	698	32	25	45	611	40	45	25	733	28
		75	25	37.5	37.5	763	25	25	50	676	34	50	25	832	19

* V_{es} = end-systolic volume; V_{ed} = end-diastolic volume.
† N_{ed} = end-diastolic count rate.
‡ N_{es} = end-systolic count rate.
§ EF = ejection fraction.
¶ Ant = anterior balloon.
** Post = posterior balloon.

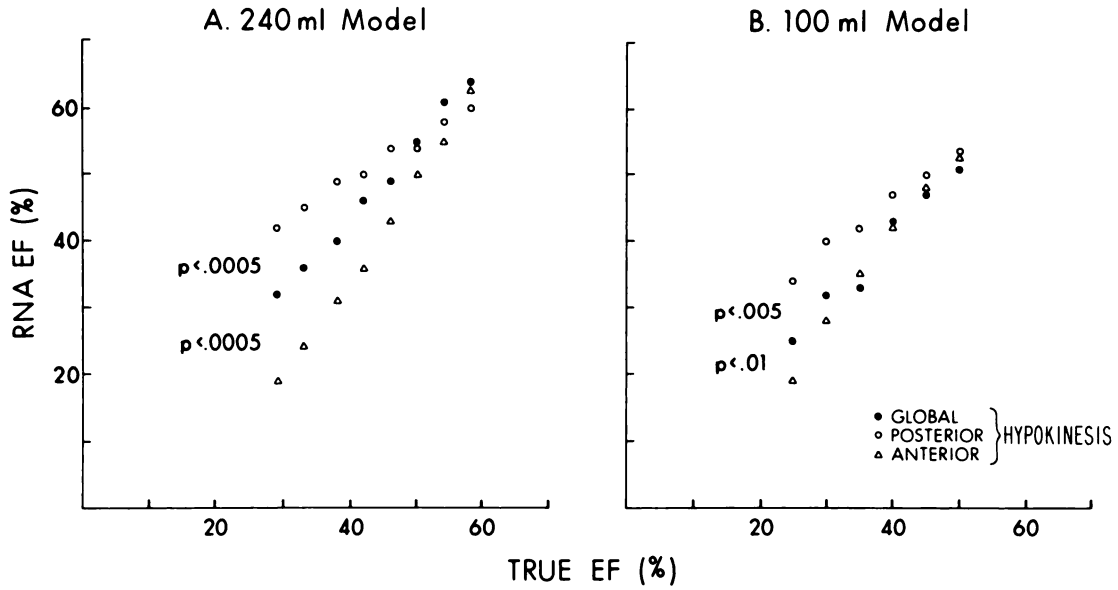

FIG. 2. Relationships between EF and true EF for heart models with end-diastolic volumes of 240 ml (A) and 100 ml (B). Slopes and y intercepts of regression lines for posterior and anterior hypokinesis are significantly different from those for global hypokinesis (p values shown).

$$\nu_{ed} \simeq N_{bld}^{-1} \cdot N_{ed} \cdot e^{\mu z}(1 + R^{-1}), \quad (6)$$

where N_{bld} is the count rate of a 1-cc "blood" sample measured with the gamma camera, N_{ed} is the background-corrected end-diastolic ventricular count rate (cps), z is the ventricular depth, and R is the ventricle-to-body concentration ratio. Using analyses similar to those of Whitehead (*6*), R is estimated from the equation:

$$R = (1 + SF)\left(1 + \frac{S}{B}\right)\frac{2 \sinh\left(\mu_b \frac{D}{2}\right) \exp\left(-\mu_b \frac{D}{2}\right)}{\mu L \exp(-\mu z)} \quad (7)$$

where SF (= 0.4) is the scatter fraction, D is the diameter of the body, L is the length of the ventricle, μ_b (= 0.1 cm^{-1}) is the effective attenuation coefficient for the background (B), and μ is the photopeak attenuation coefficient (= 0.13 cm^{-1}) (*7*). The signal-to-background ratio S/B is equal to the count rate measured within a region of interest containing the ventricle minus the measured background count rate, all divided by the background count rate. The volumes determined by Eq. (6) were used to compute RA volumetric EFs by substitution in Eq. (5).

