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ORIGINAL ARTICLE

Assessment of the arterial input function for estimation of coronary flow reserve by single photon emission computed tomography: comparison of two different approaches

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Abstract
Purpose Attempts to estimate coronary flow reserve (CFR) with single photon emission computed tomography (SPECT) tracers have been recently made. We compared two different methods for the estimation of CFR by SPECT imaging.
Methods Fourteen patients with coronary artery disease underwent dipyridamole ^{99m}Tc-sestamibi SPECT and intracoronary Doppler within 5 days. Myocardial blood flow (MBF) was estimated by measurement of first transit counts in the right pulmonary artery (PA) and left ventricular (LV) chamber, and myocardial counts from SPECT images. Estimated CFR was expressed as the ratio of stress MBF to rest MBF.
Results Rest and stress MBF obtained using first transit counts from PA were higher compared to that from LV chamber (rest: 1.05±0.38 vs 0.87±0.34 counts/pixel per s, respectively, $p<0.01$ and stress: 1.34±0.45 vs 0.91±0.20 counts/pixel per s, respectively, $p<0.05$). In the study vessels, CFR by Doppler was 1.39±0.42, and SPECT CFR obtained using first transit counts from PA and LV chamber were 1.36±0.43 and 1.16±0.39, respectively (p across categories NS). A significant relationship between SPECT CFR obtained using first transit counts from PA and CFR by Doppler was found ($r=0.85$, $p<0.001$). No relationship between SPECT CFR obtained using first transit counts from LV chamber and CFR by intracoronary Doppler was observed ($r=0.43$, p = NS).
Conclusion SPECT-estimated CFR obtained using first transit counts from right PA is more accurate and correlates better with the results of intracoronary Doppler than estimated CFR obtained using arterial input function from LV chamber.

Keywords Coronary flow reserve · Sestamibi imaging · Arterial input function

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Introduction

The assessment of myocardial ischaemia is crucial to decide which type of work-up is indicated in patients with coronary artery disease (CAD). Single photon emission computed tomography (SPECT) myocardial perfusion imaging represents a validated diagnostic tool for the evaluation of patients with suspected or known CAD [1–4]. Nevertheless, it retains some boundaries due to a limited quantitative capability, especially in patients with diffuse CAD [5, 6]. Measurement of coronary flow reserve (CFR) may be helpful in assessing the functional status of coronary vessels in order to determine disease severity

and effectiveness of implemented therapies [7–10]. The haemodynamic significance of lesions in epicardial vessels has been characterized by invasive techniques such as intracoronary Doppler which provide a direct assessment of coronary flow velocity and relative flow reserve [11, 12]. Cardiac positron emission tomography (PET) allows non-invasive and accurate quantitative measurements of myocardial blood flow (MBF) and CFR [13–15]. PET-based measurement of MBF is useful to assess coronary vasomotor alterations and preclinical but evolving atherosclerosis. However, PET technology has not been routinely employed because of economic and logistic constrains. In this context, SPECT with ^{99m}Tc-labelled tracers has played a key role for the evaluation of myocardial perfusion in patients with CAD [1–4]. Recently, efforts to estimate CFR with SPECT tracers have produced encouraging results [16–29]. In particular, a good agreement of this technique with the results obtained by invasive methods has been showed [16, 18, 19]. However, when this procedure is applied several issues might affect absolute quantitation: some related to low-resolution factors and others dealing with the accuracy of measuring arterial input function. In particular, by using dynamic planar imaging the measurement of input function may be affected by the spillover from adjacent structures and it is not possible to separate the contribution of the myocardium from the left ventricular (LV) chamber blood as well as to avoid the interference of the right ventricle and aorta. The aim of this study was to compare two different computing methods for the estimation of CFR by SPECT imaging with the results of intracoronary Doppler technique in patients with CAD.

