《原 著》

The Reproducibility and Variability of Sequential Left Ventricular Ejection Fraction Measurements by the Nuclear Stethoscope

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Abstract We evaluated the reproducibility and variability of sequential left ventricular ejection fraction (LVEF) measurements by the nuclear stethoscope in 72 patients. The group as a whole demonstrated excellent reproducibility ($r=0.96$). However, repeat LVEF measurements by the nuclear stethoscope at 5-minute interval showed around 9% absolute difference, at 95% confidence levels, from one measurement to the next. The finding indicates that a change in LVEF greater than 9% is necessary for determining an acute effect of an intervention in individual cases.

Introduction

The nuclear stethoscope is a simple, portable, non-imaging scintillation probe with an integrated microcomputer, especially designed for beside-monitoring of changes in left ventricular (LV) function. It is now being used in a broad variety of clinical and research applications, such as the evaluation of the acute effect of an intervention on LV function[1-3]. Unlike the gamma camera, however, it cannot provide a visual display of LV, so the optimal probe positioning over LV and proper background activity level is not so easy as the gamma camera. There were several reports that discussed the reproducibility and variability of sequential radionuclide angiocardiographic measurements of LV ejection fraction (EF)[4-12]. The accuracy and reproducibility of LVEF determined by the nuclear stethoscope, also, have been reported[13-15], but the change in LVEF that can be expected in sequential studies without interventions has not been defined. This information is necessary for determining whether an intervention has an effect on LVEF.

Therefore, we designed this study to investigate the reproducibility of sequential measurements of LVEF by the nuclear stethoscope and to define the limits to differentiate a true acute change induced by an intervention from a random variation in individual cases.

Materials and Methods

Seventy-two patients, 15 females and 57 males, with a mean age of 54 years (range 16 to 79 years) were studied. Twenty-seven patients had old myocardial infarction, 18 had stable angina pectoris, 13 had chest pain syndrome (CPS) without coronary artery disease (CAD), 3 had dilated cardiomyopathy (DCM), 2 had hypertrophic cardiomyopathy, and 9 had miscellaneous cardiac disorders.

All patients were studied in the supine position using the nuclear stethoscope (Bios Inc., USA) after blood-pool labelling by either 15 mCi of technetium-99m human serum albumin or 10 mCi of technetium-99m red blood cells (in vivo labelled). Following a bed rest for 20–30 minutes, that is, after fluctuations of heart rate and blood pressure being minimal, the probe was placed over the chest in 20–40 degree left anterior oblique position with 10–20 degree caudal tilt. The precordium was scanned to approximate the LV position and

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background activity. The average LV time-activity curve after background subtraction was obtained by the ventricular function mode with an acquisition period of 60 seconds. LVEF was automatically computed from the curve using the formula:

EF=(end-diastolic counts−end-systolic counts) / (end-diastolic counts−background).

LVEF measurements were repeated twice to five times at 5-minute interval in each patient. To define the intrinsic variability, we used 95% confidence limits using linear regression analysis and estimated 95% confidence limits for absolute deviations from a measurement to successive one.

In addition, we performed several interventions and assessed the effects of these interventions on LVEF according to our estimated criterion for assessing significant changes in LVEF. These interventions included sublingual administration of nitroglycerin (0.3 mg) in 28 patients with CAD, sublingual administration of nicorandil (20 mg) in 6 patients (3 with CAD and 3 with CPS), intravenous infusion of dobutamine (16 μg/min/kg) in 6 patients (4 with CAD and 2 with DCM), and hand grip sustained for 3 minutes at 30% of maximum in 6 patients (4 with CAD and 2 with DCM).

In 48 patients within this study group, contrast ventriculography was performed by injection of 30–40 m*l* of 76% meglumine sodium diatrizoate into the LV, and LVEF was calculated from volumes determined by the single plane area-length method within one week of the measurements by the nuclear stethoscope. All patients were in clinically stable condition and medications were continued without changes within this time period.

