Myocardial efficiency during calcium sensitization with levosimendan: A noninvasive study with positron emission tomography and echocardiography in healthy volunteers

Dynamic positron emission tomography (PET) with [^{11}C]acetate allows noninvasive assessment of myocardial oxygen consumption. In combination with echocardiography, PET enables determination of cardiac efficiency (defined as useful cardiac work per unit of oxygen consumption). We used this approach to compare the effects of levosimendan, a Ca^{2+}–dependent calcium sensitizer, with dobutamine and sodium nitroprusside in healthy male volunteers. The effects of levosimendan on k_{mono}, an index of oxygen consumption, and cardiac efficiency were neutral, whereas the hemodynamic profile was consistent with balanced inotropism and vasodilatation. Dobutamine enhanced cardiac efficiency at the expense of increased oxygen requirement, but the effects of nitroprusside on k_{mono} and cardiac efficiency were neutral. This study shows the feasibility of PET in phase 1 pharmacodynamic studies and suggests potential energetical advantages of calcium sensitization with levosimendan. (Clin Pharmacol Ther 1997;61:596-607.)

Heikki Ukkonen, MD, Markku Saraste, MD, Juha Akkila, MSc, M. Juhani Knuuti, MD, Pertti Lehikoinen, PhD, Kjell Någren, PhD, Lasse Lehtonen, MD, and Liisa-Maria Voipio-Pulkki, MD
Turku and Espoo, Finland

The overloaded failing heart is characterized by an imbalance between energy production and utilization. The overload itself increases energy expenditure by increasing wall stress in the dilated heart. The energy deficit of the myocardium may further aggravate both systolic and diastolic dysfunction.[1] Cardiotonic drugs modify cardiac energetics by affecting vasodilatation, inotropism, and heart rate (HR). The purely inotropic effect is associated with an increase in oxygen consumption, which may be balanced by concomitant vasodilatory properties and a decrease in heart rate. In the overloaded heart, such balanced inodilatation results in improved efficiency or ratio of oxygen consumption to useful forward work.[2,3]

In the search for the optimal inotropic agent, several different therapeutic approaches have been considered.[4] Despite beneficial short-term effects, agents that increase intracellular cyclic adenosine monophosphate (cAMP), such as β-agonists, have increased mortality.[5] In the failing heart these agents cause a rise in intracellular calcium, which in turn increases myocardial oxygen consumption.[6] Even though mechanical performance of the heart is improved, the increase in energy demand can compromise the benefits of the drug. A novel inotropic agent, levosimendan, increases the sensitivity of contractile proteins to calcium, causing an increase in the contractile response to a given level of intracellular calcium.[7-9] Compared with agents that pri-

From the Department of Medicine and Department of Nuclear Medicine, Turku University Hospital, the Radiopharmaceutical Chemistry Laboratory, Turku PET Center, and the Department of Clinical Physiology, Turku University Hospital, Turku; and the Orion Corporation, Orion Research, Espoo.
Supported by the Orion Corporation, Espoo, Finland.
Received for publication June 26, 1996; accepted Nov. 5, 1996.
Reprint requests: Heikki Ukkonen, MD, Department of Medicine, Turku University Hospital, Kiinamyllynkatu 4-8, 20520 Turku, Finland.

0009-9236/97/$5.00 + 0 **13/1/79069**

marily act by increasing cAMP levels, calcium sensitizers reduce the amount of calcium cycled with each beat and result in enhanced efficiency of the excitation-contraction coupling.[10-12] Levosimendan also acts as a peripheral vasodilatator,[13,14] and the effects on left ventricular loading conditions may augment the favorable effects of the drug on myocardial energetics.

To study the net energetical effects of levosimendan in vivo, we compared this drug with sodium nitroprusside, a vasodilatory agent, and with dobutamine, an inotropic sympathomimetic agent. In this noninvasive phase 1 study, we used [^{11}C]acetate and dynamic positron emission tomography (PET) imaging in combination with echocardiography. Myocardial metabolic rate of oxygen was indexed with PET by analysis of the myocardial elimination of [^{11}C]acetate.[15,16] Combined with echocardiographic assessment of cardiac function, PET provides a unique noninvasive approach to study myocardial energetics in vivo.[17,18]

METHODS

Subjects. Sixteen healthy male volunteers (mean ± SEM age, 25 ± 1 years; weight, 77 ± 2 kg; body mass index, 23 ± 1 kg/m^2) were included in this study. All subjects had normal medical histories, physical examinations, 12-lead electrocardiograms, and standard clinical laboratory tests. The subjects refrained from all medication for 7 days and alcohol for 4 days before the study. Written informed consent was obtained from each subject. The study protocol was approved by the Joint Commission On Ethics of the Turku University And the Turku University Central Hospital.

Study design. This was an open and nonrandomized, saline placebo–controlled study from nonactive to active treatment in the three separate drug-treatment groups. There were five subjects in the dobutamine group, five in the nitroprusside group, and six in the levosimendan group. Two similar studies were performed in each subject within 2 days: first with saline solution and then with active treatment.

Subjects were admitted to the PET unit at 9 am. Electrocardiographic recording was started and two intravenous cannulas were inserted in the antecubital veins of each subject for drug infusion and blood sampling. Echocardiography was then performed. Drug infusion was started 10 minutes before the intravenous injection of [^{11}C]acetate and dynamic PET. Echocardiography was repeated immediately after PET imaging, and the study treatment was stopped only after this echocardiography. The subjects remained in supine position during all measurements. Blood pressure and heart rate were recorded with an automated sphygmomanometer at 10-minute intervals throughout the study.

Treatments. Dobutamine (Dobuject, Leiras Pharmaceuticals, Turku, Finland) was given at a constant infusion rate of 5.0 μg/kg/min. Sodium nitroprusside (Nipride, Hoffman–La Roche, Basel, Switzerland) was given at a constant rate of 1.0 μg/kg/min and levosimendan (Orion Corporation, Espoo, Finland) as a starting bolus dose of 18 μg/kg in 10 minutes, followed by a constant infusion of 0.3 μg/kg/min. The duration of all drug infusions was 2 hours. The dobutamine dose was considered to be the smallest well-documented dose in diagnostic use.[19] According to previous dose-finding studies, the levosimendan dose was tailored to be the lowest to significantly increase cardiac output.[13] On the basis of our clinical experience and pilot dose-finding tests in two healthy volunteers, the nitroprusside dose was estimated to cause comparable vasodilation with the two other treatments.

Hemodynamics. Mean heart rate during saline and drug infusion was used in calculations. It was obtained from single observations measured at 10-minute intervals during the 2 hours of PET imaging and echocardiography. Mean systolic (SBP) and diastolic (DBP) blood pressures were calculated as the arithmetic means of blood pressure values obtained at 10-minute intervals during the imaging studies. Mean arterial pressure (MAP) was determined as follows: DBP + (SBP − DBP)/3. Systemic vascular resistance (SVR) was calculated as the ratio of mean arterial pressure and cardiac output (CO) obtained from echocardiography: SVR = MAP/CO. End-systolic blood pressure was derived from the carotid pulse tracing and simultaneous blood pressure measurements.