Materials and methods

Study population

This study included 14 consecutive patients (11 men, mean age: 54±7 years) with documented CAD in whom percutaneous coronary intervention was planned. No patients had echocardiographic evidence of LV hypertrophy. Two patients had diabetes mellitus and three patients systemic arterial hypertension. At the time of the study, all patients were in clinically stable condition, and patients were taking β-blockers (n=3), angiotensin-converting enzyme inhibitors (n=3) and nitrates (n=6). Patients with previous myocardial infarction were excluded. Within 5 days, all patients underwent an intracoronary Doppler study and ^{99m}Tc-sestamibi imaging. No clinical modification occurred or therapy change was adopted between the SPECT and the Doppler study. All patients were carefully instructed to refrain from oral intake of methylxanthines, including caffeine, during the 24 h before the SPECT and Doppler studies under dipyridamole stress. Global CFR and that computed in the culprit vessel of such patients has already been compared with CFR measured in corresponding territories of subjects with suspected CAD and normal vessels at coronary angiography in our laboratory [16]. The Ethics Committee of our university approved the protocol, and each patient gave informed consent.

Sestamibi imaging

All patients underwent dipyridamole and rest cardiac imaging. Dipyridamole was infused intravenously at a dose of 0.74 mg/kg body weight given over a 6-min period with monitoring of symptoms, blood pressure and 12-lead electrocardiography [30]. No patients had severe angina or hypotension or developed other intolerable side effects. ^{99m}Tc-sestamibi, 555 MBq, was injected intravenously as a bolus 1–2 min before completion of the stress test. Dynamic planar images were acquired for 60 s (4 frames/s) in the anterior view to measure the first transit counts in the pulmonary artery (PA) and in the LV chamber. SPECT imaging was performed 60 min later. Data were acquired with a rotating single-head gamma camera (Elscint SP4HR, Elscint, Haifa, Israel) connected with a dedicated computer system. Thirty-two projections (30 s/projection) were obtained over a semicircular 180° arc, which extended from the 30° right anterior oblique to the left posterior oblique position. A 20% symmetric energy window centred on the 140-keV peak was used. Filtered backprojection was then performed with a low-resolution Butterworth filter with a cut-off frequency of 0.5 cycles per pixel and order of 5.0. No attenuation or scatter correction was applied. Rest imaging was performed on a separate day following the same acquisition protocol.

For first-pass analysis, serial images of the first transit study were evaluated frame by frame, and on the summed image (3–5 s duration), 3 × 2-pixel regions of interest (ROI) were assigned at the main right PA and at LV chamber. After algorithm smoothing over a mean of 3 points, the area under the time-activity curve was calculated to obtain the time integral of the first-pass tracer counts for both PA and LV ($\int[C(t)dt]$). Sestamibi activity was measured on two representative short-axis tomograms (at mediobasal and medioapical levels). For each short-axis tomogram, a global ROI including the whole myocardial thickness was assigned. In addition, each tomogram was divided into six sectors of equal arc, representing the anterolateral, lateral, inferior, posteroseptal, septal and anterior myocardium, and a regional ROI was located in the corresponding sector. Tracer activity was expressed as absolute myocardial counts, and mean tracer uptake for each major coronary territory was calculated. Counts from PA, LV and myocardium were not corrected for background. To directly

compare the results of sestamibi imaging with those of intracoronary Doppler, each segment was assigned to one of the major vascular territories. In brief, the left anterior descending artery territory included the anterior and anterolateral walls and septum. The right coronary artery was assigned the posteroseptal and inferior walls. The left circumflex artery was assigned the lateral wall. Estimated MBF under stress and resting conditions was measured as myocardial counts/($\int[C(t)dt]$) considering the input function obtained from both right PA and LV. It was expressed as counts/pixel per s. Estimated CFR was expressed as the ratio of stress MBF to rest MBF. The accuracy and reproducibility of this method have been previously reported [16].

Intracoronary Doppler study

Intracoronary CFR measurements with Doppler guide wires were performed in stenotic vessels in which percutaneous coronary intervention was planned immediately before treatment. In brief, CFR was continuously evaluated starting at baseline and during dipyridamole infusion. As for sestamibi imaging, dipyridamole was infused intravenously at a dose of 0.74 mg/kg body weight given over a 6-min period with monitoring of symptoms, blood pressure and 12-lead electrocardiography [30]. No patients developed severe angina, hypotension or other intolerable side effects. FloMap 5500 (Cardiometrics Inc., Rancho Cordova, CA, USA) and Doppler flow wire (0.014-inch, 12-MHz FloWire, Cardiometrics Inc., Rancho Cordova, CA, USA) were used. The tip of the flow wire was carefully positioned as distally as possible and, in any case, beyond the stenosis. Intravascular velocity measurement was achieved at rest and during maximal vasodilatation induced by dipyridamole infusion. CFR was calculated by the ratio of mean maximal systolic-diastolic velocity at hyperaemia to the corresponding velocity at rest, by use of a machine-incorporated software system. Examinations were recorded on S-VHS videotape.