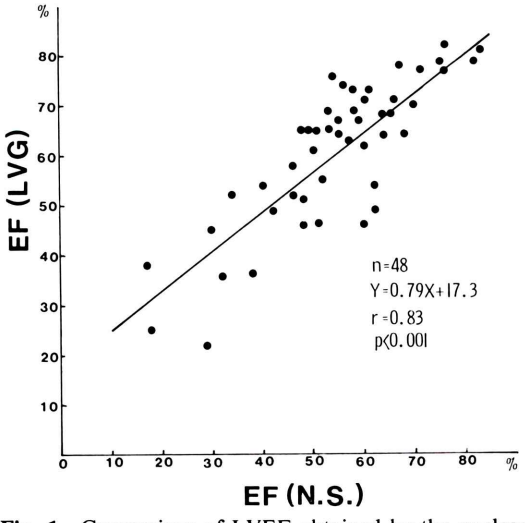

Fig. 1 Comparison of LVEF obtained by the nuclear stethoscope (N.S.) and by contrast ventriculography (LVG) in 48 patients.

Results

LVEF calculated by the nuclear stethoscope correlated with those determined from contrast ventriculography in 48 patients, with the correlation coefficient (r) 0.83 ($p<0.001$) (Fig. 1).

There was a significant correlation ($r=0.96$; $p<0.001$) between a measurement (STUDY I) and successive one (STUDY II) of the 220 paired LVEF determinations by the nuclear stethoscope in 72 patients. Figure 2 illustrates the linear regression analysis between the consecutive measurements with 95% confidence intervals for EF (STUDY II) predicted from EF (STUDY I). Figure 3 illustrates the relationship between EF (STUDY I) and absolute deviation in LVEF (ΔEF=EF (STUDY

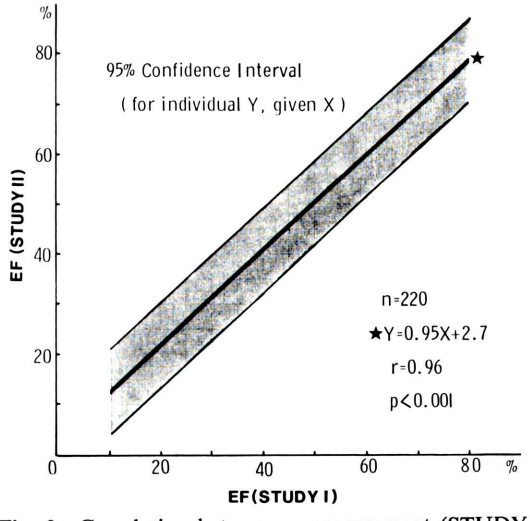

Fig. 2 Correlation between a measurement (STUDY I) and successive one (STUDY II) of the 220 paired LVEF determinations by the nuclear stethoscope in 72 patients. The regression line (★) and 95% confidence intervals (shadow) for EF (STUDY II) predicted from EF (STUDY I) are illustrated.

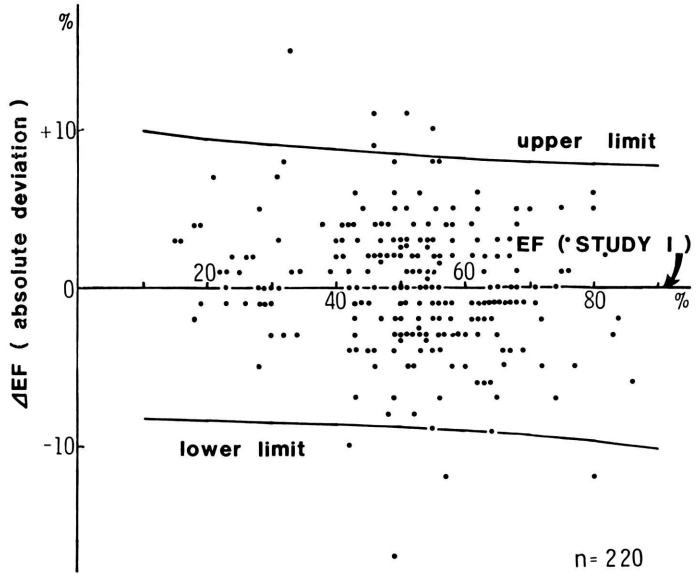

Fig. 3 Relationship between EF (STUDY I) and absolute deviation in LVEF (ΔEF= EF (STUDY II)−EF (STUDY I)). The two curves represent 95% confidence limits for ΔEF predicted from EF (STUDY I).