Biochemical analyses. Blood samples for biochemical analyses were drawn during both PET studies. Plasma glucose was analyzed using the glucose-dehydrogenase method (Granutest 250, Merck, Darmstadt, Germany). Serum free fatty acids were determined with an enzymatic colorimetric method (Nefa C test, Wako Chemicals GmbH, Neuss, Germany), and plasma lactate was determined with an enzymatic method (ACA IV discrete clinical analyzer, DuPont Company, Wilmington, Del.). Plasma epinephrine and norepinephrine were determined by means of HPLC with electrochemical detection.

Echocardiography. Echocardiography was performed with an Aloka SSD-870 (Aloka Co, Ltd, Tokyo, Japan) device and standardized ultrasonographic techniques.[20,21] Recordings were done under controlled conditions by means of two-dimensional monitoring, with the subject in the left oblique position. M-mode tracings were obtained at the speed of 100 mm/sec and adjusted to the oscillations of the simultaneously acquired electrocardiography, phonography, and carotid pulse tracing. The end-diastolic dimensions were measured at the beginning of the QRS configuration, and the end-systolic dimension was measured at the beginning of the S_2 sound. The data was digitized and analyzed with a Dextra 300 (Dextra Medical Inc., Lakewood, Calif.) digital imaging workstation. The mean of five consecutive cardiac cycles at end-expiration was used for analysis of the results.

Left ventricular (LV) end-diastolic (ed) and end-systolic (es) dimensions, posterior wall thickness at end-diastole and end-systole, and end-diastolic septal thickness were measured. M-mode recordings were used to determine left ventricular end-diastolic volume (EDV), stroke volume (SV), cardiac output (CO), and ejection fraction (EF).[22] End-diastolic volume index (EDVI) and stroke volume index (SVI) were calculated by dividing the corresponding volumes by body surface area. Left ventricular mass (LVM) was calculated according to following formula[23]:

$$LVM = [(D_{ed} + H_{ivd} + H_{pwd})^3 - D_{ed}^3] \times 1.05$$

in which D_{ed} is the end-diastolic minor-axis diameter of the left ventricle, H_{ivd} is the thickness of the interventricular septum, and H_{pwd} the thickness of the posterior wall at end-diastole. To obtain circumferential end-systolic wall stress (WS_{ci}), the following formula was used[24]:

$$WS_{ci} = 1.33 \times P \times (D_{es}/2H_{pws}) \times [1 - D_{es}^3/(2L^2 \times [D_{es} + h])]$$

in which 1.33 converts pressure from millimeters of mercury to grams per square centimeter, P is the end-systolic pressure, D_{es} is the end-systolic minor-axis diameter, L is the systolic long-axis dimension, and H_{pws} is the end-systolic wall thickness of the left ventricle. Mean velocity of circumferential fiber shortening corrected for heart rate (Vcf_c)[24] was calculated as follows:

$$Vcf_c = [(D_{ed} - D_{es})/(D_{ed} \times LVET)] \times \sqrt{RR}$$

in which LVET is LV ejection time and RR is the RR interval of the preceding cardiac cycle.

Positron emission tomography (PET). The subjects were positioned supine in an eight-ring 15-slice ECAT 931/08 tomograph (CTI, Knoxville, Tenn.). The device has a measured axial resolution of 6.7 mm and 6.5 mm in plane. To correct for tissue photon attenuation, 20-minute transmission imaging with a removable source containing ^{68}Ge was performed before the emission scanning. Twenty millicuries of [^{11}C]acetate (prepared from [^{11}C]carbon dioxide and methyl magnesium bromide[25] by a computed controlled system, as previously reported for our remote controlled system[26]) was administered as an intravenous bolus. A 49-minute dynamic emission scan was initiated simultaneously to obtain 28 dynamic frames (10 at 10 seconds, 1 at 60 seconds, 5 at 100 seconds, 5 at 120 seconds, and 7 at 240 seconds). All data were corrected for dead time, decay, and photon attenuation and were reconstructed in a 256 × 256 matrix. The final in-plane resolution of the reconstructed and Hann-filtered images was 8 mm (full width half maximum).

The reconstructed dynamic PET images were analyzed by first applying 35 to 40 regions of interest on the 15 transaxial left ventricular slices. The regional oxygen consumption index K_{mono} was derived from monoexponential fitting of the acetate washout curves after visual determination of the linear portion of the semilogarithmic plot.[15] The regions were then grouped into eight segments, as previously described[27]: anterobasilar, anterior, anteroseptal, lateral, inferoseptal, apical, inferior, and posterobasilar. Mean K_{mono} values were calculated in all segments. Mean global K_{mono} was calculated as the arithmetic mean of the segmental values. Alignment of the transaxial slices and the two sets of regions in the two studies was ascertained by two experienced investigators, and occasional discrepancies were solved by mutual consensus. Monoexponential fitting of the acetate washout curve was performed by the first author in all studies.

Myocardial efficiency. The assessment of myocardial efficiency (the relation of myocardial oxygen consumption to the useful (forward) work) was performed as follows:

$$Eficiency = (SBP \times SVI \times HR)/k_{mono} \quad (1)$$

and alternatively:

$$Eficiency = (SBP \times SV \times HR)/(k_{mono} \times LVM) \quad (2)$$

Table I. The summary of hemodynamic results

Measure	*Therapy group*		
	Dobutamine (n = 5)	*Levosimendan (n = 6)*	*Nitroprusside (n = 5)*
HR (beats/min)			
Baseline	60 ± 1.0	55 ± 3.1	53 ± 3.0
Treatment	69 ± 4.4*	57 ± 2.7*	61 ± 3.2*
SBP (mm Hg)			
Baseline	110 ± 6.4	113 ± 3.0	107 ± 2.2
Treatment	142 ± 3.7*	110 ± 3.0	99 ± 2.8*
DBP (mm Hg)			
Baseline	62 ± 4.9	62 ± 1.6	55 ± 2.7
Treatment	68 ± 3.6*	56 ± 2.6*	49 ± 2.5*
SV (ml)			
Baseline	115 ± 9.8	109 ± 6.6	118 ± 10.2
Treatment	169 ± 13.1*	121 ± 7.0*	121 ± 8.2
CO (L/min)			
Baseline	6.8 ± 0.57	5.8 ± 0.32	6.2 ± 0.48
Treatment	11.5 ± 0.59*	6.9 ± 0.40*	7.3 ± 0.46*
EF (%)			
Baseline	70 ± 2.0	70 ± 2.6	68 ± 1.8
Treatment	88 ± 2.7*	77 ± 2.8*	74 ± 3.7
Vcf_c (circ/sec)			
Baseline	1.05 ± 0.044	1.11 ± 0.084	1.07 ± 0.063
Treatment	1.79 ± 0.144*	1.33 ± 0.092*	1.19 ± 0.116
WS_{ci} (gm/cm^2)			
Baseline	138 ± 14.9	128 ± 2.2	121 ± 5.2
Treatment	104 ± 13.0*	106 ± 7.0*	89 ± 7.9*
EDVI (ml/m^2)			
Baseline	81 ± 7	82 ± 5	89 ± 8
Treatment	95 ± 8*	84 ± 8	84 ± 6
SVR (mm Hg × min/L)			
Baseline	11.8 ± 1.39	13.6 ± 0.77	11.9 ± 1.07
Treatment	8.4 ± 0.72*	11.0 ± 0.96*	9.0 ± 0.63*