In the experiments described above, depth and thickness of the heart model in the phantom were measured using the lateral images. The required front of the torso was determined by placing a small line source on the torso surface. The depth and horizontal length of the heart model at end-diastole and at each end-systole were measured. Background-corrected count rates in the heart model were computed using the semiautomatic data-processing program (described above) and were substituted in Eq. (6) to calculate volumes; the volumes were substituted in Eq. (5) to calculate volumetric EFs.

Statistics. Relationships between true EF and EF were determined by linear regression analysis. Slopes and y intercepts of these linear relationships were compared by a two-tailed t-test.

RESULTS

Studies on the heart model. Data from the model simulation of global hypokinesis, posterior-regional hypokinesis, and anterior-regional hypokinesis are presented in Table 1 for heart models with V_{ed} = 240 ml and 100 ml. A range of V_{es} values was studied, resulting in a range of true EF values. For global and posterior- and anterior-regional hypokinesis, the table presents the V_{es} values for the anterior and posterior balloons, the N_{es} values, and the resulting EF measurement. When the true EF was varied from 58 to 29 in the heart model with V_{ed} = 240 ml, by progressively adding equal volumes to each balloon to increase V_{es}, the EF ranged from 64 to 32, as measured using the semiautomatic data-analysis program during global hypokinesis. When the volume of only the posterior or anterior balloon was changed in a fashion to produce a comparable range of total V_{es}, the EF decreased to only 42 during maximum posterior hypokinesis and to 19 during maximum anterior hypokinesis. Thus, regional hypokinesis produced a disproportionate effect on EF measurements; the EF was higher than true EF during posterior hypokinesis, and lower during anterior hypokinesis.

When a comparable procedure was followed using V_{ed} = 100 ml, the true EF was varied from 50 to 25. During

global hypokinesis, the corresponding EF varied from 51 to 25. In contrast, during maximum posterior hypokinesis, the minimum EF was 34 and during maximum anterior hypokinesis, the minimum EF was 19.

Figure 2 plots EF against true EF for the three patterns of hypokinesis studied in the 240-ml (A) and 100-ml (B) phantoms. In both cases the slope of the line is significantly less for posterior hypokinesis than for global hypokinesis, indicating that with progressive posterior hypokinesis, EF increasingly overestimates true EF. Conversely, the slope of the line is greater for anterior hypokinesis than for global hypokinesis, indicating that with progressive anterior hypokinesis, EF increasingly underestimates true EF. The disproportionate effects of anterior hypokinesis, relative to posterior, are greater in the larger volume phantom.

Further model experiments revealed that the effects of regional hypokinesis on EF were not influenced by moving the center of the model (6–10 cm) from the gamma detector. Thus, the disproportionate effects of regional hypokinesis result from variable photon attenuation between the front and back of the LV chamber, and are independent of ventricular depth. Other studies demonstrated no relationship between the level of background activity and the effects of regional hypokinesis on EF.

Attenuation-corrected volumetric ejection fraction. The effects of attenuation on count rates in the heart model and background were examined by applying an attenuation-correction procedure (*4,5*) that permits calculation of absolute volumes from the multigated acquisition count rates.

The heart models with V_{ed} = 240 and 100 ml were studied first with an activity concentration ratio of 10:1 between "ventricle" and "body". As before, absolute volumes were measured at "end diastole" and at several "end-systolic" volumes (V_{es}) that simulated posterior and anterior hypokinesis. Table 2 presents attenuation-corrected computed volumes and EFs for the two V_{ed} values and for a range of V_{es} values in the anterior and posterior balloons. Attenuation-corrected volumetric EFs derived from volumes calculated during regional hypokinesis were generally very close to true EF. For both the 240-ml and the 100-ml V_{ed} heart models, the disparity between EF and true EF was reduced markedly when volumetric EF was substituted for count EF (Fig. 3). These data confirm that attenuation is the predominant factor accounting for the disproportionate effects of regional hypokinesis in the heart model.