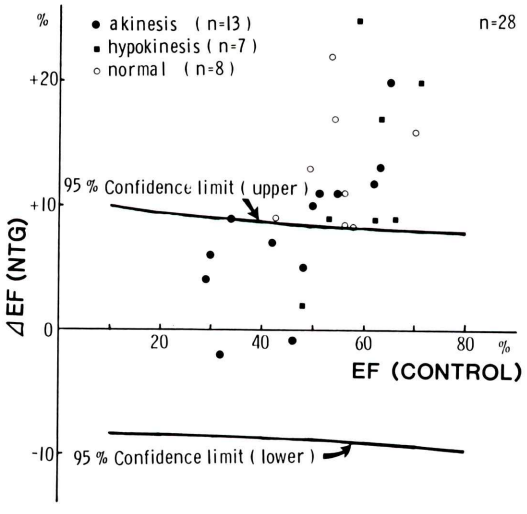

Fig. 4 Changes in LVEF induced by sublingual administration of nitroglycerin (0.3 mg).

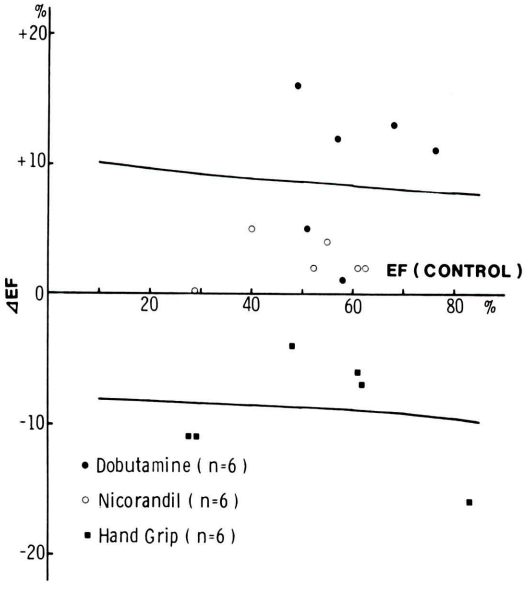

Fig. 5 Changes in LVEF induced by dobutamine, nicorandil and hand grip.

II)−EF (STUDY I)) and the curves in Fig. 3 represent 95% confidence limits for ΔEF predicted from EF (STUDY I). The upper curve varies from about 8% to about 10% with the mean 9% and the lower one from about −8% to about −10% with the mean −9%. These findings demonstrated that an absolute change greater than 9% in LVEF is more likely to represent a nonrandom rather than a random difference.

In practical terms, we selected absolute changes

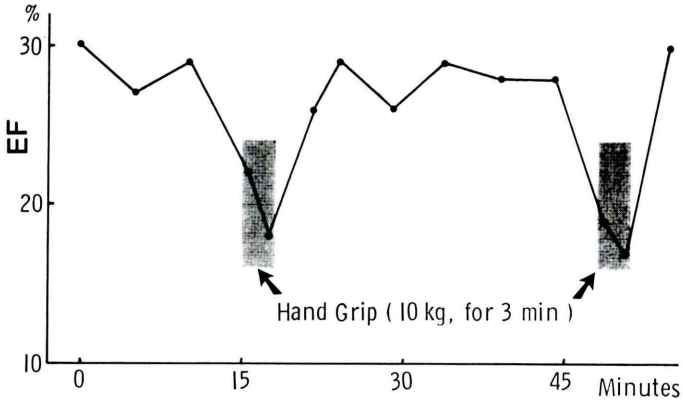

Fig. 6 Changes in LVEF induced by hand grip in a patient with dilated cardiomyopathy.

of at least 9% as limits for assessing significant alterations in LVEF in individual patients.

Figure 4 illustrates the changes in LVEF induced by sublingual administration of nitroglycerin. LVEF was measured 5 minutes after administration. According to left ventriculography, 13 patients had akinesis, 7 had hypokinesis, 8 had normal contraction. The patients with normal contraction and the patients with abnormal contraction and control EF more than 50% had ΔEF above the upper limit of 95% confidence after administration of nitroglycerin. On the other hand, there were no correlation between ΔEF and the number of coronary vessels diseased. Figure 5 illustrates the changes in LVEF induced by dobutamine, nicorandil and hand grip. LVEF was measured during infusion of dobutamine, 5 minutes after administration of nicorandil, or during hand grip. Four of 6 patients showed significant increase in LVEF during infusion of dobutamine, but in the other 2 patients dobutamine induced no significant increase in LVEF. After administration of nicorandil none of 6 patients showed significant increase in LVEF. During hand grip three of 6 patients showed significant decrease in LVEF. An example of hand grip performed twice in a patient with DCM is illustrated in Fig. 6. LVEF decreased by 11% from rest during hand grip in both examinations.