All values are mean ± SEM.
HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; SV, stroke volume; CO, cardiac output; EF, ejection fraction; Vcf_c, velocity of circumferential fiber shortening corrected for heart rate; WS_{ci}, circumferential end-diastolic wall stress; EDVI, end-diastolic volume index; SVR, systemic vascular resistance.
*$p < 0.05$ versus baseline, one-sample t test.

as the efficiency was calculated per gram of left ventricular muscle. Equation 1 is essentially equal to the concept of work-metabolic index presented by Beanlands et al.[17] Efficiency was also calculated per beat for both equations 1 and 2:

$$\text{Eficiency} = (\text{SBP} \times \text{SVI})/k_{mono} \quad (3)$$

$$\text{Eficiency} = (\text{SBP} \times \text{SV})/(k_{mono} \times \text{LVM}) \quad (4)$$

Statistical analysis

Results are expressed as mean values ± SEM. The changes from baseline in every treatment group were evaluated statistically by the one-sample t test. The conventional level of 5% was considered as the level of statistical significance. The responses of myocardial oxygen consumption and efficiency during the three treatments were analyzed separately with an analysis of covariance model (ANCOVA) that included the respective baseline measurements as a covariate. The Bonferroni correction was applied in multiple comparisons. The coefficient of variation of echocardiographic measurements was calculated. Statistical calculations were performed with the SAS statistical package.

RESULTS

Hemodynamic and biochemical data. Table I shows the summary of the hemodynamic results. A 15% increase in heart rate was observed both with dobutamine (60 to 69 min^{-1}) and nitroprusside (53 to 61 min^{-1}). Heart rate increased slightly but significantly (4%) with levosimendan (55 to 57 min^{-1}).

Table II. Biochemical data

Measure	*Therapy group*		
	Dobutamine (n = 5)	*Levosimendan (n = 6)*	*Nitroprusside (n = 5)*
P-Glucose (mmol/L)			
Baseline	5.8 ± 0.3†	5.2 ± 0.1	5.7 ± 0.3‡
Treatment	5.2 ± 0.1*	5.4 ± 0.1§	5.5 ± 0.3‡
S-Free fatty acids (mmol/L)			
Baseline	0.23 ± 0.07	0.26 ± 0.07	0.25 ± 0.09
Treatment	0.87 ± 0.15*	0.30 ± 0.07	0.44 ± 0.10
P-Lactate (mmol/L)			
Baseline	1.4 ± 0.2	1.2 ± 0.1	1.3 ± 0.2
Treatment	1.1 ± 0.1	1.2 ± 0.1	1.2 ± 0.2
P-Epinephrine (nmol/L)			
Baseline	0.12 ± 0.03	0.14 ± 0.03§	0.12 ± 0.03
Treatment	0.08 ± 0.04‡	0.12 ± 0.02	0.19 ± 0.04*
P-Norepinephrine (nmol/L)			
Baseline	0.87 ± 0.21	0.75 ± 0.06§	0.60 ± 0.02
Treatment	1.12 ± 0.18‡	0.93 ± 0.06	1.33 ± 0.19*

Data are mean values ± SEM.
*$p < 0.05$ versus baseline.
†$n = 4$; ‡$n = 3$; §$n = 5$.

Systolic blood pressure increased by 29% with dobutamine (110 to 142 mm Hg), whereas it was unchanged during levosimendan. Nitroprusside was associated with a 7% decrease in systolic blood pressure. In addition, diastolic blood pressure increased slightly during dobutamine administration, whereas both levosimendan and nitroprusside were associated with a significant decrease in diastolic blood pressure (Table I). The most prominent increase in left ventricular stroke volume (47%) was seen with dobutamine. Levosimendan was also associated with a 11% increase in stroke volume (109 to 121 ml), whereas the net effect of nitroprusside on stroke volume was neutral. The increase in cardiac output was 69% with dobutamine, 19% with levosimendan, and 18% with nitroprusside. There was also a significant increase in left ventricular ejection fraction with both dobutamine and levosimendan, but nitroprusside had no effect on ejection fraction.

Dobutamine and levosimendan increased left ventricular contractility significantly as Vcf_c increased by 70% (1.05 to 1.79 circ/sec) with dobutamine and by 20% (1.11 to 1.33 circ/sec) with levosimendan. Circumferential end-systolic wall stress decreased by 25% with dobutamine, by 17% with levosimendan, and by 26% with nitroprusside. EDVI, an estimate of preload, increased by 17% in the dobutamine group but was unchanged in the levosimendan group. EDVI tended to decrease (−6%) in the nitroprusside group. Systemic vascular resistance decreased by design in all study groups. The decrease in SVR associated with dobutamine was 29%, 19% with levosimendan, and 24% with nitroprusside.

Reproducibility of the baseline echocardiographic assessments was tested by comparing baseline 1 (saline solution) and 2 (active drug) measurements. The coefficient of variation was 2.8% for D_{ed}, 6.5% for LVM, 4.2% for ejection fraction, and 9.5% for cardiac output.

Table II summarizes the biochemical data. The serum level of free fatty acids was within the normal range at baseline in all groups. However, a statistically significant rise was observed with dobutamine, and the same tendency was observed with nitroprusside ($p = 0.08$). Free fatty acid levels did not change during administration of levosimendan. Levosimendan had no effect either on plasma norepinephrine or plasma epinephrine. Nitroprusside caused a significant rise in both plasma norepinephrine and plasma epinephrine.