Statistical analysis

Continuous data were expressed as mean ± SD. One-way analysis of variance (ANOVA) was used for comparing means between groups. Post hoc analysis with Bonferroni correction was performed. Differences between mean values were assessed by Student's t test (two-tailed probability) for paired data. Linear regression analysis was used to assess the relationship between CFR estimated by sestamibi using ROI on both PA and LV and by the intracoronary Doppler technique. A p value < 0.05 was considered statistically significant. Bland-Altman analysis was also used to evaluate the agreement between the techniques [31]. With this method, the differences between two techniques are plotted against the means of the two techniques. If the limits of agreement (mean ± 1.96 times the SD of the differences) are not clinically important, the two methods may be considered interchangeable.

Results

In each patient, Doppler flow velocity was measured in stenotic vessels in which percutaneous coronary intervention was planned. The individual study vessels and the degree of coronary artery stenosis are shown in Table 1. In the study vessel, SPECT-estimated rest and stress MBF obtained using first transit counts from PA were higher as compared to that from LV chamber (rest: 1.05±0.38 vs 0.87±0.34 counts/pixel per s, respectively, $p<0.01$ and stress: 1.34±0.45 vs 0.91±0.20 counts/pixel per s, respectively, $p<0.05$) (Fig. 1).

Table 1 Individual study vessel and degree of coronary artery stenosis from patients undergoing CFR assessment by sestamibi imaging and intracoronary Doppler

Patient	Study vessel	Coronary artery stenosis (%)
1	Right coronary artery	75
2	Left circumflex coronary artery	75
3	Left anterior descending coronary artery	90
4	Left anterior descending coronary artery	85
5	Left anterior descending coronary artery	90
6	Right coronary artery	75
7	Right coronary artery	75
8	Left anterior descending coronary artery	75
9	Left anterior descending coronary artery	75
10	Left anterior descending coronary artery	75
11	Right coronary artery	65
12	Left circumflex coronary artery	60
13	Left anterior descending coronary artery	70
14	Left anterior descending coronary artery	65

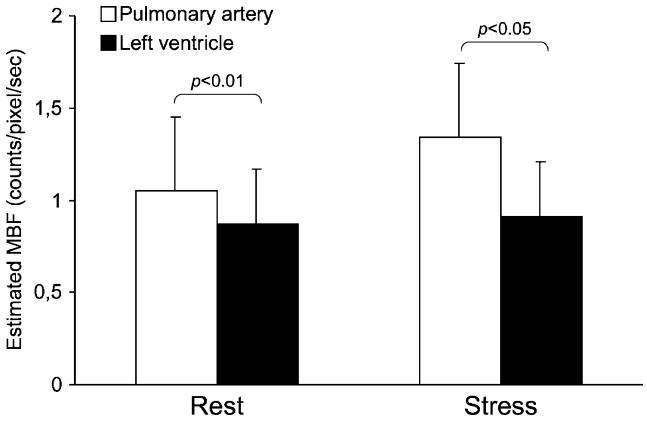

Fig. 1 Stress and rest values of ^{99m}Tc-sestamibi-estimated myocardial blood flow (*MBF*) obtained using first transit counts from pulmonary artery and left ventricle

CFR measured by intracoronary Doppler was 1.39± 0.43, and corresponding SPECT-estimated CFR obtained using first transit counts from PA and LV chamber were 1.36±0.51 and 1.16±0.33, respectively (p across categories NS). A significant relationship between SPECT-estimated CFR obtained using first transit counts from PA and CFR by intracoronary Doppler was found (r=0.85, p<0.001) (Fig. 2). On the contrary, no relationship between SPECT-estimated CFR obtained using first transit counts from LV chamber and CFR by intracoronary Doppler was observed (r=0.23, p = NS) (Fig. 3).