Discussion

Our study demonstrated that LVEF determined by the nuclear stethoscope is an accurate and reproducible index of LV performance that correlates with measurements made by contrast ventriculography. In individual patients, however, LVEF measured by the nuclear stethoscope showed rather marked sequential variation.

There have been studies of the reproducibility of LVEF measurements by contrast ventriculography. McAnulty et al.[16] reported that the group as a whole demonstrated no significant day to day changes in LVEF measured by contrast ventriculography in 14 patients, but individual patients showed rather marked day to day variation in LVEF which ranged from -0.16 to $+0.09$. Cohn et al.[17], also, demonstrated that the range in changes in sequential LVEF measurements by contrast ventriculography was -0.15 to $+0.20$ in patients with CAD.

The reproducibility of the sequential LVEF measurements by radionuclide angiocardiography has been studied and the sequential variability has been discussed[4-12]. Upton et al.[11] investigated the intrinsic variability of LVEF measurements by first-pass radionuclide angiocardiograms. In 10 normal subjects who had repeat studies 2 days apart, the variability in LVEF between studies was $4.0\pm3.8\%$ at rest and $3.2\pm2.5\%$ during exercise (mean$\pm$standard deviation of the absolute deviation of the absolute differences). Therefore, they noted that repeat EF determinations, at 95% confidence levels, should not vary by more than 8% at rest and 5% during exercise in normal subjects. Wackers et al.[12] evaluated the reproducibility of serial determinations of LVEF obtained

by multiple gated imaging and suggested that the absolute change in EF should be 10% or more in normal patients and 5% or more in abnormal patients, in order to be attributed to nonrandom physiologic alternations.

Recent studies have demonstrated the reproducibility of LVEF measurements by the nuclear stethoscope[13-15], but they have not described the limits of the intrinsic variability, which should be defined before the technique is applied to sequential studies. Because the nuclear stethoscope is adequate to monitor the short-term changes in LVEF and has been actually used to evaluate an acute effect of an intervention of LVEF, the limits to differentiate a true acute change in LVEF from a spontaneous variation must be quantified for determining whether an intervention has an effect on LVEF in individual cases.

In our study, repeat LVEF measurements by the nuclear stethoscope at 5-minute interval showed around 9% absolute difference, at 95% confidence levels, from one measurement to the next. The result is almost similar to those of the above studies by contrast ventriculography and by radionuclide angiocardiography, although in those studies the intervals of the serial measurements were longer than that in our study and it would be expected that the longer the time between sequential studies the greater the variability of LVEF measurements[17]. Such a rather marked variation in LVEF, even at a short or 5-minute interval, may be due to several factors. The first is the change in the hemodynamic states. However, this is probably not significant since hemodynamic variables such as heart rate and blood pressure were stable during sequential measurements in this study. Second is the change in the relative position between the probe and the heart due to respiration, motion of a patient, and so on. Especially, in the presence of wall motion abnormalities, which may make it difficult to determine optimal ventricular position, even small changes in the relative position between the probe and the heart may lead to considerable fluctuations of EF values in sequential measurements due to eccentric LV-positioning of the probe. In addition, a short acquisition period (60 seconds) may be another reason for the variation in LVEF measurements. The acquisition times in the reported studies[4,5,7,8,12] of gated equilibrium blood pool scintigraphy ranged from 2 minutes to 10 minutes. The long acquisition time can provide noiseless data and hence may reduce the intrinsic variability.

In conclusion, this study has demonstrated around 9% absolute differences, at 95% confidence levels, in sequential LVEF measurements by the nuclear stethoscope at 5-minute intervals. Therefore, we have proposed that a change in LVEF greater than 9% is necessary for determining an acute effect of an intervention such as an administration of a drug in individual cases when LVEF is measured by the nuclear stethoscope.

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要　旨

核聴診器を用いた左室駆出率の繰り返し測定における再現性と変動域の評価

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われわれは，核聴診器によって左室駆出率を繰り返し測定した場合の再現性と変動域について，72症例を対象として検討した．全体としての再現性は，相関係数が0.96と非常に良好であった．しかし，5分間隔での繰り返し測定での変動域は，直線回帰分析を用いた95%信頼限界で約9%と決して小さくない値であった．したがって，個々の症例において，薬剤投与や運動負荷などによって左室駆出率が9%以上変動してはじめて，有意な効果であると判定できると考えられる．

Key words: Nuclear stethoscope, Left ventricular ejection fraction, Reproducibility, Sequential, Variability.