Myocardial oxygen consumption and its correlations with hemodynamic parameters. Image quality was excellent in all PET studies. Fig. 1 shows a representative midventricular transaxial slice of the [^{11}C]acetate study and the corresponding myocardial time-activity curve. At baseline, oxygen consumption was homogenous throughout the myocar-

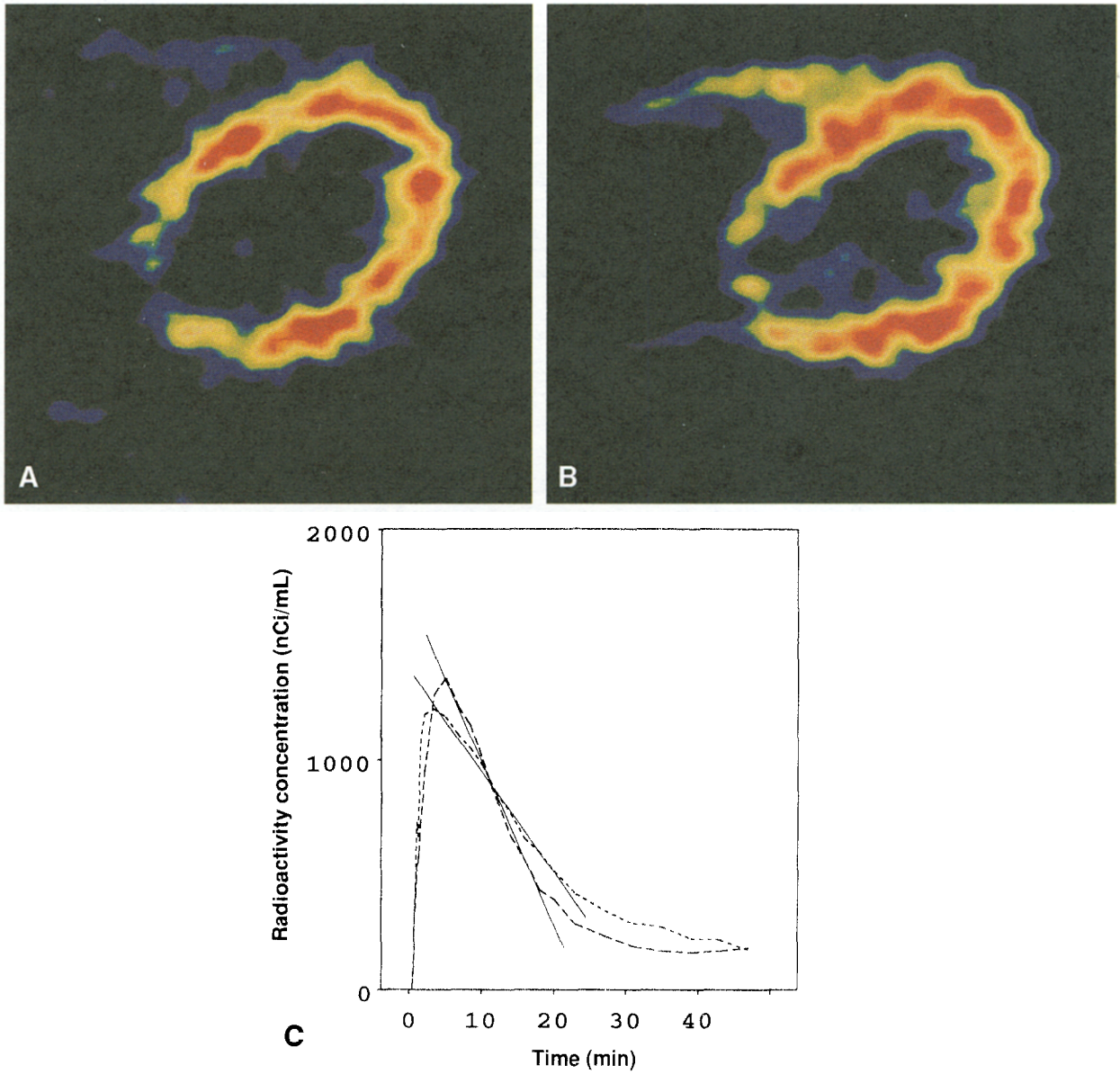

Fig. 1. Representative transaxial images showing maximal uptake of the tracer 7 minutes after [^{11}C]acetate injection at baseline **(A)** and during dobutamine administration **(B)**. Dobutamine was associated with higher myocardial peak concentration and faster washout of the tracer from the myocardium. The myocardial oxygen consumption index k_{mono} was derived by fitting the linear portion of acetate washout curve **(C)**. Dobutamine caused a marked increase in myocardial oxygen consumption becasue the k_{mono} was 0.060 L/min at baseline *(dotted line)* and 0.100 L/min during administration of dobutamine *(dashed line)*.

dium (Fig. 2, *A*). Notably, none of the treatments changed the segmental distribution of k_{mono} during stimulation (Fig. 2, *B*). During dobutamine stimulation, k_{mono} increased from 0.064 ± 0.008 to 0.100 ± 0.01 (58%; $p < 0.05$; Fig. 3). A slight increase from 0.056 ± 0.008 to 0.063 ± 0.010 (12%; $p = 0.06$) was also observed during levosimendan infusion. Oxygen consumption was unchanged in the nitroprusside group (0.058 ± 0.008 to 0.059 ± 0.005). Because the treatment effects were compared with ANCOVA (baseline k_{mono} as a covariate) the response to dobutamine differed significantly from other treat-