The mean difference between SPECT-estimated CFR obtained using first transit counts from PA and by intracoronary Doppler was 0.02, the SD of differences 0.23, and the lower and upper limits of agreement between the two techniques were −0.44 and 0.48, respectively (Fig. 4). On the other hand, the mean difference between SPECT-estimated CFR obtained using first transit counts from LV chamber and by intracoronary Doppler was 0.22, the SD of differences 0.33, and the lower and upper limits of agreement between the two techniques were −0.71 and 1.16, respectively (Fig. 5).

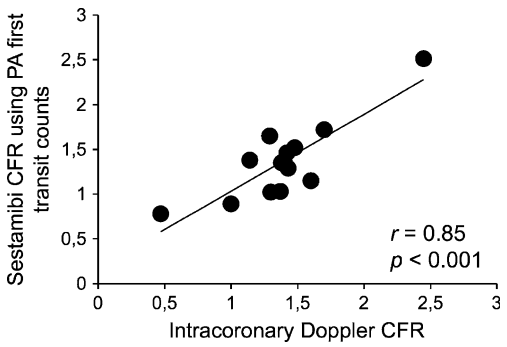

Fig. 2 Relationship between ^{99m}Tc-sestamibi-estimated CFR obtained using first transit counts from the pulmonary artery (*PA*) and intracoronary Doppler CFR

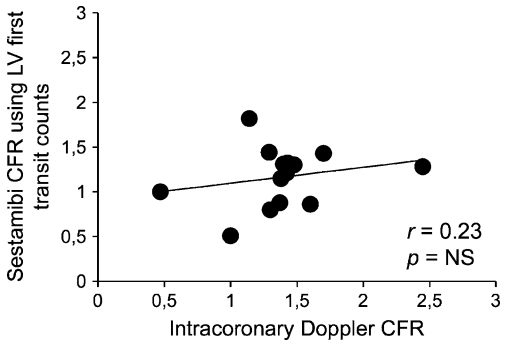

Fig. 3 Relationship between ^{99m}Tc-sestamibi-estimated CFR obtained using first transit counts from the left ventricle (*LV*) and intracoronary Doppler CFR

Discussion

Our results demonstrate that, in patients with documented CAD, CFR estimated by SPECT sestamibi imaging using first transit counts from PA is more accurate and correlates better with the results of intracoronary Doppler than CFR obtained using first transit counts from LV chamber. This study has also shown a reduction in both stress and rest estimated MBF when first transit counts are obtained from LV chamber.

The feasibility of CFR measurement has been widely investigated and its value well recognized. Gould and Lipscomb [32] originally outlined the importance of measuring CFR in clinical practice and were the first to define the relationship between CFR and the severity of coronary stenosis. Although there are some limitations,

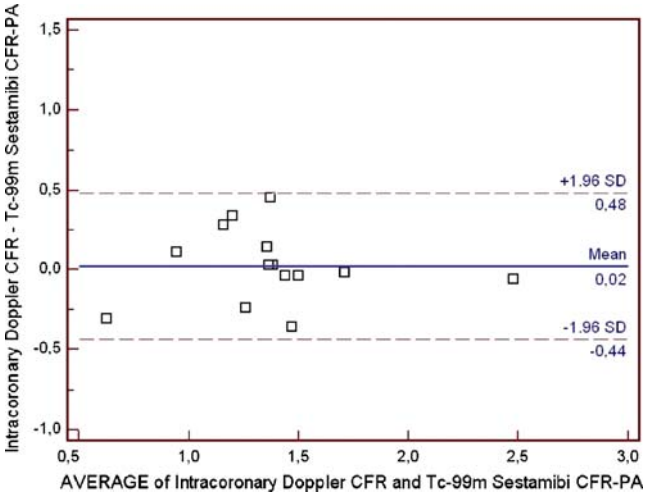

Fig. 4 Agreement between ^{99m}Tc-sestamibi-estimated CFR obtained using first transit counts from the pulmonary artery (*PA*) and intracoronary Doppler CFR by Bland-Altman analysis. The differences between the two techniques are plotted against the means of the two techniques. The *horizontal solid line* indicates the mean difference between the two techniques, and the *dashed lines* indicate the limits of agreement (mean difference ± 1.96 times the SD of the difference)