DISCUSSION

The study demonstrates that in an LV model, changes in global EF agree well with changes in true EF, but that regional hypokinesis produces disproportionate effects on the EF calculation. Posterior hypokinesis decreased movement of counts farther from the detector and had a relatively smaller effect on EF; the EF was greater than true EF. Conversely, anterior hypokinesis reduced count movement near the detector and had a greater effect on EF; the EF underestimated true EF. The extent of the overestimation or underestimation increased progressively as the true EF decreased, and was greater in larger than in smaller ventricles.

Calculation of EF by measuring absolute end-diastolic and end-systolic volumes resulted in a close correlation with true EF, not only during global hypokinesis but also during both anterior and posterior hypokinesis. This finding (Table 2 and Fig. 3) confirms that count attenuation as a function of distance is a major factor contributing to the disproportionate effects of regional hypokinesis on EF measurements.

The mathematical formulation used in the present study to measure attenuation-corrected LV volumes from multigated equilibrium count data differs from the method of Links et al. (*3*) primarily in the use of a different, empirically derived linear attenuation coefficient (μ = 0.13 cm^{-1}) (*7*) and in the calculation of the ventricle-to-body concentration ratio, R, (*4,5*) that enters the volume calculation in Eq. (6). The use of R results in volume measurements that are essentially independent of radioactivity concentrations within the ventricle and background. The present method and that of Links et al. (*3*) differ from previous approaches (*8,9*) that assumed constant attenuation and ventricle depth from subject to subject, and that estimate volumes by applying previously derived regression equations to multigated equilibrium count data. A recently described technique (*10*) determines volumes by using an esophageal point source to correct measured count rates for tissue attenuation.

Clinical application. To the extent that the human ventricle conforms to the heart model during regional hypokinesis, it is expected that similar effects on EF may result. The heart model, however, probably represents a worst-case example: i.e., the entire hypokinetic region is either directly in front of or directly behind the central point of ventricular activity. In a human heart the long axis of the ventricle is not parallel to the detector but at an angle, so that anterior or inferior hypokinesis does not occur in a strict anterior or posterior region. In the heart model the disproportionate effects were greater when the true EF was lowest and when the LV model was larger. In the clinical situation, when the EF is low and the LV volume is large, LV hypokinesis is commonly generalized, and thus is similar to the global hypokinesis model that was accurately assessed by the technique. Since regional LV asynergy is highly variable in coronary artery disease, it is expected that certain ventricles with regional asynergy will simulate the conditions of the heart model, and that in these patients the measured EF will not accurately reflect the true EF. The present

TABLE 2. ATTENUATION-CORRECTED VOLUMETRIC EJECTION FRACTIONS

V_{ed}* (ml)	ν_{ed}† (ml)	V_{es}‡ (ml)	true EF§	Posterior hypokinesis V_{es} (ml) Ant¶	Post**	count EF	ν_{es}††‡ (ml)	vol EF‡	Anterior hypokinesis V_{es} (ml) Ant	Post	count EF	ν_{es} (ml)	vol EF
240	227												
		100	58	50	50	60	88	61	50	50	63	84	63
		110	54	50	60	58	99	56	60	50	55	101	55
		130	46	50	80	54	113	50	80	50	43	122	46
		150	38	50	100	49	134	41	100	50	31	139	38
		170	29	50	120	42	154	32	120	50	19	159	30
100	100												
		50	50	25	25	53	49	51	25	25	53	49	51
		55	45	25	30	50	53	47	30	25	48	53	47
		65	35	25	40	42	62	38	40	25	35	65	35
		75	25	25	50	34	73	27	50	25	19	78	22

* V_{ed} = end-diastolic volume.

† ν_{ed} = computed radionuclide end-diastolic volume.

‡ V_{es} = end-systolic volume.

§ EF = ejection fraction.

¶ Ant = anterior.

** Post = posterior.

†† ν_{es} = computed radionuclide end-systolic volume.

†† ^{vol}EF = EF calculated from volume changes using attenuation correction.