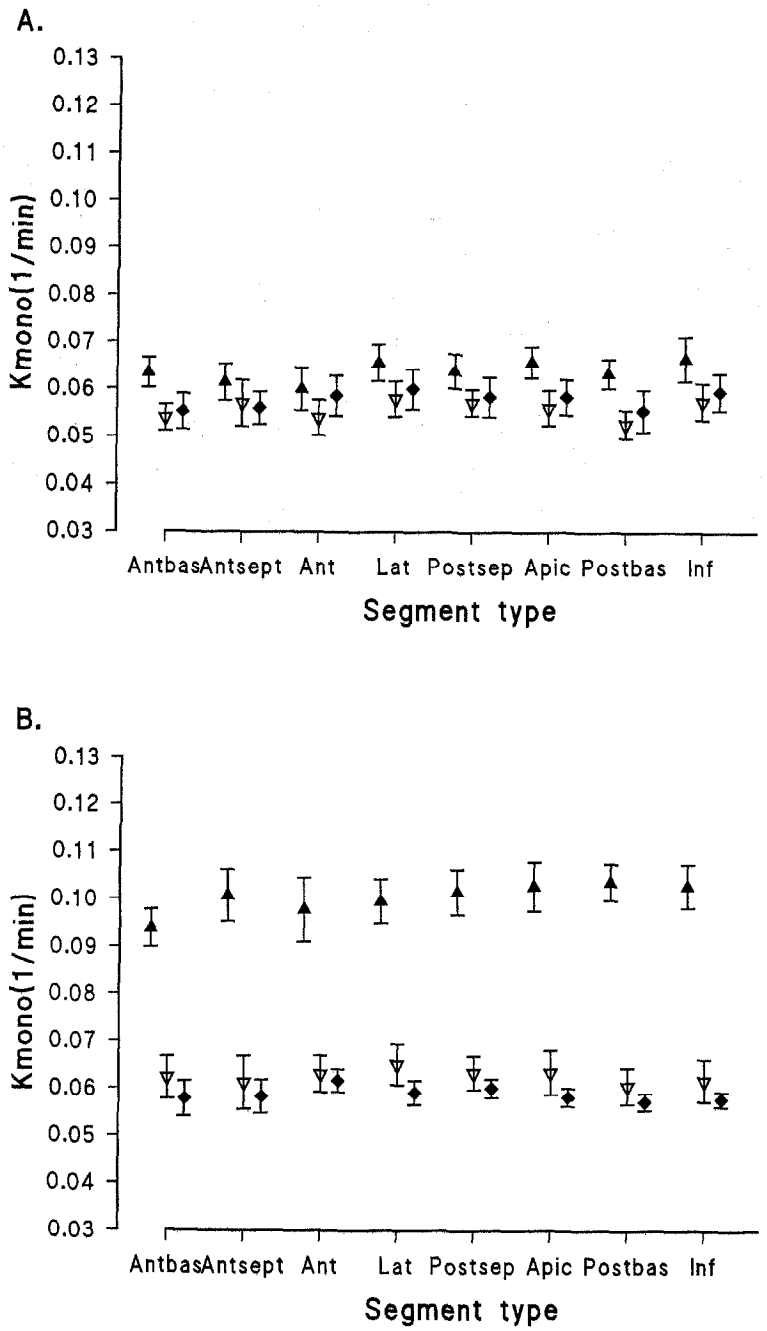

Fig. 2. Segmental distribution of [^{11}C]acetate elimination constant k_{mono} (mean ± SEM) at baseline (**A**) and during treatments (**B**) in each group (*solid triangles,* dobutamine; *open inverted triangles,* levosimendan; *diamonds,* nitroprusside). Myocardial oxygen consumption was homogenous throughout the left ventricle at rest and was comparable between all treatment groups. Although myocardial oxygen consumption was significantly higher during dobutamine, the distribution of oxidative metabolism in the left ventricle remained homogenous during all treatments in these healthy volunteers. Antbas, anterobasilar; Antsept, anteroseptal; Ant, anterior; Lat, lateral; Postsep, inferoseptal; Apic, apical; Postbas, posterobasilar; Inf, inferior.

ments ($p < 0.0001$). K_{mono} calculated per beat increased by 37% during dobutamine administration (1.07×10^{-3} to 1.46×10^{-3}; $p < 0.001$), was unchanged during levosimendan (1.03×10^{-3} to 1.10×10^{-3}), and decreased by 10% during nitroprusside (1.09×10^{-3} to 0.97×10^{-3}; $p < 0.05$).

When both baseline and stimulation data were pooled together, k_{mono} correlated well with the two measures of external work used in this study. Fig. 4, *A*, shows the relationship of k_{mono} with the rate-pressure product ($r = 0.94$; $p < 0.001$) and Fig. 4, *B*, shows the relationship of k_{mono} with the echocardiographic estimate of external work (SV × HR × SBP; $r = 0.87$; $p < 0.001$).

Myocardial efficiency. Myocardial efficiency was significantly improved with dobutamine both according to equation 1 ($5846 \pm 594 \times 10^3$ to $8090 \pm 782 \times 10^3$ mm Hg · ml · m^{-2}; +38%; $p < 0.05$; Fig. 5, *A*) and equation 2 (61,586 ± 2793 to 79,380 ± 3178 mm Hg · ml · g^{-1}; +29%; $p < 0.05$). This improvement was mainly the result of the 47% increase in stroke volume, but the 29% increase in systolic blood pressure and the 15% rise in heart rate contributed. Neither levosimendan nor nitroprusside had any impact on efficiency. The respective changes in efficiency observed with levosimendan were +5% ($6083 \pm 334 \times 10^3$ to 6406×10^3; p = NS) and +3% (62,197 ± 4779 to 64,347 ± 2160; p = NS) according to the two equations. Nitroprusside was associated with an improvement of +7% ($6027 \pm 683 \times 10^3$ to $6457 \pm 829 \times 10^3$) and +5% (58,436 ± 2514 to 61,281 ± 3708; p = NS), respectively. When the treatment effects (equations 1 and 2) were compared with use of ANCOVA (baseline efficiency as a covariate), the effect of dobutamine differed from the other two treatments ($p = 0.019$ and $p = 0.0033$, respectively).

The same pattern was seen as efficiency was calculated per beat (equations 3 and 4; Fig. 5, *B*): dobutamine, +24% (98,370 ± 10,486 to 121,371 ± 18,049 mm Hg · ml · m^{-2} · min^{-1}; $p < 0.05$) and +13% (1033 ± 42 to 1170 ± 87 mm Hg · ml · gm^{-1} · min^{-1}; $p = 0.053$); levosimendan, −1% (115,274 ± 10,414 to 113,700 ± 9815; p = NS) and −3% (1167 ± 97 to 1131 ± 36; p = NS); and nitroprusside, −9% (117,378 ± 19,793 to 107,395 ± 16,078; p = NS) and −9% (1124 ± 108 to 1022 ± 100; p = NS), respectively. However, the difference between dobutamine and the other two treatments did not reach statistical significance with use of equations 3 and 4 and ANCOVA ($p = 0.098$ and $p = 0.14$, respectively).

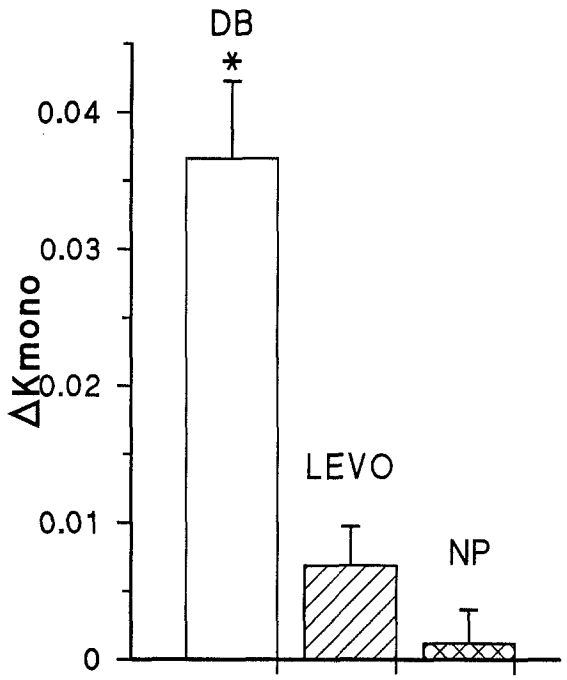

Fig. 3. Changes (mean ± SEM) in myocardial oxygen consumption during drug infusions. DB, Dobutamine; LEVO, levosimendan; NP, nitroprusside.