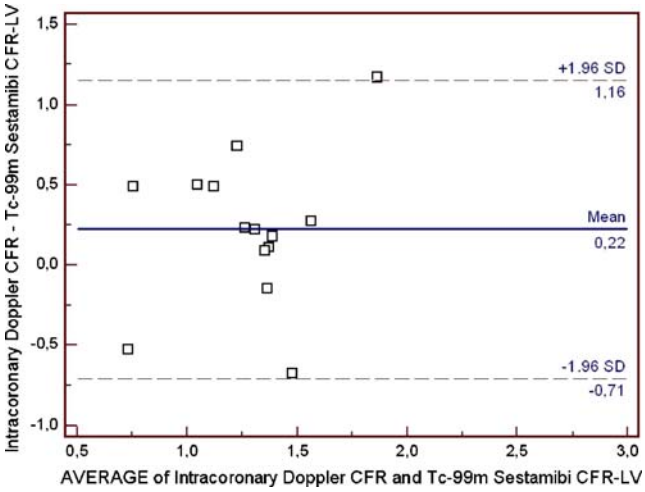

Fig. 5 Agreement between ^{99m}Tc-sestamibi-estimated CFR obtained using first transit counts from the left ventricle (*LV*) and intracoronary Doppler CFR by Bland-Altman analysis. The differences between the two techniques are plotted against the means of the two techniques. The *horizontal solid line* indicates the mean difference between the two techniques, and the *dashed lines* indicate the limits of agreement (mean difference ± 1.96 times the SD of the difference)

CFR measures can be achieved with both invasive and non-invasive procedures [22, 33–40]. Intravascular Doppler ultrasound transducer or pressure transducer attached to the end of an angioplasty guide wire system, once the system is placed into the coronary artery of interest, allows assessing CFR invasively [11, 40, 41]. Essentially, this technique evaluates coronary flow velocity reserve, which is the ratio of intracoronary mean velocity under baseline conditions to mean velocity after pharmacological induction of maximal hyperaemia. Because blood velocity is proportional to flow for a constant vessel area, coronary flow velocity reserve may be calculated from the hyperaemic flow divided by resting blood velocity in a vessel. In our study an intracoronary Doppler wire was used to assess CFR. No angiography was performed at the time of the maximal effect of the dipyridamole infusion avoiding changes in the lumen diameter of the coronary artery at the site of Doppler measurements, which would have affected volumetric flow assessment. Nevertheless, it has been demonstrated that no change or minimal changes occur in coronary diameter after intravenous adenosine or dipyridamole administration and that slight vasodilatation may occur in both normal and stenotic segments; as a result, the percent diameter stenosis is not essentially altered [42–44]. PET and SPECT represent non-invasive methods to evaluate CFR. In particular, PET imaging with ^{15}O water [13–15, 39] and ^{13}N ammonia [45, 46] represents the non-invasive gold standard for obtaining quantitative regional blood flow and CFR, whereas ^{82}Rb has been more recently proposed as a possible agent for these purposes [47, 48]. However, both intracoronary Doppler and cardiac PET, because of their economic constraints and complicated measures, may not be applied routinely in clinical assessment. Recently, estimates of CFR with single photon tracers achieved good agreement with the results obtained by invasive methods [16, 19], even if Taki et al. [18] demonstrated that the increase in myocardial retention of ^{99m}Tc-labelled agents underestimates CFR at high flow rates. For patients with CAD we reported that sestamibi imaging is an accurate and simple way to non-invasively estimate CFR with good interobserver and intraobserver reproducibility [16]. This procedure is based on the microsphere method, which makes use of the fact that sestamibi is taken up by the myocardium according to blood flow. Factors related to low resolution, such as scatter, attenuation and partial volume effects, hamper the absolute quantitation of both arterial and tissue counts, but they may be cancelled out by computing the ratio of tissue and arterial counts. In addition, first-pass studies have intrinsic difficulties such as the need for bolus integrity to obtain best-fit gamma function or the individual characteristics of great vessel anatomy in the adult population [49]. Another important factor affecting the accuracy of estimates is the noise characteristics inherent to dynamic studies. It can be a result of the movement of the patient within the scanner and respiratory movement, as well as cardiac motion.