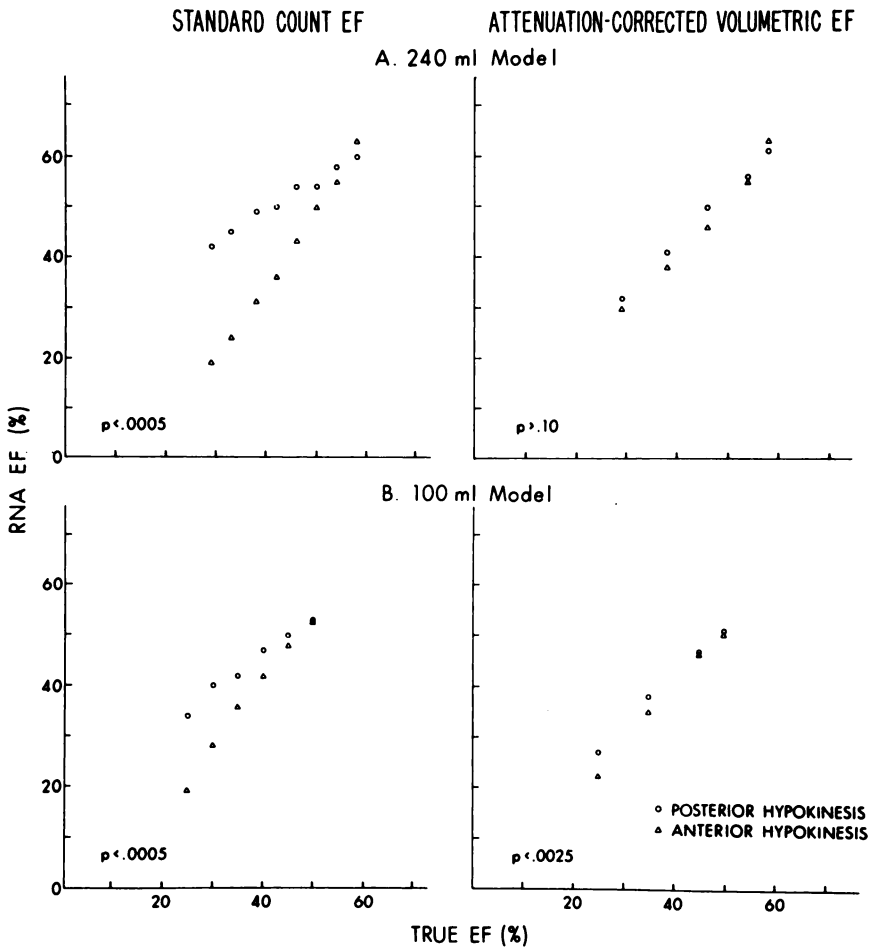

FIG. 3. Comparison of standard count EF (left panels) with attenuation-corrected volumetric EF (right panels) when each is plotted against true EF. For 240-ml heart model (A), use of volumetric EF eliminated significant difference between slopes and intercepts of regression lines derived during posterior and anterior hypokinesis (p values shown). For 100-ml model (B), disproportionate effects were reduced.

findings indicate that calculation of true volumes may correct for the disproportionate effects of regional hypokinesis on EF measurements.

We have recently performed RA in conscious dogs (*11*) subjected to acute occlusion of the left anterior descending coronary artery (anterior ischemia) or left circumflex coronary artery (inferior ischemia). Calculation of EF from attenuation-corrected ventricular volumes as described in the present study resulted in consistently higher EF in the dogs with anterior ischemia (and hypokinesis); attenuation correction did not change EF in the dogs with inferior ischemia (and hypokinesis).

We are currently examining the magnitude of possible error in standard EF in patients with regional hypokinesis, as well as the reliability of the attenuation-correction procedure. We have studied four patients with anteroapical akinesis or dyskinesis after myocardial infarction, whose EF increased an average of 9 units following attenuation correction (24 increased to 33, 29 to 37, 33 to 41, and 39 to 51). A potentially important limitation of this method when applied clinically is error in estimating ventricular depth. Studies are in progress to determine observer variability in defining depth and the magnitude of error thereby introduced into ventricular volume and EF calculations.

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