DISCUSSION

This study shows the usefulness of PET in the noninvasive assessment of myocardial efficiency. The effects of levosimendan, a Ca^{2+}-dependent calcium sensitizer with additional phosphodiesterase III–inhibiting properties, on myocardial oxygen consumption were characterized for the first time in humans. Consistent with previous reports,[13,14] levosimendan increased cardiac output by 19%, primarily by increasing stroke volume. Myocardial oxygen requirement increased to a lesser degree (12%, difference not significant). The net effect of levosimendan on cardiac efficiency, calculated either per time unit or per cardiac cycle, was neutral. The significance of this observation must be viewed against the fact that the normal heart probably operates very close to maximal efficiency at rest.[28] From the energetic point of view, any pharmacologic attempt to increase cardiac output in healthy volunteers may disturb left ventricular filling, which masks the potential benefits of the drug. The fact that cardiac energetics remained unchanged during levosimendan infusion is consistent with balanced inodilatation and holds promise for energetical advantages in the overloaded failing heart.

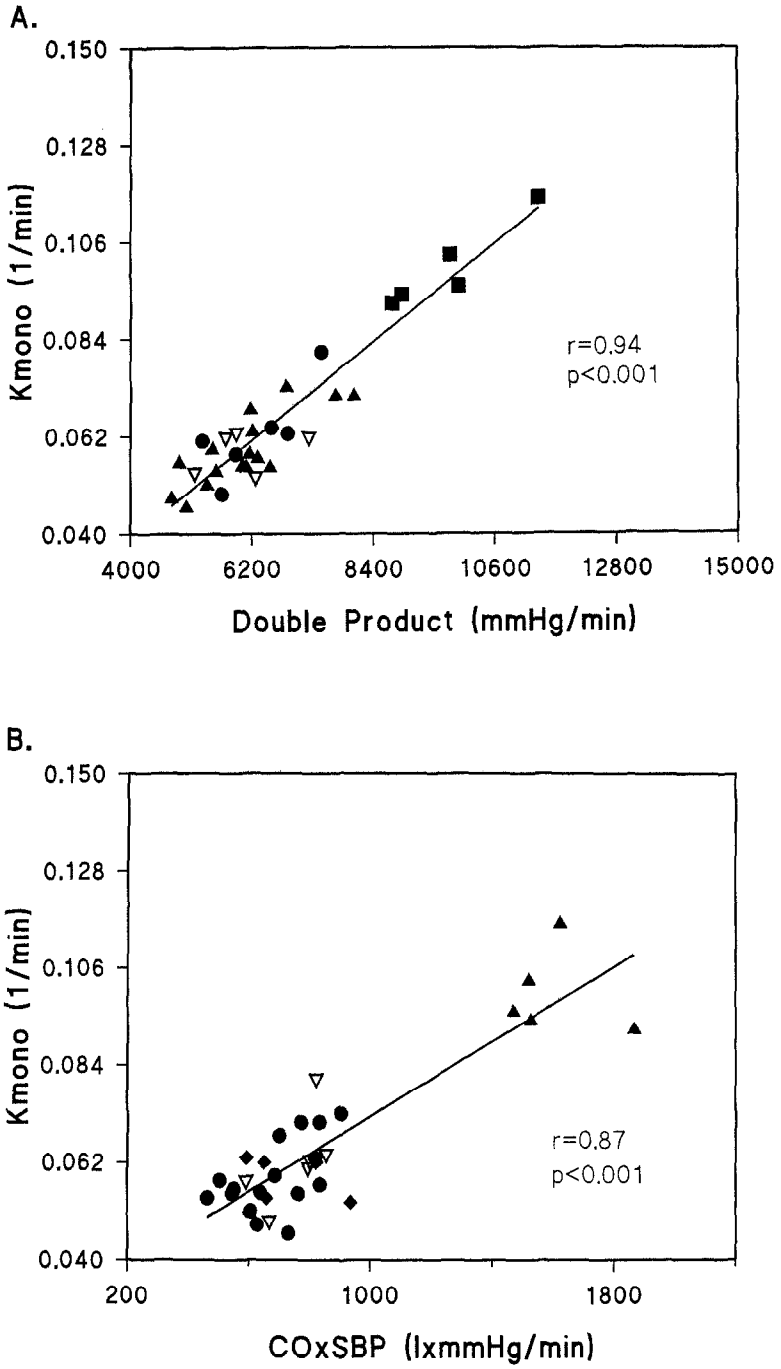

Fig. 4. Correlation of myocardial oxidative metabolism (k_{mono}) with rate-pressure product (**A**) and echocardiographic estimate of cardiac work (cardiac output [CO] × systolic blood pressure [SBP]; **B**) at rest and during study treatments. *Circles,* baseline; *solid triangles,* dobutamine; *open inverted triangles,* levosimendan, *diamonds,* nitroprusside).

We chose dobutamine and nitroprusside as comparative treatments because these model drugs of inotropism and vasodilation are commonly used to modulate cardiac function in severe heart failure. Our aim also was to decrease systemic vascular resistance comparably by the three treatments. As expected, other hemodynamic effects differed greatly. During dobutamine infusion, increased car-

diac output was associated with significantly higher heart rate, blood pressure, end-systolic volume, and contractility. Consequently, a 58% increase in oxygen demand was driven by increased double product or external work (Fig. 4) Peripheral vasodilatation (reduced afterload) and possibly other factors, such as optimal ventriculovascular coupling, balanced this effect, and a remarkably favorable net effect on cardiac efficiency was observed. Dobutamine infusion might have simulated physical exercise in the young male subjects with compliant systemic blood vessels. However, dobutamine also increased heart rate significantly. When efficiency was calculated per beat, the results were less impressive (Fig. 5, *B*).

As expected, nitroprusside acted purely as a vasodilating agent. The hemodynamic profile during nitroprusside infusion (Table I) suggested that relative hypovolemia and consequently reduced preload might have occurred. The somewhat lower end-systolic wall stress during treatment with nitroprusside than during the other two treatments probably resulted in reduced oxygen consumption independently of measurable cardiac work. Levosimendan behaved more like a true inodilatory drug (Table I), but the differences in oxygen consumption and efficiency between nitroprusside and levosimendan did not reach statistical significance. Calculation per beat tended to decrease efficiency during administration of nitroprusside, which we ascribe to the reduced preload and rise in heart rate. The net effect of levosimendan on efficiency remained practically unaltered after correction for heart rate.

Levosimendan had a neutral effect on energy-providing fuels because the serum levels of free fatty acids, lactate, and glucose were unchanged during drug infusion. In contrast, dobutamine infusion was associated with more than 200% increase in mean free fatty acids levels. Because the heart preferably uses free fatty acids that require oxygen to yield adenosine triphosphate, a neutral effect on energy substrate availability may be viewed as a favorable feature of levosimendan administration. Plasma norepinephrine and epinephrine levels were within the normal range in all groups both at baseline and during stimulation. However, nitroprusside was associated with a doubling of plasma norepinephrine. This was most likely the result of the relative hypovolemia observed during nitroprusside infusion.