From a methodological point of view, the procedure chosen to obtain the arterial input function seems to represent one of the most critical factors affecting the accuracy of measurements. In fact, the use of a ROI assigned either to the PA or to the ascending aorta has been alternatively sustained in the estimation of MBF [17, 19, 20]. Provided that appropriate ROI are selected, first-pass studies can yield reasonably accurate and reproducible determinations of cardiac output. The use of a ROI designed on the ascending aorta to measure first transit counts was supported by Ito et al. [9] since this technique may have the potential for greater reproducibility and be less dependent on the bolus administration than is measurement of the first transit counts in the PA. Conversely, the method might have the potential to cause a relatively large error in patients who have low cardiac output with a very slow time-activity curve of the aorta. In the present study all patients had an adequate time-activity curve without insufficient bolus and none of them had impaired LV function. This latter imaging approach was likely gathered from PET studies [50–53], which used a blood time-activity curve derived from a ROI drawn over dynamic PET images of the left ventricle. Results from these studies indicate that the time-activity curve obtained from the LV ROI matched well with the arterial plasma curve. It should be taking into account that ascending aorta and left ventricle represent a unique comprehensive

dynamic system as ventricular/vascular coupling can be assessed from measurements of pressure and flow in the ascending aorta (for left ventricle/systemic circulation) [54]. The integrated model of the left ventricle and aorta has been postulated theoretically [55], studied in animals [56] and investigated in humans by means of magnetic resonance [57]. Another method promotes the use of a right PA ROI to compute the arterial input function for the myocardial perfusion measurements [16, 17]. Although it assumes that the relative proportion of the tracer entering the right PA does not differ between the pharmacological stress and rest studies, differences could be detected in patients with advanced obstructive pulmonary disease or with other diseases affecting the lungs. As a result, both the above-mentioned procedures used to compute arterial input function appear to retain some concerns.

In our study we compared the values of CFR estimated by sestamibi obtained using first transit counts from both PA and LV chamber with those derived from intracoronary Doppler. Although no significant differences were found in CFR measures between the three methods, a significant relationship between CFR estimated by sestamibi using first transit counts from PA and CFR obtained by intracoronary Doppler was observed. On the contrary, no relationship between CFR estimated by sestamibi using first transit counts from LV chamber and CFR obtained by intracoronary Doppler was found. Thus, the accuracy of the arterial input function was improved by assigning a ROI at the right PA. These results endorse the concept that spillover from bordering cardiac structures may affect the accuracy of measurement by sestamibi imaging when the blood pool time-activity curve is derived from a ROI drawn in the ascending aorta or in the LV chamber. Spillover from tissue to the LV blood pool at late times is a more complicated factor when the LV curve is to be used as an input function in PET studies [49]. It depends on the usually high extraction rate of positron-emitting tracers, which does not represent a critical factor when SPECT tracers are used to obtain dynamic images. However, using sestamibi imaging, spillover to the left ventricle from the right ventricle, and atria or to the ascending aorta from the surrounding cardiac structures, should be usually encompassed. In addition, because most acquiring incidences enclose the most part of cardiac chambers some of the noise problems associated with the cardiac motion might not be completely ruled out. To substantiate this hypothesis, we considered SPECT-estimated stress and rest MBF obtained using first transit counts from PA, which were higher as compared to that from the left ventricle. A reduction in both stress and rest MBF accounts for the occurrence of spillover from bordering cardiac structures when left ventricle or ascending aorta is used. Accordingly, CFR estimated by sestamibi imaging obtained using first transit counts from PA correlated well with the results of intracoronary Doppler. Finally, it should be considered that the type of stress might influence CFR measurements [58, 59]. In our study protocol CFR was evaluated by use of dipyridamole for stress testing during both radionuclide imaging and intracoronary Doppler with similar haemodynamic changes [16]. Dipyridamole can be infused at low, intermediate and high dose [30]. Previous studies showed that the effect of intermediate- and high-dose testing does not carry a greater risk than low-dose testing [30, 60]. For the purpose of the current study we employed an intermediate (0.74 mg/kg) dipyridamole dosage.

Conclusion

SPECT-estimated CFR obtained using arterial input function from right PA counts is more accurate and correlates better with the results of intracoronary Doppler than estimated CFR obtained using arterial input function from LV chamber. Thus, the accuracy of arterial input function may be improved by assigning a ROI at PA, avoiding spillover from bordering cardiac structures that can be observed using the LV chamber.

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