Myocardial efficiency[28,29] is a practical net measure of cardiac energetics because it refers to the oxygen cost of useful (forward) cardiac work in clinically applicable terms. On the basis of clinical[3,30,31]

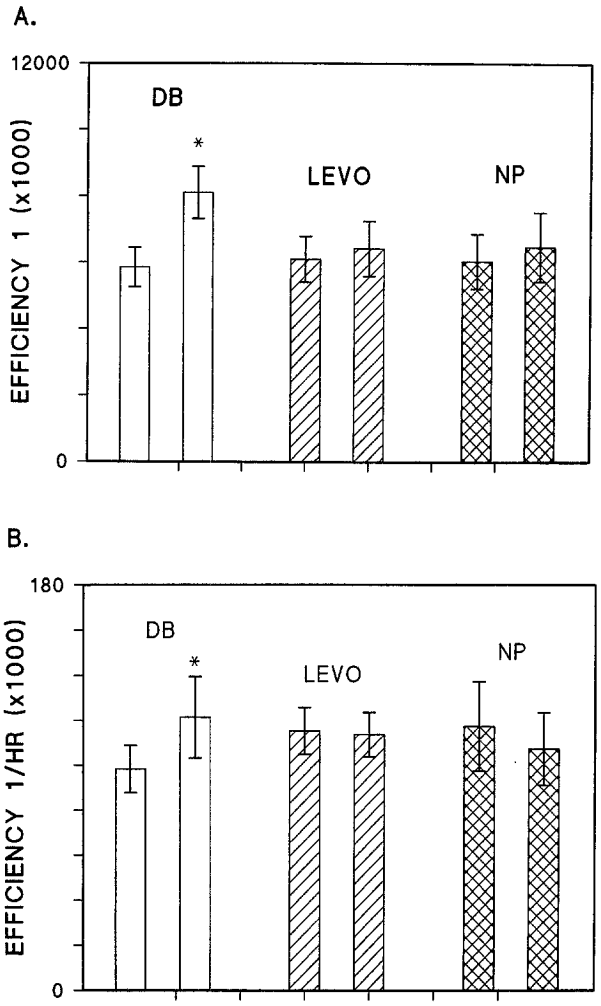

Fig. 5. A, Efficiency (equation 1, mean ± SEM) at baseline and during study treatments. Dobutamine increased myocardial efficiency by 38% ($p < 0.05$), whereas levosimendan and nitroprusside had a neutral effect on myocardial efficiency. **B,** Calculated per beat, a moderate improvement was observed with dobutamine (24%), whereas levosimendan showed a neutral effect. Efficiency per beat tended to decrease with nitroprusside (9%), possibly as a result of relative hypovolemia.

and experimental[7-9,32,33] evidence, it now appears to be justified to conclude that calcium sensitizers as a group have neutral or favorable effects on cardiac efficiency in vivo. To what extent these effects are truly reflecting changes on the contractile protein level remains to be shown. Such studies will inevitably be affected by the large individual variability of hemodynamic and energetical parameters both at baseline and during carefully adjusted treatments.

Moreover, hemodynamic and energetical results obtained in healthy volunteers must be interpreted with caution because of their limited relevance to cardiovascular disease. Abnormal myocardial wall stress and loading conditions, mitral regurgitation, reduced vascular compliance, ventricular asynergy, and restricted myocardial oxygen supply are powerful modifiers of the results as cardiotonic drugs are tested in patients with congestive heart failure.

The invasive approach to measurement of cardiac oxygen balance and efficiency carries, apart from an inherent risk to the patient, important methodologic drawbacks, particularly in the diseased heart. Estimates of myocardial oxygen consumption are sensitive to errors in measuring epicardial coronary blood flow that cannot differentiate between nutritive and non-nutritive myocardial perfusion. Estimates usually apply to only the left descending coronary artery territory, but they are extrapolated to the entire left ventricular muscle mass. Measurements of myocardial oxygen consumption by PET are necessary to evaluate cardiac efficiency by noninvasive methods. Because cardiac catheterization is not required, this approach facilitates pharmacodynamic studies in healthy volunteers and makes repeated patient studies more feasible. Moreover, PET allows assessment of nutritive myocardial perfusion and metabolism directly on the tissue level. The method assigns accurate topographic data to all vascular beds, possibly even to the right ventricle.[34] The mean baseline k_{mono} (0.059 ± 0.008) in this study was consistent with previously published values in healthy volunteers.[34] To demonstrate the regional analysis of PET data, we calculated this value as the arithmetic mean of segmental k_{mono} values. Unless the segment size is taken into consideration, this method may cause either underestimation or overestimation of global myocardial oxygen consumption in patient studies. However, in our study this did not affect the results because oxygen consumption was homogenous throughout the left ventricle.

Accurate PET estimates of myocardial oxygen consumption are currently derived from the elimination kinetics of [^{11}C]acetate.[15] The tracer yields excellent image quality and allows data analysis in relatively small myocardial segments. The noninvasiveness, unique opportunity for regional information, and quantification of oxidative metabolism at the cellular level are the advantages of PET over invasive measurements of myocardial oxygen consumption. To fully govern the complexities of cardiac energetics in vivo, alignment with other imaging modalities, such as multidimensional echocardiography and magnetic resonance imaging, are required to produce data of segmental left ventricular structure and function. Taken together, these methods may allow regional analysis of myocardial energetics in the diseased heart.

Pirjo Mills-Owens, RN, Orion Pharma Corporation, Professor Pertti Pentikäinen, University of Helsinki, and Professor Uno Wegelius, Ulla Ruotsalainen, MSc, Mika Teräs, MSc, and the personnel of the Turku PET Center are appreciated for their dedication to this study.

References

1. Katz AM. Cardiomyopathy of overload: a major determinant of prognosis in congestive heart failure. N Engl J Med 1990;322:100-10.
2. Hasenfuss G, Holubarsch C, Heiss HW, Meinertz T, Bonzel T, Wais U, et al. Myocardial energetics in patients with dilated cardiomyopathy: ifluence of nitroprusside and enoximone. Circulation 1989;80:51-64.
3. Hasenfuss G, Holubarsch H, Heiss HW, Allgeier M, Just H. Effects of pimobendan on hemodynamics and myocardial energetics in patients with idiopathic dilated cardiomyopathy: comparison with nitroprusside. J Cardiovasc Pharmacol 1989;14(suppl 2):S31-5.
4. Feldman AM. Classification of positive inotropic agents. J Am Coll Cardiol 1993;22:1223-7.
5. Remme WJ. Inodilator therapy for heart failure: early, late or not at all? Circulation 1993;87(suppl IV):IV97-107.
6. Kojima S, Wu ST, Parmley WW, Wikman-Coffelt J. Relationship between intracellular calcium and oxygen consumption: effects of perfusion pressure, extracellular calcium, dobutamine and nifedipine. Am Heart J 1994;127:386-91.
7. Pollesello P, Ovaska M, Kaivola J, Tilgmann C, Lundström K, Kalkkinen N, et al. Binding of a new Ca^{2+} sensitizer, levosimendan, to recombinant human cardiac troponin C: a molecular modelling, fluorescense probe and proton nuclear magnetic resonance study. J Biol Chem 1994:269;28584-90.
8. Pagel PS, Harkins CP, Hettrick DA, Warltier DC. Levosimendan (OR-1259), a myofilament calcium sensitizer, enhances myocardial contractility but does not alter isovolymic relaxation in conscious and anesthetized dogs. Anesthesiology 1994:81;974-87.
9. Haikala H, Linden IB. Mechanism of action of calcium sensitizing drugs. J Cardiovasc Pharmacol 1995; 26(suppl 1):S10-9.
10. Lee JA, Allen DG. EMD, 53998 sensitizes the contractile proteins to calcium in intact ferret ventricular muscle. Circ Res 1991;69:927-36.
11. Hasenfuss G, Pieske B, Kretscmann B, Holubarsch C, Alpert NR, Just H. Effects of calcium sensitizers on

intracellular calcium handling and myocardial energetics. J Cardiovasc Pharmacol 1995;26(suppl 1):S45-51.
12. Edes I, Kiss E, Kitada Y, Powers FM, Papp JG, Kranias EG, et al. Effects of levosimendan, a cardiotonic agent targeted to troponin C, on cardiac function and on phosphorylation and Ca^{2+} sensitivity of cardiac myofibrils and sarcoplasmic reticulum in guinea-pig heart. Circ Res 1995;77:107-13.
13. Lilleberg JM, Sundberg S, Leikola-Pelho T, Nieminen MS. Hemodynamic effects of novel cardiotonic drug simendan: echocardiographic assessment in healthy volunteers. Cardiovasc Drugs Ther 1994;8:263-9.
14. Lilleberg J, Sundberg S, Nieminen MS. Dose-range study of a new calcium sensitizer, levosimendan, in patients with left ventricular dysfunction. J Cardiovasc Pharmacol 1995;26(suppl 1):S63-9.
15. Armbrecht JJ, Buxton DB, Brunken RC, Phelps ME, Schelbert HR. Regional myocardial oxygen consumption determined noninvasively in humans with (1-^{11}C) acetate and dynamic positron tomography. Circulation 1989;80:863-72.
16. Henes CG, Bergman SR, Walsh MN, Sobel BE, Geltman EM. Assessment of myocardial oxidative metabolic reserve with positron emission tomography and carbon-11 acetate. J Nucl Med 1989;30:1489-99.
17. Beanlands RSB, Bach DS, Raylman R, Armstrong WF, Wilson V, Montieth M, et al. Acute effects of dobutamine on myocardial oxygen consumption and cardiac efficiency measured using carbon-11 acetate kinetics in patients with dilated cardiomyopathy. J Am Coll Cardiol 1993;22:1389-98.
18. Beanlands RSB, Armstrong WF, Hicks RJ, Nicklas J, Moore C, Hutchins GD, et al. The effects of afterload reduction on myocardial carbon 11-labeled acetate kinetics and noninvasively estimated mechanical efficiency in patients with dilated cardiomyopathy. J Nucl Cardiol 1994;1:3-16.
19. Sawada SG, Segar DS, Ryan T, Brown SE, Brown SE, Dohan AM, Williams R, et al. Echocardiographic detection of coronary artery disease during dobutamine infusion. Circulation 1991;83:1605-14.
20. Sahn DJ, DeMaria AN, Kisslo J, Weyman AE. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 1978;58:1072-83.
21. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereau R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. J Am Soc Echocardiogr 1989;2:358-67.
22. Pombo JF, Troy BL, Russell RO. Left ventricular volumes and ejection fractions by echocardiography. Circulation 1971;43:480-90.
23. Troy BL, Pombo J, Rackley CE. Measurements of left ventricular wall thickness and mass by echocardiography. Circulation 1972;45:602-11.
24. Colan SD, Borow KM, Neumann A. The left ventricular end-systolic wall stress-velocity of fiber shortening relation: a load independent index of myocardial contractility. J Am Coll Cardiol 1984;4:714-24.
25. Pike VW, Eakins MN, Allan RM, Selwyn AP. Preparation of [1-^{11}C]acetate: an agent for the study of myocardial metabolism by positron emission tomography. Int J Appl Radiat Isotopes 1982;33:505-12.
26. Någren K, Lehikoinen P, Bergman J, Hällsten U. In: Heselius SV, editor. Routine production of ^{11}C-acetate for investigations of cardiac metabolism with PET in Turku. The Åbo Akademi Accelerator Laboratory Triennal Report 1990-92. Turku, Finland, 1993:72-5.
27. Knuuti MJ, Nuutila P, Ruotsalainen U, Saraste M, Härkönen R, Ahonen A, et al. Euglycemic hyperinsulinemic clamp and oral glucose load in stimulating myocardial glucose utilization during positron emission tomography. J Nucl Med 1992;33:1255-62.
28. Burkhoff D, Sagawa K. Ventricular efficiency predicted by an analytical model. Am J Physiol 1986;250:R1021-7.
29. Baxley WA, Dodge HT, Rackley CE, Sandler H, Pugh D. Left ventricular mechanical efficiency in man with heart disease. Circulation 1977;55:564-8.
30. Remme WJ, Kruijssen DA, van Hoogenhuyze DC, Krauss XH, Bartels GL, Storm CJ, et al. Hemodynamic, neurohumoral, and myocardial energetic effects of pimobendan, a novel calcium-sensitizing compound, in patients with mild to moderate heart failure. J Cardiovasc Pharmacol 1994;24:730-9.
31. Mori M, Takeuchi M, Takaoka H, Hata K, Yamakawa H, Yokoyama M. Unique vasorelaxing properties with a new cardiotonic agent MCI-154 in human diseased heart: comparison with phosphodiesterase inhibitor [abstract]. J Am Coll Cardiol 1994;1:479.
32. Soei LK, Sassen LM, Fan DS, van Veen T, Krams R, Verdouw PD. Myofibrillar Ca^{2+} sensitization predominantly enhances function and mechanical efficiency of stunned myocardium. Circulation 1994;90:959-69.
33. Grandis DJ, DelNido PJ, Koretsky AP. Functional and energetic effects of the inotropic agents EMD-57033 and BAPTA on the isolated rat heart. Am J Physiol 1995;269:C472-9.
34. Tamaki N, Magata Y, Takahashi N, Kawamoto M, Torizuka T, Yonekura Y, et al. Oxidative metabolism in the myocardium in the in the normal subjects during dobutamine infusion. Eur J Nucl Med 1993;20:231-7.